



Contribution à la pharmacocinétique d'un antidépresseur inhibiteur de la monoamineoxydase-A en phase III: le moclobémide

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par

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Enzyme du métabolisme du médicament
- Doctorat en Pharmacie
- Maîtrise en Biologie Humaine
- M.B.A.



Sujet:

**Contribution à la pharmacocinétique
d'un antidépresseur inhibiteur de la
monoamineoxydase-A en phase III:
LE MOCLOBEMIDE**

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**Contribution à la pharmacocinétique
d'un antidépresseur inhibiteur de la
monoamineoxydase-A
en phase III:**

LE MOCLOBEMIDE

La classe thérapeutique des inhibiteurs de la monoamineoxydase (IMAO) inhibant l'enzyme du catabolisme des catécholamines présynaptiques englobe les premières drogues utilisées en neuropsychiatrie en tant qu'antidépresseur. L'utilisation de ces IMAO de première génération était limitée, d'une part, par la survenue de crises hypertensives liées à l'ingestion concomitante de tyramine dans l'alimentation, d'autre part, par leur hépatotoxicité et leur incompatibilité avec les antidépresseurs tricycliques et, enfin, par leur irréversibilité et leur manque de spécificité à l'égard de l'interaction avec la monoamine oxydase (MAO).

Il y a quelques années, des IMAO de deuxième génération ont été isolés et divisés en deux types de familles sélectives d'isoenzymes de la MAO, la MAO-A, qui désamine préférentiellement au niveau synaptique la sérotonine et la noradrénaline et sont dotés d'une activité antidépressive dominante et la MAO-B avec comme substrat préférentiel, la phényléthylamine et la benzylamine. Quant à la tyramine et à la dopamine, ce sont des substrats mixtes. L'amélioration des IMAO **irréversibles** et sélectifs de deuxième génération a conduit à une troisième génération récente d'IMAO **réversibles** et sélectifs, appelés **RIMAs** tel que le **MOCLOBEMIDE**.

Le moclobémide est une benzamide dotée d'une activité rapide, sélective, inhibiteur préférentiel et réversible de la MAO-A, spécifique et compétitif ayant des propriétés d'antidépresseur et stimulant. Cette molécule tire son originalité, d'une part, de son absence d'hépatotoxicité conduisant à une bonne tolérance même en association avec d'autres drogues, d'autre part, de sa réversibilité et de sa sélectivité à l'égard du substrat et, enfin, son effet dit "tyramine" mineur. L'activité pharmacologique et thérapeutique du moclobémide apparaît conditionnée, non seulement par son activité intrinsèque mais également par la variation des concentrations du principe actif. Ces variations conditionnent l'efficacité thérapeutique. C'est pourquoi, nous avons consacré nos travaux à la définition du profil pharmacocinétique de phase III du moclobémide.

Des études antérieures chez l'Homme ont permis de définir le profil de disposition du moclobémide après une prise orale unitaire ou intraveineuse. Après administration orale, la résorption de la molécule de moclobémide est rapide et

intense depuis le tractus gastro-intestinal vers la veine porte avec des concentrations plasmatiques maximales atteintes en moins d'une heure et plus de 90 % de la dose administrée éliminés par voie rénale. La biodisponibilité est réduite (0.55 pour 1 dose de 100 mg), en raison d'un effet de premier passage hépatique. L'administration intraveineuse révèle un volume de distribution d'environ 1.2 l/kg lié au caractère lipophile de la molécule de moclobémide.

La demi-vie plasmatique d'élimination est courte (1 à 2 h) avec une clairance systémique relativement élevée de 700 à 1200 ml/min. Cette dernière est le reflet du métabolisme et de la clairance hépatique et suggère une élimination présystémique importante. La liaison aux protéines plasmatiques, essentiellement à l'albumine, est relativement faible (50 %).

Ces données nous ont permis d'approfondir la pharmacocinétique du moclobémide et de deux de ses métabolites en étudiant, dans une première partie, le profil de disposition après administration de doses unitaires et croissantes (2) ainsi qu'une cinétique en traitement chronique permettant d'évaluer l'état d'équilibre (1).

Une deuxième partie nous a conduit à tester l'influence de la prise concomitante de repas (3) sur la cinétique du moclobémide et d'apprécier l'influence des états pathologiques associés aux populations à risques tels que l'insuffisance rénale (4), hépatique (5), l'âge (6) ainsi que l'influence des états physiologiques tel le passage du moclobémide dans le lait maternel (7), donnée importante pour la femme allaitante. En dernier lieu, nous avons voulu relier les données de la pharmacogénétique au métabolisme du moclobémide (8).

La pharmacocinétique du moclobémide durant un traitement chronique oral de 15 jours (100 mg 3x/jour) précédé et suivi d'une perfusion intraveineuse, (I.V.) nous a permis de faire les observations suivantes (étude 1): Les valeurs des paramètres obtenus après la première et deuxième dose I.V. sont respectivement (% c.v.):

Cl_s, 39,4 (15) et 29,1 (12) L/hr; t_{1/2}, 1.60 (15) et 2.00 (18) hr; V_{ss}, 84,3 (11) et 80,7 (15) L.

La réduction de la clairance systémique, avec en parallèle une augmentation du temps de demi-vie d'élimination du moclobémide, nous ont permis de conclure que le moclobémide ou un de ses métabolites pouvait inhiber son propre métabolisme. Quant aux paramètres pharmacocinétiques, après administration orale, ils révèlent une résorption rapide d'environ 0,75 h et une biodisponibilité absolue orale de 0,55 h pour la première dose, passant respectivement à 0,86 et 0,89 h la première et deuxième semaine de traitement. Ainsi, l'état d'équilibre est atteint au plus tard 8 jours après le début du traitement et l'accumulation observée après administration orale pourrait s'expliquer par une diminution de l'effet de premier passage hépatique, ainsi que par une diminution de la clairance métabolique.

Une étude de tolérance de doses unitaires croissantes du moclobémide (2) nous a permis de mettre en évidence une cinétique linéaire dans l'intervalle thérapeutique de 100 à 200 mg. Pour des doses supérieures à 200 mg, la cinétique devient non linéaire accompagnée d'une diminution de la clairance et d'un allongement statistiquement significatif du temps de demi-vie d'élimination. Ces observations reflètent un métabolisme dose-dépendant pour le moclobémide avec une saturation, soit du métabolisme pendant la phase de résorption (réduction du premier passage hépatique à doses élevées), soit de la clairance au cours de la phase qui suit immédiatement l'absorption ou des deux phénomènes simultanés. Ainsi, en traitement chronique à haute dose, on peut s'attendre à des concentrations plasmatiques supérieures à celles prévues par une cinétique linéaire. Bien que cet effet soit important en comparant les doses de 100 et 1200 mg, les conséquences cliniques aux doses thérapeutiques semblent minimales.

La deuxième partie de nos travaux est consacrée plus spécifiquement à des études d'interactions. Ainsi, l'étude de l'influence de la prise de repas sur la biodisponibilité du moclobémide (3) indique qu'en présence d'aliments la résorption est légèrement retardée (1.14 h) sans incidence sur la clinique du moclobémide. Quant à la quantité résorbée évaluée d'après les aires sous les courbes de concentrations en fonction du temps, elle est sensiblement équivalente à jeun et lors de la prise d'un repas. Le quotient des biodisponibilités orales avec et sans repas s'élève en moyenne à 0.98.

L'influence potentielle de l'insuffisance rénale sur l'excrétion du moclobémide et la relative fréquence de cette affection suffisent à justifier notre volonté de préciser le comportement pharmacocinétique du moclobémide dans cet état pathologique. Les caractéristiques de résorption et les données pharmacocinétiques de la disposition du moclobémide ont été évaluées après administration d'un comprimé de 100 mg et d'une perfusion de même dose à 13 insuffisants rénaux (4). Les paramètres obtenus ont été comparés à ceux d'une population saine et aucune différence statistiquement significative n'a été révélée. Les résultats de cette étude indiquent qu'il ne semble pas nécessaire d'ajuster la dose thérapeutique du moclobémide chez les insuffisants rénaux, car l'élimination rénale ne paraît pas influencer la résorption et la disposition du moclobémide.

La molécule de moclobémide subit un métabolisme hépatique prédominant. Ainsi, il nous a semblé primordial d'étudier l'influence de l'insuffisance hépatique sur le comportement pharmacocinétique du moclobémide (5). Pour cela, 100 mg de moclobémide par voie orale et 90 mg en perfusion ont été administrés à 12 insuffisants hépatiques chroniques atteints de cirrhose. Comparés à une population saine, les paramètres cinétiques après une dose intraveineuse montrent qu'en présence d'une insuffisance hépatique le temps de demi-vie et le temps moyen de résidence sont augmentés alors que la clairance systémique est diminuée et le volume de distribution à l'équilibre reste constant. Après administration orale, la clairance est significativement diminuée. Il en résulte des concentrations maximales plasmatiques plus élevées et une biodisponibilité absolue accrue ($F=0,84$) comparée aux sujets sains ($F=0,56$). Les variations observées sont suffisantes pour envisager une modification de posologie chez l'insuffisant hépatique et augmenter les intervalles de prise afin d'éviter une éventuelle accumulation du moclobémide.

La probabilité de prescription d'un antidépresseur chez la personne âgée étant grande, l'évaluation de la pharmacocinétique du moclobémide chez ces sujets devrait être connue. Ainsi, nous avons comparé les caractéristiques de résorption et de disposition chez 14 sujets âgés (65 - 77 ans) (groupe I), à celles de 6 sujets jeunes sains, (22 - 33 ans) (groupe II), après traitement oral chronique de 3 fois 100 mg/jour précédé et suivi d'une dose IV de 75 mg (6). Les paramètres obtenus après la voie IV indiquent que la disposition de moclo-

bémide n'est pas affectée par l'âge. Quant à la voie orale, après la première administration de moclobémide, le sujet âgé voit sa concentration plasmatique maximale augmentée et sa clairance diminuée, alors que le temps de demi-vie et la biodisponibilité absolue orale reste constante par rapport au groupe II. Après un traitement chronique de 15 jours, la clairance orale est diminuée dans les deux groupes avec augmentation de la demi-vie d'élimination. Les mêmes variations étant observées dans une étude précédente (1) chez 12 sujets sains, il semble qu'il ne soit pas nécessaire d'ajuster la posologie en gériatrie.

Après avoir examiné l'influence de deux principaux états pathologiques susceptibles d'interférer sur la disposition du moclobémide, nous avons également voulu savoir si le moclobémide était susceptible de passer dans le lait maternel, vu le caractère lipophile de cette molécule et son utilisation éventuelle dans les dépressions post-partum. L'administration d'une dose de 300 mg de moclobémide à 10 femmes allaitantes indique que seuls 0.06 % de la dose administrée se retrouvent dans le lait dans les 12 heures qui suivent la prise du moclobémide, ce qui semble sans danger pour le nouveau-né; d'autant plus, que la dose thérapeutique prévue est de 100 à 150 mg par prise (7).

Le moclobémide est éliminé à peu près exclusivement après métabolisation. La voie de dégradation prédominante se fait par des réactions d'oxydation de phase I. Au cours des études cliniques pharmacocinétiques, quelques individus isolés ont montré un temps de demi-vie très allongé avec une biodisponibilité anormalement élevée et une clairance diminuée d'un facteur 2. Ces observations peuvent être le résultat de variations interindividuelles liées à un effet de premier passage hépatique élevé mais un contrôle génétique du polymorphisme de l'activité enzymatique n'a pu être exclu. Ainsi, dans une dernière partie, nous avons abordé l'apport de la pharmacogénétique au métabolisme du moclobémide. Le phénotype d'hydroxylation a été déterminé chez 39 sujets dans nos études cinétiques par administration d'un comprimé combiné contenant 10 mg de débrisoquine, 5 métaboliseurs faibles (PM) ont pu être identifiés pour la débrisoquine.

Aucune corrélation significative entre la clairance orale ou temps de demi-vie d'élimination et le phénotypage à la débrisoquine n'a pu être mise en évidence. Les paramètres cinétiques du moclobémide des métaboliseurs efficaces englobent toutes les valeurs des métaboliseurs faibles.

Les paramètres pharmacocinétiques et le métabolisme de 5 IMAO-A réversibles chez l'Homme ont été comparés dans une étude rétrospective (Moclobémide, toloxatone, brofaromine, cimoxatone, amiflamine). Des différences sont observées dans les caractéristiques d'absorption et de disposition. Cependant, il existe une similitude entre le moclobémide et le toloxatone. A noter que les 5 IMAO-A subissent une élimination hépatique prépondérante avec moins de 1 % de substance mère éliminée dans les urines. Le catabolisme se fait principalement par oxydation.

En conclusion, ce travail nous a permis d'apporter des résultats nouveaux, d'approfondir l'aspect pharmacocinétique de la molécule de moclobémide et d'évaluer l'implication thérapeutique dans les populations à risques. La résorption du moclobémide est rapide et complète avec des concentrations plasmatiques maximales atteintes en moins d'une heure suivant l'administration orale.

Le moclobémide présente un effet de premier passage hépatique qui est à l'origine d'une biodisponibilité réduite. Cette réduction est plus prononcée après une dose unitaire ($F = 55\%$) qu'avec des doses multiples ($F = 86 - 89\%$). La clairance plasmatique s'échelonne entre 20 - 50 L/h et le temps de demi-vie d'élimination entre 1 - 2 h.

En traitement chronique, l'état d'équilibre est atteint au bout de 8 jours, avec une augmentation de la biodisponibilité liée à une diminution de la clairance hépatique. La prise concomitante d'aliment semble retarder la résorption de moclobémide mais n'influe pas sur son profil de disposition.

Le métabolisme hépatique du moclobémide étant prédominant, un ajustement de la dose thérapeutique semble nécessaire en cas d'insuffisance hépatique sévère alors que l'insuffisance rénale est sans influence sur sa pharmacocinétique. Chez le sujet âgé sain, la pharmacocinétique du moclobé-

mide n'est pas significativement différente de celle du sujet jeune sain.

Chez la femme allaitante seuls 0,06 % de la dose du moclobémide administrée passe dans le lait maternel dans les 12 h qui suivent la prise de moclobémide. Ainsi, l'allaitement ne semble pas être une contre-indication au traitement avec le moclobémide.

Enfin, l'étude pharmacogénétique suggère que le métabolisme du moclobémide n'est pas altéré chez les métaboliseurs faibles de la débrisoquine.

La pharmacocinétique du moclobémide comparée à quatre autres IMAO-A montre des similitudes avec le toloxatone (effet de premier passage hépatique). Le métabolisme hépatique est prépondérant pour les 5 IMAO-A.

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Liste des abréviations et définitions

$C_{\max}$	Concentration maximale déterminée directement par lecture des variations de concentrations en fonction du temps
CT	Concentration à la fin de la perfusion
C_t	Concentration au temps t
$T_{\max}$	Temps pour atteindre la concentration maximale
$T_{1/2}$	Temps de demi-vie
β	Constante de vitesse liée à la phase terminale
AUC_{∞}	Aire sous la courbe extrapolée à l'infini
Cl_o	Clairance orale apparente
Cl_s	Clairance totale ou systémique
F, F_{obs}	Biodisponibilité orale absolue
F_{red}	Biodisponibilité relative
$F_{\text{iv-pred}}$	Biodisponibilité attendue à partir de données obtenues après administration par voie intraveineuse
$F_{\text{po-pred}}$	Biodisponibilité attendue à partir de données obtenues après administration par voie orale
Q	Débit sanguin hépatique (valeur moyenne estimée à 1.5 L/mn)
MRT	Temps de présence moyen
MAT	Temps de résorption moyen
V_{ss}	Volume de distribution à l'état d'équilibre
f_u	Fraction de médicament non liée
f_m	Fraction métabolisée
MAO	monoamineoxydase
IMAO	inhibiteur de la monoamineoxydase
I.V.	voie intraveineuse
po	voie orale
GI	Gastrointestinal
HPLC	Chromatographie liquide à haute performance
UV	Ultraviolet

Disposition

Processus qui entrent en jeu depuis le moment où le médicament atteint la circulation jusqu'au moment où ce dernier, ou un ou plusieurs métabolites, quittent l'organisme (1).

Biodisponibilité absolue

- Fraction ou pourcentage de la dose d'un médicament en solution qui, après administration, atteint la circulation générale
- Quantité de principe actif atteignant la biophase et la vitesse à laquelle le médicament parvient au site d'action (1).

Résorption

Processus par lequel le composé passe de son lieu d'application dans la circulation générale (1).

Effet de premier passage

Perte de médicament par métabolisme avant son arrivée dans la circulation générale.

Etat d'équilibre ou Steady-State

L'état d'équilibre peut être obtenu lors de l'administration chronique du médicament. Il est atteint lorsque les quantités de substances injectées ou résorbées après chaque administration deviennent égales aux quantités éliminées entre deux administrations.

Introduction

C'est le pédiatre allemand Dost (1a) qui a utilisé pour la première fois, en 1953, le terme de "pharmacocinétique" qu'il définit comme la science des interactions quantitatives entre l'organisme et un médicament administré. Cette discipline s'est fortement développée avec, notamment, le progrès de la chimie analytique, avec l'utilisation de molécules marquées et de l'informatique qui a conduit à la description de molécules de plus en plus complexes. Peu à peu les concepts pharmacocinétiques essentiels sont apparus et leur intérêt est maintenant amplement démontré dans la mise au point des médicaments en particulier en pharmacologie expérimentale, étude de métabolisme et expérimentations cliniques, d'une part chez le sujet sain et, d'autre part en thérapeutique avec l'adaptation des posologies dans les états pathologiques tels que l'insuffisance rénale, hépatique et états physiologiques tels que le sujet âgé ou la femme allaitante. Tous ces facteurs, dont dépend l'efficacité thérapeutique, englobent l'univers de la pharmacocinétique et de ses extraordinaires ressources.

Ainsi, nous avons consacré nos travaux à la définition du profil pharmacocinétique clinique de phase III d'une nouvelle molécule médicamenteuse type benzamide appartenant à la classe thérapeutique des inhibiteurs de l'isoenzyme A de la monoamineoxydase (IMAO) inhibant l'enzyme du catabolisme des catécholamines présynaptiques tels que sérotonine et noradrénaline et utilisée en neuropsychiatrie comme antidépresseur.

Cette molécule est intéressante à différents points de vue. Elle est le fruit d'une recherche intense en pharmacologie ayant conduit à une génération récente d'IMAO réversible et sélectif au niveau de l'interaction avec la monoamineoxydase (MAO) permettant une utilisation non-restrictive de la molécule contrairement à l'ancienne génération d'IMAO dont les nombreuses interactions médicamenteuses, les crises hypertensives par ingestion concomitante de tyramine et leur hépatotoxicité limitaient sensiblement l'utilisation. Cette benzamide dotée d'une activité antidépressive rapide, sélective, inhibiteur préférentiel et réversible de la MAO, de forme A, spécifique et compétitif possède également un profil pharmacocinétique peu classique.

Après une mise au point bibliographique concernant le système MAO et ses inhibiteurs, notre démarche s'est scindée en une double approche:

- Dans la première partie de notre travail personnel, nous avons essayé de définir les caractéristiques pharmacocinétiques de la molécule de moclobémide chez le sujet sain après administration de doses unitaires croissantes et de doses multiples afin de pouvoir extrapoler le comportement de la molécule lors d'un traitement thérapeutique chronique.
- Dans la deuxième partie, nous avons recherché l'influence d'états pathologiques tels que l'insuffisance rénale ou hépatique ainsi que des états physiologiques tels que l'âge et le passage du moclobémide dans le lait maternel.

Par ce biais, nous avons été amenée à tester l'influence de la prise concomittante d'aliments sur la biodisponibilité du moclobémide.

De plus, nous nous sommes intéressée à l'influence de la pharmacogénétique sur le comportement de la molécule dans l'organisme.

Enfin, nous avons comparé le métabolisme de la molécule chez l'animal de laboratoire et l'homme afin de déceler l'existence d'une éventuelle différence métabolique qui pourrait être à l'origine d'une sélectivité de l'activité clinique MAO-A du moclobémide chez l'homme.

2. Mise au point bibliographique

2. Mise au point bibliographique

2.1. Le système monoamineoxydase (MAO) et ses inhibiteurs (IMAO)

2.1.1. Les MAO: Aspect biochimique et rôles

C'est en 1928 que fut découverte l'activité enzymatique de désamination de la tyramine (2). Dans un premier temps, cette enzyme fût baptisée "Tyramine oxydase" en relation avec la découverte de son premier substrat, puis en 1938 (3) a été défini le système enzymatique "monoamineoxydase". Depuis, l'existence de formes principales de l'enzyme ainsi que leur répartition très ubiquitaire dans l'organisme a été précisée. Il a notamment été montré que ces MAO (oxygène oxydoréductase désaminative E.C. 1.4.3.4) sont des flavoprotéines localisées sur la membrane externe des mitochondries (4,5) en particulier sur celle des synaptosomes et également présentes à des degrés différents d'activité dans presque tous les tissus des vertébrés (6) avec une préférence pour les plaquettes sanguines (7-9), le placenta (9-13), l'intestin (14, 15), le foie et le cerveau (16).

Les données biochimiques de l'enzyme indiquent que le site actif des MAO est un résidu flavine lié de façon covalente au groupe thiol d'une cystéine alors que la séquence des acides aminés dans cette région est commune aux 2 formes de l'enzyme ainsi que la présente la figure 1 (17). Les deux isoenzymes MAO-A et MAO-B possèdent au niveau de leur site actif un fragment commun (18-20) formé d'un pentapeptide lié à un groupe prosthétique flavine-adénine diphosphate (FAD). Ce site actif possède un groupement SH essentiel provenant d'une cystéine de l'apoenzyme. L'intervention des groupements α -amines provenant d'un ou plusieurs résidus lysine a également été discutée (21). Récemment à l'aide d'anticorps monoclonaux, les activités MAO-A et B hépatiques humaines ont pu être différenciées (22), dénotant une différence de structure dans la partie adjacente au site catalytique de l'enzyme où les cycles aromatiques se lient au substrat (23). Leur structure primaire a également pu être décrite à partir d'expériences de clonage (24).

Le poids moléculaire des sous-unités a été déterminé comme étant de 59700 et 58800 d pour les MAO-A et B respectivement. La comparaison de la séquence de leurs structures indique que le fragment commun constitué de 5 acides aminés portant le groupe prosthétique FAD fait partie d'une séquence de 20 acides aminés communs localisés à des positions identiques au niveau C terminal. Ces nouvelles données structurales ont stimulé des recherches en cours sur leur structure tertiaire.

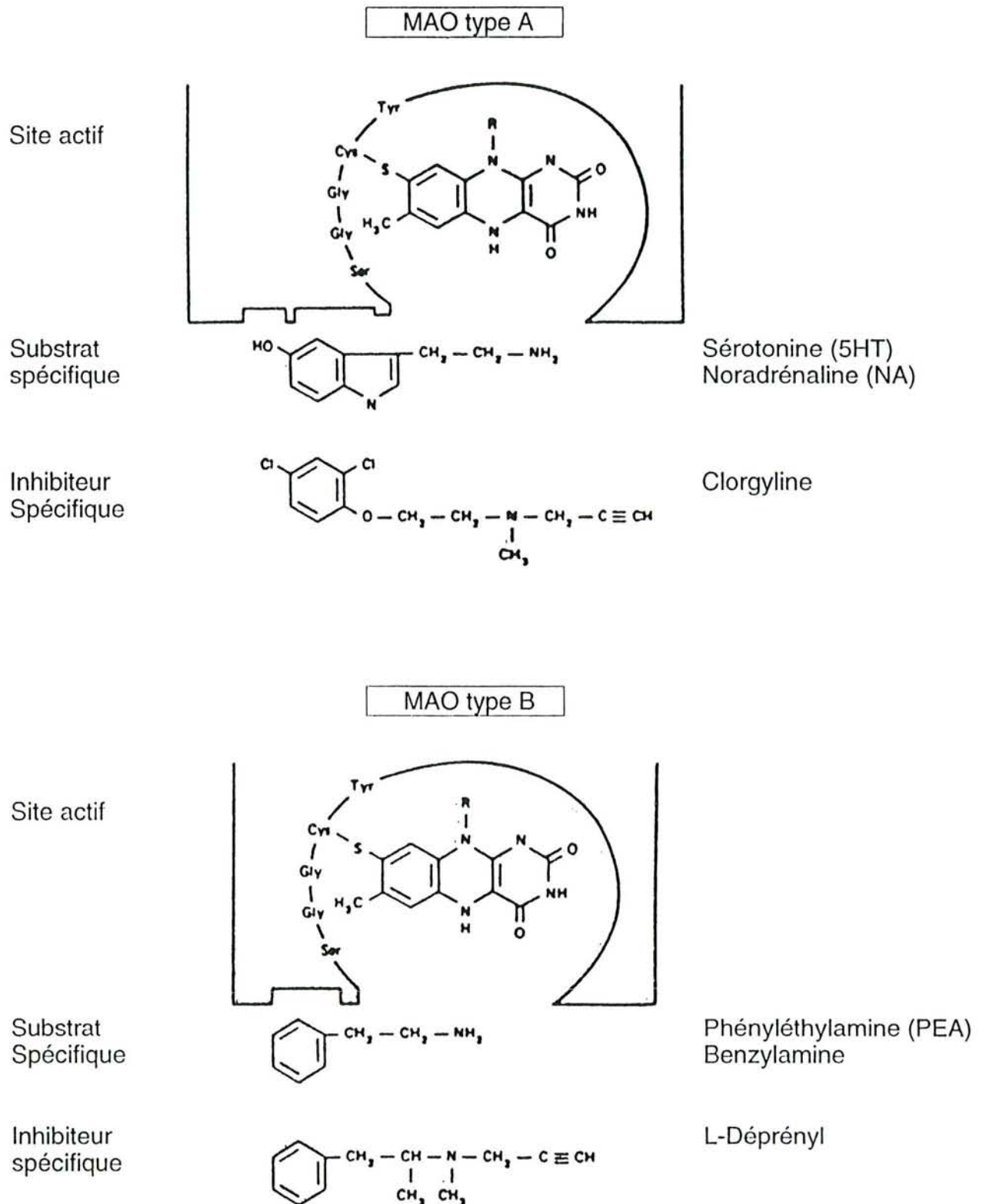


Figure 1: Représentation schématique du site actif et liaison des MAO-A et B avec leur sélectivité de substrats et leur inhibiteurs (adapté de Kalir et coll. (23)).

Le rôle des MAO en tant qu'enzymes intracellulaires est capital dans le catabolisme conduisant à l'inactivation des amines neurotransmettrices présynaptiques accumulées dans les granules ou vésicules au niveau du système nerveux central et tissus périphériques. Les neurotransmetteurs libérés par stimulation sont recaptés en grande majorité (environ 80 %) (25) et dégradés par le système enzymatique MAO (Fig. 2 et 3).

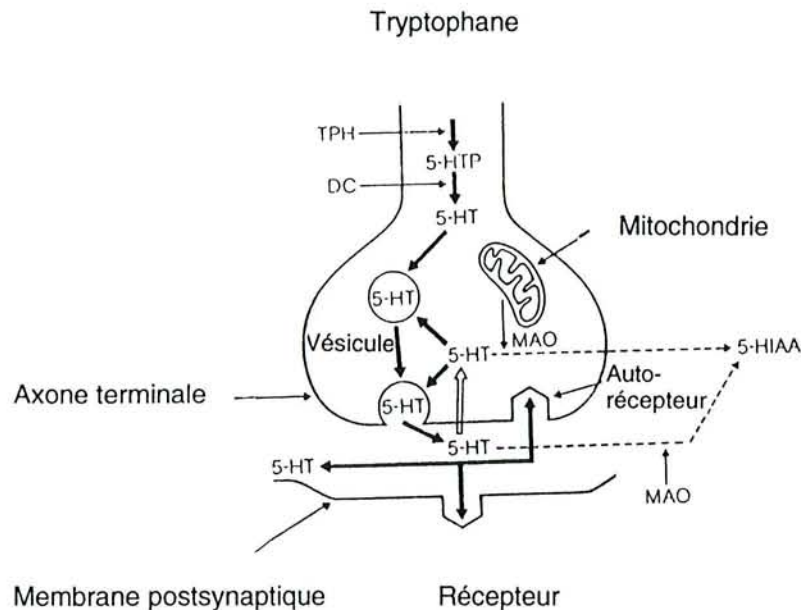


Fig. 2 - Synthèse et métabolisme de la sérotonine

La sérotonine est un substrat préférentiel pour la MAO-A. Le premier produit de dégradation produit par la MAO est l'aldéhyde 5-hydroxyindolacétique. Cet aldéhyde est principalement oxydé en acide 5-hydroxyindolacétique qui est le produit de dégradation majeur du catabolisme de la sérotonine dans le cerveau. Un faible pourcentage de l'aldéhyde est réduit en alcool, le 5-hydroxytryptophol, qui représente une voie mineure dans les conditions habituelles.

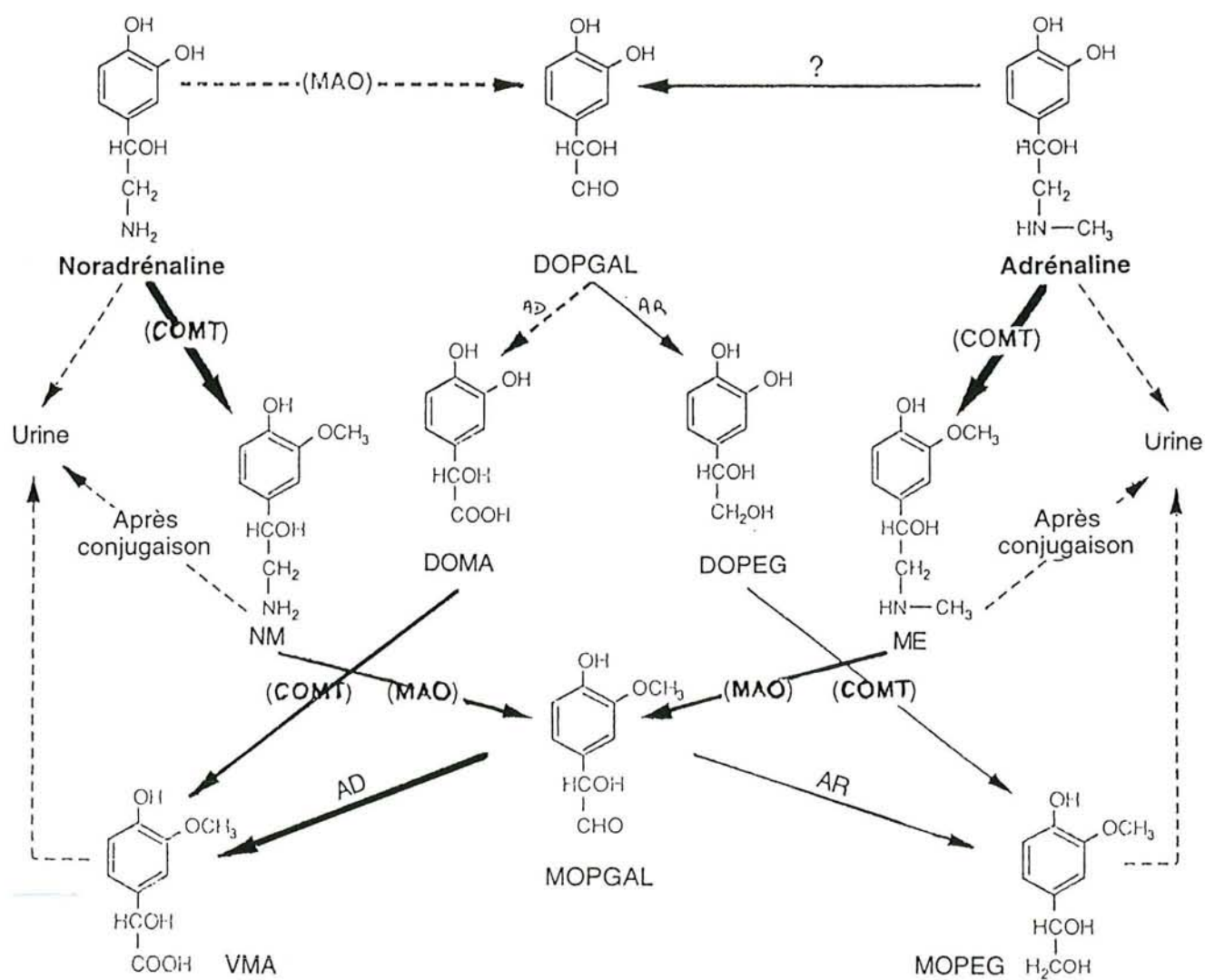


Fig. 3 Synthèse et métabolisme de la noradrénaline

Fig. 3A - Métabolisme

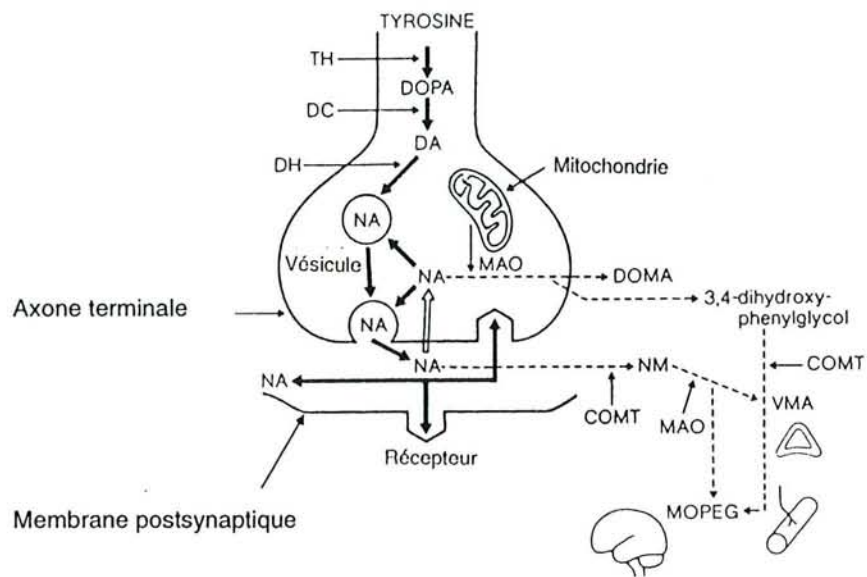


Fig. 3B Localisation neuronale

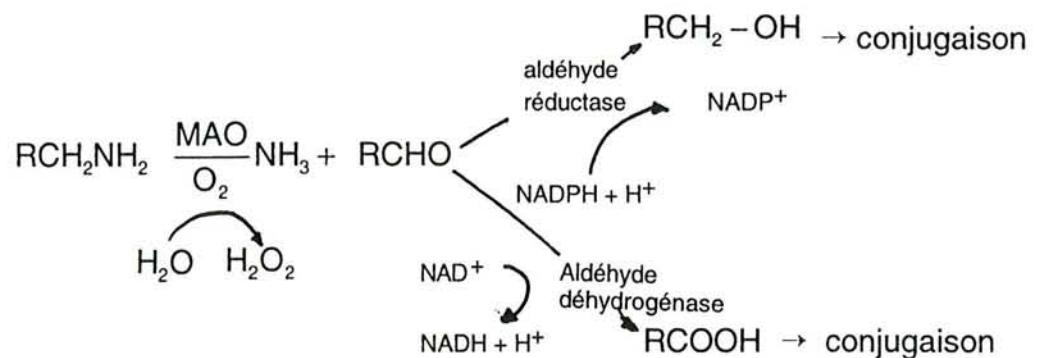
AD	Aldéhyde déshydrogénase
AR	Aldéhyde réductase
COMT	Catéchol-O-méthyltransférase (E.C. 2.1.1.6)
DA	Dopamine
DC	Dopa-décarboxylase
DH	Dopamine β-hydroxylase
DOMA	Acide 3,4-dihydroxymandélique
DOPAC	Acide 3,4-dihydroxy-phénylacétique
DOPEG	= DHPG 3,4-dihydroxy-phényl-éthylène-glycol
DOPGAL	3,4-dihydroxy-phényl-éthylène-glycolaldéhyde
5-HIAA	Acide 5-hydroxy-indol-acétique
MOPEG	= MHPG 3-méthoxy-4-hydroxy-phényl-éthylène-glycol
MOPGAL	3-méthoxy-4-hydroxy-phényl-éthylène-glycolaldéhyde
ME	Métanéphrine
Na	Noradrénaline
NM	Normétanéphrine
N-MT	N-méthyltransférase
TH	Tyrosine hydroxylase
VMA	Acide vanilmandélique = 3-méthoxy-4-hydroxy mandélate

Ainsi, une inhibition des MAO localisées dans la membrane externe mitochondriale du neurone résulte en une augmentation des concentrations présynaptiques de monoamines et de leur quantité disponible dans la synapse neuronale.

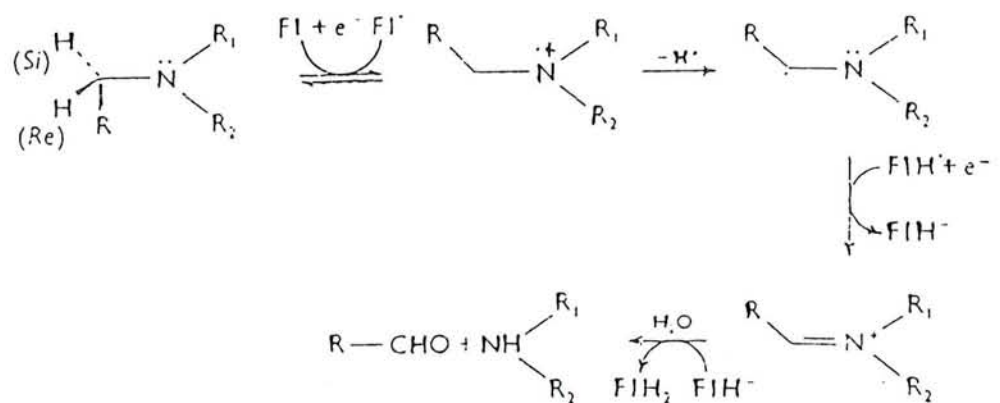
Parallèlement à l'accroissement de la concentration des monoamines, les IMAO diminuent la formation des métabolites désaminés (MHPG ou MOPEG, VMA, DOPAC, 5-HIAA)

L'activité du système enzymatique MAO consiste à catalyser la réaction de désamination oxydative sous la dépendance d'oxygène moléculaire en deux étapes (26, 27) selon l'équation de la Fig. 4:

a) Mécanisme simplifié



b) Mécanisme selon Dosert et all. (27a)



Fl = flavine oxydé

Fig. 4 Mécanisme de désamination oxydative catalysé par le système MAO

Dans l'étape initiale, le substrat est oxydé en imine, dérivé intermédiaire instable. Cet intermédiaire est immédiatement hydrolysé en aldéhyde et ion ammonium. Enfin, l'aldéhyde peut être oxydé en acide sous l'influence d'une aldéhyde oxydase, ou réduit en alcool en présence d'une aldéhyde réductase (28). Les MAO en tant que flavoprotéines (27) désaminent préférentiellement la forme non-ionisée du substrat (29-31).

Une grande variété de monoamines sont désaminées par les MAO. Les amines aliphatiques de structure $\text{CH}_3 - (\text{CH}_2)_n\text{NH}_2$, avec $n=1$ sont désaminées par les enzymes avec un maximum d'activité lorsque $n = 5$ (32-35). Les MAO désaminent également l'isoamylamine et l'isobutylamine (36) mais sont sans action sur les amines α -alkyl-substituées (32, 37). Les amines contenant un groupement aryle sont également métabolisées par cette voie, bien qu'au moins un groupement méthylène non-substitué entre l'amine et le groupement aryle soit nécessaire à l'activité (32, 37). Ainsi les neurotransmetteurs tels que les amines primaires noradrénaline (NA), dopamine (DA), 5-hydroxy-tryptamine ou sérotonine (5-HT) ainsi que les amines secondaires telles que l'adrénaline sont des substrats principaux pour les MAO, de même que les amines des produits alimentaires, telles que la β -phényléthylamine (PEA) et la tyramine (TYR) (25). Cette dernière est principalement désaminée par la MAO hépatique qu'elle atteint par la veine porte depuis son lieu d'absorption intestinale (38). Enfin, certaines amines, non trouvées dans l'organisme telles que la benzylamine sont également métabolisées par cette voie enzymatique (25). Alors que le métabolisme de la sérotonine (Fig. 2) dépend presque exclusivement de la MAO, celui des catécholamines (Fig. 3) nécessite également l'action de la catéchol-O-méthyltransférase (COMT) (39).

L'inhibition de la MAO se traduit par une accumulation de ces médiateurs et de leurs dérivés O-méthylés (3-méthoxy-tyramine, normétanéphrine et métadrénaline) et une disparition de leurs métabolites terminaux (acide 5-hydroxy indolacétique (5-HIAA) pour la sérotonine et acide homovanillique (HVA), 3-méthoxy-4-hydroxy-phénylglycol (MHPG = MOPEG), acide vanylmandélique (VMA) et acide 3,4-dihydroxyphénylacétique (DOPAC) pour les catécholamines (Fig. 3).

2.1.2. Les MAO: Evolution et naissance des IMAO. Aspect pharmacologique.

2.1.2.1. Le système enzymatique des MAO

En 1968, Johnston définit différents types de MAO (40) en étudiant un nouveau composé IMAO et en le comparant aux produits de référence. Pour ces derniers la courbe représentant le pourcentage d'inhibition de la MAO en fonction de la concentration de l'inhibiteur est une sigmoïde simple (Fig. 5).

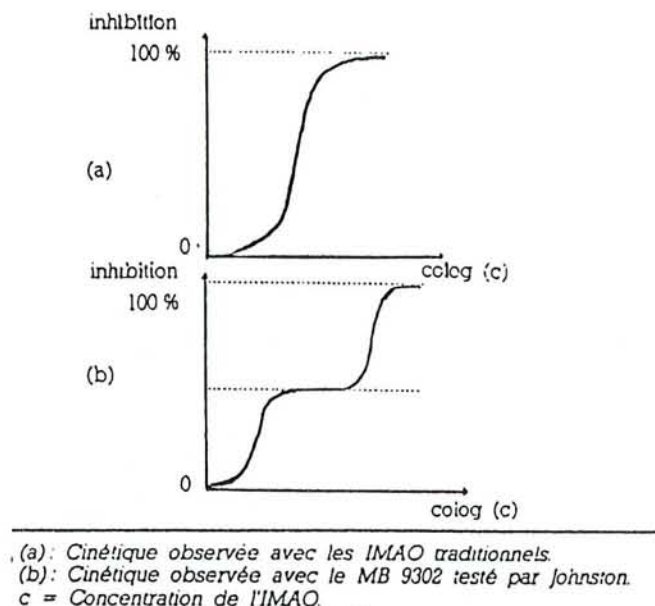


Fig. 5: Courbe d'inhibition de la MAO d'après [Johnston (40).]

Avec le produit nouveau (MB 9302), Johnston constate que la courbe devient un couple de sigmoïdes reliées entre-elles par une portion horizontale où le pourcentage d'inhibition reste constant (Fig. 5). Il en déduit que la MAO est un système binaire d'enzymes dont chacune des deux composantes a une sensibilité différente au produit testé: la première partie (à gauche) représente la courbe d'une enzyme sensible à l'inhibiteur (A), la partie horizontale représente une plage de concentrations d'inhibiteur pour lesquelles la forme (B) n'est pas encore affectée, puis la seconde sigmoïde (partie droite) représente les différents stades d'inhibition de la forme B.

De plus, les résultats de Johnston au cours de ce remarquable travail ne se sont pas limités à la constatation de la dualité de la MAO, il a en effet montré que chacune des deux isoenzymes A et B présente des spécificités de substrat différentes. Ainsi, la molécule de clorgyline inhibe l'enzyme utilisant comme substrats la noradrénaline (NA) et la sérotonine (5-HT) (41). Puis Knoll et coll. (42, 43) mettent en évidence un composé, le déprényl qui inhibe une forme de la MAO désaminant préférentiellement la benzylamine et phényléthylamine. Ainsi, deux types de MAO sont individualisés correspondant à 2 espèces majeures d'enzymes. L'existence de ces 2 formes catalytiques d'activité de la MAO a permis à Johnston d'introduire les termes de MAO-A et MAO-B pour distinguer les 2 formes d'enzymes (40). Chacune des 2 MAO admet des sélectivités ou spécificités particulières vis-à-vis des substrats (monoamines) et de leur sensibilité vis-à-vis de certains inhibiteurs (IMAO). Ainsi la forme A de la MAO réalise une désamination oxydative préférentielle de la NA (8, 16, 44) et 5-HT (8, 16, 42, 44-49), la benzylamine (8, 16) et la tryptamine (8, 16). Quant à la dopamine (DA) (8, 16) et tyramine (TYR) (8, 16), ce sont des substrats communs des formes A et B de la MAO. Des études récentes (50, 51) ont montré que cette spécificité de substrat qui est inversement proportionnelle à sa concentration pouvait être déterminée par les

valeurs relatives des paramètres cinétiques tels que K_m et V_{max} relatifs à la forme de l'enzyme par rapport au substrat (51a, 51b). A noter que cette sélectivité d'inhibition est également fonction de la concentration des médicaments, ainsi les agents inhibiteurs de la MAO très sélectifs à faible concentration deviennent non-sélectifs à haute concentration (46, 52, 53).

2.1.2.2. MAO-A et MAO-B: Leurs substrats et inhibiteurs

De nombreux travaux ont donc été consacrés à ce domaine (8, 9, 54-63) qui ont précisé quels étaient les substrats spécifiques de chacune des isoenzymes A et B et leurs inhibiteurs. Ces données sont résumées dans le tableau I.

Les MAO possèdent des substrats spécifiques de la forme A et B ou communs, de même que ses inhibiteurs peuvent être spécifiques ou mixtes avec une composante réversible ou irréversibles. Ceci signifie que les IMAO dit réversibles ont leur durée d'action inhibitrice plus courte que le temps nécessaire au renouvellement de l'enzyme. Quant aux IMAO irréversibles, ils ont une durée d'action longue.

Tableau I: MAO-A et MAO-B - Leurs substrats et leurs inhibiteurs

Substrats et inhibiteurs	MAO-A	MAO-B
Substrats spécifiques	Adrénaline Noradrénaline (NA) Sérotonine (5HT) Octopamine	Phényléthylamine (PEA) Phényléthanolamine Benzylamine O-Tyramine Milacémide Méthyl-histamine N-Acétyleputrescine MPTP n-Pentylamine Décylamine Octylamine
Substrats communs		Tryptamine (peut-être MAO-B pour certains) Dopamine (DA) surtout MAO-B dans le cerveau humain Tyramine Kynuramine 3-Méthoxy-tyramine
Inhibiteurs spécifiques réversibles	(MD 780515) Cimorexatone Toloxatone (Humoryl®) Harmaline (+) amphétamine Quipazine Moclobémide (Aurorix® - Moclamine®) P-méthoxyamphétamine Brofaromine Amiflamine	Almaxatone (MD 780236) MD 240928 (énantiomère) RO 16-6491 RO 19-6327 MDL 72145
Inhibiteurs spécifiques irréversibles	Clorgyline Lilly 51641	Déprényl (Selegiline®) Pargyline (Eutonyl®) (J-508) AGN 1133 LY 54761 MDL 72145
Inhibiteurs mixtes réversibles		Caroxazone Milacémide
Inhibiteurs mixtes irréversibles		Iproniazide (Marsilid®) Nialamide (Niamide®) Isocarboxazide (Marplan®) Iproclozide (Sursum®) Phénelzine (Nardelzine®) Octamoxine (Ximaol®) Phéniprazine (Catron®) Tranylcypromine (Tylciprine®) Benmoxine (Neuralex®)

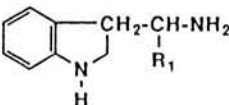
Les 2 formes de MAO individualisées diffèrent non seulement par une sélectivité de leur substrat (64) et leur inhibition (18), mais également par leur distribution tissulaire (57), leur poids moléculaire (65), leur composition en acides aminés ou leur séquence protéique (24, 65, 66) et leur comportement immunologique (67-68).

L'individualisation des 2 types de MAO a conduit à la naissance d'une nouvelle génération d'IMAO (31) de nature spécifique pour l'une des formes de l'enzyme par opposition à l'ancienne génération de nature mixte par un effet d'inhibition totale sur l'enzyme. On devait d'ailleurs constater que certains produits déjà connus pour être des IMAO s'avéraient être des inhibiteurs spécifiques (Déprényl, Clorgyline, Harmaline, Pargyline). En plus de cette **spécificité** de substrat, une seconde propriété pharmacologique importante de ces IMAO a permis de les différencier. Il s'agit de la réversibilité. Ainsi, la propriété de **réversibilité** (69, 70) ou non de l'action inhibitrice sur l'enzyme a permis de définir les inhibiteurs mixtes ou spécifiques de nature réversible ou irréversible. Toutes ces caractéristiques importantes ont permis d'établir une classification pharmacologique des IMAO présentés dans le tableau I.

2.1.3. Classification chimique des IMAO

En plus de la classification pharmacologique précédente, une deuxième classification concernant leur nature chimique s'avère être très intéressante. En effet, les différentes structures chimiques des IMAO permettent de distinguer 2 groupes divisés en 3 et 4 sous groupes respectivement (71-76). Le premier groupe englobe les dérivés des hydrazides, hydrazines et amines et le second groupe les dérivés oxazolidinones, benzofurane, benzamide et alcaloïdes de l'Harmala. Ces 2 groupes chimiques présentent une remarquable corrélation entre structure et activité des IMAO. Ainsi, à de rares exceptions près, le premier groupe avec les dérivés de l'hydrazide, hydrazine et amine est doté d'une activité **IMAO non sélective**, c'est-à-dire ont un effet d'inhibition totale sur la MAO alors que le second groupe avec les dérivés oxazolidinones, benzofurane, benzamide et alcaloïdes de l'Harmala sont des **IMAO dit sélectifs** inhibant sélectivement soit la forme A, soit la forme B de l'enzyme. (Tableaux II et III).

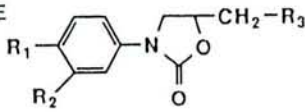
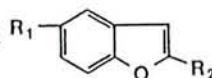
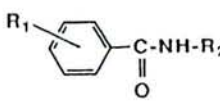
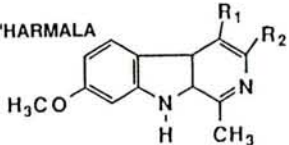
Tableau II - Structures chimiques des IMAO non sélectifs

		Spécialités [®]
HYDRAZIDE		
	$\begin{array}{c} R_1-C(=O)-NH-NH-CH(R_2)(R_3) \end{array}$	Benmoxine Iproniazide Iproclozide Isocarboxazide Nialamide Pivalylbenzhydrazine IH-3
		Neuralex Marsilid Sursum Marplan Niamide Tersavid
HYDRAZINE		
	$\begin{array}{c} R_1-CH_2-CH(R_2)-NH-NH_2 \end{array}$	Phénelzine Phéniprazine Phénoxypropazine Octamoxine
		Nardelzine, Nardil Catron Drazine Ximaol, Nimaol
AMINE		
Propargylamine	$\begin{array}{c} R_1 \\ \diagup \\ CH-N-CH_2-C \equiv CH \\ \diagdown \quad \\ R_2 \quad CH_3 \end{array}$	SU 11-739/5-508/ AGN-1133 Dinltranyl Clorgylne Abbott 21, 855 L-Déprényl, Sélégiline* Pargylne*
		Eldépryl Eutonyl, Eudltron
Cyclopropylamine	$R_1-\triangle-NHR_2$	Tranylcypromine AGN-1135* Lilly 49393 Lilly 51641** Lilly 54761* PCO
		Tylciprine, Parnate
Indolethylamine		Etryptamine
		Monase
Phenylethylamine	$\begin{array}{c} R_2 \\ \\ R_1-C_6H_4-CH_2-CH(R_3)-NH_2 \end{array}$	Amiflamine** (FLA 336)

* préférentiellement IMAO-B

** préférentiellement IMAO-A

Tableau III - Structures chimiques des IMAO sélectifs

		Spécialités®
OXAZOLIDINONE		Toloxatone(MAO-A) Almozatone(MAO-B) (MD 780236) Cimoxatone(MAO-A) (MD 780515) MD 770222 (MAO-A)
BENZOFURANE		Brofaromine(MAO-A) (CPG 11305A)
BENZAMIDE		Moclobemide(MAO-A) (Ro 11-1163) Ro 19-6327 (MAO-B) Ro 16-6491 (MAO-B)
ALCALOÏDE DE L'HARMALA		Harmine(MAO-A) Harmaline(MAO-A)

2.1.4. Localisation tissulaire des 2 isoenzymes MAO-A et B

Les formes A et B de la MAO présentes dans la plupart des tissus, à l'exception des érythrocytes, ont des caractéristiques variables selon l'espèce animale ou leur localisation. Ainsi, le cerveau de rat contient en proportion équivalente la forme A et B (16, 77), alors que dans le cerveau humain le rapport des formes A sur B est de 30/70. Les thrombocytes humaines, dont l'activité MAO est le reflet de celle de la MAO-B cérébrale, contiennent exclusivement la forme B, alors que le placenta contient exclusivement la forme A (7-9, 43, 49, 77, 78). A l'inverse, les thrombocytes de la plupart des animaux de laboratoire contiennent principalement la forme A.

Au niveau hépatique, l'activité MAO-A est légèrement supérieure par rapport à celle de la MAO-B alors que dans l'intestin l'effet est inverse (15, 79, 80). Les neurones monoaminergiques contiennent surtout de la MAO-A, à l'exception des neurones sérotoninergiques englobant des quantités importantes de MAO-B (81). Les cellules extraneuronales sont caractérisées surtout par la MAO-B (81).

Bien que la MAO intraneuronale soit surtout de type A potentialisant l'activité pharmacologique de la sérotonine (5-HT) et noradrénaline (NA), il est supposé que des traces résiduelles de la forme B peuvent coexister dans les neurones. Ainsi, lorsque la MAO-A est entièrement inhibée, les quantités de 5-HT et NA dans le cytoplasme augmentent pour atteindre des concentrations qui peuvent agir sur la constante de Michaelis et Menten (K_m) de la forme MAO-B et ainsi la désamine. Cette sélectivité dépendant de la dose a été confirmée dans plusieurs études (31, 54, 58, 59).

Dans d'autres tissus à forte concentration de MAO tels le foie, le rein et le poumon (79), l'enzyme joue un rôle de défense en inactivant les monoamines circulantes. En particulier, l'enzyme est en première ligne d'attaque contre les monamines absorbées par l'alimentation, tels la tyramine et la β -phényléthanolamine qui par leurs effets sympathomimétiques indirects induisent une crise hypertensive décrite sous le terme d' "effet fromage". A noter qu'un mécanisme similaire est actif au niveau des barrières hémato-encéphalique et gastro-intestinale (25).

Le tableau IV résume les principales localisations humaines des deux isoenzymes MAO-A et B.

Tableau IV Localisation de la monoamine oxydase de type A et B chez l'Homme.

	MAO-A	MAO-B
Périphérie	Terminaisons nerveuses pré-synaptiques sympathiques intraneuronales (82) Trophoblastes placentaires (84). Cortex et médullosurrénale (87a)	Plaquettes sanguines (83, 88, 93) Cellules médullosurrénales (87, 87a, 92)
Cerveau	Locus coeruleus (85, 86) Locus niger (87b, 89-91) Neurone riche en catécholamines	Astrocytes (cerveau, cervelet) (82) Pinealocates (épiphyse) (82) Neurones riches en sérotonines (81, 94)
Autre	Neuroblastes (84) Cellules gliales C6 (84) Cellules hépatiques (79, 85) Tissu intestinal (15, 79, 80) Plasma (83)	

2.1.5. *Aspect clinique des IMAO*

2.1.5.1. Classification des IMAO parmi les agents psychotropes

La classification française, directement inspirée de la classification clinique proposée par Delay et Deniker (95), comprend trois groupes principaux d'agents psychotropes:

- Les **psycholeptiques**, ou sédatifs psychiques.
- Les **psychoanaleptiques**, stimulants des activités mentales.
- Les **psychodysleptiques** ou perturbateurs de l'activité psychique.

Dans chaque groupe, des sous-groupes correspondent aux principaux types d'activités pharmaco-cliniques sont indiquées dans le tableau V.

Tableau V: Classification générale des psychotropes

1. Psycholeptiques ou sédatifs psychiques	A. HYPNOTIQUES	Barbituriques, non barbituriques
	B. TRANQUILLISANTS MINEURS ET SÉDATIFS	Benzodiazépines, méprobamate, etc. Bromures, belladone, etc.
	C. NEUROLEPTIQUES	Phénothiazines, réserpiniques, butyrophénones, benzamides, etc.
	D. RÉGULATEURS DE L'HUMEUR	Sels du lithium
2. Psychoanaleptiques ou stimulants psychiques	E. ANTIDÉPRESSEURS OU STIMULANTS DE L'HUMEUR	Imipraminiques et comp. tricycliques I.M.A.O.
	F. STIMULANTS DE LA VIGILANCE	Amphétamines, etc.
	G. AUTRES STIMULANTS	Phosphoriques, vitamine C, etc.
3. Psychodysleptiques ou perturbateurs de l'activité mentale	H. HALLUCINOGENES	Mescaline, lysergamide, psilocybine, cannabinoles
	I. STUPÉFIANTS	Morphiniques, cocaïne
	J. ENIVRANTS	Alcool, éther, solvants

Dans le groupe des psychoanaleptiques, ou stimulants psychiques, apparaît le sous-groupe des antidépresseurs ou stimulants de l'humeur appartenant à 2 types biochimiques différents: les composés tricycliques dérivés de l'isopramine et les IMAO. L'originalité de ce sous-groupe est son activité dans les états de dépression mentale en rapport avec un dérèglement de la fonction régulatrice de l'humeur (fonction thymique). Dans certains cas, cet effet peut dépasser le but et entraîner une véritable inversion euphorique de l'humeur. Cette action excessive qui doit être corrigée, le cas échéant, est capitale en ce qu'elle démontre l'action spécifique du médicament sur la régulation de l'humeur. Elle permet de distinguer les antidépresseurs vrais des autres médicaments utilisables dans le traitement des dépressions, en particulier des tranquillisants.

Les composés tricycliques et les IMAO, bien qu'ayant sans doute un mode d'action différent, sont des antidépresseurs vrais répondant exactement à la définition donnée ci-dessus. Les IMAO sont généralement non sédatifs et parfois plus puissants que les tricycliques, ou capables d'agir quand ceux-ci sont inefficaces (96-99).

Après avoir subi une certaine désaffection, en raison de la crainte des effets secondaires qui sont attribués aux anciennes générations d'IMAO (cf. 2.1.5.2), la nouvelle génération subit actuellement un net regain d'intérêt.

2.1.5.2. Indications cliniques des IMAO

Pendant longtemps les IMAO n'ont été qu'exceptionnellement prescrits en première intention et le psychiatre n'y avait recours que lors de contre-indications manifestes aux tricycliques ou échec à toute autre thérapeutique antidépressive plus récente du type maprotiline, miansérine, nomifensine, etc. Après avoir été pendant longtemps considéré comme antidépresseurs de second choix, les IMAO connaissent depuis 5-10 ans de nouvelles perspectives cliniques. Ainsi, ils sont considérés comme traitement de choix dans les dépressions atypiques, névrotiques et réactionnelles. De plus, l'amélioration de la sécurité d'emploi de la nouvelle génération d'IMAO-A a permis d'élargir leur spectre d'utilisation et de nombreux articles récents ont étudié les indications cliniques des IMAO (55, 96-99). Les IMAO les plus étudiés jusqu'à ce jour sont de nature irréversible. Ils sont caractérisés par un large spectre d'activité et ont été utilisés dans de nombreuses affections psychiatriques avec comme indication clinique majeure la dépression mentale dite psychogène et atypique.

Bien qu'il soit difficile de définir une classification rigoureuse des dépressions, nous avons adopté la classification suivante regroupant les plus importantes étiologies (100): Dépressions endogènes, atypiques ou psychogènes et symptomatiques.

La dichotomie classique endogène-psychogène est actuellement considérée comme trop simpliste et réductionniste; nous nous limiterons pourtant à envisager schématiquement les étiologies des syndromes dépressifs selon trois grands axes en rappelant que cette répartition reste relative et critiquable. Ces trois types de dépressions peuvent évoluer et créer une nouvelle étiologie appelée dépression résistante et dépression chronique. Ainsi, certains états dépressifs ne répondent pas favorablement à une thérapeutique adéquate et sont parfois susceptibles d'avoir une évolution particulièrement prolongée. Ces états sont caractérisés par un facteur de chronicité et de résistance.

Parmi ces étiologies, les principales sémiologies relevant de la cure d'IMAO sont les suivantes:

- Les dépressions simples ou réactionnelles sur terrain névrotique, source d'une abondante littérature (101, 102-116) et appelé dépression atypique. Cette dernière englobe une catégorie hétérogène de dépressions non majeures (103, 105, 109, 115, 117). Les états boulimiques semblent également bien réagir aux IMAO (118-121).
- Les syndromes mélancoliques francs
- Les syndromes hypocondriaques et les dépressions d'involution

A côté des dépressions proprement dites, les IMAO possèdent plusieurs autres indications telles:

En psychiatrie (Fig. 6)

- La psychasthénie avec les nombreux troubles psychiques et somatiques qu'elle entraîne
- Les attaques de panique et agoraphobie (99, 122-132) classées dans les formes anxieuses
- Les états obsessionnels (133-138)
- Les névroses dépressives et préoccupations hypocondriaques
- Les dépression du sujet âgé souvent associées à la maladie d'Alzheimer (139-142)
- Les hystéries (143)
- Le stress post-traumatique
- Les dépressions résistantes et chroniques (102)

En neurologie

- Certaines affections psychosomatiques telle que la migraine rebelle (144-152)
- L'akinésie parkinsonienne (15, 153-163)
- La schizophrénie avec prédominance de l'indifférence affective
- La narcolepsie
- L'hypotension orthostatique idiopathique (164-167)

Divers

- L'Eczéma atopique (168)
- L'Arthrite rhumatoïde (169-170)

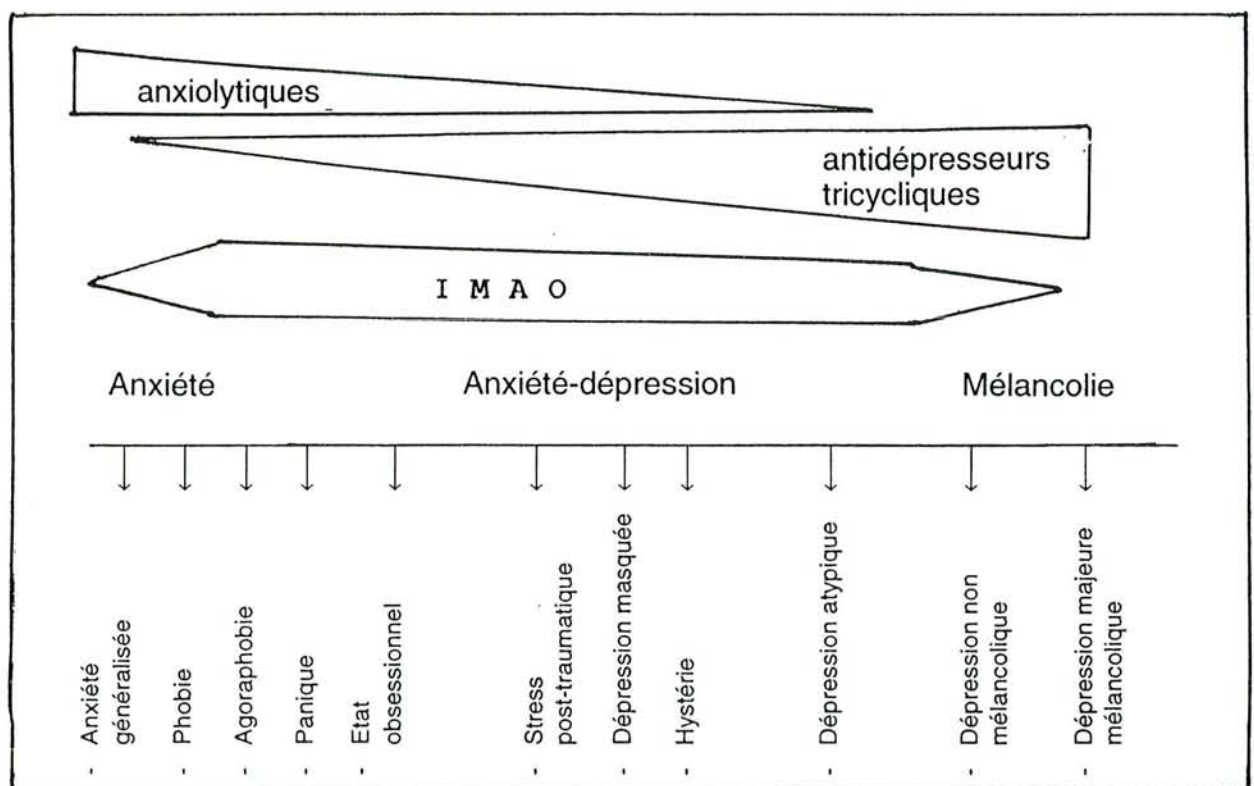


Fig. 6 Spectre d'activité des IMAO en psychiatrie selon Zisook (116)

A côté des indications mentionnées, la nouvelle génération d'IMAO sélectifs A ou B, dotés d'une maniabilité clinique significativement accrue par rapport à ses prédécesseurs a permis de mettre en évidence une activité antidépressive supérieure pour les IMAO-A par rapport aux IMAO-B (114, 171-176). Les MAO-A ont un spectre d'activité plus large que les IMAO traditionnels englobant pratiquement tous les syndromes dépressifs. Quant aux IMAO-B, ils se caractérisent par leurs propriétés anti-parkinsonniennes (175a).

2.1.5.3. Effets secondaires des IMAO classiques

Les IMAO ont longtemps été délaissés. Le désintérêt était en partie lié à leur réputation d'engendrer de nombreux effets secondaires. C'est l'imprévisibilité des réactions avec leur caractère paradoxal telle que la crise hypertensive paroxystique spontanée qui se trouve à l'origine de la véritable mythologie qui s'est développée autour des IMAO classiques.

La prise d'IMAO anciens est liée à une stricte règle de prescription qui exclue pratiquement toute comédication et nécessite pour le patient de suivre un régime diététique approprié.

Les principaux effets secondaires de ces IMAO sont regroupés dans le tableau VI.

Tableau VI - Effets indésirables des IMAO classiques

- | |
|--|
| <ul style="list-style-type: none">- Système nerveux autonome (SNA)<ul style="list-style-type: none">• Hypotension orthostatique• Crises d'hypertension artérielle paroxystique consécutive à l'administration concomitante de certains aliments riches en tyramine• Effets anticholinergiques avec rétention urinaire, constipation, sécheresse de la bouche, troubles de la vision, troubles sexuels• Hyperhydrose- Système nerveux central (SNC)<ul style="list-style-type: none">• Bouffées de chaleur et frissons• Insomnie, irritabilité ou euphorie, agitation psychomotrice• Suppression des mouvements oculaires rapides (REM), perturbation du sommeil• Hypomanie• Délire consécutif à l'ingestion concomitante de tryptophane- Divers<ul style="list-style-type: none">• Hépatotoxicité (ictère grave sous iproniazide)• Perte de poids• Oedème• Maux de tête• Paresthésie• Crampes musculaires |
|--|

Au niveau du SNA

- L'hypotension orthostatique est l'un des principaux effets secondaires des anciens IMAO qui limite fortement leur prescription (177-181). On pense que l'hypotension résulte d'une inhibition du catabolisme de la tyramine par les MAO. La tyramine subirait une β -hydroxylation en tant que "faux transmetteur" avec des effets vasopresseurs très légers (36). Cet effet apparaît au début du traitement et disparaît généralement au bout de 3-4 semaines (99, 182).
- La crise hypertensive est un effet indésirable sérieux bien que rare et est lié à l'ingestion concomitante de tyramine et amines vasopresseurs dans l'alimentation lors d'un traitement avec les IMAO. Le mécanisme de cette crise hypertensive appelée "effet fromage" ou "cheese reaction" semble être relié à la capacité de la tyramine de déplacer d'importants stocks de noradrénaline des granules présynaptiques, il en résulte un effet -adrénergique exagéré se traduisant par une élévation de la pression artérielle (183-188). Ainsi, les patients sous IMAO doivent suivre un régime appauvri en tyramine et une liste d'aliments à proscrire doit leur être procuré. Les premières listes publiées (186, 189, 190) étaient trop restrictives, ainsi une nouvelle classification basée sur le contenu en tyramine et autres amines vasopresseurs est utilisée (189, 191) telle celle présentée dans le tableau VII.
- Certains travaux suggèrent que l'inhibition de la MAO n'est pas la seule cause des crises hypertensives consécutives à l'ingestion de tyramine (192).

Au niveau du SNC

- L'insomnie n'a été qu'occasionnellement citée comme effet secondaire des IMAO bien que la majorité des prises de médicament se fassent le soir (99). Les IMAO interfèrent sur le sommeil en supprimant le mouvement oculaire rapide (102, 193) qui se traduit par une perturbation de l'électroencéphalogramme (EEG) du sommeil (102, 193). Cette perturbation s'annule dès l'arrêt du traitement (194).
- Moins de 10 % de patients sous phénelzine ou tranylcypromine souffrent d'hypomanie (177, 195, 196) lié au dosage administré.
- Dans certains cas de dépressions réfractaires, l'adjonction de tryptophane au traitement IMAO augmente l'incidence des effets secondaires sur le SNC (197, 198).
- Quelques cas sévères d'hépatotoxicité ont été décrits surtout pour l'iproniazide (47, 98, 99, 177, 185, 199).
- La prise de poids est un effet secondaire déplaisant et est surtout liée à l'ingestion de phénelzine (47, 98, 99, 177). L'incidence d'apparition d'œdème est rare (99, 177, 200). Il en est de même avec les maux de tête, les paresthésies et crampes (97, 177).

Effets secondaires peu communs

- Des cas rares d'allergie, de photosensibilisation, de leucopénie, de syndrome lupoïde, de syndrome antidiurétique, de perturbation de la sécrétion de prolactine ont été observés (201).
- Des troubles sexuels ont été enregistrés chez l'homme (47, 98, 202, 203), moins fréquemment chez la femme (196-198, 204).
- Les autres effets secondaires mentionnés dans le tableau 6 ont été rapportés dans différentes publications (98, 99, 177, 200, 205).

Parmi tous ces incidents cités, Greenblatt et coll. (94) estiment la fréquence à moins de 20 % des cas, tous troubles confondus.

Tableau VII: Restrictions alimentaires associées au traitement par les IMAO classiques (206).

Aliments à proscrire:

- Fromages fermentés
- Poissons fumés y compris hareng et caviar
- Levure, extraits de ferments
- Abats de volaille
- Fèves
- Bananes
- Saucisses, saucissons

Aliments à consommer avec modération

- Boissons alcooliques y compris vin rouge , bière et liqueurs
- Viande en conserves
- Foies de boeuf
- Sauces de soja
- Epinards
- Chocolat, café, thé, coca

Aliments pouvant être consommés normalement

- Fromages blancs, yaourts, laitages non fermentés
- Figues, oranges
- Aliment en conserves (sauf viande)

- 2.1.5.4. Interactions médicamenteuses des IMAO classiques
Le tableau VIII regroupe les associations médicamenteuses à éviter sous traitement IMAO.

Tableau VIII: Interactions médicamenteuses sous IMAO classiques	
Association dangereuse (effet potentialisateur) avec:	
Médicaments	Effets cliniques
Psychostimulants (amphétamine, cocaïne)	Crise hypertensive
Décongestifs (éphédrine, phényléphédrine, phénylpropanolamine, pseudoéphédrine)	Crise hypertensive
Antihypertenseurs (métyldopa, guanéthidine, réserpine)	Excitation, hallucination visuelle, hypotension sévère
Antidépresseurs (à l'exception de l'amitriptyline)	Potentialisation des effets cliniques
Sympathomimétiques ou amines vasopressives (dopamine, métaraminol, tyramine)	Hypotension sévère
Narcotiques (meperidine)	Excitation, hypotension, hypersudation
Anorexigènes (amphétamine)	
Anesthésiques locaux	Crise hypertensive
Anti-allergiques	Crise hypertensive
Diurétiques thiazidiques	Hypotension sévère
Association à surveiller, peut être dangereuse:	
Médicaments	Effets cliniques
Précurseurs d'amines	Potentialisation des effets sur le SNC
Narcotiques	"
Sédatifs	"
Sympathomimétiques (adrénaline, noradrénaline, isoprotérénol)	"
Anesthésiques généraux	"
Hypoglycémiant (insuline, sulphonylurée, phenformine)	Potentialisation de l'effet hypoglycémiant
Anticoagulants	
Morphiniques naturels et de synthèse type (pethidine, Dolosal [®])	

Une importante interaction médicamenteuse apparaît en associant les IMAO aux sympathomimétiques. Il en résulte une hyperactivité sympathomimétique avec crise hypertensive, maux de tête, sueur, tachycardie (99, 207). Certains médicaments bien que non métabolisés par les MAO interfèrent également avec les IMAO. Ainsi, les IMAO classiques bloqueraient d'autres enzymes que la MAO et agiraient sur le mécanisme de dégradation hépatique (47, 97, 208-210).

L'administration simultanée d'antidépresseurs tricycliques avec les IMAO a conduit à de nombreuses controverses. Au départ cette association médicamenteuse était proscrite (47), alors qu'actuellement elle est préconisée et même conseillée dans les dépressions résistantes (211-216, 217).

Après prise en compte des précautions d'interactions médicamenteuses et alimentaires, les IMAO sont habituellement bien tolérés. Cependant la prescription nécessite une surveillance étroite dès le début du traitement.

2.1.5.5. Effets secondaires et interactions médicamenteuses des IMAO-A réversibles.

Nous venons de voir que la crise hypertensive, avec les effets sur le SNA et SNC, ainsi que l'hépatotoxicité, sont les effets indésirables les plus fréquents et dangereux pour l'ancienne génération d'IMAO. Ainsi de nombreux travaux de recherche ont essayé de se concentrer sur une nouvelle génération d'IMAO non toxiques et plus maniabiles (35). Dans cette nouvelle génération la crise hypertensive a pu être contrôlée. Son incidence a fortement diminué depuis la découverte que la tyramine, principale amine du fromage, a des propriétés vasopressives dont les effets sur la tension artérielle sont potentialisés par les IMAO (3). Une restriction alimentaire appropriée a permis de faire chuter les réactions hypertensives à moins de 4 % (35).

2.2. **Propriétés pharmacologiques et apport clinique de la nouvelle génération des IMAO-A type MOCLOBEMIDE**

L'histoire des IMAO reflète en fait celle de la MAO. A la suite des travaux des équipes de Knoll et Johnston (40, 43), les fondamentalistes ont approfondi leurs connaissances dans le domaine de la biochimie cérébrale. De cette recherche est née la synthèse d'une génération de nouvelles molécules inhibitrices de la MAO (Tableaux I, II et III), douées de propriétés pharmacologiques particulières relatives à l'affinité enzyme-substrat. Nous nous limiterons à décrire les caractéristiques de la classe des IMAO de type A dont fait partie le moclobémide, la molécule que nous avons étudiée.

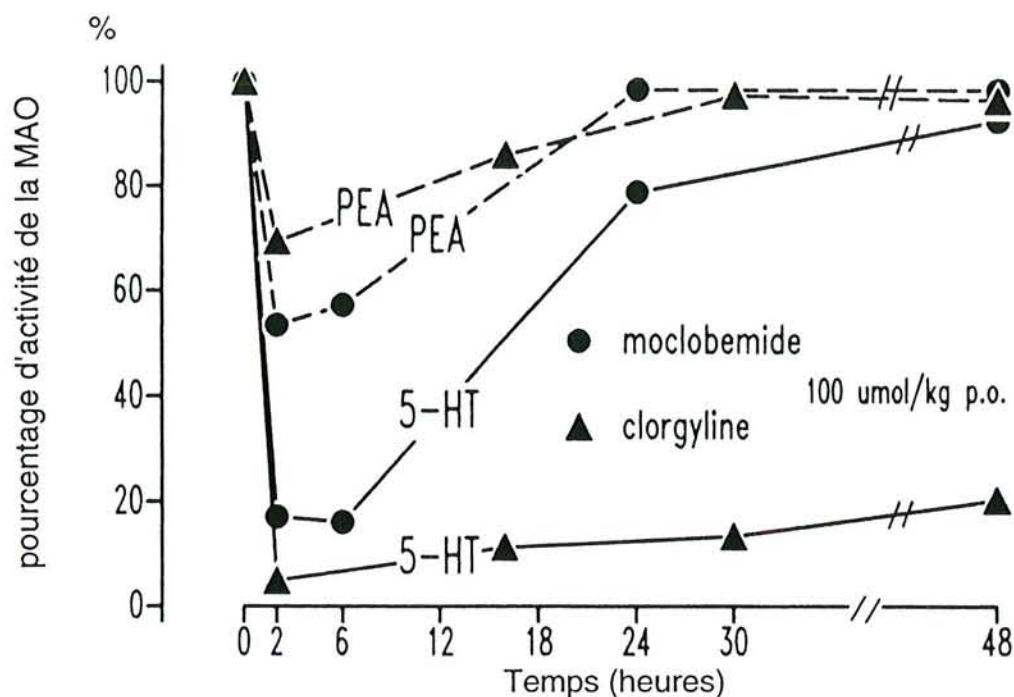
2.2.1. Sélectivité:

La nouvelle génération d'IMAO inhibe préférentiellement qu'une seule forme A ou B de la MAO contrairement à leur prédécesseurs non sélectifs. L'utilisation d'un IMAO sélectif de la forme A type moclobémide entraîne une diminution du catabolisme des monoamines impliquées dans le processus de la dépression ce qui contribue à l'augmentation de la concentration pré-synaptique en monoamines. Ainsi, l'intérêt clinique de cette sélectivité réside dans le pouvoir d'augmenter les concentrations intra-cérébrales de NA, DA, 5-HT dont le rôle est incriminé dans la pathogénie des états dépressifs.

2.2.2. Réversibilité:

La réversibilité de l'IMAO est une propriété qui induit une durée d'action inhibitrice sur l'enzyme plus courte que le temps nécessaire au renouvellement de l'enzyme, ainsi, à l'arrêt du traitement, l'activité de la MAO revient rapidement à ses valeurs initiales. Quand à l'irréversibilité des anciens IMAO liée à leur liaison covalente forte, indéplaçable avec la MAO, leur activité inhibitrice ne disparaît qu'au fur et à mesure de la synthèse d'un nouveau pool enzymatique de MAO (Fig. 7).

L'intérêt clinique de la réversibilité réside dans le fait qu'elle provoque une inhibition plus rapide de la MAO qui est levée plus rapidement, rendant caducs les problèmes de délais liés à leur durée d'action trop longue: 15-21 jours pour les IMAO classiques et 1-2 jours pour les nouvelles molécules ce qui constitue un progrès réel (100).



Substrat:

- 5-Hydroxytryptamine (5-HT)-
(substrat de la MAO-A)
- β -phényléthylamine (PEA)-
(substrat de la MAO-B)

IMAO:

- Moclobémide
(IMAO-A) réversible)
- Clorgyline
(IMAO-A irréversible)

Fig. 7 Inhibition cérébrale de la MAO-A (substrat 5-HT) et de la MAO-B (substrat PEA) chez le rat après administration par la clorgyline inhibiteur irréversible et par le moclobémide inhibiteur réversible (selon M. Da Prada et coll. 217a).

La figure 7 retrace l'inhibition cérébrale de la MAO-A chez le rat après administration d'un

- **IMAO-A réversible** type moclobémide.
Pour le substrat de la MAO-A, une inhibition enzymatique maximale est observée dès 1-2 h après administration orale, alors que l'activité enzymatique revient à ses valeurs basales.
- **IMAO-A irréversible** type clorgyline
Le maximum d'inhibition enzymatique est atteint dès les premières heures après administration orale, cette inhibition reste pratiquement constante et n'est toujours pas levée 48 h après le traitement.

A l'opposé du substrat MAO-A (5-HT), la désamination oxydative du substrat de la MAO-B (PEA) est très faible pour les 2 IMAO testés.

Ces résultats indiquent qu'avec la nouvelle génération d'IMAO-A réversibles, type moclobémide, l'inhibition enzymatique de la MAO-A est rapidement levée par opposition aux anciens IMAO irréversibles.

Le mode d'action de l'IMAO-A réversible moclobémide avec l'enzyme a été étudié par inhibition de la MAO cérébrale chez le rat ou placentaire chez l'Homme (218, 219). L'activité de la molécule de moclobémide a également été testée sur un nouveau modèle animal du rat qui permet de confirmer son efficacité dans la dépression (220, 221).

2.2.3. Compétitivité

L'activité d'un inhibiteur enzymatique est dite de type compétitif lorsque l'augmentation de la concentration du substrat sur lequel il agit est capable de rompre la liaison enzyme-inhibiteur (MAO-IMAO-A) et que l'enzyme libérée se trouve à nouveau capable d'exercer son action (89). L'absence de propriété de compétitivité des IMAO anciens est à l'origine de crises hypertensives conduisant à des accidents graves chez les malades sans traitement. Ces accidents appelés "cheese reaction" apparaissent lors d'absorption d'aliments riches en tyramine (tels que fromages, Chianti, bananes, avocats, gâteaux, abats) normalement désaminés par la MAO-A intestinale. Lors du blocage de cette MAO par un IMAO non compétitif, la tyramine n'est plus désaminée et franchit la barrière intestinale pour s'accumuler dans les terminaisons nerveuses sympathiques. Son arrivée dans la terminaison nerveuse déplace vers l'extrémité présynaptique les pools disponibles de NA. Ainsi, l'arrivée de l'influx nerveux va provoquer une libération massive de NA responsable de la crise hypertensive. Avec l'utilisation d'IMAO-A compétitifs ce type d'accident est mineur car, en cas d'absorption importante de tyramine, celle-ci primera sur l'inhibiteur, rompant la liaison faible MAO-A-IMAO-A compétitif, ce qui permet alors à la MAO à nouveau libérée de cataboliser la tyramine (222 - 224). La meilleure tolérance des IMAO-A sélectifs tel que le moclobémide par rapport aux IMAO classiques est démontré dans plusieurs études par l'absence de l'effet fromage et d'un quotient bénéfice risque positif (225 - 227).

2.2.4 Spécificité

Les IMAO nouveaux semblent plus spécifiques du seul système MAO en respectant l'intégrité des autres systèmes enzymatiques, notamment des enzymes hépatiques responsables du métabolisme de nombreux médicaments. Quant aux IMAO anciens, ils inhibent également des systèmes enzymatiques autres que la MAO tels les estérases mono-oxygénases et systèmes microsomaux hépatiques responsables de nombreuses contre-indications médicamenteuses.

2.2.5 Apport thérapeutique

Comme nous venons de le voir au chapitre précédent, les IMAO-A englobent une classe thérapeutique utilisée principalement pour leur propriétés antidépressives. Un des principaux avantages de cette nouvelle classe d'IMAO sélectifs et réversibles est la diminution des effets secondaires tels que les accidents cardio-vasculaires par ingestion concomitante de tyramine ou hépatiques en cas de surdosage.

Il en résulte une meilleure observance pour le malade et une utilisation moins restrictive du médicament thérapeutique contrairement à l'ancienne génération.

Les différentes propriétés citées respectent l'activité antidépressive et stimulante décrite depuis l'origine et constituent les étapes de découverte successive de nouvelles générations d'IMAO sélectifs et irréversibles puis réversibles. Cette dernière génération a permis un regain d'intérêt de la classe thérapeutique des IMAO. C'est ainsi que sont nés les IMAO sélectifs et réversibles de la forme A de l'enzyme avec la brofaromine (CGP 11305 A) (222, 228-233), la cimoxatone (MD 780515) (234-236), le toloxatone (Humoryl®) (236-238), l'amiflamine (FLA 336) (240) et le moclobémide (RO 11-1163) (241-247) assurant par leur courte durée d'action une aisance de manipulation sur le plan thérapeutique (248). Les nouveaux IMAO-A réversibles ont permis par leurs nouvelles propriétés de créer un nouveau concept d'IMAO appelé "RIMA" (249-252). A ce jour parmi les représentants de cette classe, le moclobémide est une des molécules les plus étudiées, bouleversant par leur nouvelle approche les théories pharmacologiques traditionnelles sur les IMAO. Ainsi, nous avons consacré ce travail à la molécule de moclobémide en développant son profil pharmacocinétique.

2.3. Propriétés du moclobémide

2.3.1. Propriétés physico-chimiques

Le principe actif de moclobémide est le p-chloro-N-(2 morpholinoéthyl)-benzamide comme l'indique la fig. 8 dont la masse moléculaire est de 268,7.

Cette molécule a les propriétés d'un acide faible de $pK_a = 6.3$. C'est un composé fortement lipophile avec un coefficient de partage n-octanol/eau de 40, à pH 7.4 (22° C). Il est également fortement soluble en milieu acide (2,6 g/100 ml de liquide gastrique artificiel de pH 1.2 à 37° C).

Toutes ces caractéristiques laissent prévoir une absorption complète après administration orale et un passage rapide à travers la barrière hématoencéphalique.

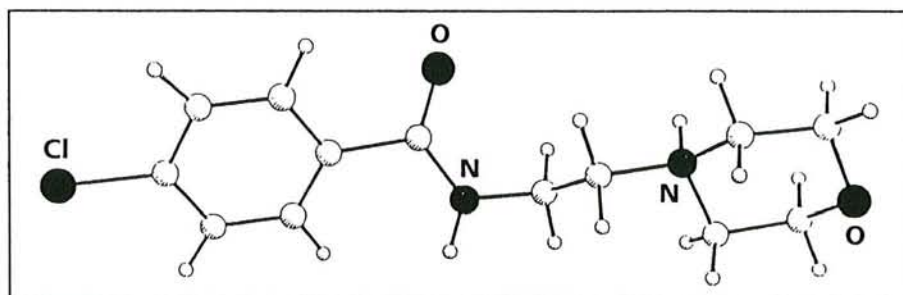


Fig. 8

Structure de la molécule de:

Nom de recherche: RO 11-1163

Nom chimique: Moclobémide

Spécialités: AURORIX® MOCLAMINE®

2.3.2. Métabolisme

2.3.2.1. Bilan d'excrétion

Après administration orale de 50 mg de moclobémide, 95 % de la dose sont excrétés dans l'urine dans l'intervalle de 96 h de collecte, dont 92 % durant les douze premières heures. Les quantités totales retrouvées dans l'urine et les faeces sont de 100 %. Avant excrétion, le moclobémide est pratiquement entièrement métabolisé. Seuls 0,4 % de la dose sont retrouvés intacts dans l'urine.

2.3.2.2 Métabolites du moclobémide dans l'urine

Les différentes voies métaboliques ont été intensément étudiées par plusieurs équipes (253).

Une multitude de métabolites du moclobémide est formée lors du catabolisme de la molécule (Tableau IX). Quatre groupes distincts de composés ont pu être identifiés: composés acides (49 % de la dose), neutres (8 % de la dose), basiques (2 % de la dose) et N-oxide (4.5 % de la dose).

Un total de 19 produits de dégradation ont été identifiés. La cascade métabolique semble initiée par quatre réactions d'oxydation primaire: l'oxydation morpholine, la désamination, la N-oxydation morpholine et l'hydroxylation aromatique (Fig. 9). Quantitativement les produits d'oxydation du noyau morpholine sont prépondérants.

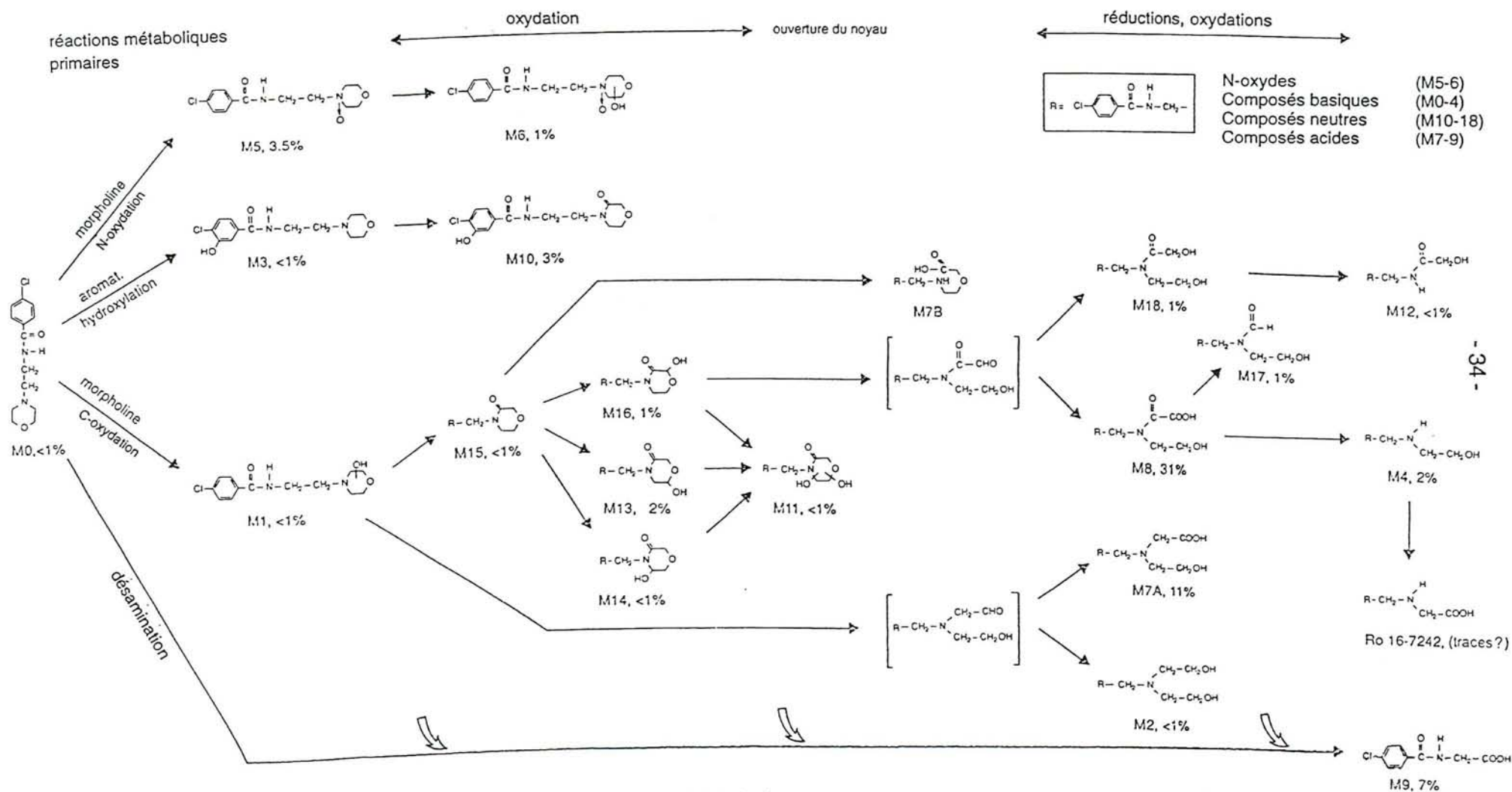
Les principaux composés excrétés dans l'urine (M8, M7A, M9) sont des acides carboxyliques correspondant à 49 % de la dose administrée.

2.3.2.3. Métabolites du moclobémide dans le plasma

Après administration orale de 50 mg de moclobémide radioactif (14 C), on peut constater qu'une grande partie de la radioactivité ne peut être attribuée à la substance inchangée.

Les métabolites retrouvés dans le plasma sont qualitativement similaires à ceux de l'urine. Parmi les métabolites identifiés dans le plasma se trouvent les métabolites principaux urinaires, les acides M8, M7A, M9, M4 et des traces du N-oxyde M5 (Fig. 9). Le métabolite principal est le dérivé Lactam M15 qui représente moins de 1 % dans l'urine.

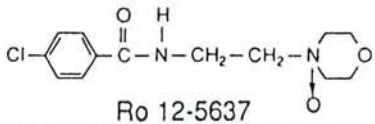
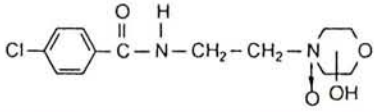
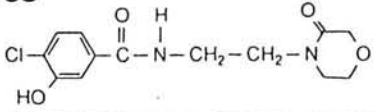
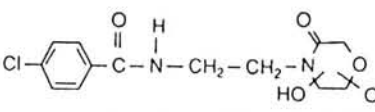
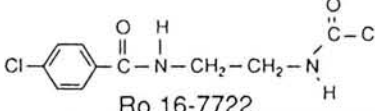
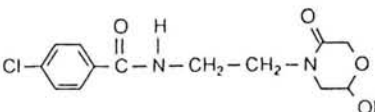
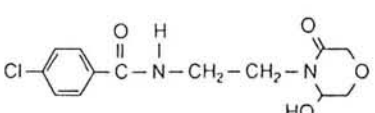
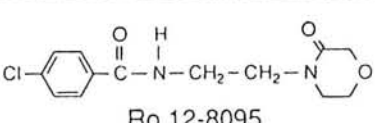
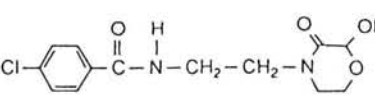
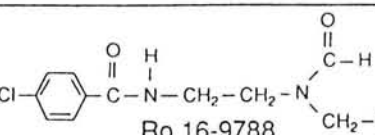
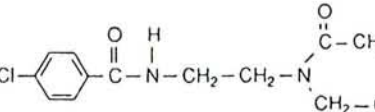
Le métabolisme du moclobémide chez l'homme se fait principalement par oxydation du noyau morpholine. Ce dernier semble être une étape intermédiaire dans la cascade métabolique (Fig. 9 - Formation de M15 et M7A) suivi d'une nouvelle oxydation et ouverture du noyau.



(Pourcentages de métabolite excrété dans l'urine par rapport à la dose administrée.)

Figure 9: Catabolisme du moclobémide chez l'Homme

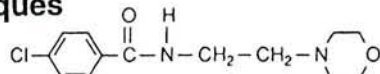
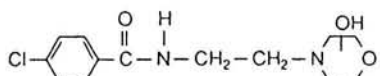
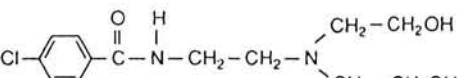
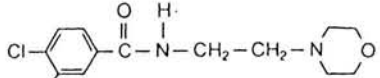
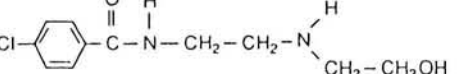
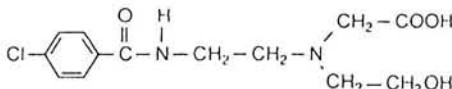
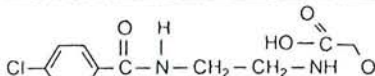
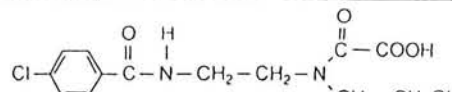
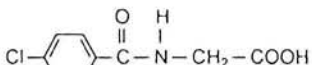
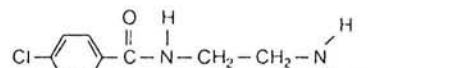
Tableau IX: Comparaison quantitative et excrétion du moclobémide et métabolites chez l'animal et l'Homme. (254).

Codes Identification 1 2 3			Structure chimique	% de la dose excrétée			
				Rat		Chien	Homme
				urine	bile		
N-Oxides							
M5			 Ro 12-5637	13 ²⁾	0.1 ²⁾	7.0 ²⁾	3.5 ²⁾
M6							1.0 ²⁾
Composés neutres							
M10	K1						3.0 ¹⁾
M11							<1 ²⁾
M12			 Ro 16-7722				<1 ²⁾
M13	S1						2 ²⁾
M14							<1 ¹⁾
M15			 Ro 12-8095	0.5 ²⁾	0.1 ²⁾	<0.2 ²⁾	<1 ²⁾
M16							1 ²⁾
M17			 Ro 16-9788				1 ²⁾
M18							1 ²⁾

1) Conjugué principalement

2) Principalement non conjugué

Tableau IX: Comparaison quantitative et excrétion du moclobémide et métabolites chez l'animal et l'Homme (254).

Codes Identification			Structure chimique	% de la dose excrétée			
				Rat		Chien	Homme
				urine	bile		
1	2	3					
Composés basiques							
M0		 Ro 11-1163	1.4 ²⁾	1.1 ²⁾	3.0 ²⁾	<1 ²⁾	
M1			0.6 ²⁾		<2 ¹⁾	<1 ²⁾	
M2		 Ro 16-5381				<1 ²⁾	
M3		 Ro 18-5075	0.25 ¹⁾	1.7	<2 ¹⁾	<1 ¹⁾	
M4	S2	 Ro 16-3177	8.4 ²⁾	4.0 ²⁾	22 ²⁾	2 ²⁾	
Composés acides							
M7	S4						
M7A		 ring opened form of Ro 17-4527			0	<11 ²⁾	
M7B		 ring opened form of Ro 12-8095	2.7 ²⁾ avec 7A	<1	3 ²⁾	avec 7A	
M8	S3	 ring opened form of Ro 16-3220	traces	<1.8 ²⁾		31 ²⁾	
M9		 Ro 11-1903	15 ²⁾	0.8 ²⁾	36 ²⁾	7 ²⁾	
		 Ro 16-7242	1.2 ²⁾		2 ²⁾	traces?	

1) Conjugué principalement

2) Principalement non conjugué

2.3.3. Toxicité

Des études de toxicité aiguë, sub-aiguë et chronique chez le rat et le chien sont incluses dans l'évaluation de la tolérance de moclobémide. La DL50, après administration orale chez le rat, est de 1000 à 2000 mg/kg.

Les études de toxicité, après administration orale répétée (resp. 12 et 18 mois chez le chien et le rat) montrent que la dose la plus élevée testée (125 mg/kg/jour chez le chien et 250 mg/kg/jour chez le rat) n'a aucun effet toxique majeur sur le foie. Le moclobémide semble dénué d'hépatotoxicité (255).

Les études de cancérogénèse chez la souris et le rat montrent que le moclobémide n'est pas cancérogène. Les études sur la reproduction chez le rat et le lapin n'indiquent aucune foetotoxicité, ni effet tératogène, de même il n'a aucun effet sur la fécondité.

2.3.4. Clinique

2.3.4.1. Efficacité

Le tableau X résume les caractéristiques de 4 études principales contrôlées à double-insu avec placebo ayant pour but de démontrer l'efficacité du moclobémide en tant qu'antidépresseur et sa tolérance (256).

Parmi ces études multicentriques l'une d'entre-elle est conduite sur 490 patients. Nous nous concentrerons sur les résultats de cette étude dont l'effectif dépasse largement celui des trois autres études menées chez 34 à 44 patients. De plus sa méthodologie est voisine de celle des études comparatives à double-insu menées avec des antidépresseurs tricycliques (257).

Tableau X - Etudes cliniques comparatives du moclobémide avec placebo.

	Nombre de patients sous moclobémide	Nombre de patients sous placebo	Autres groupes	Durée du traitement
Amérique latine (257)	164	162	<i>Imipramine</i> (N=164)	6 semaines
Danemark (260)	22	18	<i>Clomipramine</i> (N=21)	6 semaines
Italie (258)	18	16	—	4 semaines
Belgique (259)	23	21	—	4 semaines

Méthodologie

C'est une étude prospective à double-insu, comparative et randomisée, menée chez des patients répartis en trois groupes et recevant soit du moclobémide, de l'imipramine ou un placebo.

L'évaluation de la dépression du patient se fait selon les critères du DSM III. La gravité du syndrome dépressif doit être au moins modérée et le score sur l'échelle de dépression de Hamilton (EDH) (21 critères) est d'au moins 17 points avant l'étude.

Les doses de moclobémide administrées sont de 3 x 100 mg les 5 premiers jours, puis 3 x 200 mg jusqu'à la fin de l'étude.

Résultats

La figure 10 montre l'évolution chronologique du score total sur l'EDH (17 critères). Ce score diminue de façon parallèle dans les groupes moclobémide et imipramine avec une distinction du placebo dès le 14ème jour.

Aucune différence significative entre les groupes moclobémide et imipramine n'est obtenue, par contre, une différence significative existe entre les groupes moclobémide et placebo.

Echelle de Hamilton
(EDH)

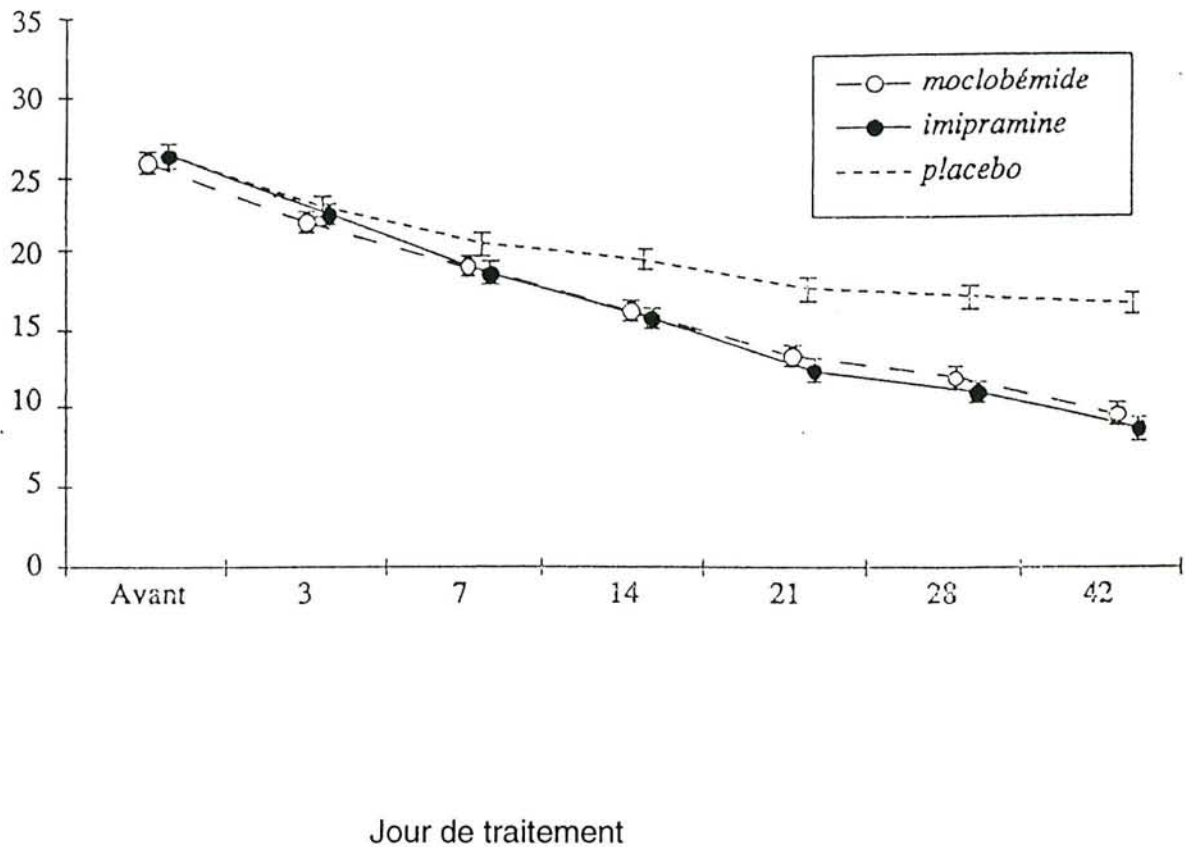
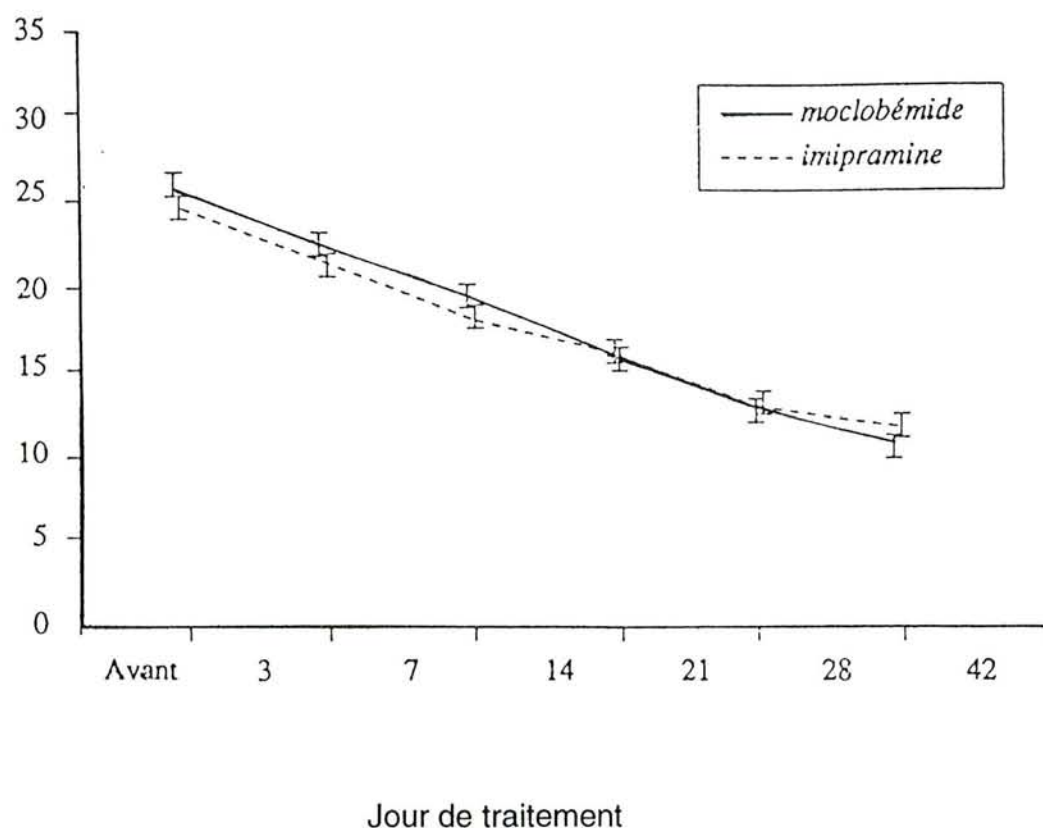


Figure 10: Score total sur l'EDH (17 critères) moyen $\pm$ ETM.
Etude multicentrique latino-américaine. (257)

- 2.3.4.2. Comparaison avec des antidépresseurs de référence
Parmi les nombreuses études cliniques comparatives du moclobémide avec l'imipramine (258), désipramine (259) clomipramine (260) et amitryptiline (261), la plus importante semble être celle menée chez 378 patients avec moclobémide et imipramine pendant quatre semaines.

Les résultats présentés à la figure 11 montrent que l'efficacité des deux composés est similaire.

Echelle de Hamilton
(EDH)



**Figure 11 : Score total sur l'EDH (17 critères) moyen $\pm$ ETM.
Etude multicentrique autrichienne. (258)**

2.3.4.3. Tolérance

Le tableau XI liste les symptômes observés au cours des études en double insu avec le moclobémide ou des antidépresseurs de référence chez plus de 5 % des patients. Les effets anticholinergiques typiques (sécheresse buccale, tremblement, hypersudation, constipation et vision floue) sont deux fois plus fréquents avec les antidépresseurs tricycliques qu'avec le moclobémide (différence significative). L'insomnie et les céphalées sont les effets indésirables les plus fréquents sous moclobémide (différence statistiquement non significative dans les deux cas) (256, 266).

Contrairement aux tricycliques, aucun effet tachycardisant systématique n'apparaît au cours des études cliniques avec moclobémide.

Aucune hypotension orthostatique importante du type de celle observée avec les IMAO irréversibles n'est observée.

Aucune interaction directe avec la tyramine n'a pu être mise en évidence parmi les rares cas d'hypertension au cours des études cliniques. Les résultats cliniques confirment ceux des études de pharmacologie humaine indiquant qu'un régime restrictif en tyramine n'est pas nécessaire durant un traitement avec moclobémide. Il est toutefois conseillé aux patients de ne pas ingérer des quantités importantes d'aliments riches en tyramine et de prendre le moclobémide en fin de repas (262-264).

Les résultats des analyses biologiques au cours des études n'indiquent aucune altération de la fonction hépatique.

En résumé, l'efficacité du moclobémide en tant qu'antidépresseur est comparable à celle des antidépresseurs tricycliques dans le traitement de diverses formes de dépression. Elle est notamment manifeste dans le traitement des dépressions endogènes. La tolérance du moclobémide ne se différencie pas de celle d'un placebo et est supérieure à celle des antidépresseurs tricycliques. Il n'exerce aucun effet sédatif, de même qu'aucune cardiotoxicité et effets anticholinergiques n'ont été démontrés.

Tableau XI: Manifestations indésirables survenues chez au moins 5 % des patients lors des études à double-insu comparant le moclobémide à des antidépresseurs tricycliques

Manifestations indésirables	<i>Moclobémide</i> (n = 694) %	atc (n = 681) %	atc/ <i>moclobémide</i> Rapport	Signification*
Sécheresse buccale	14,0	39,5	2,8	S
Tremblement	4,5	11,9	2,6	S
Hypersudation	4,3	11,2	2,6	S
Vertiges	7,8	12,3	1,6	<0,005 NS **
Constipation	3,7	11,5	3,1	S
Insomnie	6,6	5,4	0,8	NS
Fatigue	6,6	6,8	1,0	NS
Céphalées	9,1	6,6	0,7	NS
Somnolence	3,3	6,5	2,0	<0,008 NS**
Nervosité	3,6	4,8	1,3	NS
Vision floue	2,9	6,2	2,1	<0,003 <0,048 ** S
Palpitations	5,2	5,1	1,0	NS
* Test exact de Fischer ** Valeur de P corrigée selon Bonferoni				

atc = antidépresseurs tricycliques

3. Etudes personnelles

3.1. Pharmacocinétique humaine

Disposition du moclobémide lors:

3.1.1 *Etude I*

Pharmacocinétique à doses multiples du moclobémide chez le volontaire sain durant un traitement chronique

But

Cette étude est réalisée afin de pouvoir évaluer les paramètres de résorption et de disposition du moclobémide chez le volontaire sain pendant un traitement chronique. Une dose unique de 150 mg de moclobémide (RO 11-1163/004) a été administrée par voie I.V. une semaine avant et après 15 jours d'un traitement chronique oral de moclobémide (100 mg t.i.d. RO 11-1163/017) afin de pouvoir évaluer les variations éventuelles de la clairance, du volume de distribution, du temps de demi-vie et de la biodisponibilité.

Matériel et méthodes

Les concentrations plasmatiques du moclobémide et des métabolites sont dosées par une méthode CLHP (267) à détection U.V. (240 nm). Durant un traitement oral chronique avec moclobémide douze sujets sains mâles, non fumeurs, âgés de 21 à 34 ans, ont ingéré 3 fois par jour 100 mg de moclobémide pendant 15 jours (jours 8 à 22), à intervalle de 6,6 et 12 heures. Aux jours 1 et 24 de l'étude une perfusion de 150 mg est administrée durant 20 minutes.

En résumé, les échantillons à doser contenant un standard interne sont extraits du plasma baséifié (pH 11) à l'aide de dichlorométhane avec un rendement supérieur à 70 %. Les échantillons sont élués à travers une colonne remplie d'une phase hexyl Spherisorb 5 µm, à l'aide d'une phase mobile constituée d'acétonitrile, d'un tampon aqueux phosphate en proportion v/v 50:220 à pH 3,9 et à la vitesse de 1,5 ml/min.

Les limites de **quantification** pour le moclobémide et ses métabolites dans le plasma vont de 20 à 30 ng/µl avec un volume d'échantillon de 0,5 ml. Sur tout l'intervalle de dosage il existe une relation linéaire entre les concentrations et les rapports des hauteurs de pic des composés à doser. La **précision** inter-essai de la méthode calculée à partir de dosages répétées de contrôles de qualité (blancs) à différents jours est excellente avec un coefficient de variation pour moclobémide < 8 % entre 50 - 1500 ng/ml pour RO 12-5637, < 6 % entre 50 - 1500 ng/ml pour RO 12-8095, 14 % à 50 ng/ml et < 7 % entre 200 - 1000 ng/ml.

La **stabilité** des échantillons pendant 24 h à température ambiante ($\pm 20^\circ \text{C}$) après 6 et 9 mois de stockage à -20°C a été testée. Aucune chute de concentration significative (> 10 %) n'a pu être détectée.

Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques, en fonction du temps, ont été analysés en utilisant la méthode modèle indépendant.

Résultats et discussion

Les résultats des concentrations plasmatiques, en fonction du temps de moclobémide administré ou perfusion I.V. et, en traitement chronique oral, sont dans la majorité des cas suffisamment complets pour permettre d'évaluer la disposition du médicament. Le traitement oral avec le moclobémide a été réalisé durant une période suffisamment longue (15 jours) pour permettre d'atteindre l'état d'équilibre.

En revanche, la durée des prélèvements sanguins n'est pas suffisante pour permettre de caractériser la disposition des deux métabolites du moclobémide dosés, RO 12-8095 et RO 12-5637. Cette constatation apparaît lors de l'examen des profils des concentrations plasmatiques en fonction du temps qui indiquent que les métabolites sont éliminés plus lentement qu'ils ne sont formés. Une autre possibilité est que la partie terminale de la courbe d'élimination n'ayant pas été mesurée, les métabolites peuvent être formés et/ou distribués relativement lentement. Enfin, la dernière hypothèse est qu'avec des temps de prélèvement suffisamment longs, les profils des métabolites seraient parallèles à ceux du moclobémide.

Le dosage des concentrations plasmatiques du moclobémide en fonction du temps après administration I.V. et orale indique clairement des variations dépendantes du temps dans la disposition du moclobémide entre le traitement aigu et chronique. L'AUC augmente de façon significative comme conséquence d'une réduction de la clairance systémique en comparant les données obtenues à partir de la 1ère perfusion I.V. (jour 1) à celles obtenues à partir de la 2ème perfusion I.V. (jour 24). En parallèle on observe une augmentation du temps de demi-vie qui est plus le reflet d'une altération de l'élimination que du volume de distribution, car ce dernier (V_{ss}) reste constant. Le médicament étant complètement éliminé par métabolisme hépatique, la diminution de la clairance systémique signe une variation de la clairance hépatique. Ces résultats reflètent une clairance métabolique réduite, ainsi le métabolisme du moclobémide est affecté durant un traitement chronique. La clairance rénale reste inchangée entre la première et la deuxième perfusion I.V. $2,6 \pm 1,9$ et $2,4 \pm 2,8$ ml/min respectivement.

Les résultats obtenus à partir du traitement oral à l'état d'équilibre sont en accord avec les résultats obtenus à partir de la voie I.V.. Les concentrations plasmatiques de moclobémide, les AUC et $T_{1/2}$ augmentent alors que la clairance orale décroît durant la première semaine de traitement puis reste constante durant la 2ème semaine. Cette diminution de la clairance a comme conséquence une accumulation de médicament plus importante que celle prévue durant le traitement chronique oral en se basant sur la comparaison des valeurs de concentrations plasmatiques à l'état d'équilibre ou des AUC de la 2ème et 1ère semaine (Tableau XII)

Le moclobémide est rapidement résorbé après traitement oral ($T_{max} = 0,75$ h). Cette résorption reste inchangée malgré la variation de la clairance. Par contre, la biodisponibilité absolue augmente entre la première dose et après des doses multiples. La faible biodisponibilité à dose unique observée dans cette étude ainsi que précédemment (3) semble être le reflet d'une importante élimination présystémique, sûrement un effet de premier passage hépatique, car l'extraction hépatique est importante. Le médicament semble être complètement absorbé à partir du tractus gastro-intestinal, en se basant sur la bonne corrélation existant entre la biodisponibilité systémique observée et attendue. En supposant une résorption complète, un débit sanguin hépatique de 90 L/hr et un coefficient de partage sang/plasma de 1,0, la

biodisponibilité systémique attendue à partir des données I.V. (jour 1, avant traitement chronique) est de $0,56 \pm 0,06$ comparé à la valeur moyenne observée (jour 8 première dose orale avant traitement chronique et jour 1 perfusion I.V.) de $0,55 \pm 0,20$. Une bonne corrélation est également observée entre la biodisponibilité systémique attendue basée sur la première dose orale (jour 8), $0,54 \pm 0,11$ et les valeurs observées $0,55 \pm 0,20$.

Au contraire, la biodisponibilité systémique attendue basée sur la seconde dose I.V. (jour 24), $0,68 \pm 0,04$ est inférieure à la valeur observée à l'état d'équilibre (moyenne des jours 15 et 22) $0,87 \pm 0,16$. La même sous-estimation est faite pour la voie orale (jours 15 et 22) avec une biodisponibilité de $0,73 \pm 0,05$ comparée aux valeurs observées $0,87 \pm 0,16$. Ces disparités sont en réalité faibles car les valeurs obtenues sont supérieures à celles attendues, la clairance ayant varié au cours du traitement oral entre les jours 15 et 22 et la dose I.V. (jour 24). Si la clairance réduite après doses multiples revient à sa valeur de base (entre jour 22 et 24), on observe une diminution de l'AUC I.V. et une surestimation de la biodisponibilité observée (AUC oral/AUC I.V.). Alternativement, l'hypothèse d'une cinétique de 1er ordre et flux sanguin hépatique inchangé, ou autres sites de métabolisme pré-systémique, peut également expliquer les résultats obtenus.

Dans tous les cas, la biodisponibilité augmentée à l'état d'équilibre comparée à celle observée après une dose unique est en accord avec une clairance hépatique et un taux d'extraction réduit. Le mécanisme exact de cet effet et la réduction de la clairance I.V. notée après un traitement chronique (jour 24) ne sont pas connus actuellement. Il y a deux hypothèses possibles: Le moclobémide inhibe son propre métabolisme ou le métabolisme du moclobémide est inhibé par un ou plusieurs de ses métabolites. A noter que les limites étendues des paramètres et leur grande variabilité peuvent également expliquer, au moins en partie, les résultats obtenus.

En résumé, la pharmacocinétique du moclobémide a été étudiée après un traitement chronique oral à l'état d'équilibre. Le traitement chronique est précédé et suivi d'une perfusion I.V. de moclobémide. L'analyse des concentrations plasmatiques en fonction du temps indique une réduction des clairances systémiques et orales, une augmentation de la biodisponibilité systémique avec comme conséquence une accumulation du moclobémide plus élevée à l'état d'équilibre que celle attendue. Le métabolisme du moclobémide est inhibé après doses multiples par un mécanisme inconnu qui pourrait impliquer une réduction de la clairance hépatique par le composé ou le(s) métabolite(s). La diminution de la clairance du moclobémide et l'augmentation des concentrations à l'état d'équilibre ne devraient entraîner que des conséquences cliniques minimales. Le médicament montre une bonne tolérance et les ajustements des doses, pour atteindre la zone de réponse thérapeutique souhaitée, peuvent être effectués entre le 10ème et le 14ème jour qui suivent le début du traitement.

Tableau XII:
Paramètres pharmacocinétiques du moclobémide après:

- Administration intraveineuse avant (A) et après (B) un traitement oral chronique

	Moclobémide	
Paramètres	A	B
$T_{1/2}$ (h)	1.60	2.00
Cl_S (L/h)	39.4	29.1
V_{SS} (L)	84.3	80.7

- Traitement oral chronique, jours 1, 8 et 15:

	Moclobémide		
Jours / Paramètres	1	8	15
Cl_O (L/h)	83.6	35.6	33.8
F_{obs}	0.56	0.86	0.90

3.1.2. Etude II
Pharmacocinétique du moclobémide (RO 11-1163) dans une étude de tolérance à doses orales croissantes chez le volontaire sain

But

La pharmacocinétique du moclobémide et de deux de ses métabolites RO 12-5637 et RO 12-8095 sont étudiés après administration orale de 100, 200, 400, 800 et 1200 mg de moclobémide en comprimés à 12 volontaires sains, dans une étude en double aveugle randomisée. Le but de cette étude est de tester la tolérance subjective et objective, la résorption et les paramètres de disposition du moclobémide chez le volontaire sain après des doses orales croissantes, ainsi que le profil pharmacodynamique des effets secondaires après l'administration de différentes doses de moclobémide en comparaison avec le placebo. Ce rapport ne décrit que la partie pharmacocinétique de l'étude. L'étude est menée selon le protocole PK 4615 en annexe.

Matériel et méthodes

Dans une étude de tolérance en double aveugle randomisée, une dose orale de 100, 200, 400 800 et 1200 mg de moclobémide a été administrée à quatorze volontaires mâles, non fumeurs, âgés de 20 à 34 ans. Le protocole est divisé en deux études. L'étude a comprend 6 sujets dont 4 reçoivent à 3 occasions des doses de 100, 200 et 400 mg et deux du placebo. L'étude b englobe 8 sujets auxquels sont administrés des doses de 800 mg (6 vrais - 2 placebos) et 1200 mg (4 vrais - 2 placebos). Deux sujets ont quitté l'étude après la dose de 800 mg.

Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques, en fonction du temps, ont été analysés en utilisant la méthode modèle indépendant.

Résultats et discussion

Les graphiques des concentrations plasmatiques en fonction du temps du moclobémide et deux de ces métabolites (RO 12-8095 et RO 12-5637) sont étudiés sur une période de 24 heures après administration de 100, 200 et 400 mg (Etude a) et 800 et 1200 mg (Etude b) de moclobémide.

Les principaux paramètres pharmacocinétiques obtenus dans l'étude a et b indiquent que la pharmacocinétique du moclobémide est dose dépendante. Dans l'étude a, la clairance orale de moclobémide est réduite 1.6 fois (76,0 vs 47,1 L/h; $p < 0.05$) lorsque la dose passe de 100 à 400 mg. Une diminution faible mais statistiquement significative de la clairance du moclobémide est observée entre les doses de 100 et 200 mg (réduction de 1,2 fois). Elle est accompagnée d'une augmentation d'un facteur 1,4 du temps de demi-vie (1,25 vs 1,71 h; $p < 0.05$) dans le plasma. Dans l'étude b, les valeurs de la clairance orale du moclobémi-

de après des doses de 800 et 1200 mg chutent d'un facteur 2.6 et 3.4, comparé aux résultats obtenus après une dose de 100 mg.

Tableau XIII: Effet de la dose sur les paramètres pharmacocinétiques du moclobémide ($x \pm \% CV$) après administration orale

XIII a: 100 - 200 ou 400 mg

Paramètres					
Dose	Cl ₀ (L/h)	AUC (ng.h/ml)	AUC ¹ (ng.h/ml)	β (h ⁻¹)	t _{1/2} β ² (h)
100 mg (n=4)	76,0 ± 21	1361 ± 22	1361 ± 22	0,553 ± 22	1,25 ± 21
200 mg (n=4)	62,0 ± 38	3585 ± 39	1793 ± 39	0,440 ± 33	1,58 ± 37
400 mg (n=4)	47,1 ± 36	9209 ± 29	2302 ± 29	0,405 ± 24	1,71 ± 25

XIII b: 800 ou 1200 mg

Paramètres					
Dose	Cl ₀ (L/h)	AUC (ng.h/ml)	AUC ¹ (ng.h/ml)	β (h ⁻¹)	t _{1/2} β ² (h)
800 mg (n=6)	28,9 ± 53	32111 ± 33	4014 ± 33	0,253 ± 21	2,74 ± 22
1200 mg (n=4)	22,8 ± 24	55000 ± 24	4583 ± 24	0,254 ± 12	2,73 ± 12

1) Normalisé pour une dose de 100 mg de l'étude a

2) Moyenne harmonique et % CV basé sur la "pseudo" déviation standard

Ces observations indiquent que la pharmacocinétique du moclobémide est dose dépendante dans l'intervalle de dosage de 100 à 1200 mg pour le moclobémide (Tableaux XIII a et b) et apparait, soit durant la phase de résorption (réduction de l'effet de premier passage hépatique à hautes doses) et/ou est liée à la clairance systémique dans la phase "post-résorption". Bien que cet effet soit prononcé en comparant les doses de 100 et 1200 mg, les conséquences cliniques semblent minimales aux doses thérapeutiques (100 à 150 mg trois fois par jour).

3.1.3. Etude III **Effet de l'alimentation sur la biodisponibilité relative du moclobémide**

But

Le moclobémide est principalement métabolisé au niveau hépatique, sa clairance systémique est relativement grande (40L/h) et il subit un effet de premier passage hépatique élevé. L'influence de l'alimentation sur la biodisponibilité des médicaments à extraction hépatique élevée ayant été décrite, nous avons étudié l'effet d'un repas sur la résorption et la disposition du moclobémide.

Matériel et Méthodes

Une dose orale de 100 mg de moclobémide a été administrée, à deux occasions, à douze volontaires sains âgés de 27 à 47 ans. D'une part, le médicament est administré après avoir jeûné une nuit, le repas étant servi 4 heures après la prise de moclobémide. D'autre part, le médicament est administré après une nuit à jeûn, mais 30 minutes après la prise d'un repas standard consistant en 20 % de protéines, 35 % de lipides et 45 % de glucides. Un repas pauvre en lipides est servi 4 et 10 heures après la prise de médicament. Des prélèvements sanguins sont effectués durant 12 heures.

Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques, en fonction du temps, ont été analysés en utilisant la méthode modèle indépendant.

Les résultats des concentrations plasmatiques en fonction du temps sont analysés par une méthode non compartimentale pour obtenir les paramètres pharmacocinétiques et le test statistique de Student ($p < 0.05$).

Résultats et discussion

Les paramètres pharmacocinétiques obtenus après administration orale de moclobémide (Tableau XIV) montrent que sa résorption est rapide à jeun et qu'en présence d'aliments sa vitesse de résorption est légèrement diminuée, la valeur moyenne de $T_{\max}$ est de 0,71 et 1,14 h avec le repas. Quant aux valeurs de $C_{\max}$, elles restent constantes avec des valeurs moyennes de 753 ng/ml à jeun et 643 ng/ml après repas.

Ces observations en présence d'aliments peuvent s'expliquer pour différentes raisons d'une part, par un retard de la vidange gastrique avec augmentation du débit sanguin splanchnique d'autre part, par une diminution de la vitesse de dissolution et ralentissement de la diffusion du moclobémide vers les sites de résorption. Quant aux valeurs de $C_{\max}$, inchangées en présence d'aliments, elles montrent que le taux de résorption ne semble pas être altéré.

Le taux de résorption du moclobémide évalué par les aires sous les courbes des concentrations plasmatiques en fonction du temps n'est pas significativement différent avant (1752 ng.h/ml) et après repas (1676 ng.h/ml). La moyenne des quotients des biodisponibilités relatives orales (avec repas / à jeun) est de 0,98 avec un coefficient de variation

(cv) de 15 %. De même, les valeurs de la clairance orale ne sont pas influencées par la nourriture avec une valeur de la Cl_o (avec repas/à jeun) de 0,94 avec un cv de 17 %. Quant au temps de demi-vie après repas, il reste inchangé de 1,60 à 1,77 h. La valeur de C_{max} du métabolite RO 12-8095 reste inchangée en présence de nourriture, quant à T_{max} il est retardé après repas (1.64 h) comparé à jeun (1,27 h). $T_{1/2}$ varie de 2,10 à 2,39 h avec le repas. De même que pour le moclobémide, l'AUC du RO 12-8095 n'est pas significativement différente en présence d'aliments. A l'exception de T_{max} tous les rapports (avec repas/à jeun) des paramètres calculés sont proches de 1.

En résumé, la consommation d'aliments simultanément à l'ingestion de moclobémide influence sa vitesse de résorption mais n'a pas d'influence sur son taux de résorption depuis le tractus gastro-intestinal après une prise orale de 100 mg de moclobémide. Les variations minimales observées sont sans effet sur le traitement avec le moclobémide. Aussi, la prise concomitante de nourriture ne modifie pas la biodisponibilité de moclobémide.

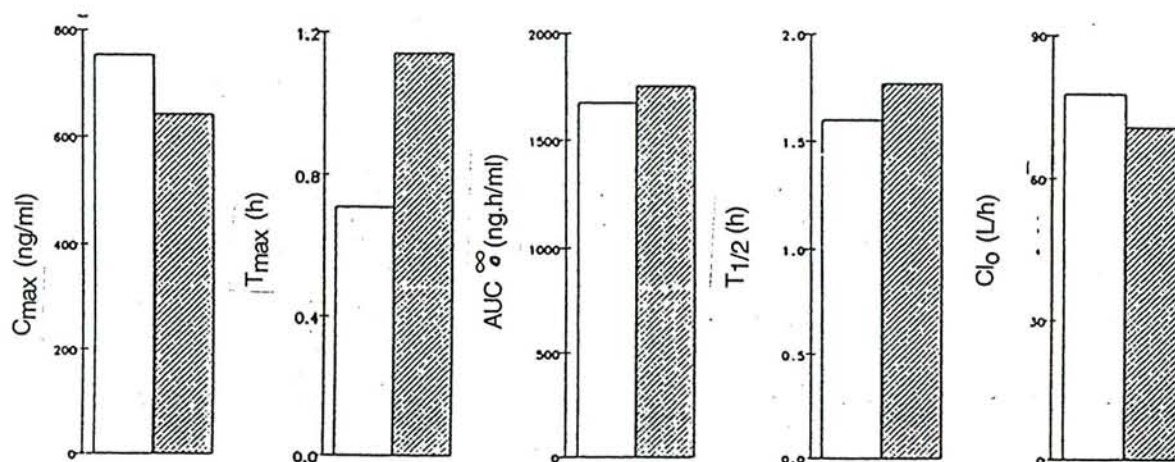
Tableau XIV
Paramètres pharmacocinétiques du moclobémide et de son métabolite principal (Moyenne $\pm$ D.S.)

Paramètre	Moclobémide				Métabolite principal			
	à jeun		Après repas		à jeun		Après repas	
C_{max} (ng/ml)	753	301	643	283	565	90	531	117
T_{max} (h)	0,71	0,21	1,14	0,65	1,27	0,70	1,64	0,75
AUC_{∞} (ng.h/ml)	1676	788	1752	788	2587	905	2770	859
$T_{1/2}$ (h)	1,60	0,32	1,77	0,37	2,10	0,53	2,39	0,69
Cl_o (L/h)	77,7	51,3	70,8	37,5	-----		----	

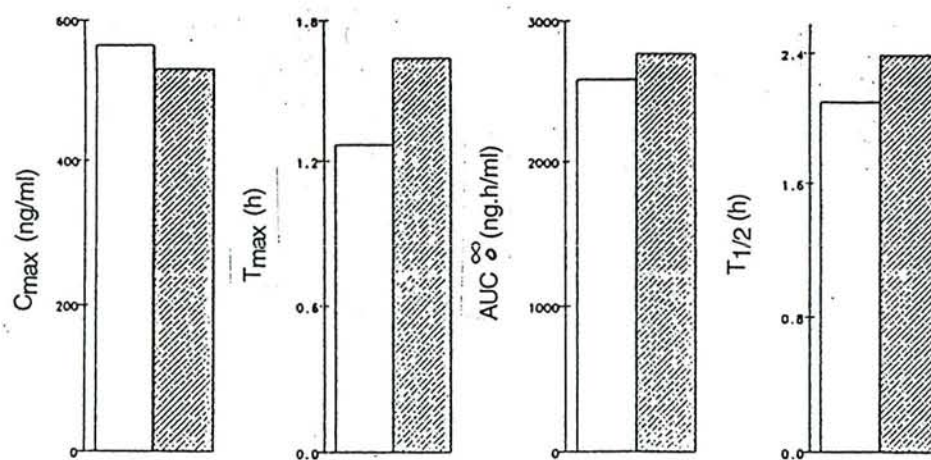
Après une dose orale de 100 mg de moclobémide avant et après un repas

Tableau XIV (suite)

Histogrammes illustrant les paramètres pharmacocinétiques de moclobémide avant et après un repas



Histogrammes illustrant les paramètres pharmacocinétiques du métabolite principal avant et après un repas



□ à jeun
▨ après un repas

3.1.4. Etude IV

Influence de l'insuffisance rénale sur la pharmacocinétique du moclobémide (RO 11-1163) et de ses métabolites RO 12-8095 et RO 12-5637

Objectif

Le but de cette étude est d'étudier l'influence de différents degrés d'insuffisance rénale sur l'absorption et la disposition du moclobémide après administration orale ainsi que de deux métabolites RO 12-8095 et RO 12-5637. Le composé a également été administré en I.V. afin de pouvoir définir les variations des paramètres de disposition. Les résultats obtenus sont comparés à ceux décrits chez le sujet sain.

Matériel et méthodes

Les caractéristiques pharmacocinétiques de résorption et de disposition du moclobémide sont étudiées suite à une administration orale d'une dose de 100 mg et une perfusion I.V. de 96,7 mg à 13 patients (9 hommes, 4 femmes) souffrant de différents degrés d'insuffisance rénale. Les sujets sont divisés en deux groupes: Groupe I avec une clairance de la créatinine de 0 à 5 ml/min (patients dialysés) et groupe II avec une clairance de la créatinine comprise entre 19 et 46 ml/min. (patients non dialysés)

Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques en fonction du temps sont analysés en utilisant la méthode modèle indépendant.

Résultats et discussion

Aucune différence n'étant apparue entre les groupes I et II dans la disposition du moclobémide, la valeur moyenne de tous les patients a été utilisée pour comparer les résultats à ceux d'une étude précédente (Etude 1) chez des volontaires sains (Tableau XV). A une exception près, aucune différence statistiquement significative dans l'absorption et la disposition du moclobémide n'a été observée en comparant le groupe des insuffisants rénaux avec les sujets sains. Les valeurs moyennes ($\pm$ DS) chez les insuffisants rénaux et sujets sains sont respectivement de: 40,3 (16,1) vs 39,4 (5,9) L/h pour la clairance systémique, 84,2 (23,6) vs 84,3 (9,3) L pour le volume de distribution à l'équilibre, 1,62 (0,53) vs 1,60 (0,24) h pour le temps de demi-vie; 2,09 (1,16) vs 2,11 (0,37) h pour le temps de présence moyen, 0,58 (0,24) vs 0,55 (0,20) pour la biodisponibilité absolue orale. Bien qu'il n'y ait pas de différence dans les concentrations maximales de moclobémide ou de la durée pour atteindre ces concentrations après une dose orale, le temps de résorption moyen est significativement prolongé chez l'insuffisant rénal comparé au sujet sain (1,05 vs 0,47 h.). La grande variabilité des paramètres obtenus chez l'insuffisant rénal, comparés à ceux des sujets sains, peut être le reflet d'une comédication et/ou d'un intervalle d'âge plus grand dans le groupe des insuffisants rénaux. Aucune corrélation entre les paramètres de disposition de moclobémide et la fonction rénale évaluée par la clairance de la créatinine n'a pu être mise en évidence.

Les caractéristiques de disposition du métabolite RO 12-8095 sont en général bien décrites et en se basant sur le temps de présence moyen et la constante d'élimination, le métabolite semble être éliminé plus rapidement que la substance mère. L'élimination de ce métabolite semble être limitée par sa vitesse de formation après prise de moclobémide et aucune différence significative entre l'insuffisant rénal et le sujet sain n'a pu être mise en évidence. Aucune corrélation entre les paramètres de disposition de RO 12-8095 (métabolite principal) et l'insuffisance rénale évaluée par la clairance de la créatinine n'a été trouvée. Peu d'informations ont pu être obtenues pour un autre métabolite, le RO 12-5637 (dérivé N-oxydé), car ce composé présente de faibles concentrations durant la durée des prélèvements.

Le résultat de cette étude montre qu'il n'est pas nécessaire d'adapter la posologie du moclobémide chez l'insuffisant rénal, la fonction rénale ne semble pas influencer les paramètres de disposition et d'absorption du moclobémide. Cette conclusion suppose qu'il existe la même corrélation dose-réponse pour les sujets sains et insuffisants rénaux.

Tableau XV

Paramètres pharmacocinétiques du moclobémide, des métabolites RO 12-8095 et RO 12-5637 et histogramme (moyenne $\pm$ DS)

Voie I.V. *	Moclobémide	
	Insuf. rénaux	Sains
$T_{1/2}$ (h)	$1,62 \pm 0,53$	$1,60 \pm 0,24^{**}$
Cl_s (L/h)	$40,3 \pm 16,1$	$39,4 \pm 5,9$
V_{ss} (L)	$84,2 \pm 23,6$	$84,3 \pm 9,3$
MRT (h)	$2,09 \pm 1,16$	$2,11 \pm 0,37$

	RO 12-8095		RO 12-5637	
	Insuf. rénaux	Sains	Insuf. rénaux	Sains
$C_{p_{max}}$ (mg/L)	$0,49 \pm 0,13$	$0,58 \pm 0,15$	$0,15 \pm 0,06$	$0,09 \pm 0,03$
T_{max} (h)	$1,63 \pm 0,83$	$1,72 \pm 0,68$	$1,66 \pm 0,60$	$0,82 \pm 0,53$

* Dose I.V. des patients insuffisants rénaux (96.7 mg) comparés à des sujets sains (Etude 1)

** Moyenne harmonique et pseudo DS

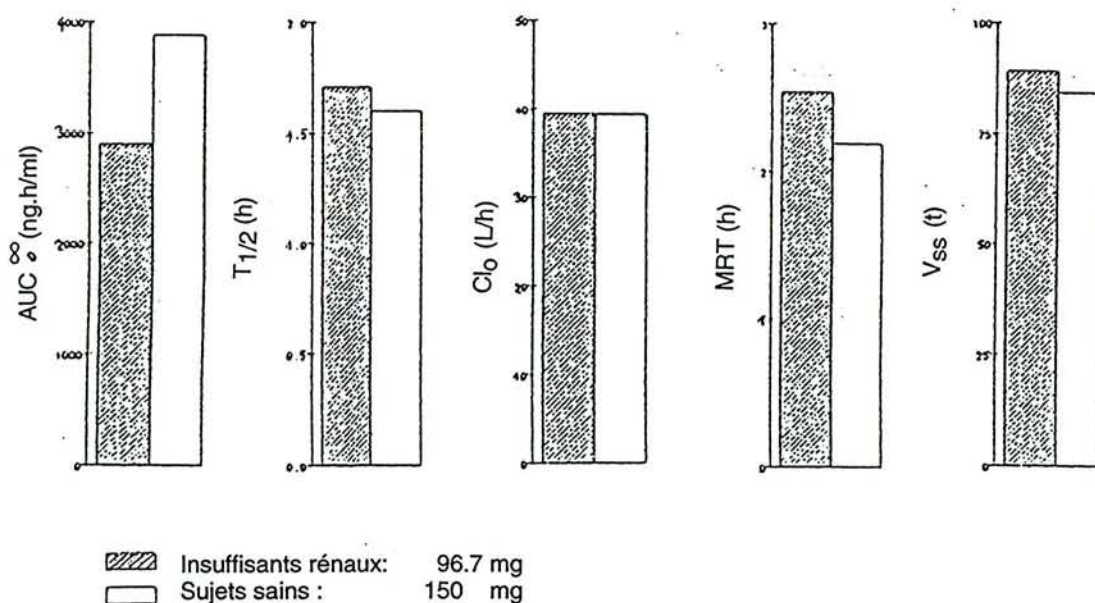
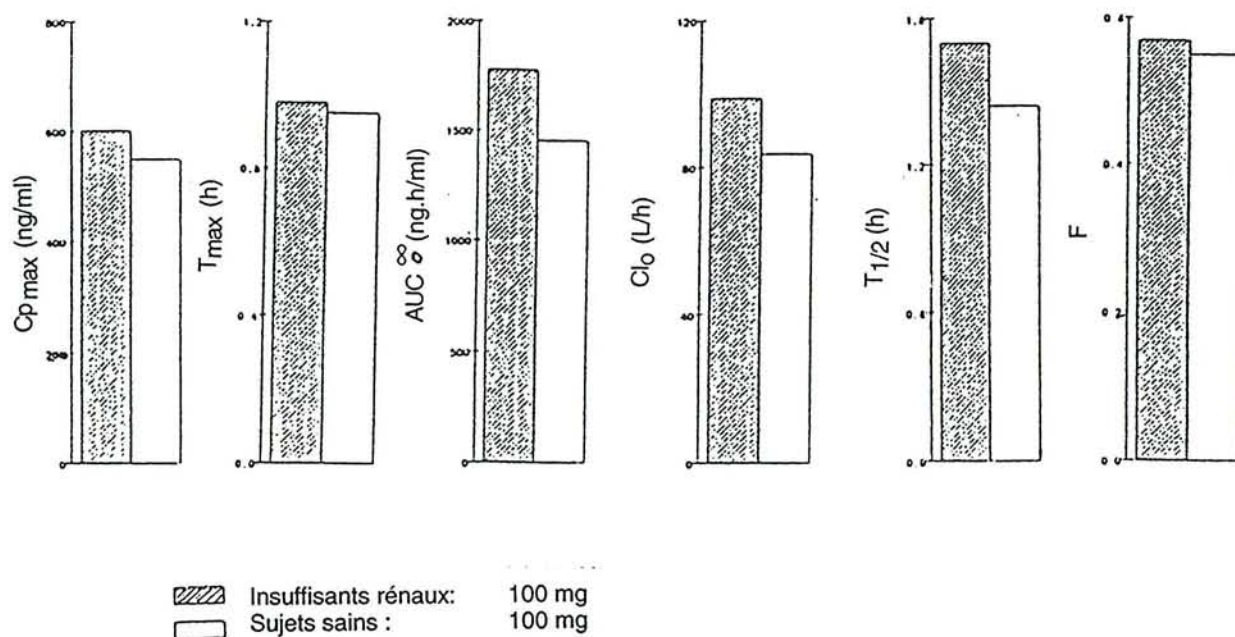


Tableau XV (suite)

Voie orale *	Moclobémide			
	Insuf. rénaux		Sains	
Cp _{max} (ng/ml)	601	288	548	214
T _{max} (h)	0.98	0.68	0.95	0.55
AUC _∞ (ng.h/ml)	1781	1407	1454	625
T _{1/2} (h)	1.70	0.61	11.44	0.36
Cl _O (L/h)	98.9	88.0	83.6	41.0
F	0.57	0.24	0.55	0.20

	RO 12-8095				RO 12-5637			
	Insuf. rénaux		Sains		Insuf. rénaux		Sains	
Cp _{max} (ng/ml)	592	154	504	142	186	67	94	29
T _{max} (h)	1.48	0.69	1.39	0.74	1.70	1.24	0.82	0.42

* Dose unique de 100 mg à des patients insuffisants rénaux comparés à des sujets sains (Etude 1)



3.1.5. **Etude V** **Influence de l'insuffisance hépatique sur la pharmacocinétique du moclobémide**

But

La résorption et la disposition du moclobémide et de deux métabolites sont examinées chez 12 patients atteints d'insuffisance hépatique chronique (cirrhose) après une perfusion I.V. de 90 mg et une dose orale de 100 mg de moclobémide.

Matériel et Méthodes

Les paramètres obtenus sont comparés aux résultats d'une étude précédente chez 12 sujets sains (Etude 1). La fonction hépatique est évaluée par la clairance du vert d'indocyanine (ICG) et la clairance de l'antipyrine (AP) et des analyses biochimiques. Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques, en fonction du temps, ont été analysés en utilisant la méthode modèle indépendant.

Résultats et discussion:

Les patients atteints de cirrhose présentent des valeurs moyennes de clairance ICG et AP de 8.24 L/h et 1.66 L/h respectivement.

Après une **dose I.V.** plusieurs paramètres sont significativement différents chez les insuffisants hépatiques comparés aux sujets sains, en particulier le temps de demi-vie ($T_{1/2}$), le temps moyen de présence (MRT), la concentration à la fin de la perfusion (C_{inf}), la clairance systémique (Cl_s) et la phase terminale d'élimination (β) résumés dans le tableau XVI.

Ainsi, en présence d'une insuffisance hépatique la valeur de Cl_s est d'environ 1/3 de celle des sujets sains, $T_{1/2}$ est prolongé par un facteur d'environ 2.4 et MRT est augmenté par un facteur >3. Tous ces paramètres ont des variations interindividuelles nettement supérieures à celles observées chez le sujet sain. Aucune différence du volume de distribution (V_{ss}) ou clairance rénale (Cl_r) n'est relevée. Ces résultats sont le reflet d'une perturbation du métabolisme dans l'insuffisance hépatique, ce qui n'est pas surprenant car la Cl_s élevée du moclobémide signe un métabolisme hépatique prépondérant. Une bonne corrélation entre les valeurs de Cl_s pour moclobémide, d'une part, et les valeurs de clairance ICG et AP, d'autre part, est observée.

Après une **administrative orale**, la clairance orale apparente Cl_o du moclobémide est significativement diminuée chez les patients insuffisants hépatiques avec des valeurs de concentrations plasmatiques maximales (C_{max}) et de biodisponibilité orale augmentées. (Tableau XVI). Comme pour la voie I.V., une bonne corrélation entre les valeurs de clairance orale apparente et celles des clairances ICG et AP est observée.

Ainsi, après un traitement oral, on peut s'attendre à une accumulation de moclobémide supérieure chez le patient souffrant d'insuffisance hépatique par rapport au sujet sain. C'est pourquoi, lors d'une insuffisance hépatique chronique, la posologie doit être réduite d'environ un quart à un tiers afin d'atteindre les concentrations de moclobémide comparables à celles du sujet sain. L'intervalle d'administration peut également être espacé du fait de l'allongement du $T_{1/2}$.

Tableau XVI Comparaison statistique des paramètres de disposition du moclobémide chez les sujets insuffisants hépatiques et sujets sains

XVI a: voie I.V.

Paramètres		Insuffisants hépatiques		Sujets sains ¹		p ²
Cl _S (l / h)						
moyenne	(% c.v.)	14.6	(77)	39.4	(15)	
limites	(n)	4.0 - 39.1	(9)	30.7 - 48.1	(11)	< 0.001
β	(h ⁻¹)					
moyenne	(% c.v.)	0.179	(64)	0.432	(15)	< 0.001
limites	(n)	0.064 - 0.392	(9)	0.296 - 0.514	(11)	
t _{1/2} (h)						
moyenne	(% c.v.)	3.87	(68)	1.60	(15)	< 0.005
limites	(n)	1.77 - 10.83	(9)	1.35 - 2.34	(11)	
V _{ss} (L)						
moyenne	(% c.v.)	75.7	(53)	84.3	(11)	ns
limites	(n)	27.0 - 165.4	(9)	63.4 - 98.0	(11)	
MRT (H)						
moyenne	(% c.v.)	7.21	(68)	2.19	(21)	< 0.005
limites	(n)	2.22 - 15.37	(9)	1.68 - 3.14	(11)	
Cl _r (l / h)						
moyenne	(% c.v.)	0.152	(33)	0.160	(70)	ns
limites	(n)	0.066 - 0.198	(8)	0.040 - 0.433	(12)	
Conc. à la fin de la perfusion (ng/ml)						
moyenne	(% c.v.)	2217	(36)	1148	(36) ³	< 0.001
limites	(n)	377 - 3371	(12)	599 - 2268	(12) ³	

1) Résultats obtenus de l'étude 1

2) Test de Student; ns = non significatif ($\alpha = 0.05$)

3) Ces valeurs sont ajustées à la différence de dose (90 mg/150 mg)

XVI b: voie orale

Paramètres		Insuffisants hépatiques		Sujets sains ¹		p ²
C _{max} (ng/ml)						
moyenne	(% c.v.)	1607	(42)	549	(39)	
limites	(n)	577 - 2959	(12)	220 - 917	(11)	< 0,001
T _{max}	(h)					
moyenne	(% c.v.)	0,87	(54)	0,95	(57)	ns
limites	(n)	0,28 - 2,00	(12)	0,50 - 2,00	(11)	
β	(h ⁻¹)					
moyenne	(% c.v.)	0,173	(64)	0,480	(25)	< 0,001
limites	(n)	0,057 - 0,393	(9)	0,326 - 0,667	(11)	
t _{1/2} (h)						
moyenne	(% c.v.)	4,00	(70)	1,44	(25)	< 0,001
limites	(n)	1,76 - 12,16	(9)	1,04 - 2,13	(11)	
AUC _∞	(ng.h/ml)					
moyenne	(% c.v.)	8864	(71)	1454	(43)	< 0,001
limites		1692 - 19760		587 - 2380		
Cl _O (l / h)						
moyenne	(% c.v.)	20,16	(88)	83,6	(49)	< 0,005
limites	(n)	5,06 - 59,10	(9)	42,0 - 170,4	(11)	
MAT (h)						
moyenne	(% c.v.)	1,16	(45)	0,47	(79)	< 0,005
limites	(n)	0,65 - 2,15	(6)	0,0 - 1,03	(12)	
F						
moyenne	(% c.v.)	0,86	(29)	0,55	(37) ³	< 0,02
limites	(n)	0,33 - 1,10	(9)	0,26 - 0,91	(11) ³	

1) Résultats obtenus de l'étude 1

2) Test de Student; ns = non significatif (α = 0.05)

3) Ces valeurs sont ajustées à la différence de dose (90 mg/150 mg)

3.1.6. Etude VI
Pharmacocinétique du moclobémide chez le sujet jeune et âgé
après une dose I.V. et orale en aiguë chronique

But

Evaluer l'influence de l'âge avancé sur la pharmacocinétique du moclobémide.

Matériel et Méthodes

Les caractéristiques de résorption et disposition du moclobémide sont examinés chez 14 sujets sains âgés (65 - 77 ans) et 6 sujets sains jeunes (22 - 23 ans). Une dose I.V. de 75 mg de moclobémide est administrée avant et après un traitement oral chronique de 15 jours de 100 mg, trois fois par jour.

Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques, en fonction du temps, ont été analysés en utilisant la méthode modèle indépendant.

Résultats et discussion

Les résultats de l'étude ne sont que partiels car les données obtenues, après administration intraveineuse avant et après le traitement oral chronique de moclobémide, n'ont pu être analysées. Il en résulte que les paramètres obtenus, après administration I.V., sont limités à deux groupes de 5 sujets jeunes et âgés ayant reçu une nouvelle dose I.V. après la fin de l'étude. A noter qu'après administration I.V. les paramètres de disposition du moclobémide tels que clairance, temps de demi-vie, volume de distribution et temps de présence moyen ne sont pas significativement différents entre les 2 groupes de sujets. De même, aucune différence significative entre les 2 groupes n'est observée dans la disposition du métabolite RO 12-8095 (Tableau XVII).

Après la première prise orale, la valeur du C_{max} des sujets âgés est augmenté de façon significative avec en parallèle une clairance orale apparente diminuée. Aucune différence entre les deux groupes n'est relevée pour les paramètres tels que le temps pour atteindre la concentration maximale, le temps de demi-vie, le temps de résorption moyen et la biodisponibilité orale absolue (Tableau XVII a). A l'état d'équilibre aux jours 15 et 22 les concentrations plasmatiques maximales sont semblables dans les deux groupes.

A la fin de la première semaine de traitement chronique, la clairance orale reste significativement supérieure chez le sujet jeune, mais cette différence devient non significative à la fin de la deuxième semaine de traitement.

Tous les autres paramètres, y compris les concentrations plasmatiques maximales sont semblables dans les deux groupes, de même que la valeur moyenne des concentrations minimales à l'état d'équilibre pour le moclobémide (Tableau XVII b) et son métabolite RO 12-8095 n'est pas différente entre les deux groupes.

Ces résultats indiquent qu'il ne semble pas nécessaire d'adapter la posologie du moclobémide lors du traitement des sujets âgés, afin d'obtenir des concentrations similaires à celles des sujets jeunes.

Dans les deux groupes, une différence significative de la clairance orale et de temps de demi-vie du moclobémide, après traitement chronique, est apparue en comparaison des valeurs obtenues après la première dose. Le même résultat de clairance diminuée et de demi-vie prolongée a été observé dans une étude précédente chez 12 sujets jeunes (Etude I).

Tableau XVII: Paramètres de disposition du moclobémide chez le sujet jeune et âgé
XVII a **Perfusion i.v. de 75 mg de moclobémide**

Sujet	Age	CT ^a ng/ml	β h ⁻¹	T _{1/2} h	AUC [∞] ng.h/ml	AUMC [∞] ng.h ² /ml	CL _s L/h	V _{ss} L	MRT ^b h
Moyenne	71	1372	0,425	1,63 ^c	2262	5307	36,3	72,8	2,10
± % c.v.	4,5	49,6	30,6	30,6	32,3	49,9	33,9	25,0	27,8
Médiane	69	1169	0,416	1,67	2319	5826	32,3	75,9	1,88
Limites	68-75	664-2461	0,257-0,563	1,23-2,69	1505-3040	2576-9188	24,7-49,8	43,5-93,7	1,51-2,99
Moyenne	29	1399	0,527	1,31 ^c	1717	3248	45,3	71,6	1,65
± % c.v.	14,1	20,0	30,0	29,9	22,1	47,3	21,0	24,9	33,9
Médiane	29	1394	0,581	1,19	1695	3222	44,3	66,7	1,61
Limites	22-33	991-1748	0,359-0,698	0,99-1,93	1296-2298	1591-5272	32,6-57,9	57,9-102,3	1,06-2,31
p < 0.05		ns	ns	ns	ns	ns	ns	ns	ns

a CT = concentration à la fin de la perfusion

b MRT = Temps de présence moyen

c = moyenne harmonique

d = Comparaison statistique (T. de student) p<0.05

ns = non significatif

XVII b **Dose orale de 100 mg de moclobémide**

Sujet	Age	C _{max} ng/ml	T _{max} h	β h ⁻¹	T _{1/2} h	AUC [∞] ng.h/ml	AUMC [∞] ng.h ² /ml	MAT ^a h	CL _o L/h	F
Moyenne	70	592	0,93	0,441	1,57 ^c	2269	6768	0,58	52,0	0,63
± % c.v.	6,1	29,8	51,0	24,6	24,3	43,9	69,1	51,3	40,6	28,6
Médiane	71	840	0,15	0,435	1,60	2142	5527	0,72	46,7	0,66
Limites	65-77	435-1313	0,50-2,00	0,202-0,627	1,11-2,65	1156-4673	2562-20673	0,23-0,86	21,4-86,5	0,36-0,79
Moyenne	29	608	0,92	0,509	1,36 ^c	1482	4408	1,16	79,1	0,66
± % c.v.	12,9	25,8	61,2	33,4	33,3	47,7	83,2	42,9	37,2	38,3
Médiane	30	584	0,75	0,537	1,29	1075	2475	1,13	93,2	0,63
Limites	22-33	428-807	0,50-2,00	0,311-0,722	0,96-2,26	931-2408	1723-10272	0,74-1,96	42,1-107,4	0,43-1,07
p < 0.05		ns	ns	ns	ns	ns	ns	ns	ns	ns

a MAT = temps de résorption moyen

XVII c
Traitement chronique (jours 15 et 22) de 100 mg de moclobémide 3 fois par jour

Sujet	Age	C _{max} ng/ml		T _{max} h		β h ⁻¹		T _{1/2} h		AUC [∞] ng.h/ml		CL ₀ L/h	
		d 15	d 22	d 15	d 22	d 15	d 22	d 15	d 22	d 15	d 22	d 15	d 22
Moyenne	70	1393	1498	0,93	0,84	0,257	0,248	2,70 ^a	2,79 ^a	5364	5571	20,2	19,7
± % c.v.	6.1	21,8	20,6	37,2	43,1	30,4	35,0	30,4	34,6	29,4	32,3	30,5	31,8
Médiane	71	1420	1493	0,88	0,75	0,255	0,274	2,73	2,54	5084	5138	19,8	19,5
Limites	65-77	927-1982	865-1911	0,50-2,00	0,50-2,00	0,114-0,371	0,084-0,370	1,87-6,08	1,87-8,25	2871-8582	2844-10117	11,7-34,8	9,9-35,2
Moyenne	29	1192	1277	0,83	0,92	0,317	0,281	2,19 ^a	2,47 ^a	3988	4406	28,5	27,4
± % c.v.	12.9	32,2	43,0	24,6	14,0	34,8	32,2	35,8	32,2	42,1	50,3	34,3	43,2
Médiane	30	1142	1199	0,88	1,00	0,285	0,291	2,49	2,38	3188	3771	31,5	26,6
Limites	22-33	758-1820	723-2124	0,50-1,00	0,75-1,00	0,207-0,463	0,176-0,399	2,13-3,35	1,74-3,94	2676-6525	2307-8245	15,3-37,4	12,1-43,4
p < 0.05		ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

a = moyenne harmonique

3.1.7. Etude VII **Passage du moclobémide dans le lait maternel**

But

Une des indications cliniques du moclobémide est la dépression post-partum. L'allaitement maternel est fortement conseillé au cours du traitement clinique or, le clinicien est souvent contraint de proposer l'arrêt de l'allaitement afin de prévenir les risques potentiels causés par le passage du médicament dans le lait maternel.

Le but de cette étude est d'évaluer le passage du moclobémide et de ses métabolites dans le lait maternel et de déterminer la quantité à laquelle est exposée le nouveau-né après une prise orale de 300 mg chez la mère.

Matériel et Méthodes

6 femmes allaitantes âgées de 24 à 36 ans ont ingéré une dose de 300 mg de moclobémide entre le 2ème et le 5ème jour post-partum. Des prélèvements sanguins et de lait maternel sont effectués durant une période de 24 heures. Le moclobémide, son métabolite actif RO 12-5637 et son métabolite principal RO 12-8095 sont dosés par une méthode HPLC.

Les paramètres pharmacocinétiques définissant le déclin des concentrations plasmatiques en fonction du temps sont analysés en utilisant la méthode modèle indépendant.

Résultat et Discussion

Après une dose orale de 300 mg de moclobémide, les concentrations de la substance mère et de son métabolite principal RO 12-8095 sont maximales au bout de 3 heures dans le plasma et le lait et ne sont plus détectables après 12 heures. Le métabolite actif RO 12-5637 n'est détecté dans aucun prélèvement de lait maternel. La quantité totale de moclobémide et de son métabolite principal RO 12-8095 excrétée dans le lait est négligeable. Le pourcentage de la dose excrétée de moclobémide et RO 12-8095 dans le lait maternel est en moyenne de 0.057 ± 0.020 % et 0.031 ± 0.011 % respectivement (Tableau XVIII). Une relation directe entre les concentrations de moclobémide dans le plasma et le lait et RO 12-8095 est mise en évidence ($r^2 \geq 0.97$). Le passage d'un médicament dans le lait maternel se fait principalement par diffusion passive à travers la membrane mammaire conduisant à un équilibre rapide du médicament entre le plasma et le lait. Le lait maternel peut donc être considéré comme un compartiment à transfert bidirectionnel entre la barrière sang-lait plutôt qu'une poche à accumulation entre deux prélèvements. Nous considérons ainsi chaque prélèvement de lait comme instantané. Le déclin parallèle des concentrations de moclobémide dans le lait et plasma soutient l'hypothèse d'un équilibre rapide entre le lait et le plasma.

En traitement chronique, il existe un risque d'accumulation de la substance mère dans le plasma et le lait, d'autant plus que chez le

La dose de 300 mg de moclobémide administrée dans cette étude est deux à trois fois supérieure à la dose thérapeutique. Ainsi, les AUC observées chez la mère allaitante après 300 mg de moclobémide reflètent les conditions à l'état d'équilibre telles qu'elles sont décrites chez le sujet sain après un traitement chronique.

En conclusion, il est peu probable que les quantités négligeables de moclobémide excrétées dans le lait maternel aient une influence clinique sur le nouveau-né.

Lait

Plasma

① = Moyenne harmonique
② = "pseudo" déviation standard

3.2. Pharmacogénétique

Etude VIII

Comparaison de la pharmacocinétique du moclobémide chez le métaboliseur faible et efficace de la débrisoquine

But

Dans plusieurs études pharmacocinétiques chez le sujet sain, le temps de demi-vie du moclobémide pour certains sujets est nettement supérieur à la moyenne de 1.5 h, de même que leur biodisponibilité semble anormalement élevée. Cette observation ne semble pas être reliée au facteur âge, mais peut être le reflet d'une variabilité interindividuelle. Ainsi, l'on ne peut exclure un éventuel contrôle génétique du polymorphisme de l'activité enzymatique.

Méthode

Au cours de trois études pharmacocinétiques les sujets ont été phénotypés avec de la débrisoquine. Une analyse rétrospective des métaboliseurs faibles auxquels a été administré du moclobémide est réalisée.

Les paramètres pharmacocinétiques, définissant le déclin des concentrations plasmatiques en fonction du temps, sont analysés en utilisant la méthode "Modèle indépendant".

Résultat et Discussion

Sur un total de 27 sujets âgés de 19 à 75 ans, 5 ont été classés comme étant métaboliseurs faibles de la débrisoquine. Bien qu'il existe une grande variabilité dans les paramètres pharmacocinétiques observés, aucune corrélation entre les paramètres pharmacocinétiques telle que la clairance orale ou temps de demi-vie d'élimination et le phénotypage par la débrisoquine n'a été obtenue. Les paramètres pharmacocinétiques des métaboliseurs faibles de la débrisoquine se situent tous à l'intérieur des limites des valeurs obtenues pour les métaboliseurs efficaces dans les études à dose unique (Cl_o , $T_{1/2}$, Cl_s) et chronique (C_{max} à l'état d'équilibre) - (Tableau XIX).

Cette analyse bien que limitée par le nombre de sujets, de même que par sa nature rétrospective suggère cependant qu'aucune variation des paramètres pharmacocinétiques du moclobémide n'est attendue chez les métaboliseurs faibles de la débrisoquine en comparaison des métaboliseurs efficaces.

Tableau XIX

Comparaison des paramètres pharmacocinétiques du moclobémide chez les métaboliseurs lents et rapides à la débrisoquine (DB) après:

A) une dose orale de 100 mg

B) une dose orale de 150 mg

C) des doses chroniques orales de 150 mg 3x/jour pendant 15 jours (jours 8 + 15)

D) une perfusion I.V. de 150 mg

Dose	Paramètre	Métaboliseur faible	Métaboliseur efficace		
A)	Cl _o (L/h)	N	5	22	
		moy.	59,74	61,56	
		D.S. % rel.	57 %	54 %	
	C _{max} (ng/ml)	lim.	26,09 - 112,8	17,11 - 214,1	
		moy.	713	706	
		D.S. % rel.	34 %	54 %	
	T _{1/2} (h)	lim.	442 - 981	210 - 2032	
		moy.	1,80	1,62	
		D.S. % rel.	29 %	26 %	
	lim.	1,35 - 2,85	1,04 - 2,81		
	B)	Cl _o (L/h)	N	3	10
			moy.	64,07	46,99
D.S. % rel.			22 %	47 %	
C _{max} (ng/ml)		lim.	50,87 - 78,02	17,32 - 83,69	
		moy.	1339	1141	
		D.S. % rel.	13 %	54 %	
T _{1/2} (h)		lim.	1218 - 1543	570 - 2622	
		moy.	1,45	1,87	
		D.S. % rel.	19 %	23 %	
lim.		1,17 - 1,67	1,35 - 2,65		
C)		Cl _o (L/h)	N	3	10
			moy.	22,42	15,33
	D.S. % rel.		15 %	41 %	
	C _{max} (ng/ml)	lim.	18,54 - 27,36	5,49 - 27,39	
		moy.	1720	2231	
		D.S. % rel.	15 %	30 %	
	T _{1/2} (h)	lim.	1424 - 2075	1572 - 4502	
		moy.	2,94	3,67	
		D.S. % rel.	20 %	30 %	
	lim.	2,28 - 3,49	2,30 - 6,44		
	D)	Cl _s (L/h)	N	4	17
			moy.	29,67	34,47
D.S. % rel.			37 %	26 %	
MRT (h)		lim.	18,60 - 40,49	17,41 - 48,2	
		moy.	2,10	2,14	
		D.S. % rel.	54 %	23 %	
V _{ss} (l)		lim.	1,53 - 4,40	1,60 - 3,29	
		moy.	62,8	73,7	
		D.S. % rel.	19 %	19 %	
T _{1/2} (h)		lim.	52,1 - 81,8	50,6 - 97,8	
		moy.	1,65	1,66	
		D.S. % rel.	46 %	19 %	
lim.	1,24 - 3,11	1,29 - 2,34			

Légende: N = nombre de sujets
moy. = moyenne géométrique
D.S. % rel. = déviation standard relative
lim. = limites

3.3 Pharmacocinétique et métabolisme comparatifs de 5 IMAO-A réversibles

Etude IX

But

Le but de cette étude rétrospective est d'évaluer la pharmacocinétique de 5 IMAO-A réversibles (moclobémide, toloxatone, brofaromine, cimoxatone et amiflamine).

Résultats et discussion

a) *Résorption*

Après administration orale, le moclobémide et le toloxatone sont rapidement résorbés. Le temps pour atteindre les concentrations plasmatiques maximales se situe entre 0,5 et 2 h. La résorption de la brofaromine, de l'amiflamine et de la cimoxatone est plus lente avec des concentrations maximales atteintes au bout de 1,5 à 4 h. La valeur de la biodisponibilité n'est connue que pour le toloxatone et le moclobémide et est comprise entre 0,5 et 0,8. Ces valeurs sont le reflet d'un taux d'extraction hépatique élevé, seuls 2/3 de la dose administrée atteignent la circulation sanguine inchangée.

b) *Distribution et fixation protéique*

La distribution d'un composé dans l'organisme est dépendant de son caractère lipophile et de la nature de sa fixation protéique. Aucune corrélation entre le coefficient de partage octanol-eau et l'un des paramètres pharmacocinétiques n'a pu être mis en évidence pour les cinq composés. La nature de la fixation aux protéines plasmatiques est différente pour chaque composé. Pour l'amiflamine elle est faible quant à la cimoxatone et la brofaromine elle est très forte. Pour le moclobémide et le toloxatone est de 50 %.

c) *Biotransformation et élimination*

Le temps de demi-vie passe de quelques heures pour le moclobémide et le toloxatone à plus de 10 heures pour la brofaromine et la cimoxatone.

Les 5 IMAO-A subissent un métabolisme hépatique prépondérant et seule une fraction négligeable de la dose (< 1 %) est éliminée inchangée dans les urines.

La voie de dégradation majeure commune aux 5 composés est l'oxydation.

Conclusion

De nombreuses différences dans les paramètres pharmacocinétiques disponibles des IMAO-A sont relevées. Cependant, une comparaison plus approfondie révèle une similitude entre le moclobémide et le toloxatone avec un taux d'extraction hépatique élevé, une biodisponibilité réduite et un temps de demi-vie d'élimination entre 1 à 3 h.

Tableau XX: Paramètres pharmacocinétiques des IMAO-A réversibles

Spécialités	Absorption		V l/kg	Distribution		T _{1/2} h	Elimination	
	F	t _{max} h		P	f _b %		Cl l/h/kg	f _e
Moclobémide	0,5–0,8	0,5–2,0	0,63–1,6	40,7	50	1–3	0,2–1,0	< 0,01
Toloxatone	0,5–0,6	0,5–1,0	1,1–1,6	11 ²⁾	50	0,9–2,5	0,46–0,86	< 0,01
Brofaromine		1,8–4,0	4,3–6,0	15,5	98	12–15	0,26–0,29	< 0,01
Cimoxatone		1,0–5,0	0,46–0,69	257	95	8,9–16	0,023–0,045	n. d.
Amiflamine		2	4,2–8,4	0,5	23	4,9–12	0,42–0,83	0,002

- 1) t_{max} = Temps d'atteinte de la concentration maximale après administration orale
 f_e : Fraction de substance inchangée éliminée par voie rénale
 f_b : Fraction de substance liée au plasma
 V : Volume de distribution apparent
 F : Biodisponibilité
 P : Coefficient de partage octanol/eau
 Cl : Clairance
 n.d. : non détectable
- 2) : Calculé d'après Hansch et Leo.

4. Conclusions

4. Conclusions

Les études pharmacocinétiques nous ont permis d'obtenir une description pratiquement complète de la résorption du moclobémide et d'examiner les différents facteurs qui peuvent influencer le taux et la vitesse de résorption chez l'homme. Le moclobémide apparaît comme un composé rapidement et complètement résorbé à partir du tractus gastro-intestinal vers la veine porte. La vitesse de résorption après administration orale est évaluée par la valeur du T_{max} (0,74 - 0,94 h) et dans certains cas, par celle du temps de résorption moyen.

Le composé apparaît comme ayant un taux d'extraction hépatique élevé qui entraîne un effet de premier passage hépatique important. La biodisponibilité orale absolue, après administration d'une dose de 100 mg, est d'environ 60 %. Avec des doses orales croissantes, un phénomène de saturation du métabolisme hépatique, par effet de premier passage hépatique apparaît, qui entraîne une augmentation de la biodisponibilité. Ce phénomène n'intervient qu'avec des doses orales d'au moins 400 mg. L'étude pharmacocinétique de doses croissantes de moclobémide (Etude II) confirme ce phénomène avec la possibilité d'une altération de la clairance systémique et temps de demi-vie observé aux hautes doses (800 et 1200 mg).

La disposition du moclobémide a été intensément étudiée au cours des différentes études. Les résultats indiquent que le moclobémide est complètement métabolisé par voie hépatique, la clairance rénale ne représentant qu'une faible fraction de la clairance systémique. Cette dernière est prépondérante. Le volume de distribution à l'équilibre d'environ 80 l est également important et implique une large distribution au-delà du système circulatoire avec une fixation tissulaire intense. Le composé est lié à 50 % aux protéines plasmatiques et a ainsi peu de chance d'être déplacé par d'autres médicaments. Son temps de demi-vie est court (1,5 à 2 h), de même que son temps de présence moyen (2,1 à 2,6 h). L'étude en traitement chronique (Etude I) montre des changements dans la disposition du moclobémide (Chute de la clairance orale) ainsi qu'une augmentation de la biodisponibilité après une semaine de traitement. Au-delà de cette période de traitement, les concentrations plasmatiques restent constantes avec des valeurs d'environ deux fois celles prédites à partir des résultats d'une dose orale.

Les concentrations plasmatiques de moclobémide augmentent de façon non proportionnelle en augmentant les doses orales de 100 à 150 mg trois fois/jour. Une explication possible de cette observation est la possibilité d'une altération de l'élimination de moclobémide par inhibition du métabolisme par le composé ou un de ses métabolites.

En pratique il devrait être proposé au clinicien d'attendre une semaine de traitement avant d'évaluer son efficacité ou d'ajuster la posologie.

L'évaluation de la prise concomitante d'un repas sur la biodisponibilité du moclobémide (Etude III) montre que la vitesse de résorption du moclobémide est légèrement retardée, par contre, le taux de résorption reste inchangé.

En ce qui concerne les **populations à risques**, les études IV et VI testent l'insuffisance rénale et l'effet de l'âge avancé sur la biodisponibilité du moclobémide et ne montrent pas de variations des concentrations plasmatiques dans ces populations.

Ainsi d'un point de vue pharmacocinétique, il ne paraît pas nécessaire d'adapter la posologie pour ces sujets. Par contre, l'insuffisance hépatique réduit fortement la capacité d'élimination de moclobémide, avec des valeurs de C_{max} et une biodisponibilité orale absolue significativement augmentée par rapport à des sujets sains. Ainsi la posologie de moclobémide doit être réduite de moitié à un tiers de la dose habituelle afin de pouvoir obtenir des concentrations semblables à celle des sujets sains lors d'un traitement chronique.

Enfin les derniers résultats sur les populations à risques que nous avons obtenus concerne les nouveaux-nés et le passage de moclobémide dans le lait maternel. Le pourcentage de substance mère passé dans le lait maternel est négligeable et sans incidence sur le nouveau-né et son allaitement (Etude VII).

Métabolisme

La principale voie de dégradation du moclobémide se fait par oxydation du noyau morpholine, conduisant à une multitude de produits d'oxydation éliminée par voie rénale. Les principaux produits de dégradation terminaux sont des acides. L'étude du polymorphisme à la débrisoquine (Etude VIII) ne montre aucune influence sur le taux d'oxydation du moclobémide.

La comparaison des caractéristiques de résorption et disposition du moclobémide à celles de plusieurs IMAO-A réversibles a permis de constater des différences par contre, tous les composés subissent un métabolisme hépatique important avec l'oxydation comme principale voie de métabolisation.

Ce travail nous a permis de montrer que d'un point de vue pharmacocinétique:

- La résorption de moclobémide à partir du tractus gastro-intestinal est rapide et complète et n'est pas influencée par l'ingestion concomitante d'aliment
- La molécule subit un effet de premier passage hépatique élevé
- La biodisponibilité orale absolue est de 60 % avec une dose de 100 mg.
- Le polymorphisme à la débrisoquine ne semble pas influencer le métabolisme du moclobémide
- La posologie doit être réduite de moitié à un tiers en présence d'une insuffisance hépatique chronique
- Il n'est pas nécessaire d'adapter la posologie chez le sujet âgé de moins de 75 ans et en bonne santé.
- L'insuffisance rénale ne perturbe pas la disposition du moclobémide
- Des quantités négligeables sont éliminées dans le lait maternel.

La molécule de moclobémide a bouleversé l'image traditionnelle des IMAO en étant l'un des précurseurs d'une nouvelle génération d'anti-dépresseur "géniale"

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6. Publications faisant l'objet de cette thèse

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1. MP. Schoerlin, M. Mayersohn, A. Korn, H. Eggers.
Disposition kinetics of moclobemide, a monoamine oxidase-A enzyme inhibitor: Single and multiple dosing in normal subjects.
Clin. Pharmacol. Ther. 1987, 42: 395-404.
2. MP. Schoerlin, M. Mayersohn, H. Eggers, V. Peuckert, G. Thieme.
Pharmacokinetics of moclobemide in a tolerability study with ascending single oral doses in healthy male volunteers.
Br. J. Clin. Pharmacol. submitted
3. MP. Schoerlin, M. Mayersohn, B. Hoevels, H. Eggers, M. Dellenbach and JP. Pfefen.
Effect of food intake on the relative bioavailability of moclobemide (RO 11-1163).
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Pharmacokinetics of moclobemide in patients with liver cirrhosis.
Pharmacol. Res. Commun 1988, 20, Suppl. 4: 122-124.
6. M. Mayersohn, MP. Schoerlin, C. Andressen.
Moclobemide absorption and disposition in healthy young and elderly subjects following single intravenous and oral dosing.
(in preparation)
- 6a. K. Stoeckel , JP. Pfefen, M. Mayersohn, MP. Schoerlin and D. Andressen
Absorption and disposition of moclobemide in patients with advanced age or reduced liver or kidney function
Acta Psychiatr. Scand. 1990: Suppl. 360: 94 - 97

7. MP. Schoerlin, A. Wischnik, G. Pons, M. Francoual, G. Olive.
Moclobemide in human breast milk.
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Comparison of the pharmacokinetics of moclobemide in poor and
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Acta Psychiatr. Scand. 1990: Suppl. 360: 98 - 100
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Pharmacocinétique des inhibiteurs de la MOA-A
Dans Neuropsychopharmaka.
Springer Verlag 1993, Vol. 3: 77-86.

Etude I

Disposition du moclobémide lors d'un traitement chronique

Etude II

Disposition du moclobémide au cours d'une étude de tolérance à doses croissantes

Etude III

Disposition du moclobémide lors de la prise concomitante d'un repas

Etude IV

Influence de l'insuffisance rénale sur la pharmacocinétique du moclobémide

Etude V

Influence de l'insuffisance hépatique sur la pharmacocinétique du moclobémide

Etude VI

Disposition de moclobémide chez le sujet âgé

Etude VII

Passage du moclobémide dans le lait maternel chez la femme allaitante

Etude VIII

Influence du phénotype d'hydroxylation de la débrisoquine sur le métabolisme du moclobémide

Etude IX

Pharmacocinétique comparative de 5 IMAO-A réversibles

ETUDE I

DISPOSITION KINETICS OF
MOCLOBEMIDE, A MONOAMINE
OXIDASE-A ENZYME INHIBITOR:
SINGLE AND MULTIPLE DOSING IN
NORMAL SUBJECTS

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Disposition kinetics of moclobemide, a monoamine oxidase-A enzyme inhibitor: Single and multiple dosing in normal subjects

The absorption and disposition kinetics of moclobemide (Ro 11-1163), a new reversible and preferential monoamine oxidase-A enzyme inhibitor, were examined in 12 normal male subjects. An intravenous infusion was administered before and after a 15-day multiple oral dosing regimen (100 mg t.i.d.). Plasma concentration-time data were obtained after each intravenous infusion, after the first oral dose, during two dosing intervals at steady state, and before the second daily dose on several days. The disposition values (percent coefficient of variation in parentheses) after the first and second intravenous infusions, respectively, were: clearance, 39.4 (15%) and 29.1 (12%) L/hr; elimination half-life, 1.60 (15%) and 2.00 (18%) hours; and volume of distribution at steady state, 84.3 (11%) and 80.7 (15%) L. The absolute oral bioavailability increased from 0.56 after the first oral dose to 0.86 and 0.90 after the first and second weeks of administration, respectively. The reduced metabolic, presumably hepatic, clearance may be the result of self-inhibition or metabolite inhibition of moclobemide clearance. (CLIN PHARMACOL THER 1987;42:395-404.)

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In recent years there has been a resurgence of interest in the use of monoamine oxidase (MAO) inhibitors for the treatment of depression. Current interest reflects the development of and encouraging findings from a new class of agents that are specific or at least preferential inhibitors of the MAO-A or MAO-B isozymes.^{1,2} In addition to the greater selectivity of action that such agents would offer, they have the advantage of being rapidly reversible enzyme inhibitors. The older, first-generation MAO inhibitors were nonspecific, irreversible enzyme inhibitors whose use has been associated with hepatotoxicity and adverse pressor response in the presence of certain amine compounds (e.g., tyramine).³ Although the latter characteristics were not common to

all MAO-inhibiting drugs, there has been a general reluctance to use those compounds and to resort to other drugs (e.g., tricyclic antidepressants).⁴

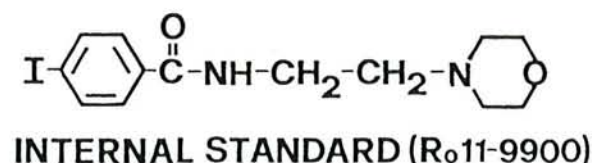
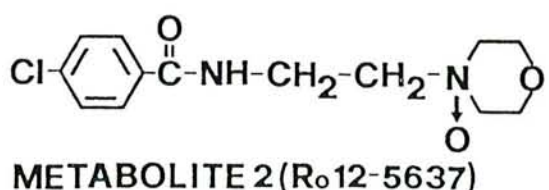
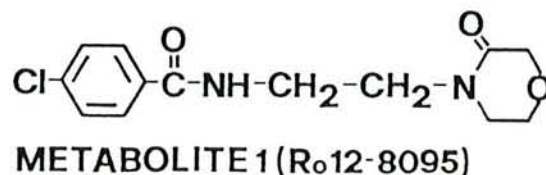
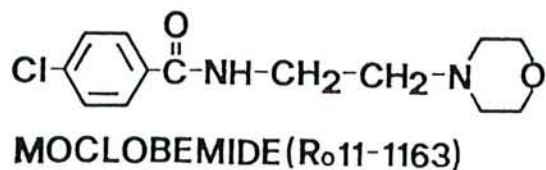
Moclobemide (Ro 11-1163) is an example of the newer class of MAO inhibitors (see structure). The compound is a short-acting, preferential, and reversible inhibitor of the MAO-A enzyme system.⁵ The compound appears to be devoid of hepatic toxicity in the rat,⁶ lacks adverse cardiocirculatory effects,⁷ and produces a mild pressor response to tyramine in rodents and humans.^{5,8,9} The antidepressant activity of moclobemide has been examined in uncontrolled¹⁰⁻¹³ and placebo-controlled¹² clinical trials and its relative efficacy has been compared with other currently used drugs (amitriptyline and clomipramine).^{14,15} The published clinical results, although limited, indicate that moclobemide, either alone or in combination with tricyclic drugs, is an effective treatment for certain forms of depression.

The disposition profile of moclobemide, especially with regard to the active pharmacologic species, has not been examined thoroughly. The compound appears to be metabolized extensively and rapidly and, based

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Structural formulas of moclobemide (Ro 11-1163), metabolite 1 (Ro 12-8095), metabolite 2 (Ro 12-5637), and the internal standard used in the assay (Ro 11-9900)

on in vitro and in vivo response measurements in the rat, it has been suggested that one or more metabolites may, at least in part, be responsible for the activity of the drug.^{5,8,16} To date there have been only two published reports concerning the disposition kinetics of the drug after single oral and intravenous doses in healthy humans.^{17,18} Those studies indicate a short elimination half-life ($t_{1/2}$) of about 1 to 2 hours and a relatively high systemic clearance (CL) (700 to 1200 ml/min). The latter value, primarily a reflection of metabolic and presumably hepatic clearance, suggests substantial presystemic elimination (i.e., first-pass hepatic metabolism). The observed absolute oral bioavailability (50 mg solution) of about 0.44 is consistent with that suggestion.¹⁷

The purpose of this report is to describe the results of a study designed to examine the absorption and disposition of moclobemide after single oral and intravenous doses before and after a multiple oral-dosing regimen and to evaluate the steady-state concentration profile of moclobemide and two known metabolites (see structure).

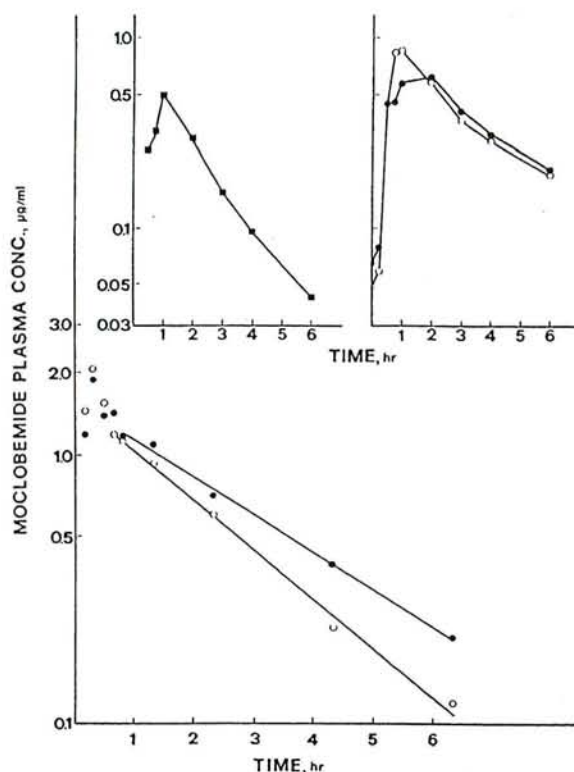


Fig. 1. Moclobemide plasma concentrations as a function of time after intravenous administration before ($\circ$, day 1) and after ($\bullet$, day 24) a multiple oral-dosing regimen of moclobemide. The inset graphs are moclobemide plasma concentration-time data after an oral dose given before ($\blacksquare$, day 8; left panel) and during ($\bullet$, day 15; $\circ$, day 22; right panel) a multiple oral-dosing regimen. The data shown are from one subject (No. 5).

METHODS

Twelve healthy, nonsmoking male subjects between the ages of 21 and 34 years participated in this study after providing written, informed consent. Health status was determined before and at the completion of the study based on medical history, physical examination, and laboratory findings. Exclusion criteria were recent drug use, history of drug abuse or drug intolerance, and any clinically significant deviation from normality in both physical examination and laboratory test results. No drugs were allowed for 2 weeks before and during the study. Alcohol ingestion was not permitted for 10 hours before and during the study. Subject ages and weights are recorded in Table I.

Eight of the 12 subjects were phenotyped with 10 mg debrisoquin and 100 mg mephenytoin according to published procedures.^{19,20} Analytic methods have been described elsewhere.^{21,22}

Table I. Disposition parameters of moclobemide after intravenous infusion before and after a multiple oral-dosing regimen of moclobemide

Subject	Age (yr)	Weight (kg)	$t_{1/2}$ (hr)		CL (L/hr)		V_d (L)	
			dl	d24	dl	d24	dl	d24
1	29	85	1.75	2.31	36.0	27.7	87.4	92.9
2	28	66	1.35	1.59	44.5	33.1	79.2	70.7
3	25	63	1.42	1.95	41.1	32.1	81.3	82.5
4	25	75	1.44	2.06	48.1	30.3	98.0	85.5
5	21	80	1.66	2.18	39.0	30.3	85.0	89.5
6	24	60	1.49	1.52	37.8	26.5	63.4	52.8
7	29	75	1.59	2.24	35.5	24.5	78.4	76.3
8	24	78	3.11	3.67	18.6	15.8	81.8	85.4
9	23	90	1.52	1.95	44.7	27.8	85.1	75.5
10	27	78	2.34	3.03	31.1	23.3	97.8	92.1
11	30	74	2.06	1.86	30.7	34.5	86.2	91.6
12	34	90	1.48	2.02	45.2	30.4	85.4	78.3
Mean*	27	76	1.60†	2.00†	39.4	29.1	84.3	80.7
% CV	13.6	12.7	15.0	18.0	15.0	12.0	11.0	15.0
P value‡			<0.001		<0.001		NS	

dl, before multiple oral-dosing regimen of moclobemide; d24, after multiple oral-dosing regimen of moclobemide.

*Data for subject 8 not included in calculation of the mean $t_{1/2}$ and CL.†Harmonic mean. Percentage coefficient of variation (% CV) on the "pseudo" SD.²⁷

‡Paired Student t test.

On day 1 of the study each subject was given an intravenous infusion of 150 mg moclobemide in a total volume of 20 ml (three vials of 50 mg/vial, batch G FER 09134). The drug was infused into an antecubital vein by a constant-rate infusion pump over a period of 20 minutes. The subjects remained supine during this time and in a sitting position for the next 2 hours; they were ambulatory thereafter. Blood samples were obtained from a contralateral vein via an indwelling venous catheter and collected into Vacutainer tubes containing ammonium and potassium oxalate. Blood samples were obtained before and 10 and 20 minutes after the start of infusion and at the following times after the end of the infusion: 10, 20, and 30 minutes and 1, 2, 4, and 6 hours. Plasma was harvested and stored frozen at -20°C until assayed. Urine was voided just before administration and complete urine collections were obtained at frequent, known intervals for up to 24 hours. Samples were stored frozen at -20°C until assayed.

One week after the intravenous dose, on day 8 of the study, each subject ingested a single 100 mg tablet of moclobemide (batch PT 9221 B56) with 120 ml water while in a sitting position. Subjects fasted overnight and until 2 hours after administration when a light standard meal, low in fat content, was served. Blood samples were obtained before, 15, 30, and 45 minutes, and 1, 2, 3, 4, and 6 hours after administration. Urine was collected for up to 24 hours.

A 15-day multiple oral-dosing regimen was initiated on day 8, at the time of the 6-hour blood sample after the first oral dose. Moclobemide tablets (100 mg) were taken three times a day at intervals of 6, 6, and 12 hours during study days 8 to 22. A concentration-time profile was obtained after the first morning dose on days 15 and 22. The blood sampling and urine collection times were the same as those used during the first single dose. Subjects fasted overnight and were served a standard meal 2 hours after the dose. A single blood sample was obtained just before the second daily dose on study days 9, 11, 13, 16, 18, and 20. On those days meals were ingested after blood sampling.

At the end of the multiple oral dosing regimen, after 1 drug-free day (day 24 of the study), a 20-minute intravenous infusion of 150 mg moclobemide was administered. Study conditions and sampling times were the same as those described above for the intravenous infusion on day 1 of the study.

Plasma and urine samples were analyzed for intact moclobemide and two metabolites (1, Ro 12-8095; 2, Ro 12-5637; see structure). Concentrations were determined by an HPLC method (Geschke et al., submitted for publication). A plasma or urine sample containing the internal standard (Ro 11-9900; see structure) was alkalized and eluted through an Extrelut 1 column (E. Merck, Darmstadt, Federal Republic of Germany) with two portions of 6 ml dichloromethane. The solvent was evaporated at 35°C under a stream of nitrogen and

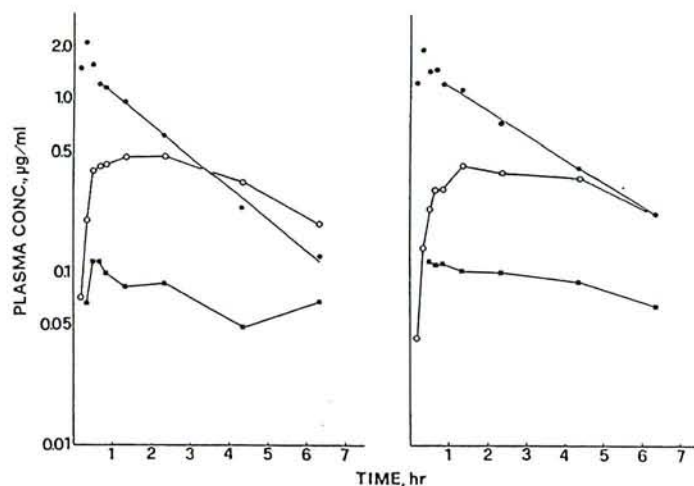


Fig. 2. Plasma concentration-time profiles after intravenous administration of moclobemide administered before (left panel) and after (right panel) a multiple oral-dosing regimen of moclobemide. The moclobemide data (●) are the same as those shown in Fig. 1 and also illustrate concentrations of metabolite 1 (○) and metabolite 2 (■). The data shown are from one subject (No. 5).

reconstituted with 300 µl mobile phase. One hundred microliters was injected onto a C_{18} reverse-phase column with a mobile phase of acetonitrile and 0.067 mol/L phosphate buffer (adjusted to pH 4.4) in the v/v ratio 50:250 and a flow rate of 1.5 ml/min. Quantitation was achieved at 237 nm with reference to a standard curve of peak height ratio vs. moclobemide or metabolite concentration. The limits of quantitation for moclobemide and metabolites 1 and 2 in plasma were 20, 40, and 40 ng/ml, respectively. The intra-assay percentage coefficients of variation for the three compounds ranged from 3% to 7% over the concentration range of 100 to 2500 ng/ml. For lower concentrations near the limits of quantitation, the percentage coefficients of variation ranged from 8% to 13% for each compound. Control samples were analyzed along with authentic samples to ensure quality control in analysis.

Moclobemide plasma concentration-time data were analyzed by area methods. The terminal disposition rate constant (β) was determined by linear regression of the log plasma concentration-time values in the postabsorptive, postdistributive phases and from which half-life was calculated ($\ln 2/\beta$). The AUC was determined by the linear trapezoidal rule until the last measured concentration (C) and extrapolation to time infinity by C/β . CL was determined from the intravenous data (dose/AUC), and the steady-state volume of distribution (V_{ss}) was calculated by moment analysis with correction for the 20-minute infusion.^{23,24} The absolute oral bioavailability (F_{obs}) after the first single oral and in-

travenous dose (days 8 and 1, respectively) was determined from the ratio of AUCs corrected for dose. F_{obs} was also determined from the oral data obtained on days 15 and 22 of the study. In that instance, because unequal dosing intervals were employed, the total AUC was calculated from: $AUC = AUC_0^6 - C_0/\beta + C_6/\beta$, where the 0- to 6-hour AUC was determined by the trapezoidal rule, C_0 and C_6 were the concentrations just before and 6 hours after administration, and β was the value determined from linear regression of the data during that dosing interval. The AUC from the oral doses on days 15 and 22 were compared with the AUC obtained from the intravenous dose on day 24 and corrected for dose. Oral clearance (CL_o) was calculated from oral dose/oral AUC. Statistical comparisons were performed with the Student paired t test.

RESULTS

No adverse effects were reported by the subjects during the study. The biochemical laboratory values were unchanged before and after completion of the study and all values were within the normal ranges. Only one of the eight subjects phenotyped with debrisoquin and mephenytoin (subject 8) gave evidence of being a poor metabolizer of debrisoquin.

Fig. 1 illustrates the moclobemide plasma concentration-time profiles after intravenous infusion and oral administration. These data are from one subject (No. 5) whose values were close to the mean of the group and are representative of the data obtained for

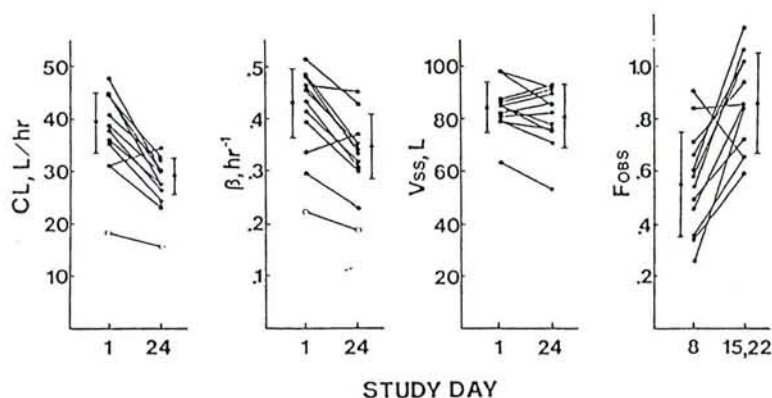


Fig. 3. Changes in the disposition parameters of moclobemide from the first intravenous dose before (day 1) and after (day 24) a multiple oral-dosing regimen of moclobemide. The F_{oss} calculated on day 8 (relative to intravenous dose of day 1) and the average of days 15 and 22 (relative to intravenous dose on day 24) are shown in the panel on the right. The open circles for CL and β are values for subject 8, which were not included in calculation of the means. The cross-hatched vertical bars represent the SD of the mean value shown to the left and right of the individual values.

all of the subjects. The intravenous data indicate a relatively short distribution phase followed by a log-linear decline in concentration. Although the drug appears to be absorbed rapidly, with a maximum concentration achieved within about 1 hour (*inset graph on left*, Fig. 1), there is no obvious distribution phase. It is apparent from Fig. 1 that there was a change in the disposition of moclobemide when comparing the first and second intravenous infusions and the first oral dose (*inset graph on left*) with the oral doses during days 15 and 22 of the study (*inset graph on right*).

The metabolite plasma concentration-time profiles after intravenous administration of moclobemide could not be completely characterized. As illustrated in Fig. 2, the 6-hour sampling time is too short to adequately describe the behavior of the metabolites. It appears that one metabolite (1) is formed relatively slowly and concentrations then begin to parallel those of moclobemide. However, sampling would need to be extended to later times to make a better judgment. In contrast, metabolite 2 appears to be formed relatively rapidly but concentrations persist, declining at a slow rate during the time of sampling. This may suggest that this metabolite is cleared more slowly than it is formed. The metabolite patterns appear similar whether moclobemide was given before or after a multiple-dosing regimen.

Table I summarizes the disposition parameters of moclobemide after the first intravenous infusion before multiple dosing (day 1) and after the second infusion given at the end of the study (day 24). The data for

subject 8 ($t_{1/2}$ and CL) were consistent with the findings of the phenotyping experiment, suggesting that this subject was a poor metabolizer of moclobemide and, based on a test for outlying data,²⁵ the data for that subject have not been included in calculation of average $t_{1/2}$ and CL. The results of the first intravenous infusion indicated that moclobemide had a relatively short $t_{1/2}$ and intermediate to large values for CL and V_{ss} . There was relatively little intersubject variability for those parameters (i.e., <16% coefficient of variation).

The data in Fig. 1 and Table I indicate changes in moclobemide disposition when comparing the results of the intravenous infusion before and after multiple oral dosing. There was a statistically significant decrease in CL and a significant increase in $t_{1/2}$. The value of V_{ss} remained unchanged from the first to the second intravenous infusion and, therefore, the change in $t_{1/2}$ is a reflection of altered CL. The individual changes in these parameters are illustrated in Fig. 3. The direction of the changes noted in CL and $t_{1/2}$ occur for virtually all of the subjects, the exception being one subject in whom CL and β increase and one subject whose value for β was unchanged. In contrast, there was no apparent trend and no significant difference in the change in V_{ss} ; the value increased in four subjects, decreased in seven, and remained unchanged in one.

Several characteristics of moclobemide disposition after oral administration are summarized in Table II, and the concentration-time profiles for one subject are illustrated as insets in Fig. 1. In comparing the results of the first oral dose to the first intravenous infusion,

Table II. Absorption parameters of moclobemide before and during a multiple oral-dosing regimen and steady-state concentrations of moclobemide and metabolites

Subject	CL_{α} (L/hr)			F_{obs}^*			Average ($\pm$ SD) minimum steady-state concentration (ng/ml) [†]		
	d8	d15	d22	d8	d15	d22	Moclobemide	Metabolite	
								1	2
1	59.7	24.1	25.1	0.60	1.15	1.10	267 (25)	194 (17)	74 (12)
2	170.4	39.4	35.7	0.26	0.84	0.93	140 (20)	222 (23)	ND
3	45.3	49.4	44.4	0.91	0.65	0.72	137 (34)	90 (13)	41 [‡]
4	133.5	51.4	48.0	0.36	0.59	0.63	141 (13)	374 (39)	ND
5	84.3	35.1	33.7	0.46	0.86	0.90	172 (33)	161 (32)	53 (12)
6	110.1	39.5	35.6	0.34	0.67	0.74	114 (34)	200 (18)	ND
7	42.0	28.5	25.3	0.84	0.86	0.97	242 (15)	232 (40)	73 (9)
8	26.1	16.7	15.8	0.71	0.94	1.00	517 (37)	212 (38)	92 (6)
9	90.7	38.7	28.5	0.49	0.72	0.98	191 (47)	400 (41)	ND
10	47.4	23.0	24.2	0.66	1.01	0.96	360 (65)	211 (11)	65 (15)
11	52.9	33.9	35.7	0.58	1.02	0.97	145 (22)	252 (32)	ND
12	83.6	28.7	35.7	0.54	1.06	0.85	164 (23)	172 (24)	ND
Mean [§]	83.6	35.6	33.8	0.56	0.86	0.90	216	227	66
% CV	49.0	26.2	22.8	35.7	20.8	15.1	54.6	37.7	26.8
P value	<0.005			<0.001					

d8, before dosing regimen; d15, 22, during dosing regimen; ND, not detectable.

* F_{obs} on day 8 with reference to intravenous administration on day 1 and days 15 and 22 with reference to intravenous administration on day 24.[†]Each value is the mean of five determinations on different days during the second week of administration.[‡]Mean of two determinations.[§]Data for subject 8 not included in calculation of mean CL_{α} .^{||}Comparison of the value on day 8 compared with the mean of days 15 and 22 by the Student paired t test.

the average CL_{α} was about twice the value of CL . In addition, there was far greater intersubject variability in CL_{α} compared with CL (26 to 170 L/hr vs. 19 to 48 L/hr, respectively). The F_{obs} after the first dose averaged 0.56 and illustrated substantial variation among the subjects (0.26 to 0.91).

Consistent with the results of the two intravenous infusions, CL_{α} decreased significantly from the first oral dose (day 8) to that seen during the second week of multiple dosing (days 15 and 22). The values for CL_{α} were essentially the same on days 15 and 22 for a given subject. As seen in Fig. 1, the concentration-time profiles for those days were superimposable (*inset graph on right*). There was a statistically significant increase in the F_{obs} of moclobemide, and in all but one subject the bioavailability increased (Fig. 3). The values of F_{obs} on days 15 and 22 were essentially the same for a given subject (Table II). Interestingly, the variability in F_{obs} during the multiple oral-dosing regimen was considerably smaller in comparison with the first oral dose (0.59 to 1.15 vs. 0.26 to 0.91, respectively).

The minimum steady-state plasma concentrations of moclobemide increased during the first week of administration and thereafter remained essentially unchanged, as illustrated for one subject in Fig. 4. This

is the same subject whose data are illustrated in Figs. 1 and 2. The average and SD of five values determined during the second week of administration are presented in Table II. The average values ranged from 114 to 360 ng/ml for 11 of the 12 subjects; subject 8, who was the poor metabolizer, had the largest value (517 ng/ml). The intrasubject variability in the minimum steady-state concentrations was not that pronounced, because the percentage coefficients of variation were <20% for nine subjects and 25% to 30% for three subjects.

Table II also presents the average minimum steady-state concentrations of two moclobemide metabolites. Metabolite 1 was present in measurable concentrations and the average values ranged from 90 to 400 ng/ml. The minimum steady-state concentrations of this metabolite were greater than those for moclobemide in six subjects and less than or about equal to moclobemide concentrations in the other six subjects. The variability in the concentrations of metabolite 1 was about that seen for moclobemide. In contrast, the minimum steady-state concentrations of metabolite 2 were detectable in only six of the 12 subjects. These concentrations were considerably smaller than those for moclobemide or metabolite 1.

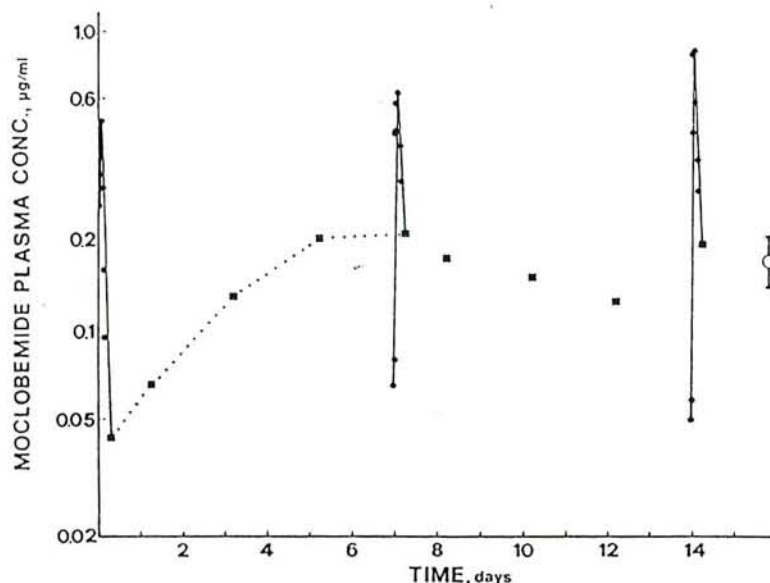


Fig. 4. Moclobemide plasma concentrations as a function of time during the multiple oral-dosing regimen of 100 mg t.i.d. The time scale refers to the oral regimen (days 1 to 15), which corresponds to days 8 to 22 of the study. Concentration-time profiles are illustrated for each of three oral doses taken during a 6-hour dosing interval ($\bullet$). The dotted line connects the minimum concentration ($\blacksquare$) just before the second daily dose during the first week of administration. The average minimum concentration ($\circ$) and SD (cross-hatched vertical bars) during the second week of administration (mean of five values) are shown on the right. These data are for one subject (No. 5), whose data are also illustrated in Figs. 1 and 2.

Moclobemide renal clearance (CL_R) remained unchanged from the first to the second intravenous infusion (2.6 ± 1.9 ml/min and 2.4 ± 0.8 ml/min, respectively). There was considerable intersubject variation in CL_R because only a small percentage of the dose ($<1\%$) was excreted in the urine as unchanged drug. The urinary recovery of metabolite 2 averaged 5.9% of the dose after the first intravenous infusion (range 2.8% to 11.3%; 33.4% coefficient of variation) and 9.1% of the dose after the second intravenous infusion (range 4.0% to 15.5%; 33.4% coefficient of variation). These values were significantly different ($P < 0.001$). The urinary recovery of metabolite 1 was too low to permit adequate quantitation.

DISCUSSION

The present study was designed to examine the absorption and disposition kinetics of moclobemide, a preferential MAO-A inhibitor, in healthy young subjects after single and multiple oral administration for 2 weeks. There have been only two published reports in a total of 12 normal subjects concerning moclobemide absorption and disposition after a single intravenous

and oral dose¹⁷ and after different single oral doses.¹⁸ The results obtained here from the first intravenous infusion and oral dose are somewhat different in magnitude from those reported previously.¹⁷ The mean values obtained in this study compared with those of a previous report after intravenous administration are: β , 0.43 vs. 0.67 hr⁻¹; CL , 39.4 vs. 55.8 L/hr; and V_{ss} , 84.3 vs. 75.6 L. Two possible explanations for this disparity are the smaller doses used in that study (50 mg administered intravenously and orally compared with 150 mg administered intravenously and 100 mg administered orally) and the shorter sampling time of only 3 hours. The former may imply some dose dependency in moclobemide disposition whereas the latter may suggest relatively greater error in the accurate determination of AUC and β . There are currently no data to support the suggestion of dose-dependent disposition. The log-linear plasma concentration-time data found in this and previous studies and the lack of change of $t_{1/2}$ with single oral doses of 50, 100, and 200 mg¹⁸ would argue against that possibility, at least over that dose range. Furthermore, the drug is bound to plasma proteins only to the extent of about 50% (Brandt R,

unpublished observation, F. Hoffmann-LaRoche & Co.) and would, therefore, be unlikely to display non-linear binding properties.

The results of these studies indicate that moclobemide has a short elimination $t_{1/2}$ and intermediate to large values of CL and V_{ss} . Because the drug appears to be totally metabolized,¹⁷ presumably by hepatic processes, CL may be viewed as being essentially equal to hepatic clearance (CL_H). The small value of CL_R (approximately 2.6 ml/min) is consistent with extensive metabolism. Assuming primarily hepatic metabolism and complete gastrointestinal absorption, the value for CL_o , which represents intrinsic clearance, is about twice that of CL. The compound would be expected to undergo first-pass hepatic elimination, and the F_{obs} after the first oral dose, 0.56, is consistent with that suggestion. The same conclusion has been reached by other investigators who report a value for F_{obs} of 0.44 after a 50 mg oral dose.¹⁷ The average values of CL_o and CL in that study were 151 and 56 L/hr, respectively. The increase in F_{obs} from 0.44 to 0.56 after single oral doses of 50 and 100 mg, respectively, may suggest saturable first-pass hepatic metabolism. Although this suggestion is limited by the small dose range, the analysis of data from other studies (oral doses from 50 to 300 mg) would lend support to that possibility (Mayersohn and Schoerlin, submitted for publication). Additional evidence for saturable presystemic metabolism comes from a study in which single oral doses of 50 to 200 mg were administered to the same subjects.¹⁸ The predicted bioavailability (F_{pred}) based on the oral data was 0.43, 0.47, and 0.59 at oral doses of 50, 100, and 200 mg, respectively. The latter values reflect a reduction in CL_o with increasing oral dose. Furthermore, as noted previously,¹⁷ there is generally good agreement between F_{obs} and F_{pred} based on intravenous and oral data. In the present study the average ($\pm$ SD) values of F_{pred} based on intravenous and oral data²⁶ are 0.58 (0.09) and 0.56 (0.13), respectively, compared with F_{obs} of 0.56. A similar good agreement is found based on the intravenous and oral data from a previous study¹⁷: 0.38 (0.13) and 0.41 (0.13), respectively, compared with F_{obs} of 0.44. This good agreement between F_{obs} and F_{pred} would support the suggestion of complete gastrointestinal absorption, for which there is some direct experimental data,¹⁷ and hepatic metabolism as being the major site of biotransformation.

Although the two metabolites of moclobemide that were measured in plasma were present at detectable concentrations after single intravenous and oral doses, the 6-hour sampling interval was insufficient to com-

pletely characterize their disposition (Fig. 2). The average maximum concentrations ($\pm$ SD) of metabolites 1 and 2 after the first single intravenous and oral dose, respectively, were: 1, 577 (152) and 487 (147) ng/ml; 2, 91 (30) and 97 (30) ng/ml. When adjusted for dose the metabolite concentrations are greater after oral compared with intravenous administration (26% greater for 1 and 59% greater for 2, relative to the intravenous concentration). Because plasma sampling was of too short a duration to clearly delineate a terminal disposition phase for the metabolites, we cannot assess whether metabolite formation is slow or rate limited by subsequent elimination. The issue of metabolite formation becomes important with regard to the chemical species responsible for producing the pharmacologic response; this point will be addressed later.

Analysis of the moclobemide plasma concentration-time data after intravenous administration clearly indicates time-dependent changes in the disposition of the drug when the results from single to multiple dosing are compared. The data in Table I and Fig. 3 illustrate the direction and magnitude of change in $t_{1/2}$ (and β), CL, and V_{ss} after intravenous infusion before and after multiple dosing. With one exception, CL decreased after multiple dosing in all subjects by an average of about 25%. Because renal excretion represented only a small fraction of the dose and CL_R was unchanged before and after multiple dosing, the reduction in CL represents a decrease in CL_H . With the exception of one subject, the decrease in β reflects altered CL because V_{ss} was essentially unchanged before and after multiple dosing. The reduction in CL_o and the consequent increase in F_{obs} (Table II; Fig. 3) are consistent with reduced CL_H . The alteration in CL_H appeared to occur gradually during the first week of administration because concentrations before the second daily dose increased during that time and remained relatively constant thereafter (Fig. 4).

The exact mechanism of this alteration in CL_H is not known at present but would appear to involve either self-inhibition or metabolite inhibition of moclobemide clearance. The mechanism and time course of this effect need further investigation. Some data obtained here may pertain to the nature of altered moclobemide clearance on multiple dosing. The urinary excretion of one of the metabolites measured in urine, referred to as metabolite 2, increased significantly after the second intravenous infusion compared with the first infusion. These results would indicate increased formation of that metabolite after multiple dosing with moclobemide. To be consistent with reduced CL of moclobemide, one or

more of the other metabolites of moclobemide must be formed to a smaller extent. This would suggest a preferential alteration in the metabolic pattern and therefore metabolite 2 would not appear to be involved in the metabolic steps associated with the inhibition of moclobemide metabolism.

The metabolic profile of moclobemide may be an important consideration in therapy for two reasons: the nature of the chemical species responsible for the pharmacologic effect, as a result of decreased moclobemide clearance, and the consequent alteration of metabolite formation. Studies in rats have shown that moclobemide per se is a relatively weak MAO inhibitor in vitro.⁵ This observation and comparison with the results from ex vivo experiments have led one group of investigators to conclude that one or more of the metabolites of moclobemide is responsible for producing the pharmacologic response.^{5,8,16} Although the in vitro activity of six identified metabolites of moclobemide has been shown to be low,⁸ moclobemide may be serving as a prodrug, at least in part, in producing the desired response. Our current understanding of the pharmacologic profile of the drug suggests that it acts rapidly and is a readily reversible preferential inhibitor of the MAO-A enzyme system. Although the chemical form(s) responsible for the effect and its potential alteration as a result of inhibition of moclobemide clearance are of fundamental interest, the clinical data currently available support the therapeutic efficacy of the drug.

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ETUDE II

ABSTRACT

1. The pharmacokinetics of moclobemide, a new reversible inhibitor of the monoamine oxidase-A isozyme, were assessed following single oral doses (100, 200, 400, 800 and 1200 mg) to 14 young, healthy male volunteers as a part of a double blind, randomized placebo-controlled dose tolerance study. Dose was escalated in a scattered sequence when tolerance of the preceding dose was acceptable. This trial was divided into two study components. Study 1 involved six subjects participating in three dosing sessions (100, 200 and 400 mg of moclobemide) with each dosing session consisting of four moclobemide and two placebo treated subjects. Study 2 involved eight subjects participating in two moclobemide dosing sessions (800 mg [6 moclobemide and 2 placebo] and 1200 mg [4 moclobemide and 2 placebo]). Two subjects dropped out of Study 2 following the 800 mg dose.
2. Plasma concentrations vs time profiles of moclobemide and two of its metabolites (RO 12-8095 and RO 12-5637) were evaluated over a 24 hour period following the single oral dose administration of 100, 200 and 400 mg (Study 1) and 800 and 1200 mg (Study 2) of moclobemide.
3. All major pharmacokinetic parameters obtained in Studies 1 and 2 indicated dose dependent behavior for moclobemide. In Study 1, the Cl_o of moclobemide was reduced 1.6 fold (76.0 vs 47.1 L/h; $P < 0.05$) as the dose was increased from 100 to 400 mg. A modest but statistically significant lower Cl_o of moclobemide was observed between the 100 and 200 mg doses (1.2 fold reduction). This was accompanied by a 1.4 fold increase (1.25 vs 1.71 h; $P < 0.05$) in

plasma half-life. In Study 2, oral clearance values of moclobemide following 800 and 1200 mg doses were 2.6 and 3.4 fold lower compared to those obtained after administration of 100 mg dose (from Study 1).

4. Our observations are consistent with dose dependent metabolism of moclobemide occurring either during absorption (reduction in first-pass effect at higher doses) and/or as a function of systemic clearance. Although this effect appears dramatic, particularly when contrasting the 100 and 1200 mg doses, the clinical consequences are expected to be minimal at the dosage range to be employed therapeutically.

INTRODUCTION

Moclobemide is a benzamide derivative which has a preferential ability to reversibly inhibit the monoamine oxidase-A isozyme (DaPrada et al., 1981). This compound, unlike earlier monoamine oxidase inhibitors, is devoid of hepatotoxicity in rodents (Schlappi, 1985) and produces only a mild pressor response to tyramine in rodents (DaPrada et al., 1981; DaPrada et al., 1984) and humans (Korn et al., 1986). This antidepressant drug following oral administration to humans is rapidly absorbed and undergoes first pass metabolism resulting in a bioavailability of approximately 55% following a single 100 mg oral dose. Preliminary observations with moclobemide indicated that the bioavailability of this compound increases with higher oral doses (Schoerlin et al., 1987). Therefore, the purpose of the present study was to assess the impact that escalating single oral dose of moclobemide has on its pharmacokinetics and safety over a dosing range of 100 to 1200 mg.

METHODS

The pharmacokinetics of moclobemide were assessed following single oral doses (100, 200, 400, 800 and 1200 mg) to fourteen young (20 to 34 years), healthy male volunteers as a part of a double blind, randomized placebo-controlled dose tolerance study. All subjects gave their written informed consent and the study was approved by the local Ethics Committee. All volunteers were non-smokers and in general good health as evidenced by a normal medical history, physical examination and laboratory profile. Subjects received escalating doses of moclobemide in a scattered sequence when the tolerance of the preceding dose was acceptable. This trial was divided into two study components. Study 1 involved six subjects participating in three dosing sessions (100, 200 and 400 mg of moclobemide)

with each dosing session consisting of four moclobemide and two placebo treated subjects. Study 2 involved eight subjects participating in two moclobemide dosing sessions (800 mg [6 moclobemide and 2 placebo] and 1200 mg [4 moclobemide and 2 placebo]). Two subjects dropped out of Study 2 following the 800 mg dose. One of the two drop-outs was associated with dose intolerability. A one week washout period was imposed between treatments for each of the subjects.

All subjects were housed at the study facility at least 12 hours prior to dosing through the 24 hour blood sample. Subjects were dosed following an overnight fast at approximately 08:00. Immediately prior to dosing, a venous catheter was inserted into each subject's arm for the purpose of blood withdrawal. Each subject ingested their assigned tablet with 200 ml of water. Blood samples (10 ml) were collected in ammonium oxalate tubes at the following times: pre-dose, 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours after drug administration. Blood samples were immediately centrifuged and the plasma harvested and placed into glass tubes and stored at -20°C until analysis.

Plasma concentrations of moclobemide and two of its metabolites, the active RO 12-5637 and the main metabolite in plasma RO 12-8095, were determined by HPLC (Geschke et al., 1987). Briefly, this assay involves extraction of the three main components from alkalinized plasma with dichloromethane followed by chromatographic separation with a reversed-phase HPLC system and quantitation by UV detection. The lower limits of assay sensitivity for moclobemide, RO 12-5637 and RO 12-8095 were 20, 25, and 30 ng/ml, respectively. Inter-day coefficient of variation studies performed on quality control samples of moclobemide, RO 12-5637, and RO 12-8095 were 3.5, 7.7, and 4.2%, respectively.

Pharmacokinetic data analysis was performed according to noncompartmental methods. The maximum plasma moclobemide concentrations (C_{max}) and time to reach maximum moclobemide concentrations (T_{max}) were determined directly by observation of the data. The AUC was determined by the trapezoidal rule. The values were extrapolated to infinity by dividing the last measured plasma concentration by β , the negative slope of the terminal elimination phase obtained by least-squares linear regression. The terminal plasma elimination half-life ($t_{1/2 \beta}$) was calculated as $t_{1/2 \beta} = 0.693/\beta$. Apparent oral clearance (Cl_o) was determined by: $Cl_o = \text{dose}/\text{AUC}$. Statistical analysis of log-transformed data from Study 1 was analyzed using a 2-way ANOVA (SAS). If appropriate, the least square means of the dose effects were then compared in a pairwise manner (option LS means of GLM of SAS). Statistical analysis for Study 2 involved a t-test procedure which compared differences between the following treatment group: 800 vs 100 mg; 1200 vs 100 mg. This latter approach was employed because of the relatively high drop out rate ($n = 2$) at the 1200 mg dosage level. Statistical significance was defined as $P < 0.05$ throughout the study.

RESULTS

Figures 1, 2, and 3 represent mean plasma concentration vs time data of moclobemide, RO 12-8095, and RO 12-5637, respectively following oral administration of 100, 200, 400, 800, and 1200 mg of moclobemide. Moclobemide was rapidly absorbed with T_{max} values in the range of 0.5 to 2.0 hours and appeared independent of the dose administered. Table I provides a summary of the major pharmacokinetic parameters obtained from Study 1. Statistically significant differences were observed for all parameters between dosing groups in Study 1 suggestive of dose-dependent

pharmacokinetics for moclobemide. Table II summarizes the pharmacokinetic parameters determined from Study 2. As expected, all of these parameters were statistically different from those compared to the 100 mg treatment group in Study 1. Figure 4 reveals the relationship between oral moclobemide dose and its AUC. A disproportionate increase in AUC with increasing dose can also be appreciated by examining normalized AUC values in Tables I and II. Half-life values also tended to increase with increasing dose (1.25 h [100 mg dose] vs 2.73 h [1200 mg dose]).

The pharmacokinetics of moclobemide's main inactive (RO 12-8095) and pharmacologically active (RO 12-5637) metabolites are summarized in Table III. Like moclobemide, the terminal half-life of RO 12-8095 and RO 12-5637 increased with increasing moclobemide dose. The magnitude of the terminal half-life for the two metabolites were similar to each other at the five doses studied. Both metabolites had terminal half-lives slightly longer than that of the parent compound, moclobemide.

DISCUSSION

The present study shows that the pharmacokinetics of oral moclobemide, a new reversible monoamine oxidase inhibitor, are markedly altered as a function of dose. Moclobemide has been shown to be extensively metabolized by the liver to a large number of metabolites. Its relatively low oral bioavailability has been attributed to an extensive first pass metabolism effect. Dose-dependent bioavailability has been observed with several compounds (Bai et al., 1983; Twamoto et al., 1985; Jusko et al., 1976). Most notably, the dose-dependent bioavailability of propranolol has been extensively evaluated in man (Shand & Rangno, 1982; Evans & Shand, 1973) and animals (Bai et al., 1983; Suzuki et al., 1981).

In an earlier study (Wiesel et al., 1985), the predicted bioavailability of moclobemide based on oral data increased from 0.43 to 0.59 over a single oral dose range of 50 to 200 mg suggestive of a reduction in oral clearance with increasing dose. In a more recent report (Schoerlin et al., 1987), it was shown that the systemic clearance of moclobemide decreased after chronic oral dosing. It was also observed that a reduction in Cl_o occurred during a multiple dosing regimen of 100 mg three times a day. It was suggested from this study that moclobemide's non linear behavior may be due to either self-inhibition or metabolite inhibition of moclobemide clearance. Our study suggests that a saturable first pass effect and reduction in systemic clearance is occurring over the single dose administration range of 100 to 1200 mg.

We observed a significant reduction (3 fold between 100 and 1200 mg doses) in the oral clearance of moclobemide with increasing dose. This can be best visualized by examining the relationship between oral dose and AUC (see Figure 4). This data suggests that saturable first pass metabolism may exist with moclobemide.

It is also possible that a reduction in systemic clearance (Cl_s) with increasing dose may also be contributing to moclobemide's nonlinear characteristics. In fact, a saturable first pass phenomena alone cannot, by itself, account for the three fold reduction in oral clearance. Previous studies have shown that the oral bioavailability of moclobemide following a single oral 100 mg dose is approximately 55%. Consequently, a decrease in moclobemide's oral clearance from 76.0 L/h [100 mg] to 22.8 L/h [1200 mg] can't be explained solely on the basis of increased bioavailability. Such a change could only occur if moclobemide's oral bioavailability exceeded 180%. This unrealistic bioavailability value supports the argument that decreases in moclobemide's oral clearance with

increasing dose is likely attributed to a decrease in both the first pass effect and systemic clearance. Further support for a nonlinear elimination process can be found in the consistent trend toward prolonged half-life values (1.25 [100 mg] vs 2.73 [1200 mg] hours) with increasing dose. If this 2.2 fold increase in half-life reflected a comparable reduction in systemic clearance, then a more reasonable increase in absolute bioavailability to 88% would explain the data. Differences in our observed half-lives could partially be attributed to the fact that at the higher doses we were able to sample for a longer period of time resulting in a better estimate of our terminal slope. It is interesting to note that the increases in moclobemide's terminal elimination half-life paralleled those observed with the two metabolites studied (see Table III). Finally, limitations in the study design (incomplete crossover design Study 1 and two dropouts from Study 2) may have exaggerated our observation of nonlinear behavior with moclobemide. Because there was no overlap between subjects in Study 1 (100, 200, 400 mg doses) and Study 2 (800, 1200 mg doses), a considerable portion of our nonlinear profile could be attributed to intersubject variability in moclobemide's metabolism.

Table III provides a summary of the pharmacokinetics for two of moclobemide's metabolites. As mentioned previously, the half-lives of both metabolites (RO 12-8095 and RO 12-5637) increased with increasing dose. The terminal elimination half-lives of both metabolites were slightly longer than that of their parent compound, moclobemide. This would suggest that their terminal elimination half-lives are elimination and not formation dependent.

In summary, moclobemide appears to possess dose-dependent pharmacokinetic characteristics over the dosage range of 100 to 1200 mg. It appears that this nonlinear behavior is the consequence of saturable metabolic processes either during absorption (reduction in first-pass effect at higher doses) and/or systemic clearance in the post-absorptive phase. Although the effect appears dramatic (i.e. comparison of data between 100 and 1200 mg doses), the clinical consequences are expected to be minimal at the dosage range (100 to 150 mg three times a day) to be employed therapeutically.



Robert A. Blum



September 9-



Dr. F. Eiserling (signed for G. Thieme)

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FIGURE LEGENDS

Figure 1: Semilogarithmic plots of the mean moclobemide concentrations (ng/ml) in relation to time: 100 mg ($\square$); 200 mg (O); 400 mg (Δ); 800 mg (∇); 1200 mg ($\diamond$).

Figure 2: Semilogarithmic plots of the mean RO 12-8095 concentrations (ng/ml) in relation to time (symbols same as Figure 1).

Figure 3: Semilogarithmic plots of the mean RO 12-5637 concentrations (ng/ml) in relation to time (symbols same as Figure 1).

Figure 4: Effect of moclobemide dose on moclobemide area under the plasma concentration vs time curve.

Table 1: Effect of dose (100, 200 and 400 mg) on the pharmacokinetic parameters ($\bar{X} \pm \% \text{ CV}$) of oral moclobemide.

Dose	Parameters				
	Clo	AUC	AUC ¹	β	$t_{1/2} \beta^2$
	(L/h)	(ng·h/ml)	(ng·h/ml)	(h ⁻¹)	(h)
100 mg (n=4)	76.0 ± 21	1361 ± 22	1361 ± 22	0.553 ± 22	1.25 ± 21
200 mg (n=4)	62.0 ± 38	3585 ± 39	1793 ± 39	0.440 ± 33	1.58 ± 37
400 mg (n=4)	47.1 ± 36	9209 ± 29	2302 ± 29	0.405 ± 24	1.71 ± 25

¹Normalized to a 100 mg dose.

²Harmonized mean and % CV based upon the "pseudo" standard deviation.

Table II: Effect of dose (800 and 1200 mg) on the pharmacokinetics ($\bar{X} \pm \% \text{ CV}$) of oral moclobemide.

	Clo	AUC	AUC ¹	β	$t_{1/2} \beta^2$
Dose	(L/h)	(ng·h/ml)	(ng·h/ml)	(h ⁻¹)	(h)
800 mg (n=6)	28.9 ± 53	32,111 ± 33	4014 ± 33	0.253 ± 21	2.74 ± 22
1200 mg (n=4)	22.8 ± 24	55,000 ± 24	4583 ± 24	0.254 ± 12	2.73 ± 12

¹Normalized to a 100 mg dose from Study 1.

²Harmonized mean and % CV based upon the "pseudo" standard deviation.

Table III: Summary of plasma half-life values of moclobemide, RO 12-8095, and RO 12-5637 with increasing moclobemide dose ($\bar{X} \pm \% \text{ CV}$).

<u>Dose (mg)</u>	<u>Moclobemide</u>	<u>RO 12-8095</u>	<u>RO 12-5637</u>
100	1.25 $\pm$ 21	2.16 $\pm$ 17	ND
200	1.58 $\pm$ 37	2.02 $\pm$ 32	1.97 $\pm$ 36
400	1.71 $\pm$ 25	2.48 $\pm$ 38	2.76 $\pm$ 36
800	2.74 $\pm$ 22	3.64 $\pm$ 24	3.38 $\pm$ 20
1200	2.73 $\pm$ 12	3.68 $\pm$ 20	3.24 $\pm$ 29

Figure 1

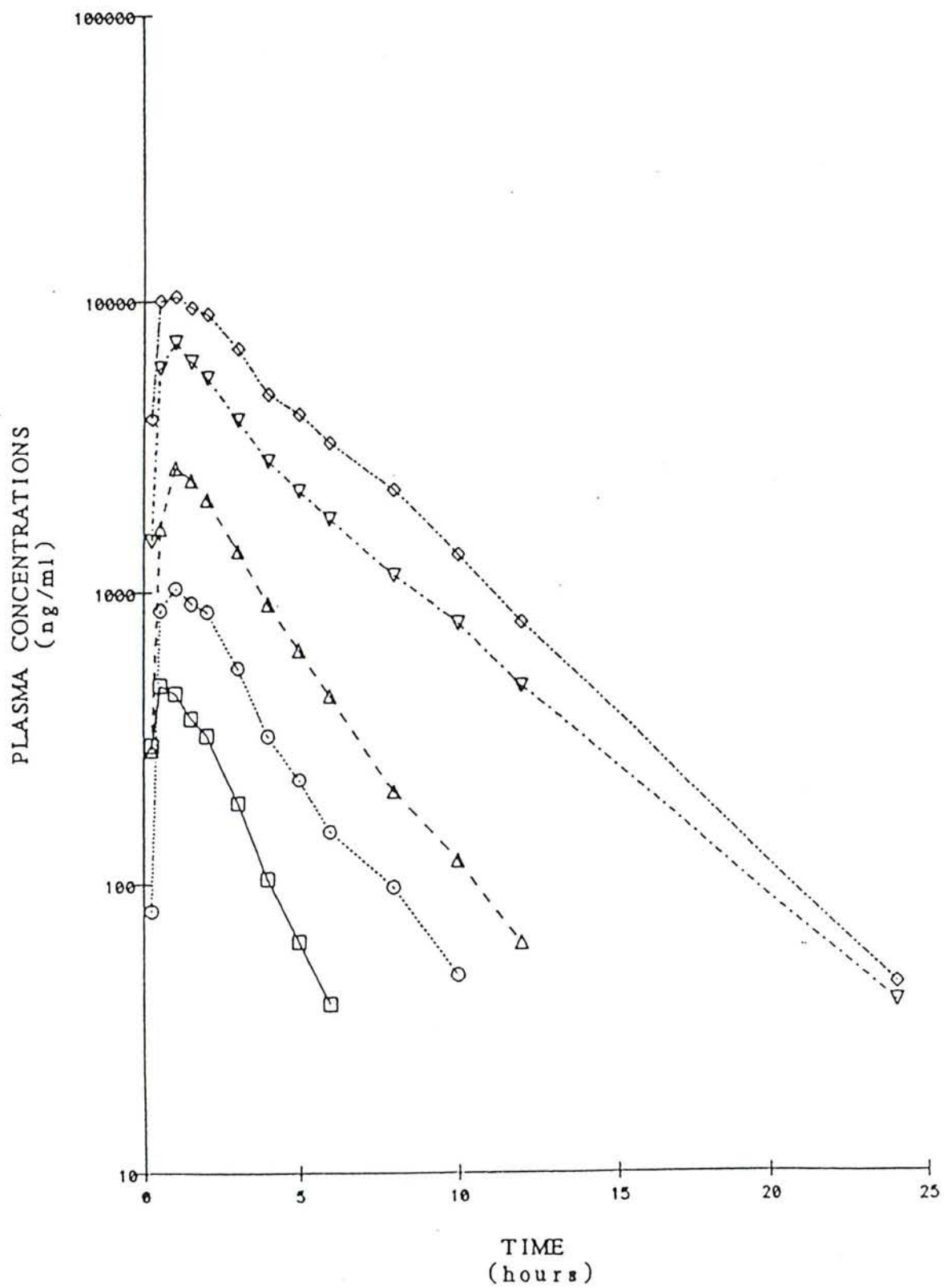


Figure 2

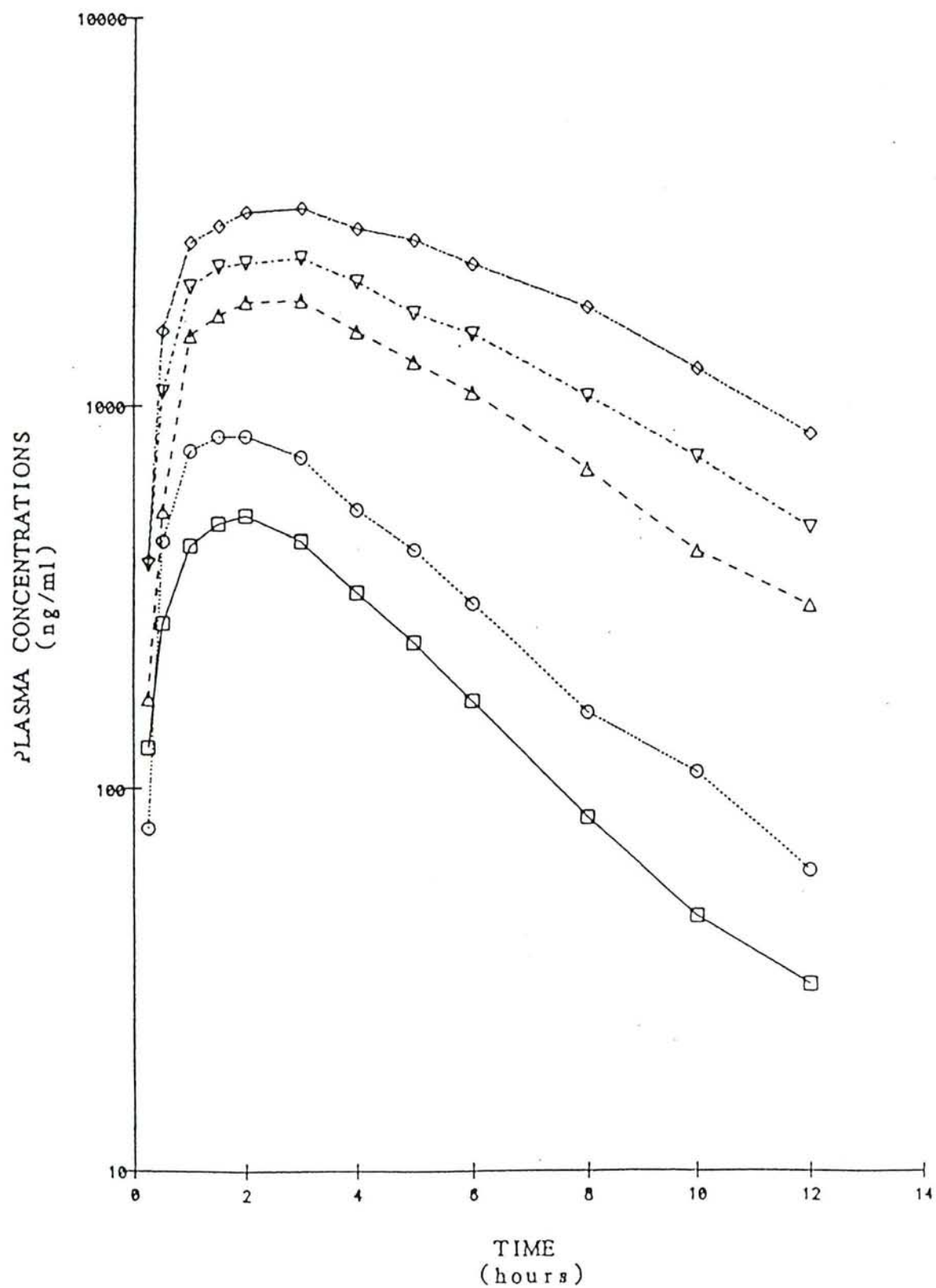


Figure 3

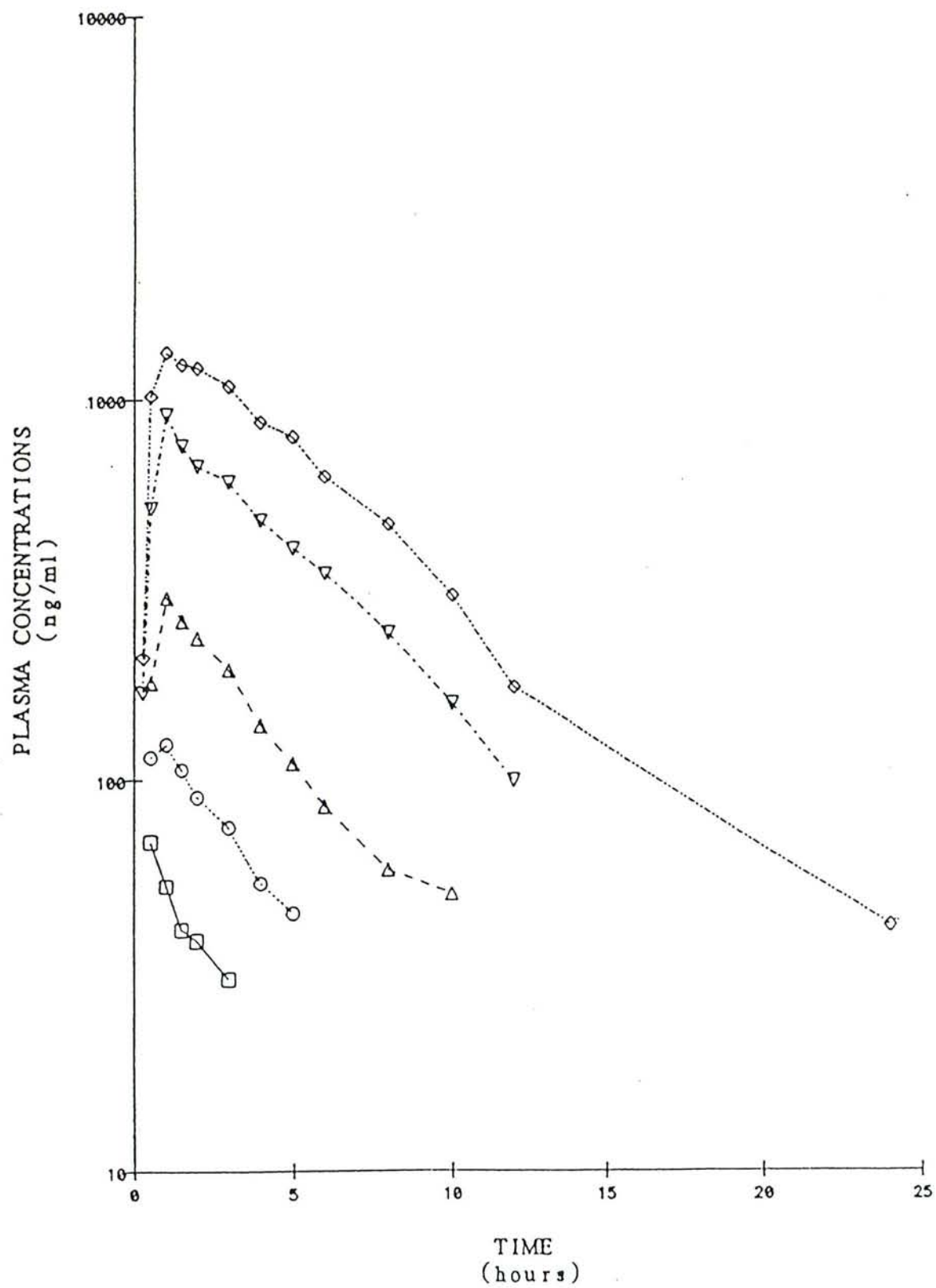
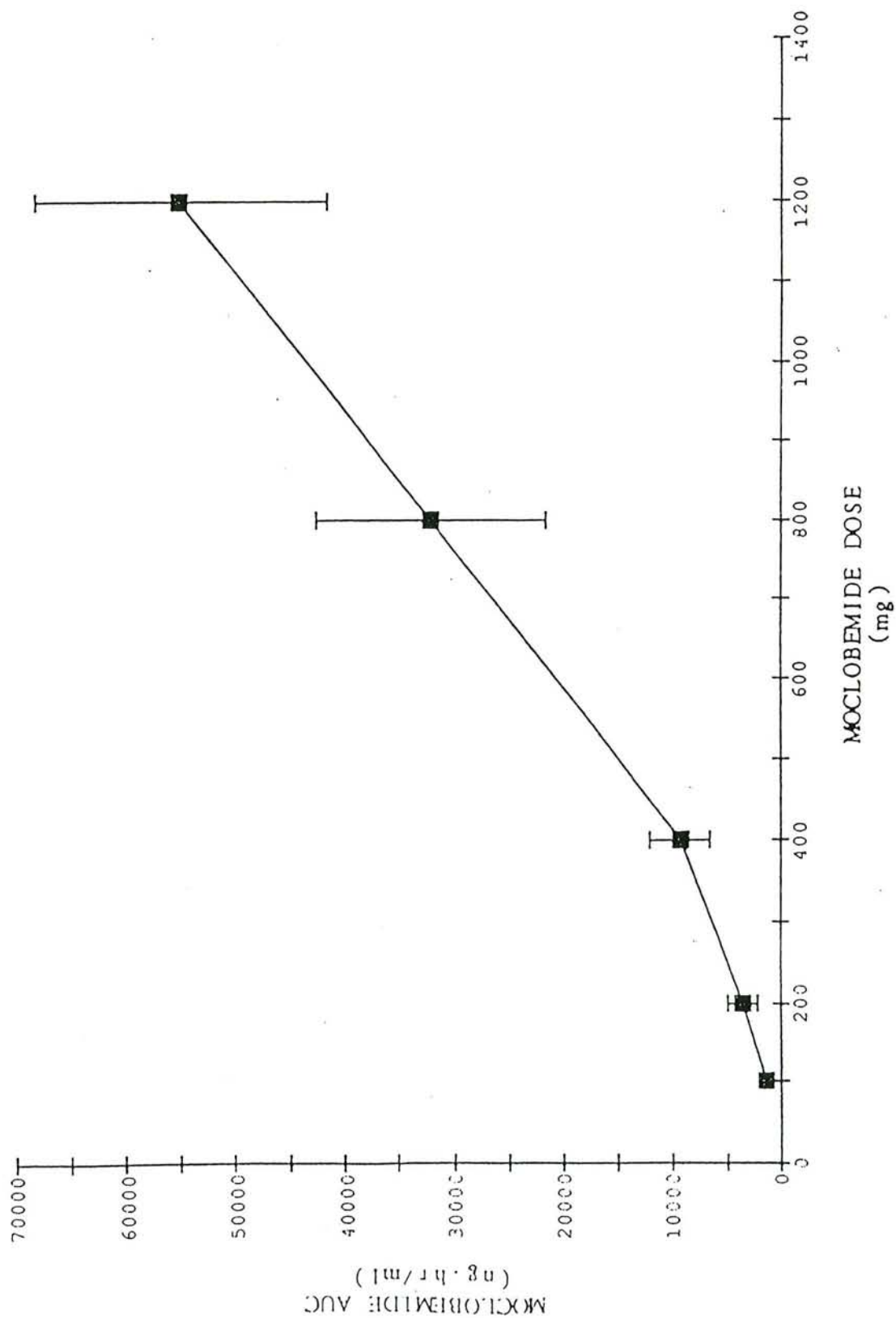


Figure 4



ETUDE III

Effect of food intake on the relative bioavailability of moclobemide (Ro 11-1163)

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Summary. Twelve healthy adult volunteers received a single 100-mg tablet of moclobemide in an open-label crossover study designed to determine the influence of food on moclobemide absorption. Moclobemide was administered 30 min after a standard breakfast as well as under fasting conditions. Moclobemide absorption was rapid in the absence of food. Bioavailability parameters obtained when drug was taken 30 min after the meal suggested that the rate of absorption was slightly decreased in the presence of food (mean T_{max} 0.71 h vs. 1.14 h), while the extent of absorption of moclobemide given with food was unaltered. The decreased absorption rate in the presence of food is not expected to be of clinical significance.

Introduction

Moclobemide (Ro 11-1163), a benzamide derivative (Fig. 1) is a novel monoamine oxidase (MAO)-inhibitor with predominant inhibition of MAO-A. In contrast to classical MAO-inhibitors, this drug is characterized by the reversibility of MAO-inhibition. Pharmacokinetic data obtained after single doses indicate that moclobemide has a short terminal disposition half-life of between 1 and 2 h, an intermediate value for systemic plasma clearance (31–48 L/h), and a large steady-state volume of distribution (1–1.5 L/kg). The drug appears to be totally metabolized by the liver with only a small value for renal clearance. As a result of substantial first-pass hepatic metabolism, the absolute oral bioavailability of a 100-mg single dose averages about 56% (Schoerlin et al., 1987). However, bioavailability appears to be dose-dependent, increasing as dose increases, possibly as a result of saturable hepatic metabolism during the absorption step (Mayersohn et al., unpublished).

High first-pass hepatic extraction or "presystemic" elimination after oral ingestion is a property shared with a variety of other drugs, including pro-

pranolol (Evans et al., 1973), lidocaine (Shand et al., 1975), nifedipine (Mc Allister, 1982), verapamil (Schomerus et al., 1976), and imipramine (Abernethy et al., 1984). When such drugs are ingested with food, systemic bioavailability may increase. This has been reported for propranolol, metoprolol, lidocaine, propoxyphene, and hydralazine (Rawlins et al., 1977; Melander et al., 1977a-c). The mechanism of increased bioavailability during food ingestion is not well

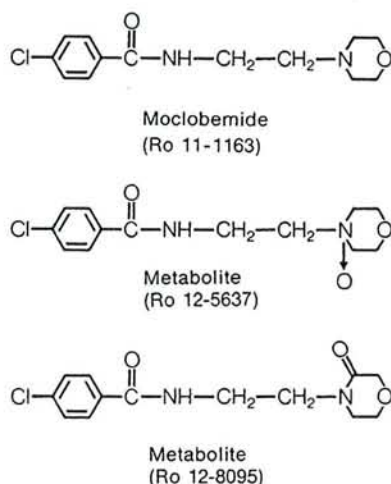


Fig. 1. Structure of moclobemide and metabolites

defined, but may be related, at least in part, to altered splanchnic or hepatic blood flow (Svensson et al., 1983). On the other hand, food may also be associated with a decrease or delay in drug absorption (Welling, 1977; Polasa and Krishnaswamy, 1983; Colburn et al., 1983), but examples of a lack of effect or increased absorption have been reported as well (Welling, 1977; Melander, 1978).

The present single-dose study was conducted to determine the relative bioavailability of moclobemide in the presence and absence of food.

Methods

Subjects

Twelve healthy non-smoking male volunteers ranging in age from 23–47 years, weighing 68.5–93.5 kg, and taking no other medications were included in the trial. All subjects provided written informed consent.

Protocol

In an open-labelled, crossover design, the volunteers received a single 100-mg tablet of moclobemide on an empty stomach after an at least 10-hour overnight fast (treatment A) and on a second occasion, 30 min after a standard breakfast¹ (treatment B). Six subjects

¹ Standard breakfast contained a total energy of 1840 kJ (= 440 kcal); 20% protein, 35% fat and 45% carbohydrate.

started with treatment A, the other six subjects with treatment B; the subjects were randomly assigned to one of the treatment sequences. The two treatments were separated by a wash-out period of at least one week.

The time of moclobemide dosage always was between 6.00 and 8.00 a.m. After each dose, venous blood samples were drawn into Vacutainer tubes containing EDTA prior to the dose and during twelve hours post drug administration. A light standardized low-fat meal was eaten after the 4-h and 10-h blood sampling. Blood specimens were centrifuged, the plasma separated and stored at -20°C until analysed.

Analytical methods

Plasma concentrations of moclobemide, and two metabolites were measured by a HPLC method (Eggers et al., 1987). A Spherisorb[®] C₆, 5 μm , 125 $\times$ 4 mm (Phase Separation) steel column was used with a flow rate of 1.0 ml/min for the mobile phase (mixture of acetonitrile and aqueous phosphate buffer solution 30:320 (v/v), pH 3.9). The column effluent was monitored with a UV-detector at 240 nm. The limit of sensitivity was 20, 30, and 30 ng/ml for moclobemide (Ro 11-1163), the main metabolite (Ro 12-8095), and an active metabolite (Ro 12-5637), respectively (see Fig. 1). The mean inter-assay reproducibility (% CV) for the quantitation of these three compounds in plasma calculated from quality control samples were 4.1 (range 3.4–5.0), 4.8 (range 3.4–6.0), and 11.0% (range 6.0–14.4), respectively, over the concentration range 50 to 1250 ng/ml for Ro 11-1163, 100 to 1250 ng/ml for Ro 12-8095, and 50 to 220 ng/ml for Ro 12-5637. For lower concentrations near the detection limits, the coefficients varied between 8 and 20% for the compounds.

Data analysis

Pharmacokinetic analysis

Plasma concentration-time (C, t) data for moclobemide Ro 11-1163 and the main metabolite Ro 12-8095 after the two administration modes were first plotted for visual inspection. Maximum plasma concentration (C_{max}) and time of its occurrence (T_{max}) were determined directly from the C, t data. Other pharmacokinetic parameters were calculated by "model-independent" (area) methods. The terminal disposition rate constant was determined by linear regression analysis of the terminal log-linear phase in the concentration-time profile. The terminal disposition half-life ($t_{1/2}$) was calculated from $\ln 2/\beta$. The total area under the plasma concentration-time curve ($\text{AUC}_{0 \rightarrow \infty}$) was determined by the linear trapezoidal rule applied up to the time of the last concentration and extrapolation thereafter ($\bar{C}_n/\beta$), where $\bar{C}_n$ is the last concentration on the regression line. The bioavailability of moclobemide post-prandial (B) relative to pre-prandial (A), F_{Rel} (uncorrected and corrected for differences in the terminal disposition rate constants), was calculated as

$$F_{\text{Rel}} = \frac{\text{AUC}_{0 \rightarrow \infty}(\text{B})}{\text{AUC}_{0 \rightarrow \infty}(\text{A})}$$

$$F_{\text{Rel corrected}} = \frac{\text{AUC}_{0 \rightarrow \infty}(\text{B})}{\text{AUC}_{0 \rightarrow \infty}(\text{A})} \times \frac{\beta_{(\text{B})}}{\beta_{(\text{A})}}$$

The oral clearance (Cl/F) after oral administration was calculated as

$$\text{Cl/F} = \frac{\text{dose}}{\text{AUC}_{0 \rightarrow \infty}}$$

Statistical analysis

The Wilcoxon matched-pairs signed-ranks test was used to test for a statistical significance in changes in pharmacokinetic parameters $AUC_{0 \rightarrow \infty}$, $t_{1/2}$, β , Cl/F , T_{max} , C_{max} obtained in the absence or presence of food ($\alpha = 0.05$).

Results

Fig. 2 shows moclobemide and Ro 12-8095 plasma concentrations during the trial for a representative subject.

Table 1 compares mean pharmacokinetic parameters obtained for parent drug after the two administration modes. The values for one subject (number 5) were not included in the calculation of the mean values, since this subject was characterized as a poor metabolizer (mephenytoin). The half-life of the drug in this subject was unusually high (5.17 h) and was beyond two standard deviations of the mean of the other subjects. However, the value is consistent with what one finds for poor metabolizers (Schoerlin et al., 1987).

The plasma concentrations of the metabolite Ro 12-5637 were low, and in many cases near the limit of detection throughout the sampling period. No graphical representation or pharmacokinetic analysis for this compound is provided.

Moclobemide is absorbed rapidly after oral dosing. No significant differences in the mean maximum plasma concentration was observed between fasting

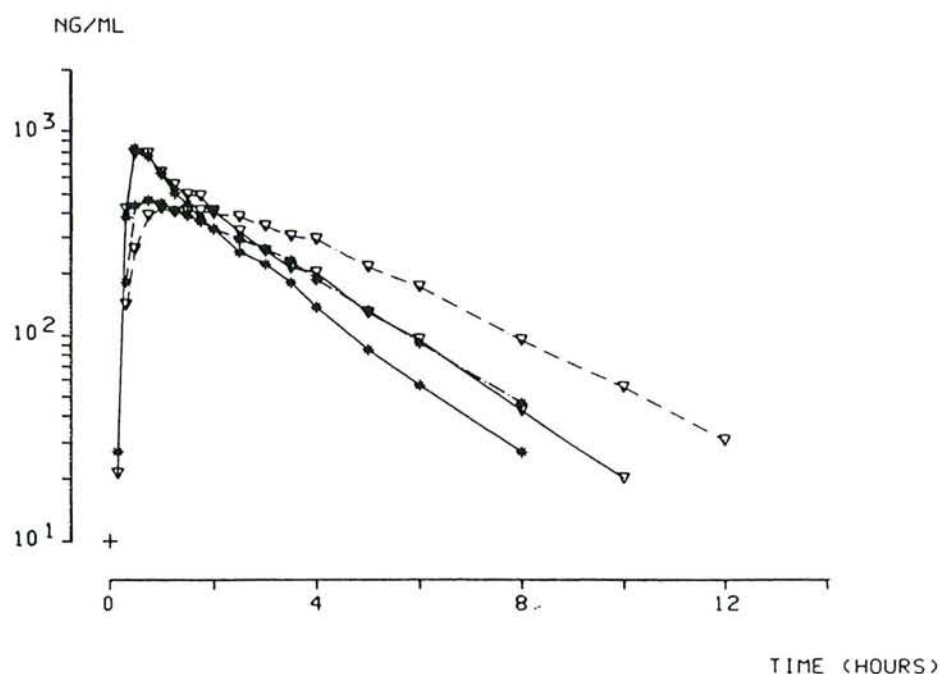


Fig. 2. Plasma concentration-time profiles of moclobemide (—) and Ro 12-8095 (---) in a healthy volunteer following a 100-mg oral dose in absence (*) and in presence (▽) of food

Effect of food intake on the relative bioavailability of moclobemide (Ro 11-1163) 119

Table 1. Absorption and disposition parameters of moclobemide after a single 100-mg oral dose in the absence (A) and presence (B) of food in twelve subjects

Parameters in the extensive metabolizers	Mean $\pm$ CV% and (range)			p-value for A = B ¹
	A	B	ratio B/A	
β (h ⁻¹)	0.433 $\pm$ 20 (0.319–0.541)	0.392 $\pm$ 21 (0.258–0.509)	0.91 $\pm$ 14 (0.72–1.17)	<0.05
$t_{1/2}$ (h) ²	1.60 $\pm$ 20 (1.28–2.17)	1.77 $\pm$ 21 (1.36–2.69)	1.12 $\pm$ 13 (0.86–1.38)	<0.05
$C_{\max}$ (ng/ml)	753 $\pm$ 40 (210–1 270)	643 $\pm$ 44 (229–1 290)	0.89 $\pm$ 30 (0.55–1.45)	>0.05
$T_{\max}$ (h)	0.71 $\pm$ 29 (0.33–1.00)	1.14 $\pm$ 57 (0.50–2.50)	1.74 $\pm$ 69 (0.67–4.55)	<0.05
dose/AUC _{0$\rightarrow$$\infty$} (L/h)	77.7 $\pm$ 66 (31.4–214.1)	70.8 $\pm$ 53 (30.9–149.5)	0.95 $\pm$ 16 (0.70–1.17)	>0.05
AUC _{0$\rightarrow$$\infty$} (ng · h/ml)	1 676 $\pm$ 47 (467–3 183)	1 752 $\pm$ 45 (669–3 241)		>0.05
F_{Rel} ³			1.10 $\pm$ 18 (0.86–1.43)	
F_{Rel} ⁴ corrected			0.98 $\pm$ 15 (0.77–1.32)	

Table 1 (continued)

Parameters in subject 5 (poor metabolizer)						
	β (h ⁻¹)	$t_{1/2}$ (h)	$C_{\max}$ (ng/ml)	$T_{\max}$ (h)	Cl/F (L/h)	AUC _{0$\rightarrow$$\infty$} (ng · h/ml)
A	0.134	5.17	1 331	0.50	13.9	7 211
B	0.113	6.13	1 032	1.50	10.1	9 942

¹ Wilcoxon matched-pairs signed-ranks test.

² Harmonic mean and %CV based upon the “pseudo” standard deviation (Lam *et al.*, 1985).

³ $F_{\text{Rel}} = \text{AUC}_{0 \rightarrow \infty (B)} / \text{AUC}_{0 \rightarrow \infty (A)}$ [data for subject 5 (poor metabolizer) incl.].

⁴ $F_{\text{Rel}}^{\text{corrected}} = \text{AUC}_{0 \rightarrow \infty (B)} / \text{AUC}_{0 \rightarrow \infty (A)} \times \beta_{(B)} / \beta_{(A)}$ [data for subject 5 (poor metabolizer) incl.].

($C_{\max}$ 753 ng/ml) and non-fasting (643 ng/ml) conditions. However, with the meal the rate of absorption was slightly decreased ($T_{\max}$ 0.71 h vs 1.14 h), while the relative extent of absorption was unaltered (98%).

However, a large inter-subject variation was seen in these parameters. There were no significant changes with food in total areas under the concentration-time curve, either uncorrected or when corrected for varying half-lives. Furthermore, no difference was seen in apparent oral clearances (Cl/F fasting 77.7 L/h, non-fasting 70.8 L/h). The relative oral bioavailability of moclobemide in the presence of food relative to fasting conditions was 0.98 ($\pm 15\%$). There was a consistent increase in the terminal disposition half-life ($t_{1/2}$) in the presence of food with a harmonic mean of 1.77 h and ranging from 1.36 to 2.69 h. Although the difference compared to fasting conditions was small (difference of average values, 0.17 h) it reached statistical significance. Since it is likely that the change seen is due to changes in clearance, AUCs corrected for changing half-lives were used to calculate the relative availability of the drug.

Discussion

Moclobemide absorption is rapid in the absence of food. On average, the rate of absorption was slightly decreased in the presence of food (mean $T_{\max}$ 0.71 h vs. 1.14 h), while the extent of absorption was unaltered. The extent of moclobemide absorption as judged by the corrected AUCs was not significantly different in the absence and presence of food. The lack of a significant change in $C_{\max}$ in the presence of food supports the contention of unaltered extent of absorption when moclobemide is given with a meal. The relative oral bioavailability F_{Rel} (food/no food) averaged 0.98 with a CV of only 15%. Consistent with this finding, no significant influence of food on the apparent values of oral clearance was found. It is apparent from the absorption and disposition parameters of moclobemide (Table 1) that for all measured parameters except $T_{\max}$, the CV values are similar in the presence and absence of food. Only for $T_{\max}$ did the CV increase by a factor of 2, from 29 to 57% with food. Increased variability in rate of absorption with food is generally seen in bioavailability studies and is not unique for moclobemide. Even though $T_{\max}$ is affected by food intake, the increase is small. Maximum concentrations were reached within 2.5 h in all subjects.

Similar observations for the variability of moclobemide could be made for the disposition parameters associated with the metabolite Ro 12-8095: little differences in variability around the means of the parameters $t_{1/2}$, $C_{\max}$, $\text{AUC}_{0 \rightarrow \infty}$, but a greater CV for $T_{\max}$. As exemplified for subject 8 (Fig. 2), $C_{\max}$ for this metabolite is slightly (but not statistically significantly) decreased, and $T_{\max}$ is increased in presence of food.

We conclude that food, at least of the composition used in this study, has no clinically significant influence on the gastrointestinal absorption of moclobemide following a single oral 100-mg dose.

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ETUDE IV

Disposition Kinetics of Moclobemide, a New Mao-A Inhibitor, in Subjects with Impaired Renal Function

Marie-Paule Schoerlin, PhD, Fritz F. Horber, MD, Felix J. Frey, MD,
and Michael Mayersohn, PhD

A single intravenous and oral dose of moclobemide (Ro 11-1163) was administered to 13 subjects with varying degrees of renal impairment (creatinine clearances ranging from 0 to 40 mL/min). The resulting disposition and absorption parameters of moclobemide were more variable than but, with the exception of mean absorption time, were not significantly different from values obtained in another study conducted in 12 normal healthy subjects. There were no relationships between any of the disposition parameters and renal function as measured by creatinine clearance. The disposition of two metabolites of moclobemide were partially characterized from plasma data. One of these (Ro 12-8095) appears to be formation rate-limited and, from available data, behaves in a manner similar to what has been observed in normals. The other metabolite (Ro 12-5637) has a long apparent disposition half-life and is present in greater concentrations in the renally impaired compared to the normal subjects. The latter observation may reflect reduced elimination clearance in the renally impaired subjects. Based upon the results of this study there does not appear to be any need to alter the normal dosing regimen of moclobemide in subjects with renal impairment in order to achieve drug concentrations similar to those in healthy subjects.

Moclobemide (Ro 11-1163; Figure 1) is a new drug entity which shows preferential and reversible inhibition of the A-isozyme of the monoamine oxidase enzyme system.¹ Unlike many of the earlier generation monoamine oxidase enzyme inhibitors, moclobemide is devoid of hepatic toxicity in the rat² and it produces only mild pressor response to tyramine in rodents and humans.^{1,3,4} The antidepressant activity of the drug in humans has been examined in several uncontrolled and placebo controlled studies.⁵⁻⁸ The relative efficacy of moclobemide compares favorably with other currently used antidepressant agents.^{9,10}

The absorption and disposition characteristics of moclobemide have been studied in normal human subjects following single intravenous and oral doses

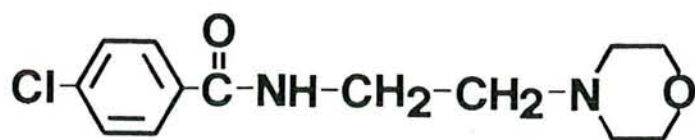
and after multiple oral dosing.¹¹⁻¹³ The overall findings of those studies indicate that moclobemide has a relatively short disposition half-life of 1-2 hours and intermediate to large values of systemic clearance and steady state volume of distribution (ca., 40 L/hour and 80 L, respectively). The drug appears to be primarily metabolized, presumably by the liver, as renal clearance is only a small fraction of systemic clearance (<1%).¹³ The relatively large hepatic extraction ratio results in substantial first-pass hepatic metabolism, providing an absolute bioavailability of about 55% from a single 100 mg oral dose. The oral bioavailability appears to be dose-dependent, increasing as the dose increases above 100 mg, possibly as a result of saturable first-pass metabolism (Mayersohn and Schoerlin, unpublished).

Multiple oral dosing results in a reduction in moclobemide clearance and an increase in oral bioavailability.¹³ The exact mechanism of this phenomenon is not known but it may involve moclobemide and/or metabolite inhibition of metabolism.

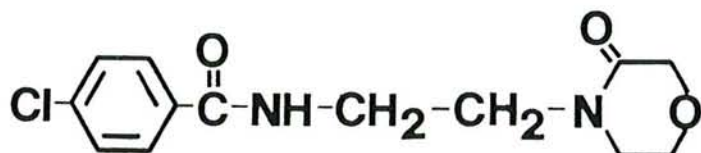
There are suggestions that one or more of the metabolites of moclobemide may be partially responsi-

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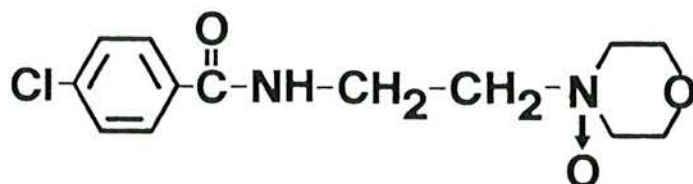
DISPOSITION KINETICS OF MOCLOBEMIDE



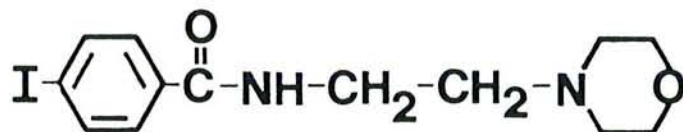
MOCLOBEMIDE (Ro11-1163)



METABOLITE 1 (Ro12-8095)



METABOLITE 2 (Ro12-5637)



INTERNAL STANDARD (Ro11-9900)

Figure 1. Structural formulas of moclobemide and two metabolites and the internal standard used in the assay.

ble for producing the pharmacologic effect.^{1,3} Since those metabolites may be partially excreted by the kidney, the influence of renal impairment on the disposition of moclobemide and its metabolites needs to be examined. The purpose of this investigation was to study the absorption and disposition of moclobemide and two known metabolites (Ro 12-8095 and Ro 12-5627; Figure 1) in renal impaired subjects following single oral and intravenous doses and to compare the results to findings in normal healthy subjects.

METHODS

Protocol

This study was approved by the investigators' institutional human research committee and all subjects provided informed consent. Thirteen subjects (4 women, 9 men) with varying degrees of renal impairment and between the ages of 27 and 75 years participated in the study. The subjects have been arbitrarily divided into two groups according to renal status; Group I, creatinine clearance values of

0–5 mL/min; Group II, creatinine clearance values of 19–40 mL/min. Subjects in Group I were maintained on hemodialysis. Subject characteristics are summarized in Table I. The values for creatinine clearance represent the average of two measurements, one of which was determined prior to and the other after the end of the study. The individual values were similar. All subjects provided a medical history, underwent a physical examination and blood chemistry tests were performed. There was no evidence of impaired liver or gastrointestinal function. Subjects were allowed to continue taking any medication necessitated by their medical condition. Exclusion criteria were: smoking more than 10 cigarettes per day; unstable renal function; anemia (beyond what is expected for the degree of renal insufficiency); pregnancy and any history of drug abuse (other than excessive consumption of analgesics).

An open treatment design was used. On one of two experimental interdialysis days, separated by at least one week, each subject ingested a single 100 mg tablet of moclobemide (Ro 11-1163/017, batch PT 2935 B 51) with 4 ounces of water. On another occasion 12 of the 13 subjects received a 96.7 mg dose of moclobemide as an intravenous infusion over 20 minutes (Ro 11-1163/004, batch G FER 09 134). The infusion (30 mL) was administered via an antecubi-

tal vein at a constant rate using a previously calibrated infusion pump. The drug was administered between 5 and 9 AM following a 10-hour period during which alcohol, caffeine, and tyramine-containing foods were not permitted. The drug was ingested 1.5 hours after a light snack (tea, bread and jam) and an additional snack (2 biscuits and fruit juice) was served 4 hours after dosing. A light standard meal was ingested 8 hours after dosing. Food was always ingested after the appropriate blood sample was obtained.

The subjects remained in a sitting position for the first 2 hours following dosing. Blood samples were obtained from an arm vein and, in the case of the infusion, from a contralateral vein. Blood samples were obtained prior to, 10, and 20 minutes after the start of the infusion and at the following times after the end of the infusion: 10, 20, 30, 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, and 8 hours. For oral dosing, blood samples were obtained prior to and at the following times after drug ingestion: 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, and 8 hours. Samples were obtained via an indwelling venous catheter at early times and by venipuncture at later times. Blood was collected into Vacutainer tubes containing EDTA and centrifuged to obtain plasma. The plasma was stored frozen until analyzed for moclobemide and metabolites.

TABLE I

Subject Characteristics

Subject	Sex	Age (yr)	Weight (kg)	CLcr* (mL/min)	Diagnosis
Group I					
1	M	48	50	0	Nephrotuberculosis
2	M	27	67	0.4	Glomerulonephritis
3	M	42	57	0.4	Glomerulonephritis
4	M	31	69	0.4	Glomerulonephritis
5	M	54	71	1.1	Analgesic nephropathy
6	F	52	77	2.9	Glomerulonephritis
7	F	64	60	4.1	Analgesic nephropathy
8	F	59	63	4.4	Analgesic nephropathy
Group II					
9	M	62	66	19	Nephroangiosclerosis
10	F	75	75	27	Diabetic nephropathy, Hyperparathyroidism
11	M	48	75	30	Glomerulonephritis
12	M	36	63	35	Glomerulonephritis
13	M	61	62	40	Analgesic nephropathy

* CLCr = creatinine clearance. Values are the mean of two measurements determined prior to and after the completion of the study.

Analytical Methods

Plasma samples were analyzed for intact moclobemide and two metabolites whose structures are illustrated in Figure 1. Plasma concentrations were determined by a high performance liquid chromatographic method.¹⁴ Briefly, a plasma sample containing the internal standard (Ro 11-9900; Figure 1) was alkalized and eluted through an Extrelut 1 column with two portions of 5 mL dichloromethane. The solvent was evaporated at 35°C under a stream of nitrogen and reconstituted with 250 µl of mobile phase. One hundred µl were injected onto a C-18 reversed phase column (µ-Bondapak, Waters, Milford, MA) using a mobile phase of acetonitrile and 0.067 M phosphate buffer (adjusted to pH 3.8) in the v/v ratio of 55:255 and a flow rate of 1.5 mL/min. Quantitation was achieved by measuring absorbance at 237 nm with reference to a standard curve of peak height ratio vs moclobemide or metabolite concentration. The lower detection limits for quantitation of moclobemide and metabolites 1 and 2 in plasma were 20, 35 and 40 ng/mL, respectively. The intra-assay percentage coefficient of variation for the three compounds ranged from 2 to 6% over the concentration range of 100 to 3,000 ng/mL. For lower concentrations near the limits of detection, the percentage coefficients of variation ranged from 5 to 13% for each compound. Control samples were analyzed along with authentic samples to ensure quality control in analysis.

Data Analysis

Plasma concentration-time data for moclobemide and metabolites were analyzed by noncompartmental or area methods. The data in the terminal post-absorptive, post-distributive phases were analyzed by linear regression to obtain estimates of the terminal disposition rate constant (β) and from which the disposition half-life was obtained ($\ln 2/\beta$). The total area under the concentration-time curve (AUC) was determined by the linear trapezoidal rule with extrapolation from the last measured concentration on the regression line (C_n) to time infinity (C_n/β). Systemic or total body clearance (CLs) and the steady state volume of distribution (Vss) were determined from the intravenous (iv) data by:

$$CLs = \text{iv dose}/AUC \quad [1]$$

$$Vss = [(iv \text{ dose} \cdot AUMC)/(AUC)^2] - [(iv \text{ dose} \cdot T)/2(AUC)] \quad [2]$$

where AUMC is the total area under the first mo-

ment of the plasma concentration-time curve and T is the duration of infusion.

The mean residence time (MRT) following iv infusion was determined from:

$$MRT = [AUMC/AUC] - T/2. \quad [3]$$

The initial or central volume of distribution (V_c) of moclobemide following iv infusion was determined by applying the method of residuals to the post-infusion data in order to estimate the rate constants and coefficients. The coefficients associated with an iv bolus were then calculated¹⁵ and from which an estimate of V_c was obtained by dividing the iv dose by the sum of the coefficients.

The mean residence time of the metabolite, Ro 12-8095, was determined from the iv data for the metabolite and moclobemide from the relationship,¹⁶

$$MRT (\text{metabolite}) = [AUMC/AUC] \text{ metabolite} - [AUMC/AUC] \text{ moclobemide.} \quad [4]$$

The maximum plasma concentration (C_{max}) and time to achieve the maximum (T_{max}) were determined directly from the concentration-time data. The observed absolute oral bioavailability (Fobs) was calculated from:

$$Fobs = [(AUC \text{ oral})/(AUC \text{ iv})] \times [(iv \text{ dose})/(oral \text{ dose})] \quad [5]$$

The apparent clearance after oral administration (oral clearance, CL_o) was determined from the ratio of the oral dose to the corresponding AUC. The mean absorption time (MAT) was calculated by,

$$MAT = [(AUMC) \text{ oral}/(AUC) \text{ oral}] - MRT \quad [6]$$

The absolute oral bioavailability was predicted from the iv data ($F_{pred: iv}$) and the oral data ($F_{pred: oral}$) based upon the following relationships:

$$F_{pred: iv} = 1 - [CLs/Qh] \quad [7]$$

$$F_{pred: oral} = Qh/[CL_o + Qh] \quad [8]$$

where Qh is the hepatic blood flow assumed to be 90 L/h and CLs was assumed to be equal to hepatic clearance.

The Student's unpaired t-test was used to compare parameter values between the two renal impaired groups and between the renal impaired and normal subjects. A value of $P < .05$ was considered to suggest a statistically significant difference.

RESULTS

There were slight but clinically insignificant changes in blood pressure and pulse rate noted only

during the first 2 hours following dosing. Apart from one subject who developed tachycardia which lasted for about 10 minutes, there were no adverse effects experienced by any of the subjects to the single iv and oral dose of moclobemide. These effects were not different from those seen in normal subjects who received single iv and oral doses of 150 and 100 mg, respectively, and who were given 300 mg moclobemide per day for 2 weeks.¹³

The subjects were arbitrarily divided into two groups according to renal status (Table I). These groups had significantly different creatinine clearance and serum creatinine values but, with the exception of the relative proportion of men and women, there were no significant differences between the groups. There were no statistically significant differences between the two groups for any of the disposition parameters to be discussed and, for that reason, comparisons to findings in normals will be based upon the values for all of the renal impaired subjects. Data reported here for normal subjects, (12 male subjects, 21 to 34 years) have been obtained from another study in which a single iv (150 mg) and oral (100 mg) dose of moclobemide was administered prior to multiple dosing.¹³

Figure 2 illustrates the plasma concentration-time profiles of moclobemide and two metabolites following iv infusion and oral administration (inset graph). The data shown are for one subject (number 1) whose values for moclobemide disposition were similar to the group mean, however, this subject was essentially anephric. The 8-hour sampling time was sufficiently long to characterize moclobemide disposition and that of one metabolite (Ro 12-8095). In most cases, distribution was rapid but somewhat more prolonged in some subjects. The maximum plasma concentration of moclobemide at the end of the iv infusion varied over a four-fold range (775 to 3109 ng/mL) and the average was greater in Group II subjects compared to those in Group I (mean and range: Group I, 1.56, 0.78 to 3.11 mg/L; Group II, 2.39, 1.86 to 2.98 mg/L) but this difference was not significant. There was a nonlinear inverse correlation between the maximum moclobemide concentration and estimates of the initial or central volume of distribution obtained in these subjects (data not shown).

In order to perform a similar analysis between the renal impaired and normal subjects, the maximum moclobemide concentration was adjusted for differences in iv dose and further adjusted to a body weight of 70 kg since the normal subjects had a greater body weight. The average maximum concentrations (% coefficient of variation) for the renal impaired and normal subjects were 1.79 mg/L (42%)

and 1.38 mg/L (24%), respectively. These differences were not significant but the normal subjects had a lower average value and a smaller range of values.

The disposition parameters of moclobemide following iv administration are summarized in Table II which also includes values obtained in normals. One subject (number 2) did not receive the iv dose for reasons unrelated to the drug. There were no significant differences between the renal impaired and normal subjects for the iv disposition parameters listed in Table II. For each of those parameters, however, there is greater variation among the renal impaired subjects compared to the normals. The latter comparisons are best seen in Figure 3.

Moclobemide is rapidly absorbed following oral administration with maximum concentrations being achieved within 1 to 2 hours. The range of the maximum concentrations were greater than that observed for the iv dose (0.11 to 1.08 mg/L; mean and % CV, 0.60 mg/L, 47%). A similar mean and range of values have been noted in normals following the same 100 mg oral dose (mean and % CV, 0.55 mg/L, 39%; range, 0.22 to 0.92 mg/L). The absorption parameters associated with the oral moclobemide dose are summarized in Table II. The absolute oral bioavailability ranged from 0.19 to 0.93 with an average (0.58) essentially identical to that observed in normals (0.55). The apparent oral clearance (one value not used in the calculation of the mean) had a large range of values (21.7 to 174.5 L/h) but the mean was similar to that seen in normals and there were no significant differences between the two groups. The oral clearance was about twice the value of systemic (iv) clearance. The mean absorption time, which included several values of zero for both subject groups, was significantly greater in the renal impaired compared to the normal subjects. The latter was the only parameter that was different between the two groups. As noted for the iv data, the oral parameters have far greater variation among the renal impaired subjects. This is best illustrated in Figure 4.

With regard to the disposition of the two metabolites of moclobemide that were measured in this study, only one of those (Ro 12-8095) provided a concentration-time profile that permitted analysis. The sampling time was generally sufficient to characterize disposition, as noted in Figure 2. In several instances (subjects 9 and 10) the parameter values were estimations only, as the metabolite had a long terminal phase. The maximum concentrations of this metabolite following iv dosing were not significantly different from those seen in the normal subjects after adjusting for dose and to a body weight of 70 kg (renal impaired, 0.45 mg/L, 23% CV; normals,

DISPOSITION KINETICS OF MOCLOBEMIDE

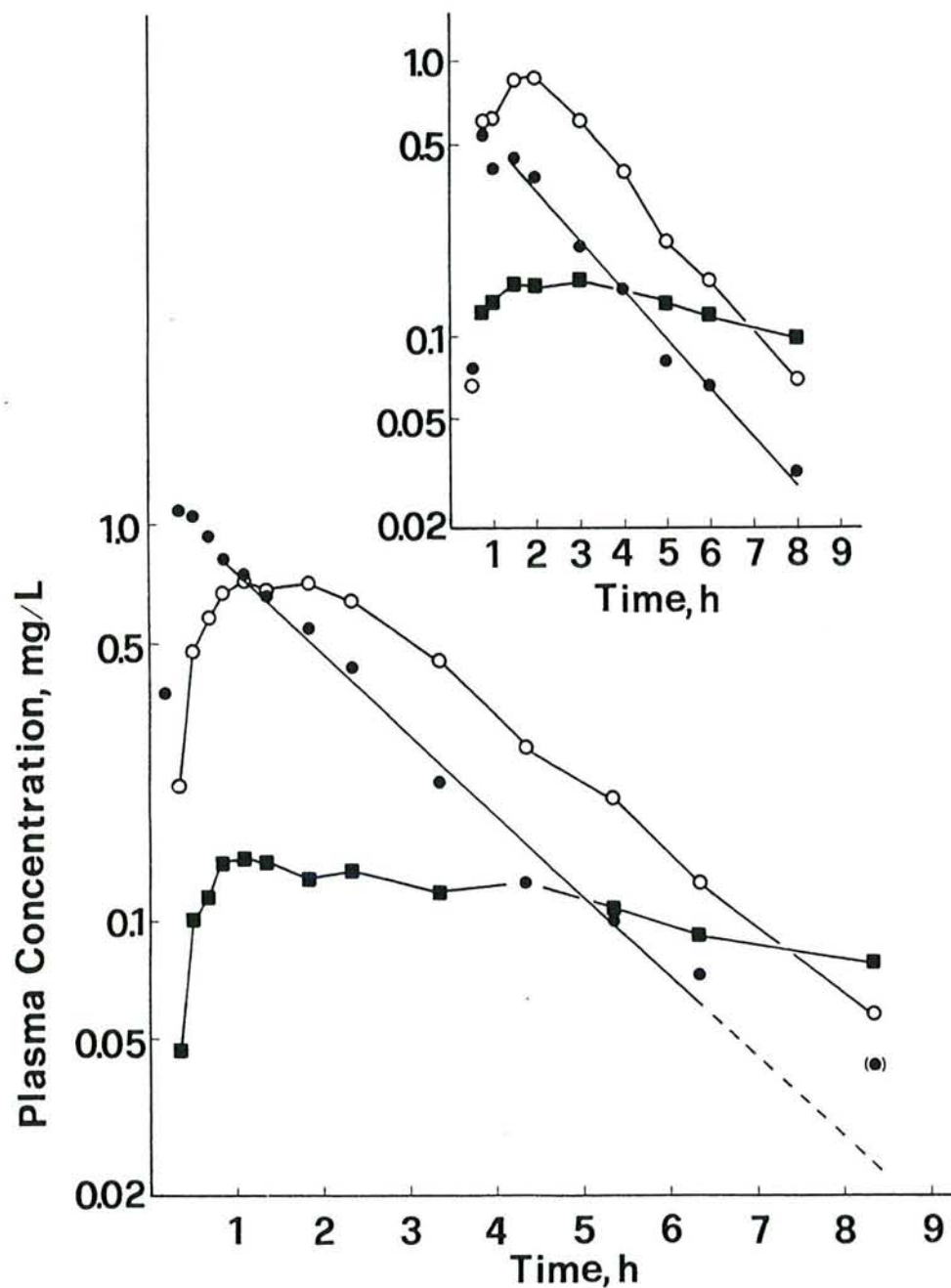


Figure 2. Plasma concentration of moclobemide (●), metabolite 1 (Ro 12-8095; ○) and metabolite 2 (Ro 12-5637; ■) as a function of time following an iv infusion in one subject (number 1). The solid line is based upon linear regression analysis of the moclobemide data in the terminal phase. One point in parentheses was not used in fitting the data. Metabolite concentrations are connected by straight line segments. The inset graph illustrates the concentration-time data following an oral dose of moclobemide in the same subject.

TABLE II
Moclobemide Disposition and Absorption Parameters

Subject	IV				F	ORAL	
	CLs (L/h)	Vss (L)	T _{1/2} (h)	MRT (h)		CLo (L/h)	MAT (h)
Group I							
1	39.2	92.6	1.66	2.36	0.58	68.1	0.70
2*	—	—	—	—	—	119.2	—
3	32.8	71.6	1.58	2.18	0.92	35.7	1.38
4	52.4	105.4	1.74	2.01	0.46	113.1	—†
5	29.7	85.2	2.16	2.87	0.68	43.6	1.99
6	64.0	144.1	1.64	2.25	0.70	91.9	1.99
7	28.3	73.6	2.16	2.60	0.40	71.7	—†
8	67.5	92.8	0.94	1.37	0.19	354.6‡	0.92
Group II							
9	17.3	67.8	2.82	3.92	0.80	21.7	0.79
10	20.4	75.3	2.77	3.69	0.93	22.0	2.14
11	49.3	72.1	1.38	1.46	0.55	90.0	0.55
12	48.9	79.7	1.43	1.63	0.61	79.7	1.62
13	34.0	50.7	1.15	1.49	0.19	174.5	0.55
Mean	40.3	84.2	1.62§	2.09§	0.58	77.6	1.05
SD	16.1	23.6	0.53	1.16	0.24	45.0	0.76
Normals							
Mean	39.4	84.3	1.60§	2.11§	0.55	83.6	0.47
SD	5.9	9.3	0.24	0.37	0.20	41.0	0.37
p value [¶]	NS	NS	NS	NS	NS	NS	<.05

* This subject did not receive an iv dose.

† Value approximately equal to zero and included in the calculation of the mean.

‡ Value not included in calculation of the mean.

§ Harmonic mean and "pseudo" SD.¹⁹

^{||} Data taken from Schoerlin et al. (based upon 11 subjects).¹³

[¶] Unpaired Student's t-test for the comparison between renal impaired and normal subjects (NS = not significantly different).

0.40 mg/L, 28% CV). The maximum concentrations were achieved within 2 hours after dosing and these values were similar in both groups (renal impaired, 1.63 hours, 51% CV; normals, 1.72 hours, 40% CV). Table III lists the actual values of C_{max} and T_{max} along with estimates of half-life and mean residence time. The two latter parameters could not be compared with normals as an insufficient sampling time did not permit their estimation. The half-life values for this metabolite are similar to those for moclobemide (Table II) but the estimated mean residence time is shorter than that for moclobemide.

The other metabolite, Ro 12-5637, was present in low concentrations in plasma and, as noted in Figure 2, the concentrations persisted at relatively constant values during the sampling time. We were unable to obtain adequate estimates of the terminal half-life of that metabolite. The maximum concentrations and time to maximum are summarized in Table III. After

adjusting the C_{max} values for differences in dose and to a 70 kg body weight, the renally impaired subjects had a significantly greater concentration compared to the normal subjects (renally impaired 0.14 mg/L, 35% CV; normals, 0.07 mg/L, 32% CV). The time to achieve this maximum concentration was also significantly longer in the renally impaired subjects.

The metabolite plasma concentration-time data after an oral dose of moclobemide provided profiles similar to those seen after iv administration (Figure 2). The maximum concentrations of Ro 12-8095 were not significantly different when comparing the renal impaired and normal subjects (renal impaired, 0.59 mg/L, 26% CV; normals, 0.49 mg/L, 30% CV). The time to achieve the maximum concentration in the renal subjects (1.46 hours, 47% CV) was not different from the normals (1.44 hours, 30% CV). In contrast, and as noted following iv dosing, the maximum concentrations of Ro 12-5637 were signifi-

DISPOSITION KINETICS OF MOCLOBEMIDE

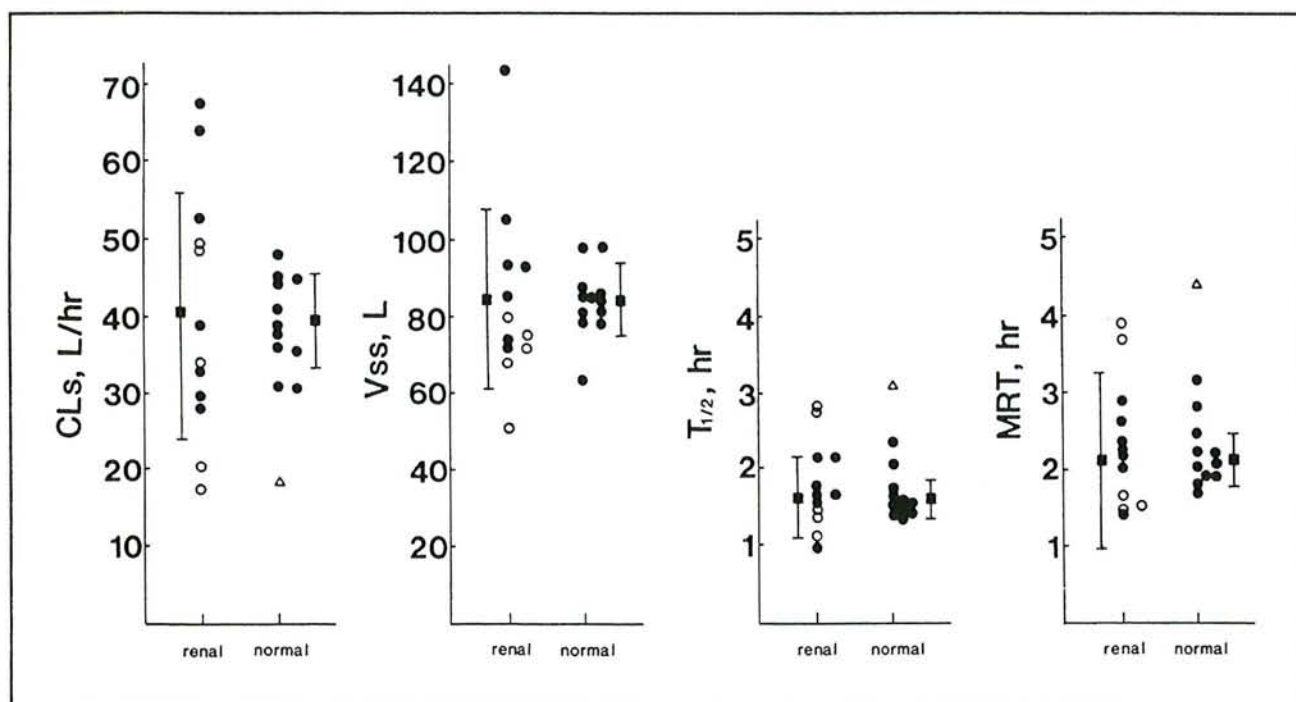


Figure 3. Disposition parameters of moclobemide in renal impaired subjects (●, Group I; ○, Group II) and normal subjects following a 20-minute iv infusion of moclobemide. The data for the normal subjects have been taken from Schoerlin et al¹³. Several values for one normal subject (Δ) have not been included in the calculation of the mean. The harmonic mean is shown for $T_{1/2}$ and MRT. The cross-hatched vertical bars represent the standard deviation of the mean values (■) shown to the left or right of the individual values.

cantly greater in the renal impaired subjects (0.19 mg/L, 36% CV) compared to the values in normals (0.10 mg/L, 31% CV). The time to achieve the maximum concentration was also significantly greater in the renal impaired subjects (1.70 hours, 73% CV) compared to the normals (0.83 hours, 47% CV).

There were no correlations between any of the disposition parameters of moclobemide or its metabolites and renal function based upon creatinine clearance.

DISCUSSION

The purpose of this investigation was to examine the absorption and disposition characteristics of the MAO-A inhibitor moclobemide and several of its metabolites in subjects with impaired renal function following a single iv and oral dose. These results could then be compared to findings obtained in normal healthy subjects in order to assess differences in disposition and the need for adjustment of dosing regimens.

The subjects in this study had different degrees of renal function with creatinine clearance values

ranging from 0 to 40 mL/min. While an arbitrary division, the subjects were separated into two groups according to the degree of renal impairment. These groups differed significantly with regard to creatinine clearance and serum creatinine concentration but there were no differences with respect to age or weight. It should be recognized, however, that these groups were not balanced in terms of the number of subjects per group nor with regard to gender. Based upon the results of this study, however, there were no differences between these groups with respect to absorption or disposition parameters and, therefore, comparisons with normals were based upon the average values for all of the renal impaired subjects.

Moclobemide appears to be essentially completely metabolized, presumably by hepatic enzymes. The renal clearance of the drug is low in normal human subjects (less than 1% of systemic clearance)¹³ and, on that basis, renal impairment per se would not be expected to alter disposition of the parent drug. There are suggestions, however, that renal impairment may directly influence hepatic enzyme activity as has been observed for certain drugs.¹⁷ Altered

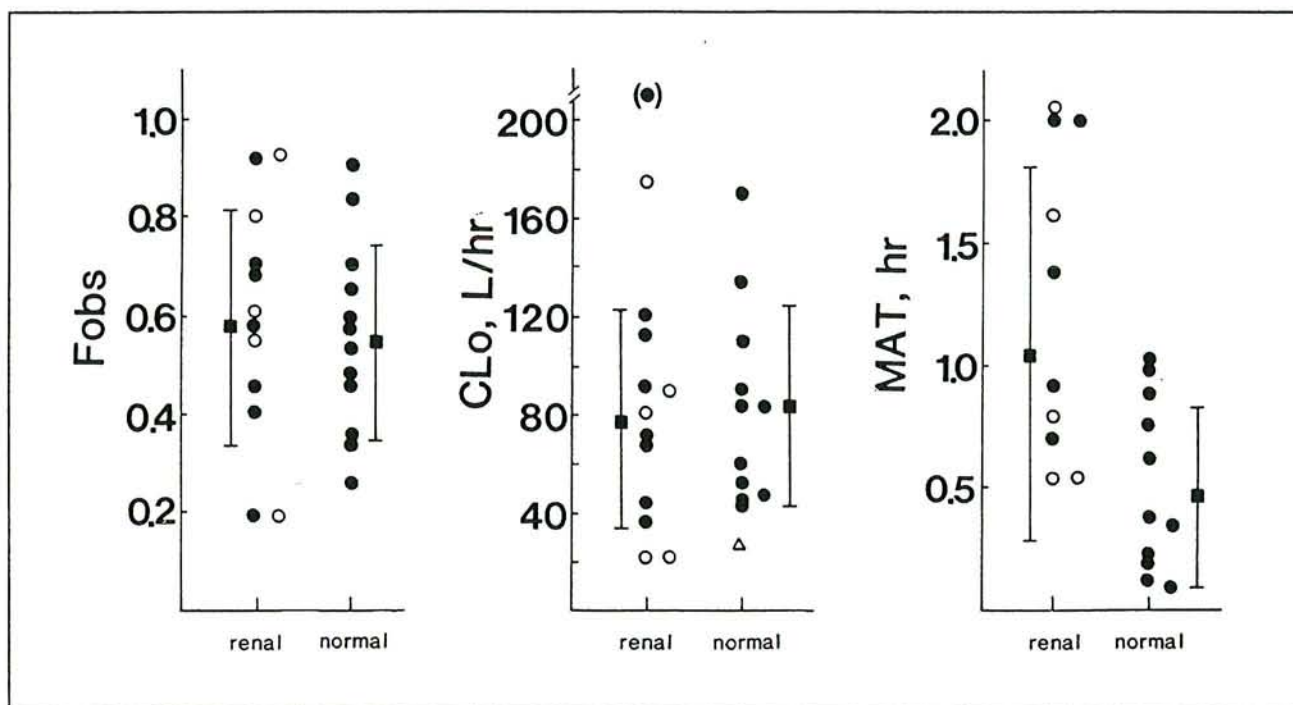


Figure 4. Absorption parameters of moclobemide in renal impaired subjects (●, Group I; ○, Group II) and normal subjects following an oral dose of moclobemide. The values for the normal subjects have been taken from Schoerlin et al¹³. Two values were not used in calculation of the mean C_{Lo} (one value in parentheses and not drawn to scale and the open triangle). The average value of MAT includes several values of zero (not shown). The cross-hatched vertical bars represent the standard deviation of the mean value (■) shown to the left or right of the individual values.

renal function in the absence of liver impairment may influence disposition by indirect or secondary mechanisms. These would include a change, most often a decrease, in plasma protein binding which may alter systemic clearance, apparent volume of distribution and disposition half-life. Renal impairment may also cause a change in tissue protein binding of the drug and thereby alter the apparent volume of distribution and disposition half-life. Altered renal function would be expected to have a direct effect upon the excretion of metabolites which are partially or completely eliminated by the kidney. The latter consideration is of concern when the metabolite(s) are either pharmacologically active or toxic. One of the metabolites measured in this study (Ro 12-5637) appears to exhibit some activity^{1,3} and about 6 to 10% of an iv dose is excreted into the urine in that form.¹³

The disposition parameters of moclobemide following iv dosing are essentially the same in the renal impaired and normal subjects (Table II). In both groups of subjects moclobemide had a relatively short disposition half-life of about 1.6 hours and intermediate to large values for systemic clearance

(ca., 40 L/h) and steady state volume of distribution (ca., 84 L). A similar conclusion is reached with regard to the absorption parameters of moclobemide. With the exception of mean absorption time, which is longer in the renally impaired subjects, there are virtually no differences between the two groups with respect to absolute oral bioavailability or apparent oral clearance. However, for all of those parameters, there is greater variability among the renal impaired subjects compared to the normals (Figures 3 and 4).

It is unlikely that renal function would be responsible for this greater variation within the renal impaired subjects because the drug is primarily eliminated by metabolism. It is possible that plasma or tissue binding differences between these groups could, at least in part, explain some of this variation. Plasma binding was not determined in this study but moclobemide is bound only to the extent of about 50% (R. Brandt, F. Hoffmann-LaRoche and Co., personal communication). There are, however, two possible explanations for this greater variability among the renal impaired subjects. First, that group had a greater average and range of ages (51: 27 to 75 years)

DISPOSITION KINETICS OF MOCLOBEMIDE

TABLE III

Disposition Parameters of the Metabolites of Moclobemide Following IV Administration of Moclobemide

Subject	Ro 12-8095				Ro 12-5637	
	C _{max} (mg/L)	T _{max} (h)	T _{1/2} (h)	MRT (h)	C _{max} (mg/L)	T _{max} (h)
Group I						
1	0.71	1.83	1.70	0.76	0.15	1.08
2*	—	—	—	—	—	—
3	0.47	1.08	1.78	1.02	0.28	1.08
4	0.36	0.67	1.49	0.65	0.10	1.83
5	0.33	2.33	2.76	1.84	0.18	6.33†
6	0.39	1.83	1.86	1.19	0.09	2.33
7	0.58	1.83	2.01	0.98	0.17	1.83
8	0.67	1.33	1.18	0.91	0.09	1.83
Group II						
9	0.62	3.33	9.05†	—‡	0.20	1.08
10	0.51	2.33	6.85†	7.23†	0.14	2.33
11	0.50	0.50	2.01	1.68	0.10	0.83
12	0.34	0.67	1.78	1.36	0.12	2.22
13	0.41	1.83	1.61	1.59	—‡	—‡
Mean	0.49	1.63	1.74§	1.08§	0.15	1.66
SD	0.13	0.83	0.40	0.38	0.06	0.60
Normals						
Mean	0.58	1.72	—‡	—‡	0.09	0.82
SD	0.15	0.68	—	—	0.03	0.53
P value [¶]	NS	NS	—	—	<.001	<.005

* This subject did not receive an intravenous dose.

† Value not used in calculation of the mean nor in the statistical comparison.

‡ Value could not be determined.

§ Harmonic mean and "pseudo" standard deviation.¹⁹^{||} Data taken from Schoerlin et al. (based upon 11 subjects).¹³[¶] Unpaired Student's t-test for the comparison between renal impaired andnormal subjects (NS = not significantly different). The comparisons of C_{max} are based upon the values adjusted for differences in dose and body weight (values listed are unadjusted). The adjusted C_{max} values for Ro 12-8095 (SD) in the renal impaired and normal subjects were, 0.45 (0.10) and 0.40 (0.11) mg/L, respectively. The adjusted C_{max} values for Ro 12-5637 (SD) in the renal impaired and normal subjects were, 0.14 (0.05) and 0.07 (0.02) mg/L, respectively.

compared to the normal subjects (27: 21 to 34 years). While we have not yet established the influence of age on the disposition of moclobemide, it would not be unlikely to observe a greater range of disposition values in association with a larger range of ages. The disposition parameters, however, did not correlate with age. Second, while there were no obvious clinical laboratory findings to suggest altered hepatic function among the renally impaired subjects, the measurements used for that purpose (typically elevation in certain enzyme concentrations) will not by themselves rule out that possibility. Interestingly, normal serum liver enzyme concentrations have been noted in renal impaired subjects even though there was a diminished non-renal (i.e., hepatic) clearance for several drugs.¹⁸ In addition, all subjects continued to take their medication and no attempt was made to interfere with required therapy. While

we cannot predict the possible alteration of moclobemide disposition in the presence of other drugs, it would not seem unreasonable to expect greater variation in disposition within a population taking other drugs compared to a drug-free group (as were the normals). We have noted, for example, an interaction between moclobemide and cimetidine (Mayer-son et al., unpublished).

As mentioned previously, with the exception of mean absorption time, the absorption parameters were not different between the two groups. Since many of the renally impaired subjects were ingesting antacids, it is possible that the significantly longer mean absorption time in that group was related to an antacid-induced reduction in absorption rate. However, the completeness of absorption and apparent oral clearance, while more variable in the renal impaired group, were essentially identical in

both groups. The apparent oral clearance was about twice the value of systemic clearance. Since the oral dose appears to be completely absorbed from the gastrointestinal tract into the portal circulation,¹¹ that observation is consistent with an absolute oral bioavailability of less than one and suggests an hepatic first-pass effect. Equating systemic clearance with hepatic clearance, moclobemide has a substantial hepatic extraction ratio which would be consistent with presystemic elimination. The bioavailability may be predicted from the iv or oral data and, in both cases, the predictions agreed well with the observed bioavailability of 0.58. The average (% CV) value predicted from the iv data was 0.55 (33%) and that from the oral data was 0.55 (33%). The relationship between the predicted and observed values may be seen in Figure 5 which includes data from the renal impaired and normal subjects. The values are randomly distributed about the line of identity (solid line) but there is far less variation noted with the oral compared to the iv prediction. The same conclusion has been made for moclobemide based upon more extensive data obtained from several other studies; the oral prediction is less variable than the iv prediction but both give the same aver-

age value (Mayersohn et al., unpublished). These correlations tend to support the assumptions of complete gastrointestinal absorption from the oral tablet and that systemic clearance is essentially equivalent to hepatic clearance.

The plasma concentration-time profiles of the two metabolites of moclobemide were similar to those noted in normal subjects,¹³ however, the sampling time in the former study was insufficient to completely characterize their disposition. In the present study we were better able to characterize the disposition of one of the two metabolites, Ro 12-8095, but not the other (Ro 12-5637). The former metabolite reached maximum concentrations within 1-2 hours following dosing and then appeared to decline in parallel with moclobemide. The average ratio of the terminal disposition rate constants (Ro 12-8095 to moclobemide) was 0.90. Based upon that information and the fact that the calculated mean residence time for that metabolite was less than that of moclobemide, the elimination of Ro 12-8095 would appear to be formation rate-limited. Unfortunately, we are not able to compare disposition half-life or mean residence time of that metabolite with values in normals, for the reason given above. However, since

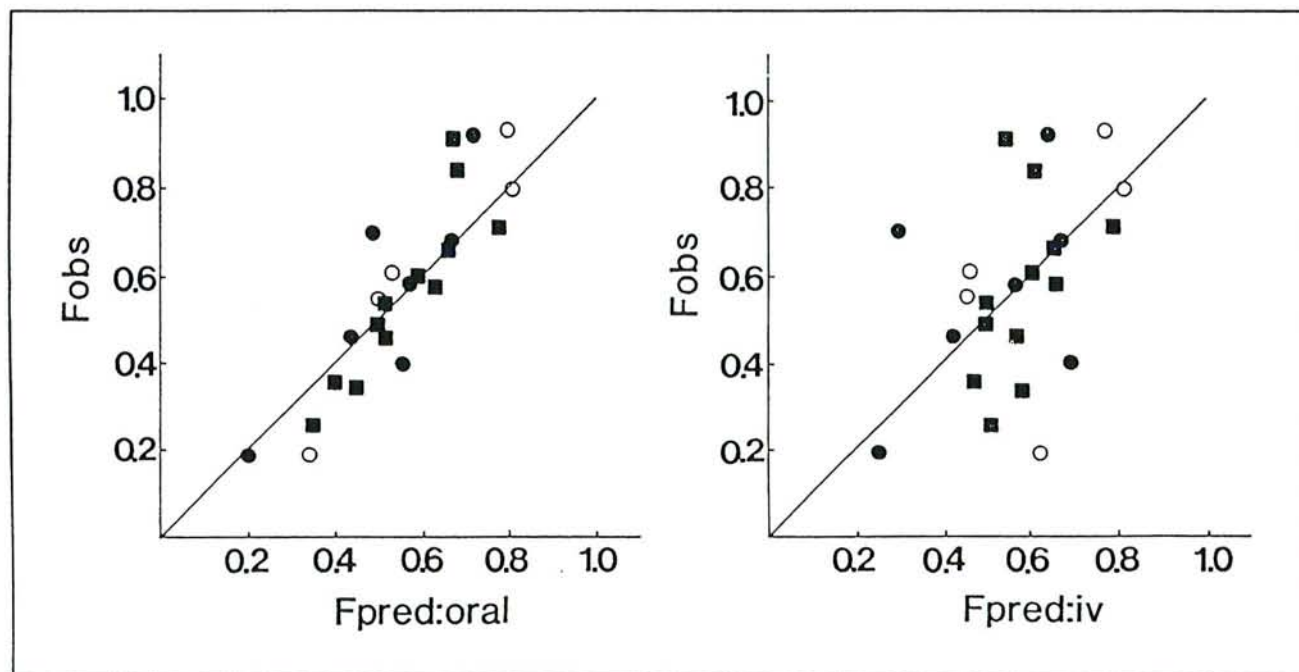


Figure 5. The observed absolute oral bioavailability (F_{obs}) of moclobemide in renal impaired subjects (●, Group I; ○, Group II) and normal subjects (■) as a function of the bioavailability predicted from the oral data ($F_{pred: oral}$) and iv data ($F_{pred: iv}$). The data for the normal subjects have been taken from Schoerlin et al.¹³ The solid lines are the lines of identity. The slopes of the regression lines forced through the origin are: $F_{pred: oral}$, 1.05; $F_{pred: iv}$, 1.05.

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the elimination appears to be limited by metabolic formation, renal insufficiency is not expected to influence the disposition or accumulation of that metabolite.

Less information has been obtained about the other metabolite, Ro 12-5637, since the disposition half-life was relatively long and blood samples were not obtained for a sufficient time. The maximum concentrations of that metabolite were found within 1-2 hours after dosing, but the concentrations remained small and persisted during the period of sampling. We were unable to determine the disposition half-life in the renal impaired and normal subjects and it is, therefore, difficult to evaluate the influence of renal impairment on the disposition and accumulation of that metabolite. Based upon the relatively long half-life, at least in comparison to moclobemide, it would appear that the elimination of the metabolite is rate-limited by its further elimination (either metabolism and/or renal excretion). Since, in a previous study,¹³ a small fraction of the metabolite was excreted into the urine in that form (ca., 6 to 10%), elimination would appear to be limited by subsequent metabolism rather than renal excretion. However, renal function appears to influence the disposition of the metabolite, at least to some extent. The latter conclusion is based upon the significantly greater maximum concentrations and the longer time to achieve those concentrations in the renally impaired compared to the normal subjects (Table III). Those differences may be caused by alterations in formation and/or elimination clearances of the metabolite. Reduction in the elimination clearance, rather than an increase in formation clearance, is a more reasonable explanation and that value would appear to be reduced in subjects with renal impairment. The significance of this observation and the presumed mechanism, in terms of effective moclobemide therapy, is difficult to evaluate. Although this metabolite has been suggested to be pharmacologically active, it is present at low concentrations. Following multiple oral dosing in normal subjects,¹³ the metabolite does not accumulate and steady state concentrations are low. It is likely that accumulation following multiple dosing in subjects with renal impairment would still result in low concentrations of the metabolite and not result in substantially greater clinical effect compared to normals.

In conclusion, we have examined the disposition kinetics of moclobemide and two of its metabolites in subjects with renal impairment following a single iv and oral dose. The results have been compared with findings from a previous study in normal subjects. Although there was greater variability among

the renally impaired subjects there were no important or significant differences in the disposition or absorption parameters of moclobemide when compared to normal subjects. The disposition of one metabolite (Ro 12-8095) was examined and, with the available data, the characteristics of that metabolite were the same in both the renally impaired and normal groups. The disposition of another metabolite, Ro 12-5637, could not be completely described because of a relatively long half-life but the renally impaired subjects had greater maximum concentrations and it took longer to achieve those concentrations compared to the normal subjects. It does not appear to be necessary to alter the dosing regimen of moclobemide in subject with renal impairment; existing regimens in normals should provide adequate therapy provided that there is no alteration in response.

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ETUDE V

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Clinical Pharmacologist

PharmD, PhD, or MD to run Clinical Drug Testing Center within Division of Clinical Pharmacology. Emphasis on Phase I studies, strong background in pharmacokinetics a must. Academic appointment and research interest required. Send curriculum vitae and bibliography to: Division of Clinical Pharmacology, The Chicago Medical School, 3333 Green Bay Road, North Chicago, IL 60064; 312-578-3415.

ETUDE V

PHARMACOKINETICS OF MOCLOBEMIDE (RO 11-1163) IN PATIENTS WITH LIVER CIRRHOSIS

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Key words: moclobemide, liver cirrhosis, pharmacokinetics

Moclobemide (Ro 11-1163) is an effective anti-depressant drug which is a rapidly acting and reversible inhibitor of the MAO-A enzyme system. The drug has a relatively large systemic clearance (ca. 40 l/h) and undergoes substantial hepatic first-pass metabolism after its oral administration. Moclobemide is entirely metabolized before its elimination from the body and it was of interest to examine the influence of liver disease on the disposition of the drug. The absorption and disposition of moclobemide and disposition of its metabolites Ro 12-5637 (active) and Ro 12-8095 (inactive) have therefore been examined in six male and six female patients with chronic liver disease following a single IV infusion (90 mg over 20 min) and a single oral dose (100 mg) of moclobemide. Liver function was evaluated on the basis of biochemical blood tests, indocyanine green clearance (ICG) (mean 8.24 l/h, $\pm$ CV 55%) and antipyrine clearance (1.66 l/h, $\pm$ 74%). The estimated hepatic blood flow averaged at 16.3 l/h ($\pm$ 53%) and 57% of that flow was calculated to perfuse the functional mass of the liver.

Following the IV dose pharmacokinetic parameters, such as half-life ($T_{1/2}$), mean residence time (MRT), the concentration at the end of the infusion (C_{inf}), the systemic clearance (Cl_s) and the terminal disposition rate constant (β) summarized in Table 1 were significantly changed in the liver impaired subjects compared to those of healthy subjects in a previous study (Schoerlin et al., 1987). This was due to impaired metabolism of the

drug in liver patients. The steady-state volume of distribution (V_{ss}) and renal clearance (Cl_r) were unchanged in liver disease as shown in Table 1. There were good correlations between moclobemide systemic clearance and ICG and antipyrine clearance.

Following a single oral dose apparent oral clearance (Cl_o) of moclobemide was significantly lower in the diseased patients than in healthy subjects with greater maximum plasma concentrations (C_{max}) and increased absolute oral bioavailability (F) (Table 1). Although there were no differences in the time needed to achieve the maximum concentration, the mean absorption time (MAT) was significantly greater in the liver impaired subjects. Consistent with the IV dose, moclobemide apparent oral clearance correlated well with both ICG and antipyrine clearances. The results of this study indicate that subjects with chronic liver impairment handle moclobemide in a quantitatively and significantly different manner from healthy subjects. Therefore, the oral dose needs to be reduced when treating such patients to avoid drug accumulation.

Table 1: Average ($\pm$ CV) Pharmacokinetic Parameters of Moclobemide in Patients with Liver Cirrhosis Compared to Healthy Volunteers

STUDY POPULATION	INTRAVENOUS INFUSION / 90 mg							ORAL DOSE / 100 mg			
	$T_{1/2}$ (h)	MRT (h)	C_{inf} (ng/ml)	Cl_s (l/h)	β (h ⁻¹)	V_{ss} (l)	Cl_r (l/h)	Cl_o (l/h)	C_{max} (ng/ml)	F	MAT (h)
Patients with liver cirrhosis (n = 12)	3.87 68%	7.21 68%	2271 36%	14.6 77%	0.179 64%	75.7 53%	0.15 33%	20.2 88%	1607 42%	0.84 29%	1.16 45%
Healthy volunteers (n = 12)	1.67 21%	2.37 32%	1148 36%	37.7 22%	0.415 21%	84.1 11%	0.16 70%	78.8 54%	582 40%	0.56 35%	0.47 79%

Reference: Schoerlin M.-P., Mayersohn M., Korn A., Eggers H.
Clin. Pharmacol. Ther. 1987; 42: 395-404.

ETUDE VI

Absorption and disposition of moclobemide in patients with advanced age or reduced liver or kidney function

Stoeckel K, Pfefen JP, Mayersohn M, Schoerlin MP, Andressen C, Ohnhaus EE, Frey F, Guentert TW. Absorption and disposition of moclobemide in patients with advanced age or reduced liver or kidney function.

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Three different studies were conducted to assess the pharmacokinetics of moclobemide in subjects with conditions complicating dose determination. The first examined the absorption and disposition of moclobemide in an elderly population and compared these with results obtained in a group of normal young subjects. No significant differences were found between the groups in the intravenous (i.v.) parameters of disposition, and no differences with regard to disposition of the metabolite, Ro 12-8095. In addition, the minimum steady-state concentrations of moclobemide and the main plasma metabolite did not differ between the elderly and younger patients. In the second study, clearance tests in patients with cirrhosis of the liver confirmed that hepatic function is drastically reduced in this group of patients; it is therefore possible that moclobemide absorption and distribution might be influenced. In only 3 of the 12 patients investigated, slowly declining plasma concentrations after administration pointed to a severely limited elimination capacity for moclobemide. In the remaining 9 subjects, average values of several parameters changed significantly ($t_{1/2}$, MRT and Cl), whereas V_d and renal clearance were not significantly altered. In patients with kidney dysfunction, there were no differences in kinetics between patients undergoing hemodialysis and those who were not. Compared with normal healthy volunteers, no differences were found for renal patients, with the exception of the mean absorption time, which was significantly prolonged. From these studies it can be concluded that, pharmacokinetically, neither age nor renal impairment require adjusting the dosage of moclobemide. Patients with liver cirrhosis, however, need to have the usual dose reduced to one half or one third, or else the dosage intervals can be increased to prevent cumulation.

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Key words: antidepressant; moclobemide; pharmacokinetics; elderly patients; liver cirrhosis; renal impairment

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Impaired capacity of excretory pathways in advanced age or different disease states may increase the risk of side effects of any drug treatment. Three different studies were undertaken to assess the pharmacokinetics of moclobemide in populations with conditions complicating drug dose adjustments.

Elderly people often suffer from depression and moclobemide may therefore be useful in treating depression in the aged population. There is considerable evidence that elderly subjects may dispose of drugs differently than young subjects (1). Unfortunately, and unlike the renal excretion of drugs, no generalizations can be made on the influence of age on drug metabolism. Therefore, a first study

examined the absorption and disposition of moclobemide in an aged population and compared the results with those obtained in a group of normal young subjects.

Moclobemide appears to be completely metabolized by hepatic enzymes. Liver impairment may change the elimination characteristics of the drug and dosage alterations may be required when treating patients with such conditions. It was of interest, therefore, to examine the absorption and disposition of moclobemide in subjects with reduced liver function.

Renal excretion accounts for only a small portion of the total elimination of moclobemide. Nevertheless, absorption and disposition of moclo-

bemide was studied in renal disease patients, since renal impairment may alter hepatic metabolism by affecting intrinsic enzymatic activity (2, 3). Furthermore, several of the metabolites of moclobemide appear to be eliminated by renal mechanisms, and the metabolites may therefore accumulate to a different degree depending on renal function. The latter may be important if any of the metabolites exert activity or alter the elimination of the parent drug.

Material and methods

Study outlines

When the influence of age was assessed, 14 healthy elderly subjects (10 women, 4 men; 65–77 years; 46–78 kg) were administered oral moclobemide as single doses of 100 mg and multiple doses of 100 mg 3 times daily. Five subjects received additional moclobemide intravenously (i.v.) (75 mg as infusion over 20 min). The panel of liver cirrhosis patients examined (6 women, 6 men; 34–80 years; 56–103 kg) also received single oral doses of moclobemide (100 mg) and an i.v. infusion (90 mg over 20 min). Antipyrine and indocyanine green (ICG) were administered to assess total hepatic blood flow and the degree of shunting (4, 5). Patients with renal insufficiency (4 women, 9 men; 27–75 years; 50–77 kg) were grouped according to severity of the kidney impairment (group I: Cl_{Cr} 0–5 ml/min, on hemodialysis; group II: Cl_{Cr} 19–40 ml/min, no hemodialysis). Again a single oral dose (100 mg) and i.v. infusion (96.7 mg over 20 minutes) were administered to every study subject. Although the pharmacokinetic characteristics of moclobemide seen in the liver or kidney disease patients

were contrasted to those in healthy volunteers by a historical comparison, the study on elderly volunteers included a parallel group of young subjects (2 women, 4 men; 22–33 years; 62–74 kg) that underwent the same protocol as the elderly subjects.

Pharmacokinetic evaluation

In all 3 studies plasma was collected at various times after drug administration to determine pharmacokinetic parameters suitable for characterization of absorption and disposition by model-independent methods: area under concentration-time curve (AUC); elimination half-life ($t_{1/2\beta}$) or associated rate constant (β); mean residence time (MRT); clearance (Cl) and steady-state volume of distribution (V_{ss}) after i.v. dosing; maximum concentrations (C_{max}) and oral clearance (Cl/F) after oral administration. In the studies on liver and renal patients, urine was also collected to determine the renal elimination characteristics of unchanged drug and metabolites. Parameters between different study groups were statistically compared by using Student's unpaired *t*-test ($\alpha=0.05$). The analytical method employed to quantify moclobemide in plasma and urine (6) allowed not only unchanged drug but also the MAO-A active N-oxide metabolite (Ro 12-5637) and the main metabolite in plasma with a lactam structure (Ro 12-8095) to be determined.

Results and discussion

In Fig. 1 $t_{1/2}$ and AUC values observed in elderly subjects, liver and renal disease patients are all compared with values reported earlier (7) for a group of healthy young volunteers.

When the elderly study group was compared with the young volunteers investigated in parallel using the same trial protocol, there were no significant differences in the i.v. parameters of disposition between the subjects with advanced age (mean $\pm$ SD: Cl 36.3 ± 12.3 l/h; $t_{1/2\beta}$ 1.63 ± 0.50 h; MRT 2.10 ± 0.58 h; V_{ss} 72.8 ± 18.2 liter) and the young control group (Cl 45.3 ± 9.5 l/h; $t_{1/2\beta}$ 1.31 ± 0.39 h; MRT 1.65 ± 0.56 h; V_{ss} 71.6 ± 17.8 liters). In addition, there were no significant differences between these groups with regard to the disposition of the moclobemide metabolite, Ro 12-8095, following i.v. moclobemide administration. Following the first oral dose, the elderly subjects had a significantly greater C_{max} and smaller Cl/F, but there were no significant differences between the groups for time of peak concentrations, $t_{1/2\beta}$, MRT and absolute bioavailability. Unlike the results of the first oral dose, the C_{max} values during multiple dosing

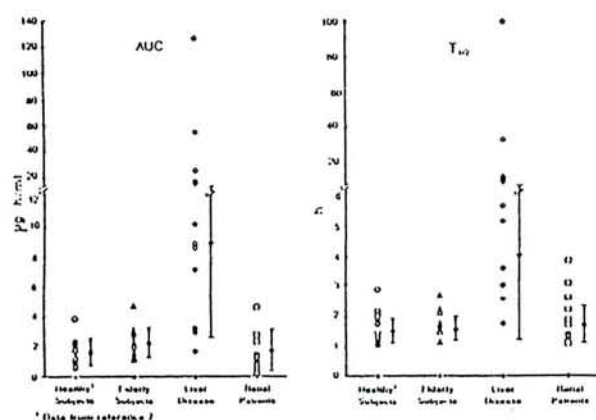


Fig. 1. Influence of advanced age, liver or renal impairment on pharmacokinetic parameters of moclobemide after single 100-mg doses. Bars represent mean $\pm$ SD; parameters from 3 liver disease patients with extreme values not included in calculation of mean.

at steady state were not significantly different between the elderly (1446 ± 243 ng/ml) and the young (1235 ± 448 ng/ml) subjects. At the end of the first week of multiple dosing the oral clearance remained significantly greater in the young subjects, but that parameter was not different at the end of the second week of dosing (19.7 ± 6.3 l/h vs 27.4 ± 11.8 l/h). No other parameter showed significant differences. In addition, the average minimum steady-state concentrations of moclobemide and its main plasma metabolite (Ro 12-8095) were not different between the groups.

Clearance tests performed in the liver cirrhosis patients confirmed that hepatic function in this group was drastically reduced, thus allowing a possible influence on moclobemide absorption and disposition to be investigated. Based upon ICG and antipyrine measurements, we estimated that, in these subjects, the total hepatic blood flow averaged 16.3 l/h and 57% of that flow was calculated to perfuse the functional mass of the liver. The variability in kinetic parameters seen in liver disease was much greater than that observed in other subject groups and may reflect heterogeneity in the disease among the patients. For 3 subjects, only slowly declining plasma concentrations after administration were observed, indicating a drastically reduced elimination capacity for moclobemide. An exact assessment of pharmacokinetic values was not possible because of time limitations in the sample collection period. Even when parameters obtained for these subjects are excluded from statistical tests, several parameters were still significantly changed on average in the remaining 9 liver impaired subjects compared with healthy volunteers: $t_{1/2\beta}$ (3.87 ± 2.62 h vs 1.67 ± 0.35 h) and MRT (7.21 ± 4.93 h vs 2.37 ± 0.77 h), both calculated after the i.v. dose. Systemic clearance, Cl, was significantly lower compared with normals (14.6 ± 11.2 l/h vs 37.7 ± 8.2 l/h). No significant differences in moclobemide V_{ss} (75.7 ± 40.3 liters vs 84.1 ± 9.0 liters) or renal clearance (0.152 ± 0.050 l/h vs 0.160 ± 0.112 l/h) were found. There were good correlations of moclobemide clearance with ICG and antipyrine clearance ($n=12$). Following a single oral dose, moclobemide Cl/F was significantly smaller than in normals (20.2 ± 17.8 l/h vs 78.8 ± 42.5 l/h) and this resulted in higher C_{max} (1607 ± 669 ng/ml vs 582 ± 234 ng/ml) and greater absolute oral bioavailability compared with the normal subjects (0.84 ± 0.25 vs 0.56 ± 0.20). Moclobemide apparent oral clearance correlated well with both ICG and antipyrine clearance.

When renal patients with various degrees of kidney impairment were studied, no differences in moclobemide kinetics between patients with and without hemodialysis were noted. The mean for all

subjects was therefore used to compare the results with those from a previous study in normal healthy volunteers (7). With one exception, there were no statistically significant differences in moclobemide disposition and absorption parameters when the renal impaired patients were compared with the normal group. The mean values for the renal impaired subjects were: Cl, 40.3 ± 16.2 l/h; V_{ss} , 84.2 ± 23.5 liters; $t_{1/2\beta}$, 1.62 ± 0.55 h; MRT, 2.32 ± 0.84 h; absolute oral bioavailability, 0.58 ± 0.25 . Although there were no differences in C_{max} or the time to reach it following an oral dose, the mean absorption time was significantly longer in the renal-impaired than in the normal subjects. The greater variability for any given parameter within the renal-impaired subjects compared with the normals may reflect the use of other drugs and/or the greater average age and age range among the renal-impaired group. There were no relationships between any of the disposition parameters of moclobemide and renal function as measured by creatinine clearance. The elimination kinetics of the metabolite Ro 12-8095 appear to be formation rate-limited after moclobemide administration and there were no significant differences in the comparisons that could be made between the renal-impaired and normal subjects. Little information could be obtained about another metabolite, the N-oxide derivative, since that compound was present at low concentrations only persisting at relatively constant levels during the sampling period.

From a pharmacokinetic point of view, neither advanced age nor renal impairment require dose adjustments when depressive disorders are treated with moclobemide. Patients with liver cirrhosis, however, handle moclobemide differently than do normal subjects; the oral dose of moclobemide in such patients needs to be reduced to one half or one third of the usual dose, or the dosing interval may be prolonged to avoid accumulation of the drug after chronic dosing.

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Title Moclobemide Absorption and Disposition in Healthy Young and Elderly Subjects Following Single Intravenous and Oral Dosing and Multiple Oral Dosing (PK-4577)

M. Mayersohn, GCR B-116'078

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1. INTRODUCTION

Moclobemide (Ro 11-1163) is a preferential inhibitor of the monamine oxidase-A isozyme (1). The compound is a rapid acting and reversible inhibitor of that enzyme system (1). The anti-depressant activity in humans has been examined in several clinical studies and the results support the drug's therapeutic efficacy (2-5). The absorption and disposition of the compound has been reasonably well defined in normals following single oral and iv doses and after multiple oral dosing (6-8). Other studies have examined moclobemide absorption and disposition in renally and hepatically impaired subjects (9, 10) as well as in the presence of food (11) and cimetidine (12). These studies indicate that moclobemide has a relatively short elimination half-life of about 1 to 2 hour in normals and intermediate to large values of clearance (ca., 40 L/hr) and steady-state volume of distribution (ca., 80 L). Since the drug is primarily metabolized by the liver and, because of its relatively large hepatic clearance, moclobemide undergoes rather substantial first-pass metabolism. Although moclobemide appears to be completely absorbed into the portal circulation from the solid oral dosage forms examined, the bioavailability increases with dose, probably as a result of saturable hepatic metabolism (13). There is generally good agreement between the observed and predicted absolute oral bioavailability following single doses.

Because moclobemide may find use in the elderly population, it is of interest to determine if absorption and disposition in that population is different from that in young subjects. Such differences may suggest the need to alter a dosing regimen of the drug in the elderly subjects assuming the same concentration-response relationship as in the young. There is now considerable evidence that elderly subjects are different from young subjects with regard to anatomic and physiologic parameters and, therefore, the elderly may handle drugs differently (14). Unfortunately, and, unlike the renal excretion of drugs, no generalizations can be made concerning the influence of age on drug metabolism. This leaves little choice but to examine the disposition of the drug of interest in the elderly population and compare the findings with those obtained in a young group of subjects.

2. OBJECTIVES

The purpose of this study was to examine the absorption and disposition of moclobemide in groups of healthy young and elderly subjects following single iv and oral doses and after multiple oral dosing.

3. MATERIALS AND METHODS

3.1. Trial Center

This study was conducted by Dr. C. Andressen of AFB, Klinische Pharmakologie GmbH, D-1000 Berlin, according to trial plan PK 4577. The staff of that company was responsible for subject recruitment,

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drug administration, blood collection and plasma separation.

3.2. Test Preparations

Moclobemide for iv administration was given in a dose of 75 mg (3 ml of 50 mg/2 ml; Ro 11-1163; batch GFER 09134) dissolved in sterile water to make a final volume of 20 ml.

Moclobemide tablets (100 mg; Ro 11-1163/017; batch 2963 B51) were used for single and multiple oral dosing (3 x 100 mg per day for 15 days).

3.3. Subject Characteristics

Fourteen healthy non-smoking elderly male and female subjects between the ages of 65 and 77 years and six healthy young non-smoking subjects between the ages of 22 and 33 years participated in this study. Subject characteristics are summarized in Table 1. Health status was established by medical history, physical examination including a 12-lead ECG and biochemical laboratory tests. The biochemistry test results are summarized in Appendix 1 and the normal values in Appendix 2.

Exclusion criteria included: any deviation from normal with respect to gastrointestinal, hepatic, respiratory, renal or cardiac functions; any deviation from normal in the physical examination; any clinically significant allergic disease; any history of drug exposure which amounts to drug abuse; smoking; drug or alcohol addiction. No other medication should be taken during the 2 weeks preceeding and during the study. Alcoholic beverages were not allowed for 10 hours prior to dosing and during the blood sampling period.

Ten of the twenty subjects were phenotyped with 10 mg debrisoquine and 100 mg mephenytoin (Table 1) (15, 16).

3.4. Ethical Considerations

The present study was conducted in accordance with the principles laid down in the declarations of Helsinki, Tokyo and Venice concerning biomedical research involving human subjects. The study protocol was aproved by the institutional ethical review board and written informed consent was obtained from every subject prior to inclusion in the study. The volunteers were free to withdraw from the study at any time.

3.5. Study Design

Each subject received a single 20 minute iv infusion of 75 mg moclobemide on two occassions: one week prior to and two days after a 15 day multiple oral dosing regimen of moclobemide. Moclobemide 100 mg tablets were ingested three times a day at intervals of 6, 6, and 12 hours for a total of 15 days.

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Five elderly and five young subjects repeated the single dose iv experiment 11 weeks after the initial study.

3.6. Clinical Procedures

On day 1 of the study each subject received 75 mg moclobemide (in 20 ml sterile water) as a 20-minute iv infusion into a forearm vein using a calibrated syringe infusion pump. Subjects remained supine during the infusion. Blood samples (10 ml) were to be obtained from a contralateral arm vein and collected into Vacutainer tubes containing ammonium oxalate and sodium fluoride. Blood samples were taken prior to dosing (blank), 10 minutes after the start of the infusion and at the end of the infusion and at the following times after the end of the infusion: 10, 20 and 30 minutes and 1, 2, 3, 4, 5, 6, 8 and 10 hours. Blood was centrifuged within 30 minutes of collection at 3000 rpm for 15 minutes. Plasma was transferred to glass tubes and stored at -20 C until analysis.

One week after the first iv dose, on day 8 of the study, a 15 day multiple oral dosing regimen was begun. Moclobemide tablets (100 mg) were ingested three times a day with 120 ml of water at intervals of 6, 6 and 12 hours. A concentration-time profile was obtained during a dosing interval on days 8, 15 and 22 (days 1, 8 and 15 of the multiple dosing regimen). Blood samples were collected into Vacutainer tubes at the following times after the first morning dose: 0, 15, 30 and 45 minutes and 1, 2, 3, 4, 5 and 6 hours. On study days during which multiple blood samples were obtained, the subjects came to the clinic after an overnight fast. Two hours after the morning dose a light breakfast was served which was limited in fat content. Caffeine-containing beverages were allowed but were restricted to the absolute minimum. For 10 hours prior to and as long as blood samples were obtained, alcoholic beverages were not allowed. During sampling days the meals were eaten after the appropriate blood samples were obtained.

A single blood sample was obtained just prior to the second daily dose on days 8, 10, 13, 16, 18 and 20 (days 1, 3, 6, 9, 11 and 13 of the oral regimen).

. At the end of the multiple oral dosing regimen and following one drug-free day (day 24 of the study), a second 20 minute iv infusion of 75 mg moclobemide was administered. Study conditions and sampling times were the same as described above for the first iv infusion.

A copy of the study protocol is attached in Appendix 3.

3.7. Analytical Methods

Moclobemide and one of its metabolites, Ro 12-8095, were determined in plasma using a HPLC method (15). The main steps of the assay involve extraction of the two components from alkalized plasma with dichloromethane, followed by chromatographic separation with a reverse phase system and quantitation by uv detection.

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The detection limits for the quantitation of moclobemide and Ro 12-8095 in plasma were 20 and 40 ng/ml, respectively, starting with 0.5 ml of plasma. The intra-assay reproducibility for the quantitation of these compounds in plasma, calculated from quality control samples, ranged from 3 to 8% over the concentration range of 30 to 2,400 ng/ml.

3.8. Pharmacokinetic Data Analysis

Plasma concentration-time data for moclobemide and its metabolite were analyzed by noncompartmental methods. The data in the terminal post-absorptive, post-distributive phases were analyzed by linear regression to obtain the terminal disposition rate constant (β) from which the half-life ($t_{1/2}$) was calculated ($\ln 2/\beta$). The total area under the plasma concentration-time curve (AUC) was determined by the linear trapezoidal rule with extrapolation from the last measured concentration on the regression line (C_n) to time infinity (C_n/β). Systemic clearance (CLs) and steady-state volume of distribution (Vss) were determined from the iv data by,

$$CLs = iv \text{ dose}/AUC$$

$$Vss = [(iv \text{ dose} \cdot AUMC)/(AUC)^2] - [(iv \text{ dose} \cdot T)/(2 \cdot (AUC))]$$

where AUMC is the total area under the first moment of the plasma concentration-time curve and T is the duration of infusion. The mean residence time (MRT) following iv infusion was determined from,

$$MRT = [AUMC/AUC] - [T/2]$$

The mean residence time of the metabolite, Ro 12-8095, was determined from the iv data for moclobemide and metabolite from the relationship (18),

$$MRT (\text{metabolite}) = [AUMC/AUC] \text{ metabolite} - [AUMC/AUC] \text{ moclobemide}$$

The maximum plasma concentration (C_{max}) and the time of its occurrence (T_{max}) were determined directly from the data. The absolute oral bioavailability of moclobemide (F_{obs}) was determined from,

$$F_{obs} = [(AUC)_{oral}/(AUC)_{iv}] \cdot [(dose)_{iv}/(dose)_{oral}]$$

Apparent oral clearance (CL_o) was determined as the ratio of oral dose to the corresponding AUC.

Predicted values for the absolute oral bioavailability of moclobemide were calculated from the iv data ($F_{pred:iv}$) and the oral data ($F_{pred:oral}$),

$$F_{pred:iv} = 1 - [CLs/Q_h]$$

$$F_{pred:oral} = [(Q_h)/(Q_h + CL_o)]$$

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where Q_h is liver blood flow (assumed to be 90 L/hr) and assuming that CL_s is equal to hepatic clearance.

The total AUCs on days 15 and 22 of the study (at steady-state) were determined from,

$$AUC = (AUC)^{0-6} - C^0/\beta + C^6/\beta$$

where C^0 is the concentration just prior to the dose and C^6 is the concentration at the end of the dosing interval. The value of β used was the one determined from the concentration-time data during the dosing interval on either day 15 or 22. Since C^0 was not experimentally measured, it was calculated from a concentration prior to that time by,

$$C^0 = C(\text{previous}) \cdot e^{-\beta \cdot t}$$

where $C(\text{previous})$ is the concentration taken at some time prior to C^0 , and t is the time difference between those two concentrations.

CL_o and $F_{pred:oral}$ were determined from the AUC values calculated on days 15 and 22 using the equations described above.

3.9. Statistical Analysis

Statistical comparisons within a subject were performed on the first vs. the multiple oral dosing data on days 15 and 22 using the paired Students t-test for: β , $T_{1/2}$, AUC and CL_o . However, such comparisons were only made in the cases where a difference between observation days was indicated by a Friedman test. Comparisons among subjects were performed using the unpaired Students t-test. A p-value of <0.05 was suggested to indicate a significant difference.

4. RESULTS

4.1. Adverse Effects

Table 3 summarizes the adverse events reported by the subjects during the course of the study. These effects were noted by only some subjects and only on certain and few occasions. The reported effects appeared to be transient in any one subject for a given effect as they were not present on more than 1 or at most 3 days. Subject 15 reported 9 different events.

The biochemical laboratory values were essentially unchanged prior to and after the completion of the study and these values were within the normal ranges (Appendix 1). Vital signs are reported in Appendix 4.

4.2. Deviations from Protocol

The study was completed using essentially the protocol as described in Study Design (3.5). Upon completion of the study it became apparent that the plasma concentrations of moclobemide following iv dosing were extremely high and totally inappropriate for the dose given, based

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upon the results of previous studies. It appeared that the investigators sampled blood from the same catheter used to infuse the drug. The iv data from that portion of the study, therefore, had to be discarded. Therefore, an iv dose was given to 10 of the subjects (5 young and 5 elderly) after the completion of the original study. That dose then served as the base-line iv study (i.e., comparable to day 1 of the study). In addition, time zero blood samples were not obtained during the dosing intervals on days 15 and 22. The time zero values had to be calculated from a concentration prior to that time. Only 10 of the 20 subjects underwent the phenotyping study. The original 20 subjects initially enrolled completed the study.

4.3. Analytical

All plasma samples were analyzed at least twice and, in some instances, 3 to 5 times. Spiked control plasma samples were analyzed daily together with authentic samples to obtain a measure of reproducibility. The results of the quality control analyses are summarized in Table 2. The results indicate excellent reproducibility for moclobemide and the measured metabolite. The % CV was less than 8% in all cases and the values of % bias are quite small. A representative HPLC chromatogram is shown in Appendix 5.

4.4. Pharmacokinetic Analysis

The moclobemide and metabolite (Ro 12-8095) plasma concentration-time data following the 75 mg iv infusion of moclobemide are presented in Tables 4 and 5 and are shown graphically in Figures 1 to 10. The moclobemide plasma concentration-time data following the first single 100 mg oral dose and during a dosing interval on days 15 and 22 are summarized in Tables 6 to 8, and the corresponding metabolite data are presented in Tables 9 to 11. These data are shown graphically in Figures 11 to 30. The moclobemide and metabolite plasma concentration-time data during the multiple dosing regimen are presented in Tables 12 to 15.

The moclobemide and metabolite concentration-time data were generally quite regular in their graphical display and at least 4 and upto 6 points could be used to estimate the terminal disposition rate constant. The same was true following the first single oral dose (day 8). As a result, the data were generally sufficient to completely characterize disposition and absorption of moclobemide and the disposition of one major metabolite (Ro 12-8095). Fewer points were used in estimating the terminal rate constant of moclobemide and metabolite during the two oral dosing intervals at steady-state (days 15 and 22) since blood samples were obtained for only 6 hours. The resulting estimates must be considered to be only reasonably good approximations of the true value. Furthermore, it was necessary to calculate a time zero concentration at the beginning of the dosing intervals since a sample was not obtained at that time. This was done by multiplying the concentration prior to time zero by the exponential, $e^{-\beta t}$, where β was the value estimated during the interval and t was the time between that concentration and at time zero. Both

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of the above approximations add error to the estimates of AUC which were obtained during each of the two dosing intervals.

The analysis of the iv experiments conducted in only 5 young and 5 elderly subjects is summarized in Table 16. There was substantial variation among most parameters for both the young and elderly subjects, but there was less variation of the concentration at the end of the infusion, AUC and CLs among the younger subjects. This can be seen with reference to Figure 31 which illustrates the comparisons among $\bar{C}$, V_{ss} , CLs and MRT. In all cases the standard deviations overlap when comparing the two groups. There were no statistically significant differences in any of the parameters when comparing both groups of subjects (Table 21). Figure 32 illustrates the age relationship for the disposition parameters.

Table 17 summarizes the disposition parameters of the metabolite, Ro 12-8095, following the iv infusion of moclobemide. As noted for moclobemide, there is large variation among most parameters in both groups of subjects. There were no significant differences for any of the parameters when comparing the young and elderly subjects (Table 21). The values for C_{max} , $\bar{C}$ and MRT are shown in Figure 33.

The results of the analysis of moclobemide absorption and disposition following the first oral 100 mg dose (day 8) are summarized in Table 18. The analysis of several of these parameters could be compared among 14 elderly and 6 young subjects. The maximum concentration range was greater among the elderly compared to the young subjects and there was a significant difference between the groups ($p < 0.05$; Table 21). In contrast, the average T_{max} values were similar and encompassed an identical range (0.5 to 2.0 hours). The mean absorption time could only be determined in those subjects who received the iv infusion and, while the values were lower in the elderly subjects, there were no significant differences between the groups (Table 21). The comparisons among C_{max} and MAT are shown in Figure 34.

The apparent oral clearance could be calculated for all of the subjects and the elderly had a significantly smaller value for CL_o compared to the young subjects ($p < 0.05$; Table 21). This can be seen with reference to Figure 35. As with MAT, the absolute oral bioavailability of moclobemide could only be determined in subjects who received the iv infusion. There were no significant differences in that parameter between the two groups although the young group had greater variation (Figure 35).

The relationships between C_{max} , MAT, CL_o and F_{obs} and age are illustrated in Figure 36.

Table 19 summarizes the absorption and disposition parameters of moclobemide during the multiple dosing phase of the study. The data for all subjects could be used to compare the two age groups. There were no significant differences between the two groups for a given parameter on day 15 or on day 22 with the exception of CL_o on day 15

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(Table 21). The latter comparison is shown in Figure 35.

Comparisons of the oral data for day 8 versus days 15 and 22 within a group, however, indicate that there are significant changes in C_{max} , β , $T_{1/2}$, AUC and CL_o (Table 22). These comparisons for CL_o and β can be seen graphically in Figure 37. The comparison of CL_o on days 15 and 22 between the elderly and young subjects is illustrated in Figure 35.

The results of the minimum steady-state concentrations of moclobemide and Ro 12-8095 are summarized in Table 20 along with the ratio of those concentrations. There were no significant differences between the two groups with respect to the concentrations or ratio of concentrations (Table 21).

5. DISCUSSION

The purpose of this study was to examine and compare the absorption and disposition of moclobemide among a group of healthy young and elderly subjects. Moclobemide was given as a single iv dose prior to and following a multiple oral dosing regimen of moclobemide. The study design was identical to that used previously in a group of young healthy subjects (8).

The results of this study are not complete. The reason for this situation is the fact that the samples obtained for the iv portions of this study were taken from the same catheter used for drug administration. This resulted in unusually large artifactual values for moclobemide concentrations which could not be relied upon to give accurate results. A single iv dose was therefore given to 5 of the elderly and 5 of the young subjects once more several months after completing the study and the resulting data were used to compare disposition data between the two groups. Thus, several parameters could only be compared between 5 young and 5 elderly subjects (viz., CLs , MRT , $T_{1/2}$, MAT and F). This, of course, represents a small population from which one can only obtain limited information. The data from the multiple oral dosing phases of the study, however, could be analyzed and it permitted a valid comparison between the 14 elderly and 6 young subjects.

Moclobemide disposition parameters following the iv dose to 5 young and 5 elderly subjects are summarized in Table 16. The average age of the elderly group was 71 years (68 to 75 years) and that of the young group was 29 years (22 to 33 years). There were no significant differences between the two groups for any of the parameters listed (Table 21). Figure 31 illustrates the individual data and, as is apparent, there is substantial variation within any given parameter for both groups. In all cases, however, the range of values overlap.

The values obtained here can be compared to those determined in another study where 12 healthy young subjects received a 150 mg iv dose of moclobemide (8). The average and range of ages in that study were 27 years and 21 to 34 years, respectively. The mean values determined in that study were: $T_{1/2}$, 1.60 hr; CLs , 39.4 L/hr; V_{ss} , 84.3

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L; MRT, 2.19 hr. The latter values agree very well with those obtained in the young and elderly subjects in this study and the range of values for any given parameter overlap between the two studies.

The graphical display of the above iv parameters as a function of age is shown in Figure 32. No attempt was made to perform a correlation analysis of these data because there are only a total of 10 points and because the data encompass a small range of ages at either extreme of age. Additional data points covering a larger range of ages would be needed to perform such a meaningful analysis.

One of the metabolites of moclobemide, Ro 12-8095, was quantitated following moclobemide dosing. The disposition parameters of that metabolite are summarized in Table 17 and the individual values are illustrated in Figure 33. As for moclobemide following iv administration, there were no significant differences in the disposition of this metabolite when comparing the 5 elderly and 5 young subjects (Table 21). For all of the parameters of this metabolite shown in Figure 33 (C_{max} , β and MRT) there is overlap for any given parameter between the two groups. The values for C_{max} at the end of infusion are similar to those seen in 12 normal healthy subjects (8) when adjusting for differences in moclobemide dose (75 vs. 150 mg). The average (% CV) C_{max} adjusted for dose was 289 ng/ml (26 % CV) compared to the means reported here for the young (248 ng/ml) and elderly subjects (304 ng/ml). We are not able to calculate the values for T and MRT from the previous study as insufficient data were available and, therefore, comparisons cannot be made with the findings of the present study.

The terminal elimination rate constant of Ro 12-8095 as a function of the terminal elimination rate constant of moclobemide following iv moclobemide dosing is illustrated in Figure 38 for the 5 elderly and 5 young subjects. The slope of this line forced through zero is 0.706 with relatively little variation about the line of regression. Since this slope is less than one, the data suggest that this metabolite is eliminated more slowly than it is formed. Although similar data are not available in normal subjects, the same analysis performed in subjects with renal impairment gave a slope of 0.90 (unpublished) with points randomly distributed about the line of identity (slope = 1.0). Based upon the latter value and the fact that the MRT for Ro 12-8095 was less than the MRT for moclobemide, a tentative conclusion reached was that the metabolite was formation rate-limited. In the present study, albeit based upon fewer points, the smaller slope and the nearly equal MRTs for moclobemide and Ro 12-8095 (Tables 16 and 17) suggest elimination rate-limited elimination of the metabolite. This comparison is flawed by the fact that we are contrasting results from normals with those from renally impaired subjects. An unequivocal conclusion cannot be reached at this time about the precise rate-limiting step for the decline of metabolite Ro 12-8095 concentrations. The terminal elimination rate constant of the metabolite appears to be about equal to or less than that for moclobemide.

Since only 10 subjects out of a total of 20 received the iv dose of

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moclobemide, the analysis of the oral absorption data is incomplete. As a result, values for F and MAT after the first oral dose could only be calculated for the 10 subjects who received the iv dose. Table 18 summarizes the results of the analysis. The average C_{max} of moclobemide after the first single oral dose was greater in the elderly subjects (843 ng/ml) compared to the value in the young subjects (608 ng/ml) and this difference just reached statistical significance ($p < 0.05$; Table 21). The individual values are shown in Figure 34. In contrast, there were no significant differences in T_{max}, D, T_{1/2}, or MAT. The latter value, however, could only be compared in 5 elderly and 5 young subjects and the mean values were close to but were not significantly different. Figure 34 illustrates the values for MAT which gives the impression that absorption rate is more rapid in the elderly subjects. The apparent oral clearance (C_{Lo}) was significantly greater in the young subjects compared to the elderly subjects (79.1 vs. 52.0 L/hr, respectively) as seen in Figure 35 ($p < 0.05$; Table 21). Figure 35 also illustrates the absolute oral bioavailability of moclobemide among the 10 subjects who received the iv dose. There were no significant differences between the two groups with respect to that parameter.

Several of the above absorption parameters can be compared with results obtained in 12 normal young subjects who received the same 100 mg oral dose of moclobemide (8). The values for those parameters in the previous study compared to those in the young subjects in the present study (%CV) are: C_{max}, 549 (39%) vs. 608 (26%) ng/ml; T_{max}, 0.95 (57%) vs. 0.92 (61%) hr; MAT, 0.47 (79%) vs. 1.16 (43%) hr; C_{Lo}, 83.6 (49%) vs. 79.1 (37%) L/hr; F, 0.55 (37%) vs. 0.68 (38%). With the exception of MAT, the values are essentially identical from both studies in normal young subjects. The MAT was considerably smaller in the previous study compared to this study but this may reflect the smaller number of subjects in the present study upon which that average is based.

The greater C_{max} among the elderly subjects compared to the young subjects may reflect a greater rate of absorption based upon the smaller MAT values, although there were no differences in T_{max}. The basis for that argument, however, is somewhat limited because MAT was only determined in 5 of the 14 elderly subjects. Based upon a fairly substantial literature, it is unusual to observe a greater rate of absorption in the elderly compared to young subjects (14). There are numerous factors that would suggest a slower and not a more rapid rate of absorption in the elderly. A more likely explanation for the greater C_{max} is the difference observed in C_{Lo}. The elderly have a significantly smaller C_{Lo} value compared to the young subjects. This would result in a reduced hepatic first-pass effect and lead to a greater C_{max}. In contrast to this suggestion is the observation that there were no differences in the absolute oral bioavailability of moclobemide when comparing the elderly and young subjects. However, the latter comparison, unlike the comparison of C_{Lo}, is based only upon data from 5 elderly subjects. While it is not possible to say with any certainty, it is conceivable that if values for F were available for all of the elderly subjects that there would have been a

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larger value for that parameter compared to the young subjects. Such an observation has been made for the drug propranolol which also undergoes substantial first-pass hepatic metabolism (19). Additional studies might be required to support this suggestion.

A reduced oral clearance in the elderly for drugs with a high hepatic clearance has been noted, as mentioned above, for propranolol but other similar drugs have not been studied in that regard. The reduced oral clearance may be a general observation among the elderly as a result of decreased metabolic efficiency, but to date no general conclusion can be reached. Conclusions with regard to moclobemide absorption in the elderly is necessarily limited by the data obtained in the present study. The elderly may be expected to have somewhat greater maximum concentrations following a single oral dose perhaps as a result of a lower oral clearance but more important will be the Cmax value following multiple oral dosing and this is discussed below.

The relationships between the observed absolute oral bioavailability of moclobemide (Fobs) and the values predicted from the oral data (Fpred:oral) and iv data (Fpred:iv) are shown in Figure 39. Although these data are limited, the oral prediction provides a better relationship to Fobs compared to that seen with the iv prediction. For the former plot there is far less variation about the line of identity compared to the latter graph. This is an observation that we have made in a previous study (8) and, with the exception of one subject who had an unusually large value for Fobs, the oral data appear to provide a good prediction of the observed absolute oral bioavailability of moclobemide after a single oral dose. Furthermore, the data for the elderly and young subjects illustrate similar variability in the oral and iv predictions.

The results of the multiple oral dosing study are summarized in Table 19. Two comparisons need to be made here; elderly vs. young and results as a function of the time of study within each group (i.e., day 8 vs. days 15 and 22). There were no significant differences between the elderly and young group with regard to parameters on day 15 of the study (i.e., after one week of oral dosing) with the exception of CLo which was significantly greater in the young group. There were no significant differences among the parameters on day 22 of the study (two weeks of oral dosing) when comparing both groups. The significant difference in CLo on day 15 is consistent with the results obtained from the first oral dose (day 8). On day 22 of the study the comparison of CLo between the two groups just misses being significantly different. The average of CLo on days 15 and 22 indicates a significantly greater value for the young subjects compared to the elderly. As seen in Figure 35 there is a large amount of variability associated with that average value, especially among the 6 elderly subjects.

Unlike the results of the first oral dose, the Cmax values during multiple dosing on days 15 and 22 were not significantly different between the elderly and young subjects. This would appear to reflect the fact that oral clearance decreases in both groups with continued

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dosing and the fact that the values have become similar. On day 8 the CLo values for the elderly and young were 52.0 and 79.1 L/hr, whereas on days 15 and 22 they were 20.2 and 28.5 and 19.7 and 27.4, respectively. This suggests that moclobemide will accumulate to about the same extent in the elderly and young subjects and produce similar plasma concentrations. Further evidence for this is shown in Table 20 which presents the average minimum steady-state concentrations of moclobemide and the metabolite Ro 12-8095. Although the elderly tended to have greater concentrations, there were no statistically significant differences between the elderly and young groups (Table 21). Nor was there a significant difference in the ratio of the concentrations of the metabolite to moclobemide. The latter ratio was considerably more variable among the elderly subjects (0.49 to 1.91) compared to the young subjects (0.47 to 0.93). This would appear to reflect a greater range of metabolic efficiencies among the elderly in the formation of the metabolite.

The second important comparison that needs to be made is that between the disposition parameters within each group on day 8 compared to days 15 and 22. Friedman's test indicated differences in Cmax, β , $T_{1/2}$, $AUC_{0-\infty}$ and CLo but not in Tmax. Multiple comparisons between observation days for each one of these parameters by the paired t-test are summarized in Table 22. There were significant differences in Cmax, β , $T_{1/2}$, AUC and CLo when comparing day 8 to day 15 and day 8 to day 22. Figure 37 illustrates the values of CLo and β on day 8 compared to the average value on days 15 and 22 for the elderly and young subjects. It is clear that upon multiple dosing oral clearance and β decrease substantially and this happens for both the young and elderly subjects. We have noted the same phenomenon in a similar multiple dosing study among 12 young healthy subjects (8). While the exact mechanism of this effect is not as yet known it would appear to reflect reduced moclobemide clearance as a result of self-inhibition or metabolite-inhibition of metabolism.

In conclusion, we have examined the absorption and disposition of moclobemide in a group of healthy young and elderly subjects following a multiple oral dosing regimen. The study results have been compromised by the fact that the iv data prior to and at the end of the dosing regimen could not be analyzed. As a result, the data are somewhat limited and only 5 young and 5 elderly subjects received an iv dose subsequent to the completion of the study. The results of the study indicate that there were no differences between the young and elderly subjects with regard to the iv disposition parameters of moclobemide or of its metabolite Ro 12-8095. Following the first oral dose, the elderly had a significantly greater Cmax value and smaller CLo compared to the young subjects. The oral clearance on day 15 of the study remained greater in the young subjects, however, there were no other significant differences between the groups for any of the parameters obtained on either days 15 or 22 of the study. In particular there were no significant differences in Cmax values between the two groups. The average minimum steady-state concentrations of moclobemide and Ro 12-8095 during the multiple dosing regimen were not different between the two groups. As noted in a previous study the oral clearance and elimination of moclobemide

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decreased in both groups upon multiple dosing compared to the first oral dose. Based upon these results it would appear that after a given oral dosing regimen elderly subjects will achieve steady-state plasma concentrations of moclobemide similar to those achieved in young subjects. There is no pharmacokinetically-based need to alter the dosing regimen of moclobemide for elderly subjects.

6. DATA RETRIEVAL

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TABLE 1 : Subject Characteristics

Subject Number	Sex ^{a)}	Age yr	Weight kg	Height cm	Phenotype ^{b)}	
					Debrisoquine	Mephenytoin
1	M	74	78	169	ND	ND
2	F	65	69	162	ND	ND
3	F	77	65	165	ND	ND
4	F	65	69	152	ND	ND
5	F	72	70	168	ND	ND
6	M	72	70	158	ND	ND
7 ^{c)}	F	69	46	160	PM	EM
8 ^{c)}	F	68	62	157	EM	EM
9 ^{c)}	F	75	65	159	EM	EM
10 ^{c)}	F	68	70	174	EM	EM
11	F	65	64	157	ND	ND
12	F	66	60	160	ND	ND
13	M	76	60	178	ND	ND
14 ^{c)}	M	73	75	172	EM	EM
Mean		70	66	164		
+ %CV		6	12	5		
Range		65-77	46-78	152-178		
15 ^{c)}	M	30	74	190	EM	EM
16 ^{c)}	M	22	63	184	EM	EM
17	F	31	62	172	ND	ND
18 ^{c)}	F	33	74	174	EM	EM
19 ^{c)}	M	29	65	179	EM	EM
20 ^{c)}	M	29	67	184	EM	EM
Mean		29	68	181		
+ %CV		13	8	4		
Range		22-33	62-74	172-190		

a) M = male, F = female

b) PM = poor metabolizer, EM = extensive metabolizer, ND = not determined

c) Subjects studied once more after completion of initial study (iv infusion)

TABLE 2 : Reproducibility of the Quality Control Plasma Samples

Compound	Concentration Added ng/ml	Number of Samples	Concentration measured		% Bias ^{a)}		
			mean ng/ml	%CV			
Ro 11-1163	40.0 200.0 800.0 2000.0	IV Samples					
		5	41.1	4.0	2.75		
		6	202.0	2.5	1.00		
		6	806.0	1.6	0.75		
		8	2003.0	1.6	0.15		
		Ro 12-8095	6	99.2	2.9	- 0.80	
			6	393.0	1.8	- 1.75	
			8	965.0	2.0	- 3.50	
		Ro 11-1163	32.0 52.5 104.9 139.9 599.4 700.0 750.8 1501.6 2247.8 2400.0	Oral Samples			
				61	32.4	8.0	1.25
15	53.2			7.5	1.33		
12	106.8			7.5	1.81		
59	142.4			5.4	1.79		
62	597.2			1.4	- 0.37		
5	685.2			1.5	- 2.10		
12	743.0			1.5	- 1.04		
16	1490.3			1.6	- 0.75		
64	2234.3			2.8	- 0.60		
Ro 12-8095	52.0 69.9 104.0 299.7 350.0 375.4 750.8 1223.9	12	2329.3	1.8	- 2.95		
		15	50.8	6.7	- 2.31		
		59	70.8	7.5	1.29		
		12	100.4	3.0	- 3.46		
		61	294.8	3.2	- 1.63		
		6	336.9	3.3	- 3.70		
		11	365.5	2.9	- 2.64		
		16	720.3	1.7	- 4.06		
		64	1111.6	2.4	- 9.18		

a) % Bias =
$$\frac{\text{Conc. measured} - \text{Conc. added}}{\text{Conc. added}} \times 100$$

TABLE 3 : Summary of Reported Adverse EventsElderly subjects

Symptom	Patient No.	Day of Treatment
1. Headache	2	03 05
	5	09
	6	02
	8	02 10 18
=====		
2. Fatigue	2	09 16 18
	4	01
	5	02
	8	01 16
=====		
3. Insomnia	3	03
	6	07
	11	05 07
=====		
4. Tinnitus	5	12
	6	12
=====		
5. Dizziness	6	12
=====		
6. Numbness	8	02
=====		

Young Subjects

Symptom	Patient No.	Day of Treatment
1. Fatigue	15	01 09
	18	18
	19	16 18
=====		
2. Headache	15	02 03 05
	17	02 10
=====		
3. Somnolence	15	16
	18	01 02
	19	01 02
=====		
4. Acathisia	15	03 07
=====		
5. Nausea	18	03 07
=====		
6. Dizziness	15	01
=====		
7. Weightlessness	15	01
=====		
8. Agitation	15	03
=====		
9. Numbness	15	18
=====		
10. Stomache	15	02
=====		

TABLE 4 : Plasma Concentrations of Moclobemide (ng/ml) in Five Elderly Subjects (7-14) and in Five Young Subjects (15-20) Following an Intravenous Infusion of 75 mg Moclobemide

Time Hours	Subject No.									
	7	8	9	10	14	15	16	18	19	20
-0.05	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.00	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.08	552	494	392	37	440	568	1038	345	280	992
0.17	1346	725	801	382	1098	1091	1295	590	534	1408
0.25	1959	1424	1070	518	2053	1410	1278	816	914	1584
0.33	2461	1052	1169	664	1516	1748	1324	991	1394	1539
0.50	1369	766	977	692	896	947	717	627	919	763
0.67	1041	560	786	593	807	739	483	524	739	559
0.83	938	529	712	541	729	654	421	468	683	455
1.33	771	395	551	476	562	535	284	404	503	315
2.33	503	248	353	274	421	312	149	265	291	186
3.33	224	107	205	134	249	192	72	159	147	84
4.33	130	61	140	81	192	122	37	106	88	44
5.33	95	42	105	55	141	89	N.D.	73	50	28
6.33	53	25	67	31	109	65	N.D.	51	28	N.D.
8.33	28	N.D.	37	N.D.	64	35	N.D.	26	N.D.	N.D.
10.33	N.D.	N.D.	21	N.D.	42	N.D.	N.D.	N.D.	N.D.	N.D.

N.D. = not detectable

TABLE 5 : Plasma Concentrations of Moclobemide Metabolite, Ro 12-8095 (ng/ml), in Five Elderly Subjects (7-14) and in Five Young Subjects (15-20) Following an Intravenous Infusion of 75 mg Moclobemide

Time Hours	Subject No.									
	7	8	9	10	14	15	16	18	19	20
-0.05	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.00	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.08	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.17	34	43	N.D.	N.D.	N.D.	42	52	N.D.	N.D.	35
0.25	125	168	47	N.D.	42	106	90	N.D.	56	152
0.33	231	152	77	57	79	159	176	69	133	98
0.50	345	300	175	153	137	232	239	122	222	224
0.67	340	278	222	209	203	235	208	128	262	201
0.83	360	310	239	233	207	256	225	141	267	198
1.33	381	327	253	263	247	261	198	179	291	169
2.33	332	290	281	256	269	268	156	191	321	127
3.33	231	206	243	200	246	235	116	187	252	87
4.33	156	131	195	140	219	178	70	158	186	54
5.33	113	89	157	99	185	156	40	131	131	37
6.33	71	59	115	68	159	127	N.D.	105	86	N.D.
8.33	35	N.D.	65	33	104	77	N.D.	56	47	N.D.
10.33	N.D.	N.D.	37	N.D.	71	41	N.D.	38	N.D.	N.D.

N.D. = not detectable

TABLE 6: Plasma Concentrations of Moclobemide (ng/ml) in Elderly Subjects (1-14) and Young Subjects (15-20)
Following the First 100 mg Oral Dose of Moclobemide on Study Day 8¹

Time Hours	Subject No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.00	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.25	36	N.D.	55	N.D.	N.D.	N.D.	23 ²	N.D.	133	200 ²	75	58	N.D.	N.D.	93	N.D.	141	N.D.	N.D.	N.D.
0.50	125	455	507	342	393	433	150	N.D.	571	634	1005	1249	178	1086	647	372	781	N.D.	258	585
0.75	287	1086	841	885	892	754	426	516	838	N.S.	1067	1313	676	1057	807	466	550	173	398	498
1.00	376	828	781	890	860	673	641	485	819	443 ³	1033	1128	577	835	679	372	426	432 ⁴	428	349
2.00	435	532	583	756	1025	406	414	373	560	369	720	648	308	632	519	336	274	582	279	253
3.00	259	231	303	425	678	218	181	165	286	145	391	365	142	355	288	134	80	423	137	91
4.00	167	134	199	261	459	136	110	87	165	83	254	239	86	287	209	95	43	289	76	57
5.00	112	87	127	174	393	97	72	56	144	55	210	189	49	215	139	43	29	198	51	30
6.00	78	64	92	136	299	56	48	32	106	55	N.S.	129	27	155	117	29	N.D.	173	31	N.D.

1 N.D. = not detectable, N.S. = no sample

2 Actual sample time 0.28 hr

3 Actual sample time 1.50 hr

4 Actual sample time 0.97 hr

TABLE 7: Plasma Concentrations of Moclobemide (ng/ml) in Elderly Subjects (1-14) and Young Subjects (15-20) on Study Day 15 Following a Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times A Day¹

Time Hours	Subject No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.00	293	77	380	391	539	207	147	60	257	44	394	388	106	364	254	32	86	355	45	43
0.25	254	56	349 ²	328 ²	504	202	448	243	265	276	624	582	89	475	228	87	162	343	324	96
0.50	423	1058	1339	1351	469	795	1083	1040	1128	869	1346	1753	411	1634	871	629	1226	451	454	724
0.75	594	1385	1499	1410	780	1135	1250	1108	1554	909	1710	1982	738	1375	1225	891	923	1406	758	1016
1.00	821	1306	1562	1454	1629	1163	1196	1029	1481	927	1643	1792	1048	1205	1399	846	1017	1820	757	1058
2.00	1092	1070	1203	1169	1422	985	1060	821	1119	594	1389	1389	964	1034	1108	644	747	1247	617	625
3.00	830	667	720	924	1130	679	621	451	796	368	921	949	617	789	770	406	367	895	473	387
4.00	555	463	552	652	841	531	459	348	624	252	757	771	513	650	612	274	294	678	296	195
5.00	424	369	472	554	781	399	369	243	556	192	730	623	363	529	496	168	231	621	232	168
6.00	424	257	388	447	638	310	275	175	419	143	637	585	273	490	440	113	177	532	173	N.S. ³

1 Values reported at time 0.00 actually correspond to sample times prior to dosing

2 Actual sample time 0.33 hr

3 N.S. = no sample

TABLE 8: Plasma Concentrations of Moclobemide (ng/ml) in Elderly Subjects (1-14) and Young Subjects (15-20) on Study Day 22 Following a Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times A Day¹

Time Hours	Subject No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.00	377	450	249	N.D.	109	N.D.	99	65	245	103	505	217	167	483	281	46	70	762	148	40
0.25	562	528	290	28	110	27	219	240	238	606	544	199	202	491	N.S.	109	78	755	103	47
0.50	1177	1583	1193	1252	631	150	1197	1190	1649	1617	1565	1040	1258	796	620	570	633	1339	278	317
0.75	1310	1911	1525	1201	173	865	1352	1461	1888	1429	1624	1752	1678	1181	614	717	1673	2104	578	746
1.00	1237	1647	1458	1029	317	793	1290	1271	1622	1193	1870	1652	1545	1350	1328	723	1079	2124	1069	685
2.00	1023	1524	1172	1066	1144	630	977	902	1248	772	1557	1352	986	1348	1178	568	689	1567	923	530
3.00	710	955	768	672	867	369	617	469 ²	754	421	969	843	650	876	728	423	437	1284	614	389
4.00	527	632	538	433	693	312	446	364	610	339	822 ³	648	488	736	628	268	339	1081	467	247
5.00	467	523	456	371	569	217	344	262	511	231	856	613	367	599	523	195	260	820	363	176
6.00	369	422	367	290	506	160	277	196	480	197	727	485	317	585	427	143	207	815	282	107

¹ Values reported at time 0.00 actually correspond to sample times prior to dosing. N.D. = not detectable

² Actual sample time 3.13 hr

³ Actual sample time 4.08 hr

TABLE 9: Plasma Concentrations of the Moclobemide Metabolite, Ro 12-8095 (ng/ml), in Elderly Subjects (1-14) and in Young Subjects (15-20) Following the First 100 mg Oral Dose of Moclobemide on Study Day 8¹

Time Hours	Subject No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.00	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
0.25	34	N.D.	N.D.	N.D.	N.D.	N.D.	45 ²	N.D.	49	180 ²	N.D.	N.D.	N.D.	N.D.	37	N.D.	149	N.D.	N.D.	N.D.
0.50	110	323	245	184	127	311	202	N.D.	265	494	323	489	262	300	239	270	572	N.D.	250	456
0.75	252	792	523	479	271	578	450	492	451	N.S.	466	645	766	384	413	458	564	91	437	481
1.00	350	846	525	569	320	634	649	702	490	540 ³	587	678	806	391	385	371	499	223 ⁴	516	374
2.00	501	739	499	671	538	511	539	687	449	498	663	634	674	402	455	380	365	478	472	272
3.00	406	533	377	575	500	363	307	415	341	280	602	534	436	351	391	213	189	478	292	138
4.00	299	391	284	426	448	256	193	263	244	187	500	435	301	307	332	156	115	409	219	80
5.00	225	295	210	324	423	173	123	182	216	151	467	373	197	254	256	89	68	337	151	54
6.00	172	226	157	258	350	114	91	110	145	107	N.S.	307	125	209	230	52	40	294	104	N.D.

1 N.D. = not detectable, N.S. = no sample

2 Actual sample time 0.28 hr

3 Actual sample time 1.50 hr

4 Actual sample time 0.97 hr

TABLE 10: Plasma Concentrations of the Moclobemide Metabolite, Ro 12-8095 (ng/ml), in Elderly Subjects (1-14) and in Young Subjects (15-20) on Study Day 15 Following a Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times A Day¹

Time Hours	Subject No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.00	247	212	215	354	433	205	117	158	187	50	242	323	239	238	197	33	71	252	52	N.D.
0.25	219	185	177	304	427	210	168	169	179	122	229	343	214	242	182	48	81	276	132 ²	38
0.50	269	421	343	496	393	331	329	416	261	344	314	482	308	393	251	214	359	288	193	157
0.75	287	558	420	542	466	441	403	528	354	409	387	564	409	393	303	348	336	381	298	241
1.00	329	614	451	583	584	468	413	561	370	450	396	572	550	383	369	379	388	472	322	273
2.00	454	815	447	597	640	507	459	612	373	383	454	591	686	392	385	357	372	457	340	222
3.00	446	755	382	560	615	439	354	540	367	319	419	543	658	371	360	290	265	419	333	167
4.00	404	686	339	479	582	402	274	470	319	246	388	494	576	323	322	211	208	407	247	98
5.00	350	646	320	460	568	335	233	391	318	197	380	429	516	307	281	130	186	397	219	97
6.00	339	534	269	383	506	269	195	340	253	159	335	410	427	280	283	97	153	341	178	N.S.

¹ Values reported at time 0.00 actually correspond to sampling times prior to dosing. N.D. = not detectable, N.S. = no sample

² Actual sample time 0.33 hr

TABLE 11: Plasma Concentrations of the Moclobemide Metabolite, Ro 12-8095 (ng/ml), in Elderly Subjects (1-14) and in Young Subjects (15-20) on Study Day 22 Following a Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times A Day¹

Time Hours	Subject No.																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.00	287	518	200	N.D.	149	N.D.	87	117	223	112	299	158	291	290	222	33	60	478	164	N.D.
0.25	306	516	198	N.D.	143	N.D.	106	163	198	220	255	139	294	280	N.S.	48	63	479	126	N.D.
0.50	432	663	341	301	253	154	332	401	359	462	365	273	513	314	274	166	163	521	171	115
0.75	490	799	435	343	161	399	424	562	449	522	382	396	647	381	288	262	426	557	257	243
1.00	472	825	462	394	209	441	449	550	449	486	421	443	724	423	389	274	388	647	392	244
2.00	540	870	465	540	445	441	448	534	457	433	488	484	689	461	478	262	316	587	450	228
3.00	471	782	406	452	504	356	374	470	408	330	461	428	622	421	405	210	283	628	418	198
4.00	427	633	346	400	470	303	297	388	354	304	432	375	549	372	376	167	235	608	357	130
5.00	387	603	320	359	427	244	238	335	328	223	424	338	479	330	337	120	190	499	313	98
6.00	338	519	262	307	405	201	201	284	321	194	407	296	424	337	285	96	156	488	278	65

1 Values reported at time 0.00 actually correspond to sampling times prior to dosing. N.D. = not detectable, N.S. = no sample

2 Actual sample time 3.13 hr

3 Actual sample time 4.08 hr

TABLE 12: Trough Levels of Moclobemide (ng/ml) on Days 8-15, 16-22 in Fourteen Elderly Subjects
During a 15 Day Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times a Day

Days	Time hours	Subject No.													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
8	12	167	137	194	246	500	126	80	49	204	86	220	270	67	232
9	36	321	330	342	770	1013	580	564	769	369	226	669	590	1003	947
11	84	555	443	615	605	1269	486	664	199	409	336	1218	588	418	1024
13	132	552	1324	580	110	1021	48	768	604	407	267	668	925	840	662
15	180	567	427	538	601	731	391	389	246	515	184	624	635	338	750
16	204	617	743	828	826	998	601	783	160	733	935	748	590	348	415
18	252	942	795	604	616	953	308	533	270	752	155	1139	578	499	1007
20	300	1024	1083	691	125	535	53	167	289	593	273	662	129	560	959
22	348	545	662	752	616	959	364	343	236	560	258	689	496	362	704

TABLE 13: Trough Levels of Moclobemide (ng/ml) on Days 8-15, 16-22 in Six Healthy Subjects
During a 15 Day Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times a Day

Days	Time hours	Subject No.					
		15	16	17	18	19	20
8	12	188	33	52	222	58	31
9	36	361	81	102	626	147	120
11	84	626	510	342	951	222	83
13	132	834	416	727	1677	414	374
15	180	531	113	162	619	193	122
16	204	701	666	541	809	286	342
18	252	670	704	445	755	619	739
20	300	828	326	678	939	277	528
22	348	415	128	213	784	270	133

TABLE 14: Trough Levels of the metabolite, Ro 12-8095 (ng/ml), in Fourteen Elderly Subjects
During a 15 Day Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times a Day

Days	Time hours	Subject No.													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
8	12	238	338	195	367	466	161	117	166	193	144	406	360	175	251
9	36	321	698	307	622	636	447	469	931	254	278	535	528	986	409
11	84	472	674	388	516	666	362	455	501	338	407	433	456	633	493
13	132	532	940	337	174	649	59	442	928	288	316	336	495	853	380
15	180	363	624	292	412	534	288	233	412	312	194	356	412	464	350
16	204	413	958	432	494	666	422	440	497	462	740	415	335	552	249
18	252	452	1015	360	484	625	337	352	537	440	249	402	390	664	450
20	300	467	960	393	145	489	82	119	514	411	347	320	134	739	457
22	348	402	613	410	489	493	353	234	336	362	224	436	339	517	364

TABLE 15: Trough Levels of Metabolite, Ro 12-8095 (ng/ml), in Six Healthy Subjects
During a 15 Day Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times a Day

Days	Time hours	Subject No.					
		15	16	17	18	19	20
8	12	288	52	84	343	137	44
9	36	399	124	150	452	240	121
11	84	336	393	321	483	300	61
13	132	406	341	425	679	366	180
15	180	301	98	144	384	179	72
16	204	341	469	407	429	309	158
18	252	397	382	289	463	519	266
20	300	460	238	358	450	284	288
22	348	262	105	174	491	243	89

TABLE 16: Moclobemide Disposition Parameters in Young and Elderly Subjects
Following a 75 mg i.v. Infusion of Moclobemide

Subject Number	Age yr	C_T^a ng/ml	β hr^{-1}	$T_{1/2}$ hr	AUC_0^∞ ng.hr/ml	$AUMC_0^\infty$ ng.hr ² /ml	CL_s L/hr	V_{ss} L	MRT^b hr
7	69	2461	0.416	1.67	3040	5867	24.7	43.5	1.76
8	68	1052	0.563	1.23	1533	2576	48.9	74.0	1.51
9	75	1169	0.345	2.01	2319	5826	32.3	75.9	2.35
10	68	664	0.542	1.28	1505	3080	49.8	93.7	1.88
14	73	1516	0.257	2.69	2915	9188	25.7	76.8	2.99
Mean	71	1372	0.425	1.63 ^c	2262	5307	36.3	72.8	2.10
$\pm$ % CV	4.5	49.6	30.6	30.6	32.3	49.9	33.9	25.0	27.8
Median	69	1169	0.416	1.67	2319	5826	32.3	75.9	1.88
Range	68-75	664-2461	0.257-0.563	1.23-2.69	1505-3040	2576-9188	24.7-49.8	43.5-93.7	1.51-2.99
15	30	1748	0.359	1.93	2298	5272	32.6	69.5	2.13
16	22	1324	0.698	0.99	1296	1591	57.9	61.4	1.06
18	33	991	0.361	1.92	1695	4206	44.3	102.3	2.31
19	29	1394	0.581	1.19	1812	3222	41.4	66.7	1.61
20	29	1539	0.634	1.09	1485	1950	50.5	57.9	1.15
Mean	29	1399	0.527	1.31 ^c	1717	3248	45.3	71.6	1.65
$\pm$ % CV	14.1	20.0	30.0	29.9	22.1	47.3	21.0	24.9	33.9
Median	29	1394	0.581	1.19	1695	3222	44.3	66.7	1.61
Range	22-33	991-1748	0.359-0.698	0.99-1.93	1296-2298	1591-5272	32.6-57.9	57.9-102.3	1.06-2.31

a C_T = concentration at the end of infusion

b MRT = mean residence time

c Harmonic mean. % CV based upon the "pseudo" standard deviation (reference 20)

TABLE 17: Disposition Parameters of the Moclobemide Metabolite Ro 12-8095 in Young and Elderly Subjects Following a 75 mg i.v. Infusion of Moclobemide

Subject Number	Age yr	C _{max} ng/ml	β hr ⁻¹	T _{1/2} hr	AUC ₀ [∞] ng.hr/ml	AUMC ₀ [∞] ng.hr ² /ml	MRT hr
7	69	381	0.377	1.84	1627	5365	1.37
8	68	327	0.402	1.72	1374	4360	1.49
9	75	281	0.281	2.46	1696	7893	2.19
10	68	263	0.361	1.92	1264	4697	1.67
14	73	269	0.190	3.65	2137	13521	3.18
Mean	71	304	0.322	2.15 ^a	1620	7167	1.98
± % CV	4.5	16.4	26.9	26.0	20.9	53.2	37.4
Median	69	281	0.361	1.92	1627	5365	1.67
Range	68-75	263-381	0.190-0.402	1.72-3.65	1264-2137	4360-13521	1.37-3.18
15	30	268	0.243	2.86	1796	8745	2.58
16	22	239	0.532	1.30	769	2012	1.39
18	33	187	0.246	2.82	1362	7277	2.86
19	29	321	0.342	2.03	1609	6264	2.11
20	29	224	0.389	1.78	674	1941	1.57
Mean	29	248	0.350	1.98 ^a	1242	5248	2.10
± % CV	14.1	20.3	34.1	36.4	40.3	59.3	30.0
Median	29	239	0.342	2.03	1362	6264	2.11
Range	22-33	187-321	0.243-0.532	1.30-2.86	674-1796	1941-8745	1.39-2.86

a Harmonic mean. % CV based upon the "pseudo" standard deviation (reference 20)

TABLE 18: Moclobemide Absorption and Disposition Parameters in Young and Elderly Subjects Following the First Single 100 mg Oral Dose of Moclobemide

Subject Number	Age yr	C _{max} ng/ml	T _{max} hr	β hr ⁻¹	T _{1/2} hr	AUC _{0-∞} ng.hr/ml	AUMC _{0-∞} ² /n1	MAT ^a hr	CL ₀ L/hr	F
1	74	435	2.00	0.401	1.73	1544	5042	-	64.8	-
2	65	1086	0.75	0.428	1.62	2032	4872	-	49.2	-
3	77	841	0.75	0.456	1.52	2260	6011	-	44.2	-
4	65	890	1.00	0.383	1.81	2854	8751	-	35.0	-
5	72	1025	2.00	0.262	2.65	4573	20673	-	21.4	-
6	72	754	0.75	0.478	1.45	1693	4228	-	59.1	-
7	69	641	1.00	0.441	1.57	1451	3697	0.79	68.9	0.36
8	68	516	0.75	0.597	1.15	1156	2744	0.86	86.5	0.56
9	75	838	0.75	0.311	2.23	2428	7463	0.72	41.2	0.79
10	68	634	0.50	0.627	1.11	1322	2783	0.23	75.6	0.66
11	65	1067	0.75	0.481	1.44	2945	7428	-	34.0	-
12	66	1313	0.75	0.389	1.73	3162	8505	-	31.6	-
13	76	676	0.75	0.592	1.17	1188	2562	-	84.2	-
14	73	1086	0.50	0.332	2.09	3057	9986	0.28	32.7	0.77
Mean	70	592	0.93	0.441	1.57 ^b	2269	6768	0.58	52.0	0.63
± % CV	6.1	29.8	51.0	24.6	24.3	43.9	69.1	51.3	40.6	28.6
Median	71	840	0.15	0.435	1.60	2142	5527	0.72	46.7	0.66
Range	65-77	435-1313	0.50-2.00	0.202-0.627	1.11-2.65	1155-4673	2562-20673	0.23-0.86	21.4-86.5	0.36-0.79
15	30	807	0.75	0.311	2.23	2377	7742	1.13	42.1	0.78
16	22	466	0.75	0.537	1.29	1097	2526	1.24	91.2	0.63
17	31	781	0.50	0.722	0.95	1052	1723	-	95.1	-
18	33	582	2.00	0.307	2.26	2408	10272	1.96	41.5	1.07
19	29	428	1.00	0.537	1.29	1026	2423	0.75	97.5	0.43
20	29	585	0.50	0.642	1.03	931	1763	0.74	107.4	0.47
Mean	29	608	0.92	0.509	1.35 ^b	1482	4408	1.16	79.1	0.66
± % CV	12.9	25.8	61.2	33.4	33.3	47.7	83.2	42.9	37.2	38.3
Median	30	584	0.75	0.537	1.29	1075	2475	1.13	93.2	0.63
Range	22-33	428-807	0.50-2.00	0.311-0.722	0.96-2.26	931-2408	1723-10272	0.74-1.96	42.1-107.4	0.43-1.07

a MAT = mean absorption time

b Harmonic mean. % CV based upon the "pseudo" standard deviation (reference 20)

TABLE 19: Moclobemide Absorption and Disposition Parameters in Young and Elderly Subjects on Days
15 and 22 of a Multiple Oral Dosing Regimen of 100 mg Moclobemide Three Times a Day

Subject Number	Age yr	C_{max} , ng/ml		T_{max} , hr		p , hr ⁻¹		$T_{1/2}$, hr		AUC_0 , ng.hr/ml		CL_o , L/hr	
		d 15	d 22	d 15	d 22	d 15	d 22	d 15	d 22	d 15	d 22	d 15	d 22
1	74	1092	1310	2.00	0.75	0.336	0.246	2.06	2.82	4362	4679	22.9	21.4
2	65	1385	1911	0.75	0.75	0.344	0.264	2.01	2.63	4744	6039	21.1	16.6
3	77	1562	1525	1.00	0.75	0.201	0.284	3.45	2.44	5414	5280	18.5	18.9
4	65	1454	1252	1.00	0.50	0.243	0.320	2.85	2.17	5858	4786	17.1	20.9
5	72	1629	1144	1.00	2.00	0.197	0.181	3.52	3.83	7093	6130	14.1	16.3
6	72	1163	865	1.00	0.75	0.284	0.327	2.44	2.12	4508	2844	22.2	35.2
7	69	1250	1352	0.75	0.75	0.266	0.311	2.61	2.23	4754	4649	21.0	21.5
8	68	1108	1461	0.75	0.75	0.371	0.370	1.87	1.87	3541	4036	28.2	24.8
9	75	1554	1888	0.75	0.75	0.232	0.153	2.99	4.53	5919	7034	16.9	14.2
10	68	927	1617	1.00	0.50	0.350	0.333	1.98	2.08	2871	3859	34.8	25.9
11	65	1710	1870	0.75	1.00	0.114	0.084	6.08	8.25	8582	10117	11.7	9.9
12	66	1982	1752	0.75	0.75	0.166	0.171	4.17	4.05	7585	7303	13.2	13.7
13	76	1048	1678	1.00	0.75	0.305	0.284	2.27	2.44	4179	4995	23.9	20.0
14	73	1634	1350	0.50	1.00	0.189	0.142	3.67	4.68	5685	6247	17.6	16.0
Mean	70	1393	1498	0.93	0.84	0.257	0.248	2.70 ^a	2.79 ^a	5364	5571	20.2	19.7
± % CV	6.1	21.8	20.6	37.2	43.1	30.4	35.0	30.4	34.6	29.4	32.3	30.5	31.8
Median	71	1420	1493	0.88	0.75	0.255	0.274	2.73	2.54	5084	5138	19.8	19.5
Range	65-77	927-1982	865-1911	0.50-2.00	0.50-2.00	0.114-0.371	0.084-0.370	1.87-6.08	1.87-8.25	2871-8582	2844-10117	11.7-34.8	9.9-35.2
15	30	1399	1328	1.00	1.00	0.229	0.178	3.03	3.89	5673	5692	17.6	17.6
16	22	891	723	0.75	1.00	0.436	0.353	1.59	1.96	2677	2639	37.4	37.9
17	31	1226	1673	0.50	0.75	0.243	0.292	2.85	2.37	3409	3583	29.3	27.9
18	33	1820	2124	1.00	1.00	0.207	0.176	3.35	3.94	6525	8245	15.3	12.1
19	29	758	1069	0.75	1.00	0.326	0.290	2.13	2.39	2967	3959	33.7	25.3
20	29	1058	746	1.00	0.75	0.463	0.399	1.50	1.74	2676	2307	37.4	43.4
Mean	29	1192	1277	0.83	0.92	0.317	0.281	2.19 ^a	2.47 ^a	3988	4404	28.5	27.4
± % CV	12.9	32.2	43.0	24.6	14.0	34.8	32.2	35.8	32.2	42.1	50.6	34.3	43.2
Median	30	1142	1199	0.88	1.00	0.285	0.291	2.49	2.38	3188	3771	31.5	26.6
Range	22-33	758-1820	723-2124	0.50-1.00	0.75-1.00	0.207-0.463	0.176-0.399	2.13-3.35	1.74-3.94	2676-6525	2307-8245	15.3-37.4	12.1-43.4

^a Harmonic mean, % CV based upon the "pseudo" standard deviation (reference 20)

TABLE 20: Minimum Steady-State Plasma Concentrations of Moclobemide and Metabolite (Ro 12-8095) During the Multiple Oral Dosing Regimen^a

Subject Number	Minimum steady-state conc. ($\pm$ S.D.), ng/ml		Ratio Ro 12-8095/Moclobemide
	Moclobemide	Ro 12-8095	
<u>Elderly</u>			
1	739 (226)	419 (41)	0.57
2	742 (237)	834 (198)	1.12
3	683 (115)	377 (55)	0.55
4	557 (259)	405 (149)	0.73
5	835 (198)	561 (80)	0.67
6	343 (197)	296 (129)	0.86
7	443 (231)	276 (123)	0.62
8	240 (49)	459 (84)	1.91
9	631 (106)	397 (61)	0.63
10	361 (325)	351 (225)	0.97
11	772 (210)	386 (47)	0.50
12	486 (206)	322 (110)	0.66
13	421 (101)	587 (112)	1.39
14	767 (236)	374 (85)	0.49
Mean	573	432	0.83
% CV	33.3	33.7	48.2
Median	594	392	0.67
Range	240-835	276-834	0.49-1.91
<u>Young</u>			
15	629 (160)	352 (78)	0.56
16	387 (285)	258 (165)	0.67
17	408 (218)	274 (114)	0.67
18	781 (115)	443 (40)	0.57
19	329 (166)	307 (128)	0.93
20	372 (264)	175 (99)	0.47
Mean	484	302	0.64
$\pm$ CV	37.1	30.1	25.0
Median	398	291	0.62
Range	329-781	175-443	0.47-0.93

^a Each value is the average of 5 determinations made during the second week of dosing. The samples were obtained prior to the third daily dose on days 8, 9, 11, 13 and 15.

TABLE 21: Unpaired Statistical Comparison of Moclobemide and Metabo-
lite (Ro 12-8095) Absorption and Disposition Parameters:
Elderly vs Young Subjects

Level of Significance ^a Parameter (p value)		Level of Significance ^a Parameter (p value)	
I.V. Moclobemide		Oral Moclobemide on Day 15	
C_T	ns	C_{max}	ns
β	ns	T_{max}	ns
$T_{1/2}$	ns	β	ns
AUC_o^∞	ns	$T_{1/2}$	ns
$AUMC_o^\infty$	ns	AUC_o^∞	ns
CL_s	ns	CL_o	< 0.05
V_{ss}	ns		
MRT	ns		
Ro 12-8095 Following I.V. Moclobemide		Oral Moclobemide on Day 22	
C_{max}	ns	C_{max}	ns
β	ns	T_{max}	ns
$T_{1/2}$	ns	β	ns
AUC_o^∞	ns	$T_{1/2}$	ns
$AUMC_o^\infty$	ns	AUC_o^∞	ns
MRT	ns	CL_o	ns
Oral Moclobemide on Day 8		Moclobemide } ns	
C_{max}	< 0.05	$C_{min.ss}$	
T_{max}	ns	Ro 12-8095 } ns	
β	ns	$C_{min.ss}$	
$T_{1/2}$	ns	Ratio of } ns	
AUC_o^∞	ns	Ro 12-8095	
$AUMC_o^\infty$	ns	$C_{min.ss} /$	
MAT	ns	Moclobemide	
CL_o	< 0.05	$C_{min.ss}$	
F	ns		

a Based upon the unpaired Student's t-test

TABLE 22: Paired Statistical Comparison of Moclobemide Absorption and Disposition Parameters: First Oral Dose (d 8) vs Oral Multiple Doses (d 15 and 22)

Parameter	Level of Significance ^a (p value)	
	<u>Elderly</u>	<u>Young</u>
C _{max} : d 8 <u>vs</u> d 15	<0.001	<0.01
	d 8 <u>vs</u> d 22	<0.001
T _{max} :	ns	ns
β : d 8 <u>vs</u> d 15	<0.001	<0.05
	d 8 <u>vs</u> d 22	<0.001
T _{1/2} : d 8 <u>vs</u> d 15	<0.001	<0.02
	d 8 <u>vs</u> d 22	<0.005
AUC ₀ [∞] : d 8 <u>vs</u> d 15	<0.001	<0.005
	d 8 <u>vs</u> d 22	<0.001
CL ₀ : d 8 <u>vs</u> d 15	<0.001	<0.005
	d 8 <u>vs</u> d 22	<0.001

a Based upon the Student's paired t-test

Figures 1-4 : Plasma concentration-time profiles of moclobemide (*—*) and Ro 12-8095 (▽...▽) following a 75 mg intravenous infusion of moclobemide.

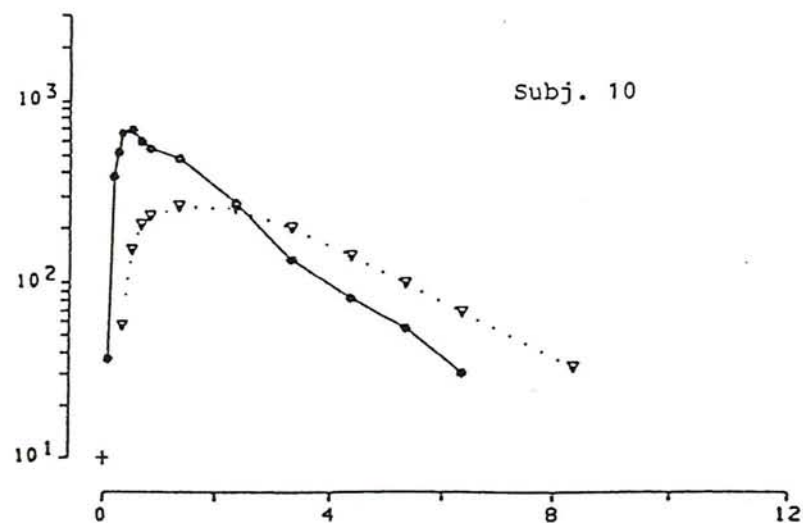
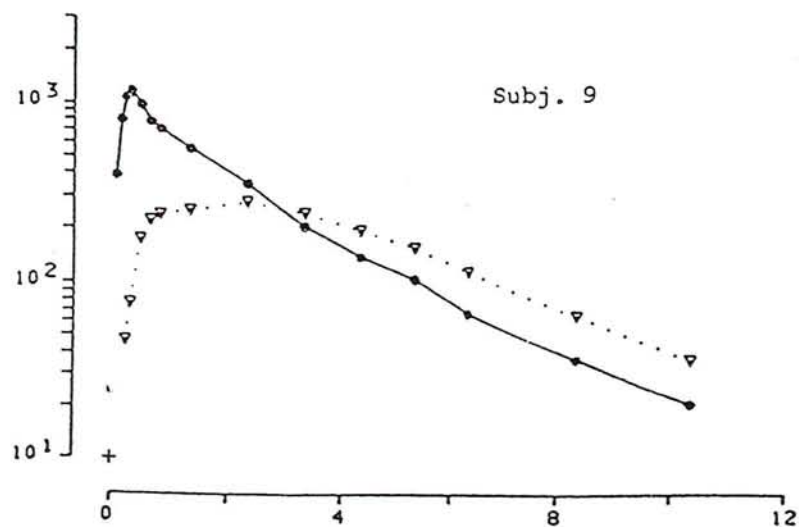
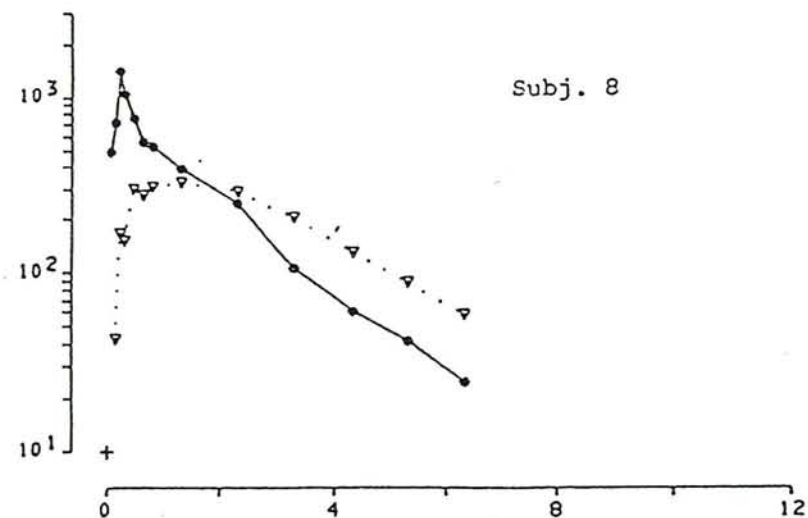
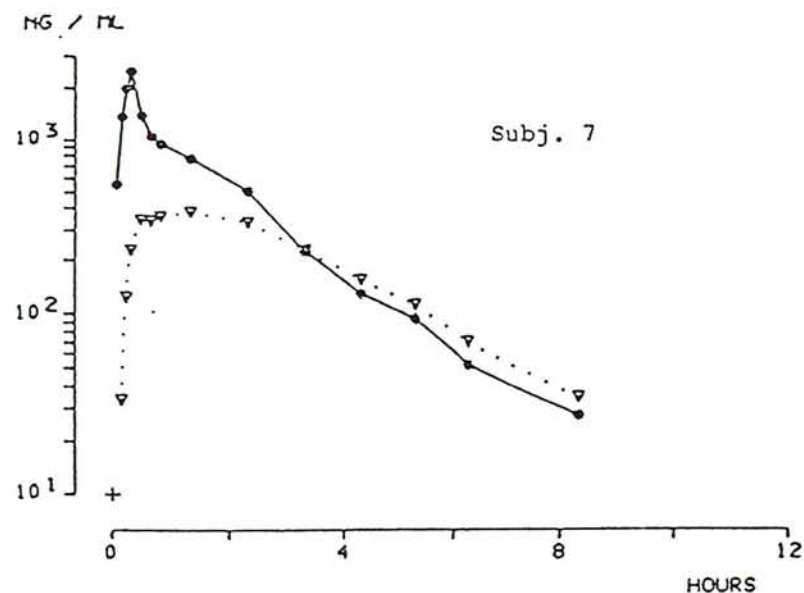
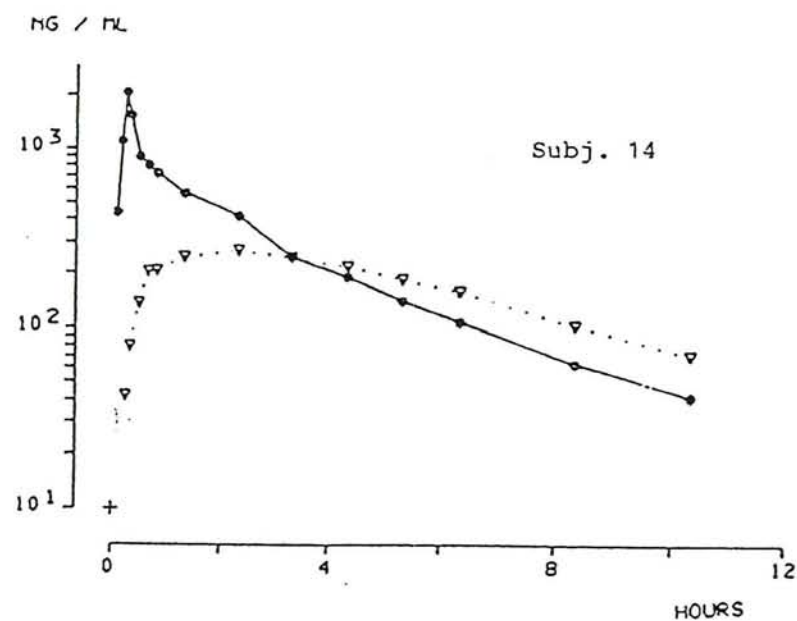


Figure 5 : Plasma concentration-time profiles of moclobemide (*—*) and Ro 12-8095 (▽...▽) following a 75 mg intravenous infusion of moclobemide.



Figures 6-9 : Plasma concentration-time profiles of moclobemide (*—*) and Ro 12-8095 (▽...▽) following a 75 mg intravenous infusion of moclobemide.

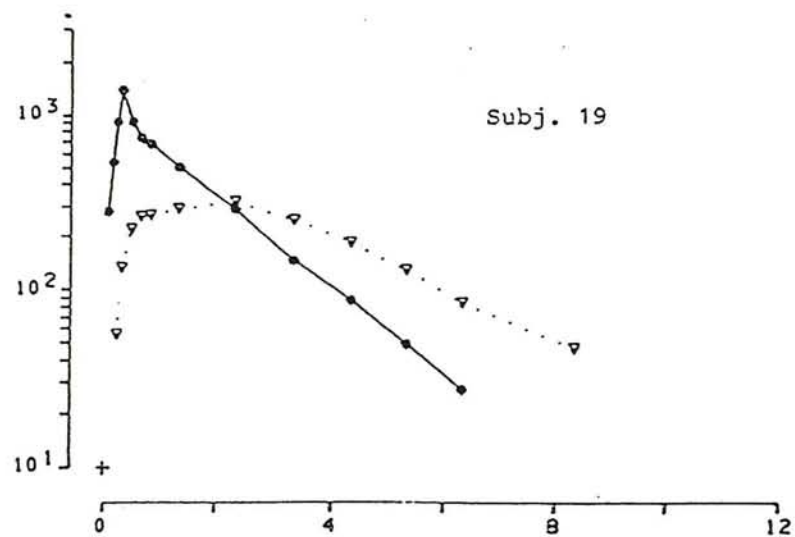
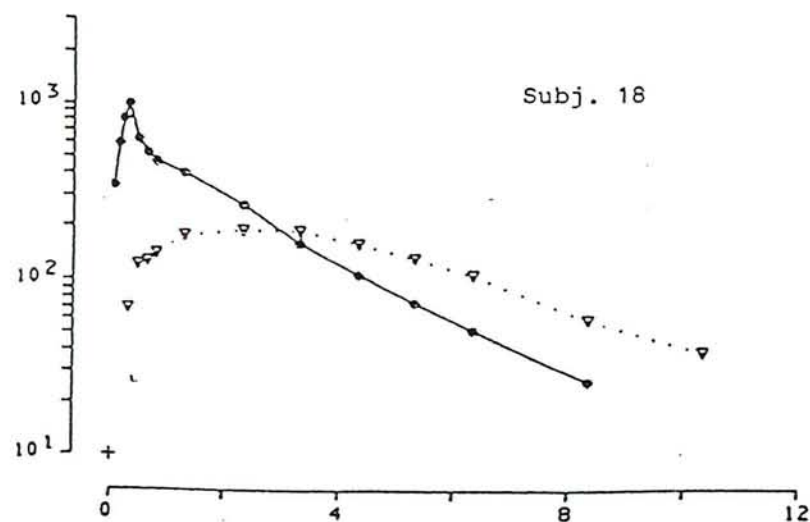
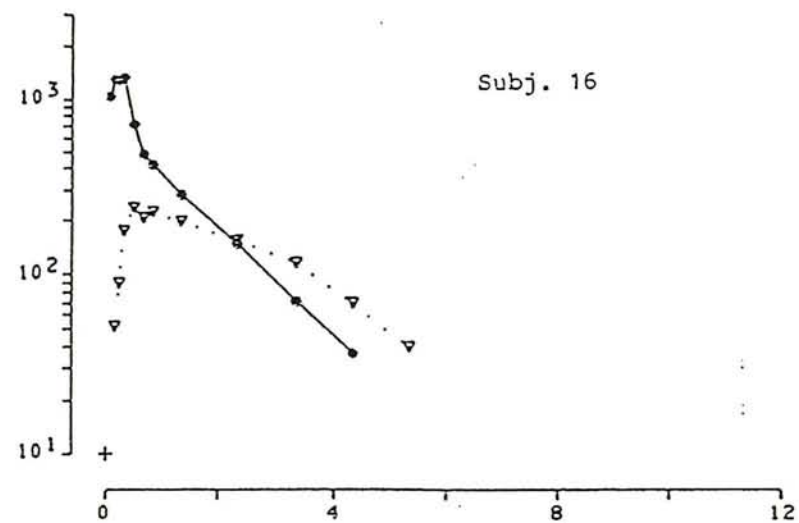
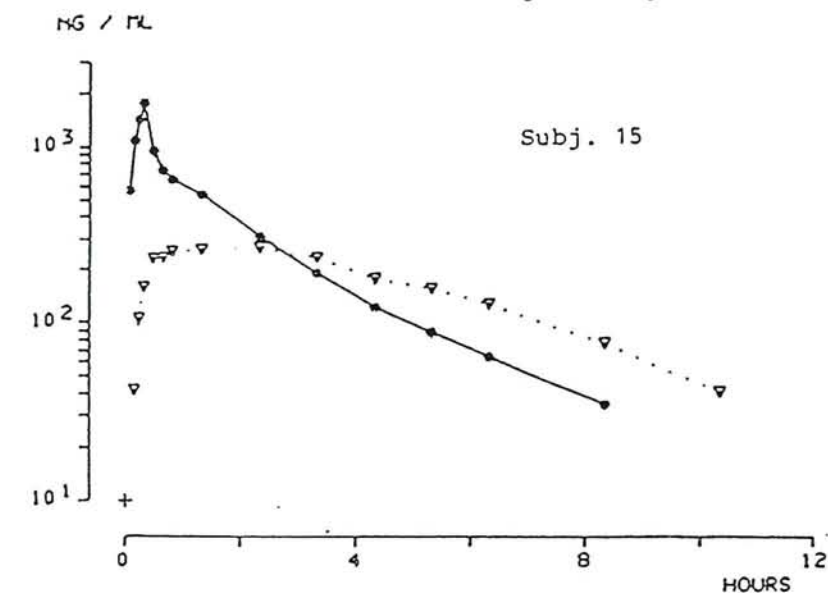
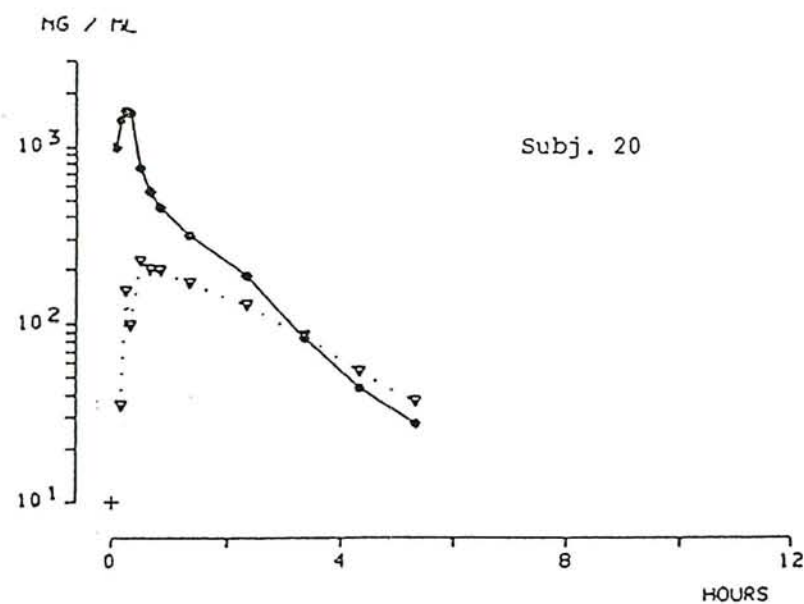
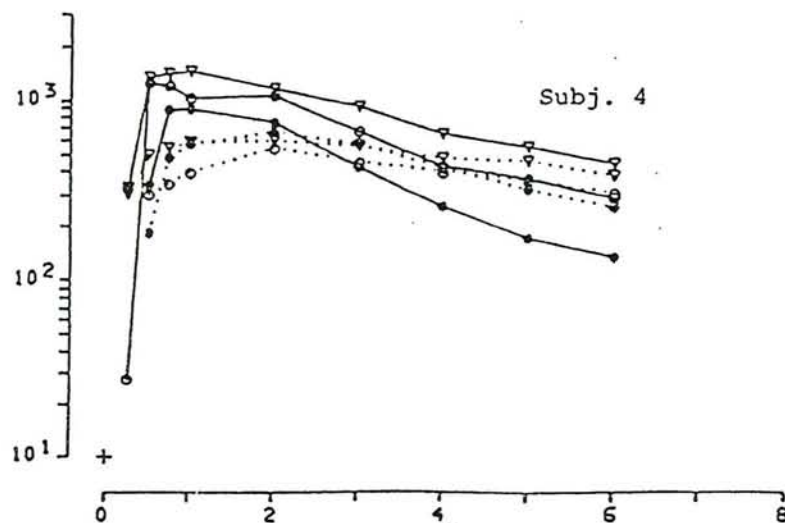
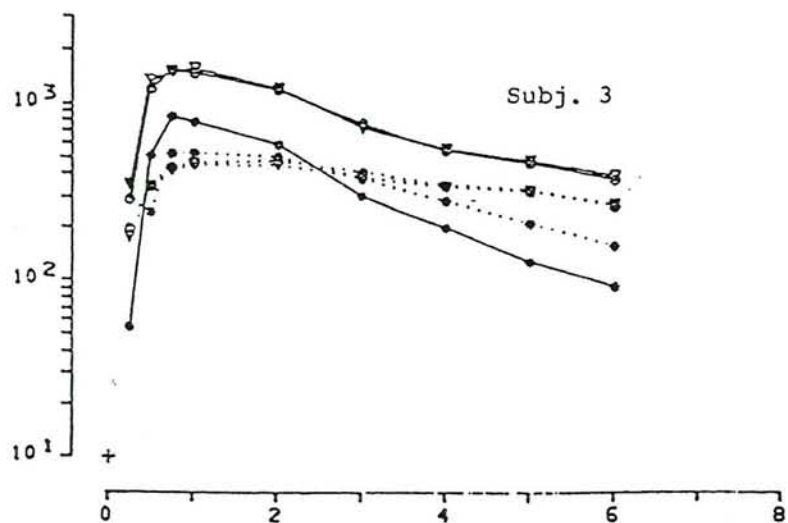
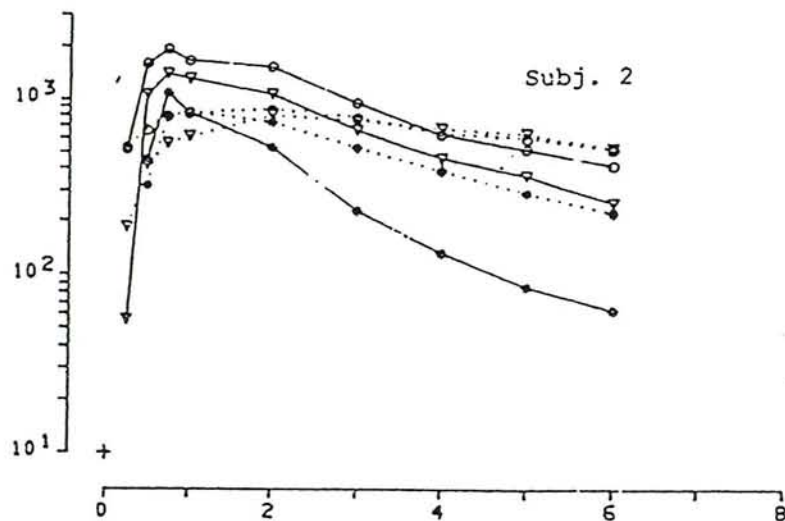
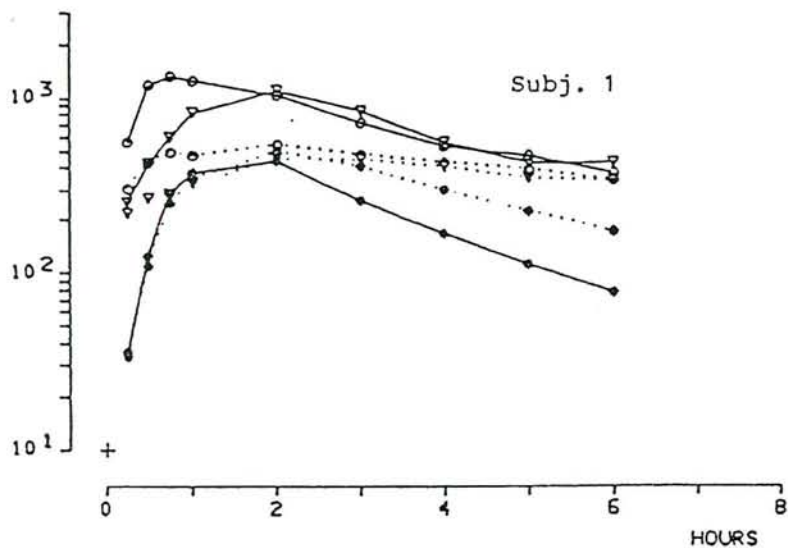


Figure 10 : Plasma concentration-time profiles of moclobemide (*—*) and Ro 12-8095 (▽...▽) following a 75 mg intravenous infusion of moclobemide.



Figures 11-14 : Plasma concentration-time profiles of moclobemide and Ro 12-8095 on days 8, 15 and 22 following a multiple oral dosing regimen of moclobemide.

MG / ML



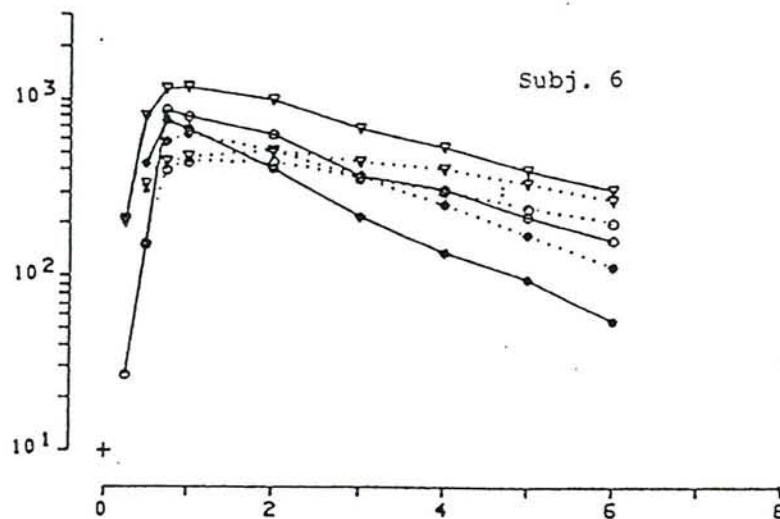
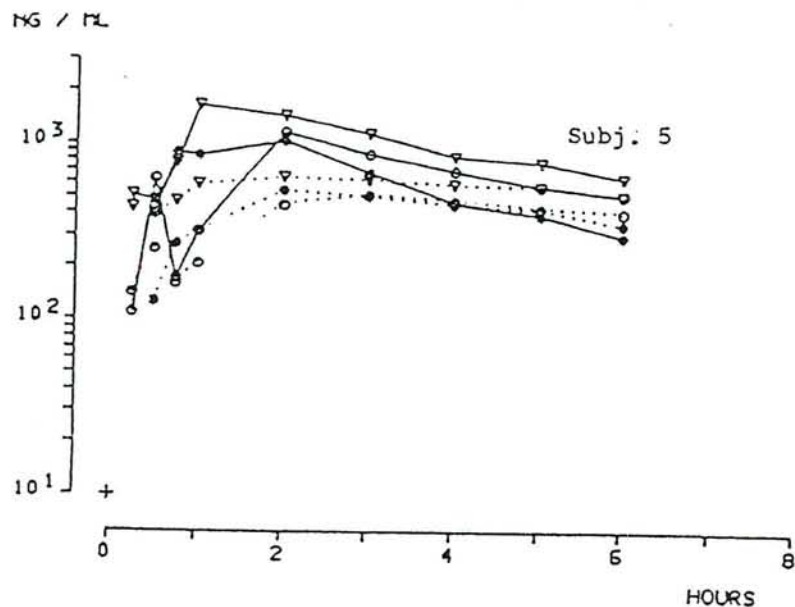
Ro 11-1163

day 8 *—*
day 15 ▽—▽
day 22 ○—○

Ro 12-8095

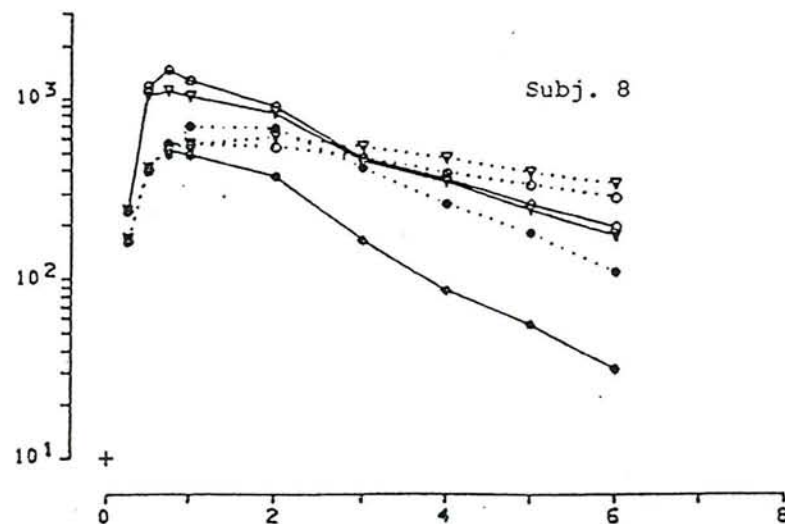
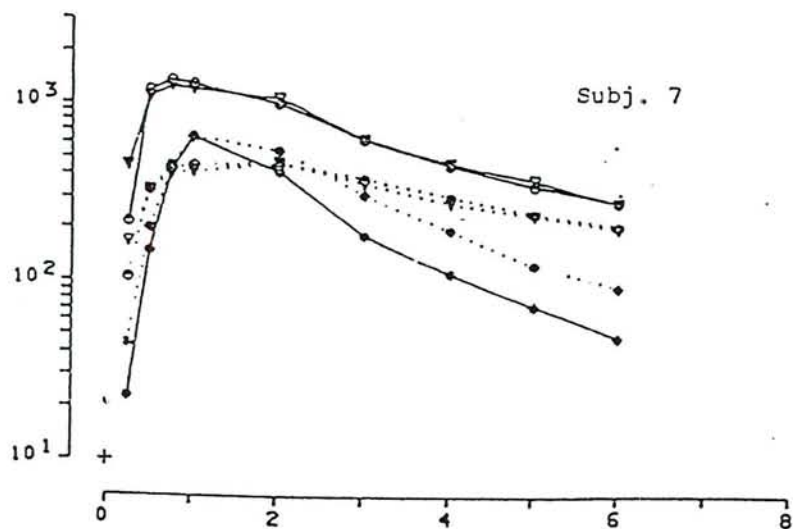
day 8 *.....*
day 15 ▽.....▽
day 22 ○.....○

Figures 15-18 : Plasma concentration-time profiles of moclobemide and Ro 12-8095 on days 8, 15 and 22 following a multiple oral dosing regimen of moclobemide.



Ro 11-1163

day 8 *—*
day 15 ▽—▽
day 22 ○—○

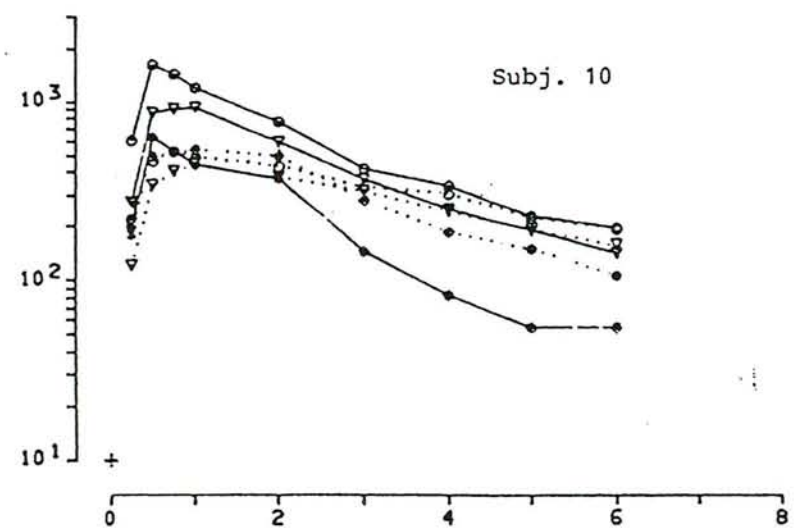
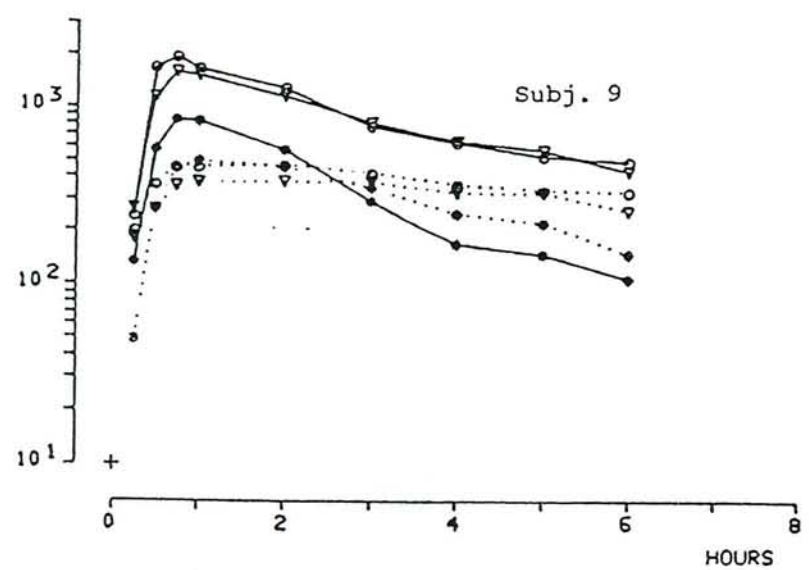


Ro 12-8095

day 8 *.....*
day 15 ▽.....▽
day 22 ○.....○

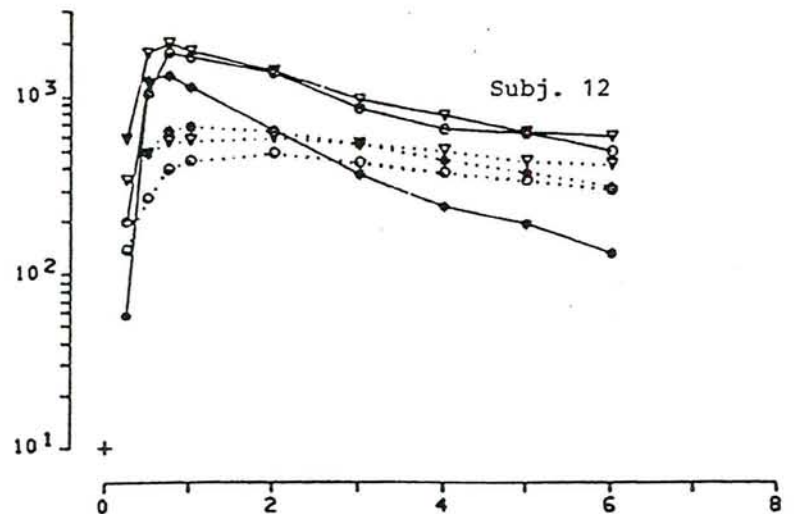
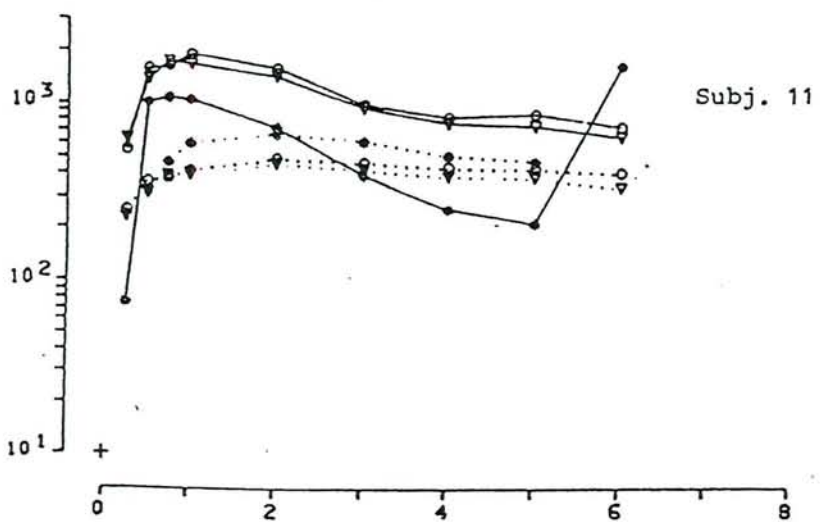
Figures 19-22 : Plasma concentration-time profiles of moclobemide and Ro 12-8095 on days 8, 15 and 22 following a multiple oral dosing regimen of moclobemide.

NG / ML



Ro 11-1163

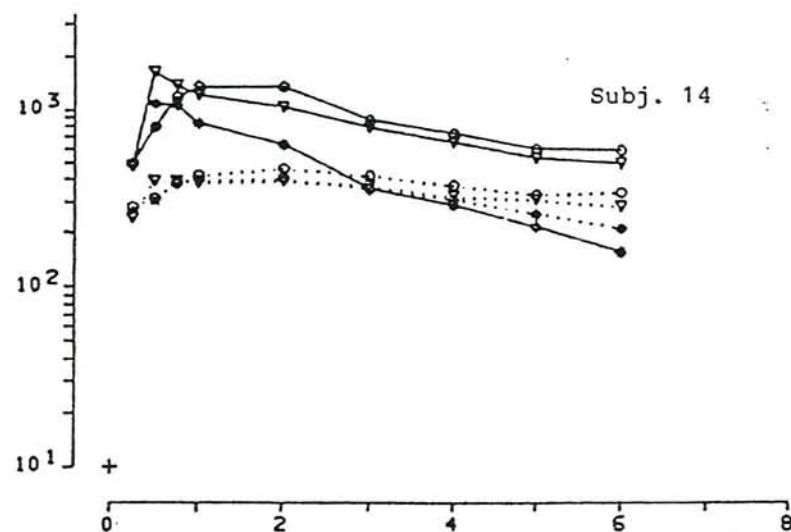
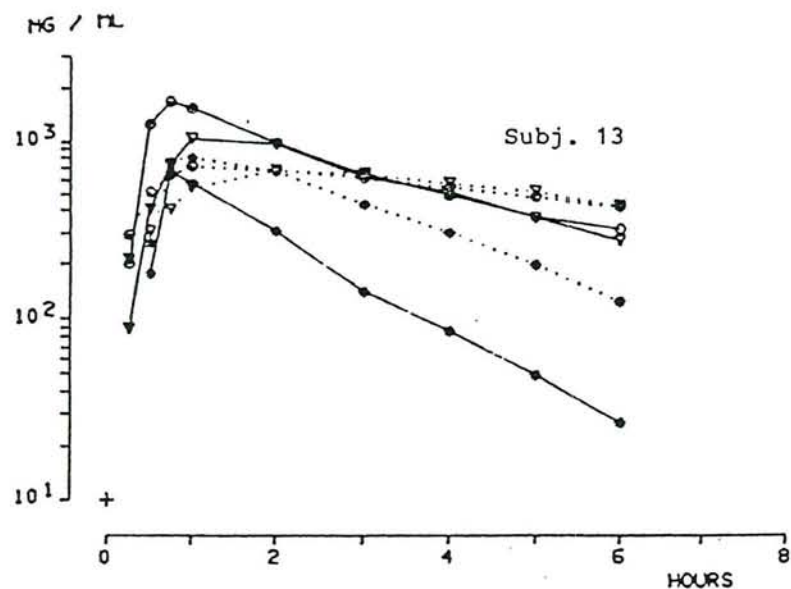
day 8 *—*
day 15 ▽—▽
day 22 ○—○



Ro 12-8095

day 8 *.....*
day 15 ▽.....▽
day 22 ○.....○

Figures 23-24 : Plasma concentration-time profiles of moclobemide and Ro 12-8095 on days 8, 15 and 22 following a multiple oral dosing regimen of moclobemide.



Ro 11-1163

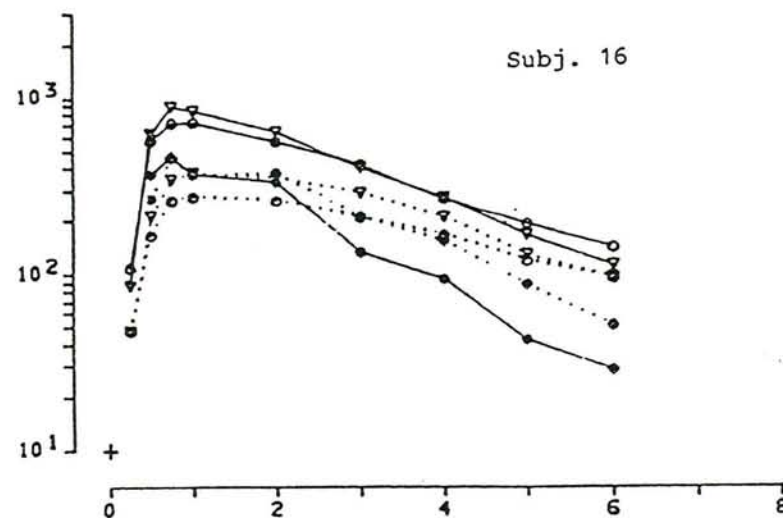
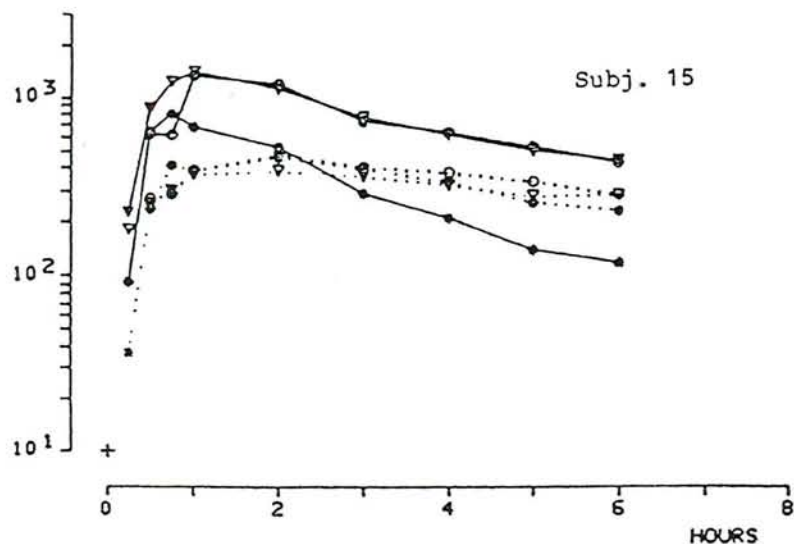
day 8 *—*
day 15 ▽—▽
day 22 ○—○

Ro 12-8095

day 8 *.....*
day 15 ▽.....▽
day 22 ○.....○

Figures 25-28 : Plasma concentration-time profiles of moclobemide and Ro 12-8095 on days 8, 15 and 22 following a multiple oral dosing regimen of moclobemide.

MG / ML

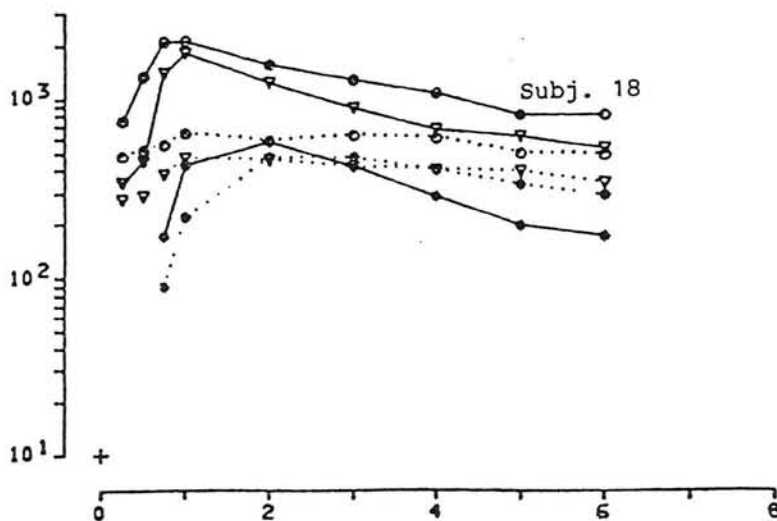
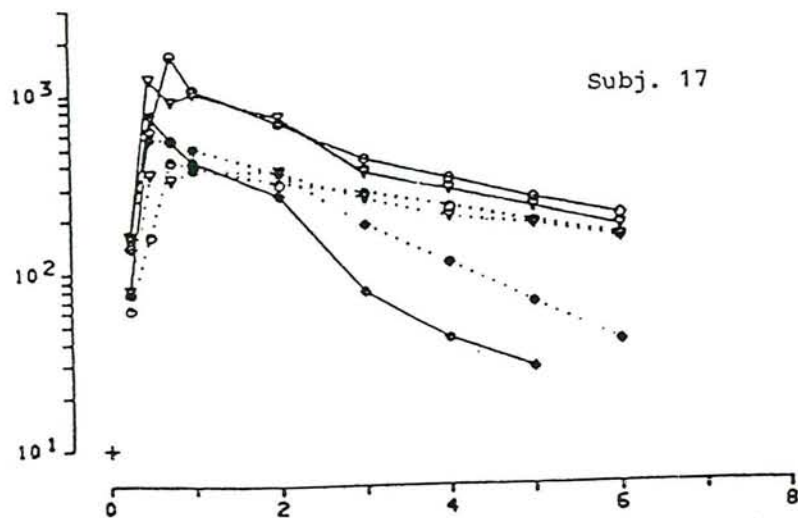


Ro 11-1163

day 8 *—*

day 15 ▽—▽

day 22 ○—○



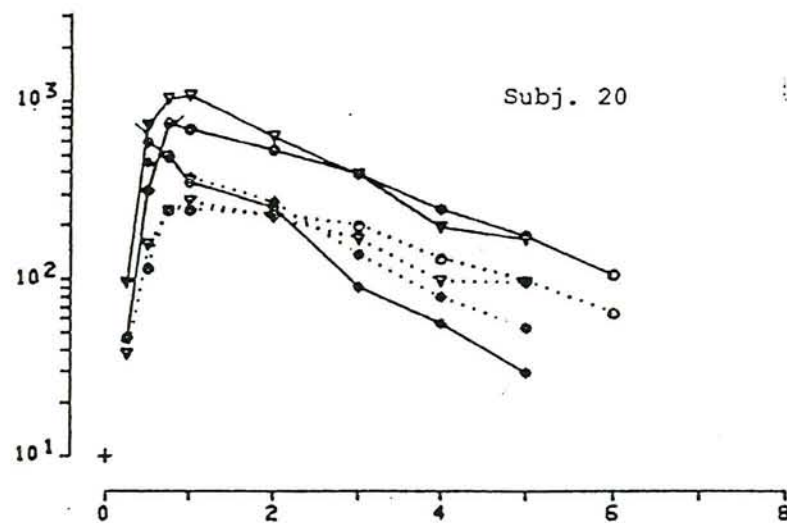
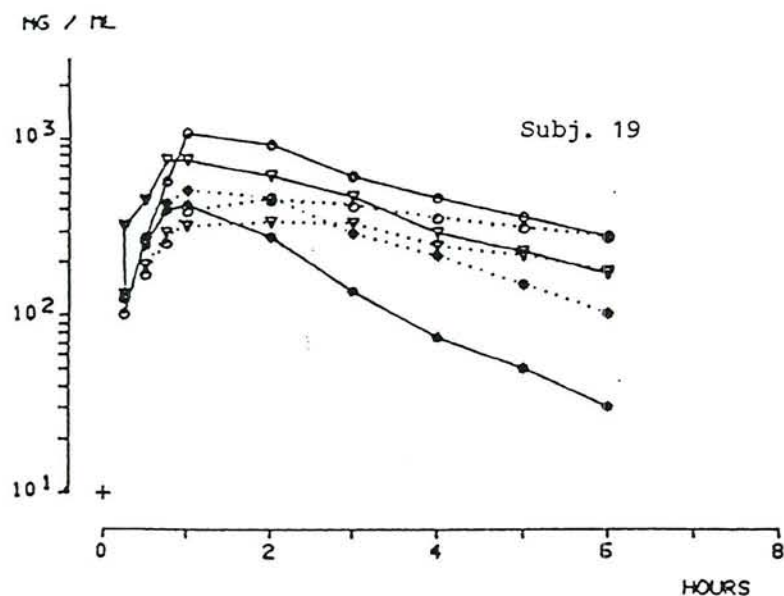
Ro 12-8095

day 8 *.....*

day 15 ▽.....▽

day 22 ○.....○

Figures 29-30 : Plasma concentration-time profiles of moclobemide and Ro 12-8095 on days 8, 15 and 22 following a multiple oral dosing regimen of moclobemide.



Ro 11-1163

day 8 *—*
day 15 ▽—▽
day 22 ○—○

Ro 12-8095

day 8 *.....*
day 15 ▽.....▽
day 22 ○.....○

Figure 31 : Disposition parameters of moclobemide following a single 75 mg intravenous infusion of moclobemide in elderly (E) and young (Y), subjects. The cross-hatched vertical bars are the standard deviations of the mean shown to the left and right of the individual values.

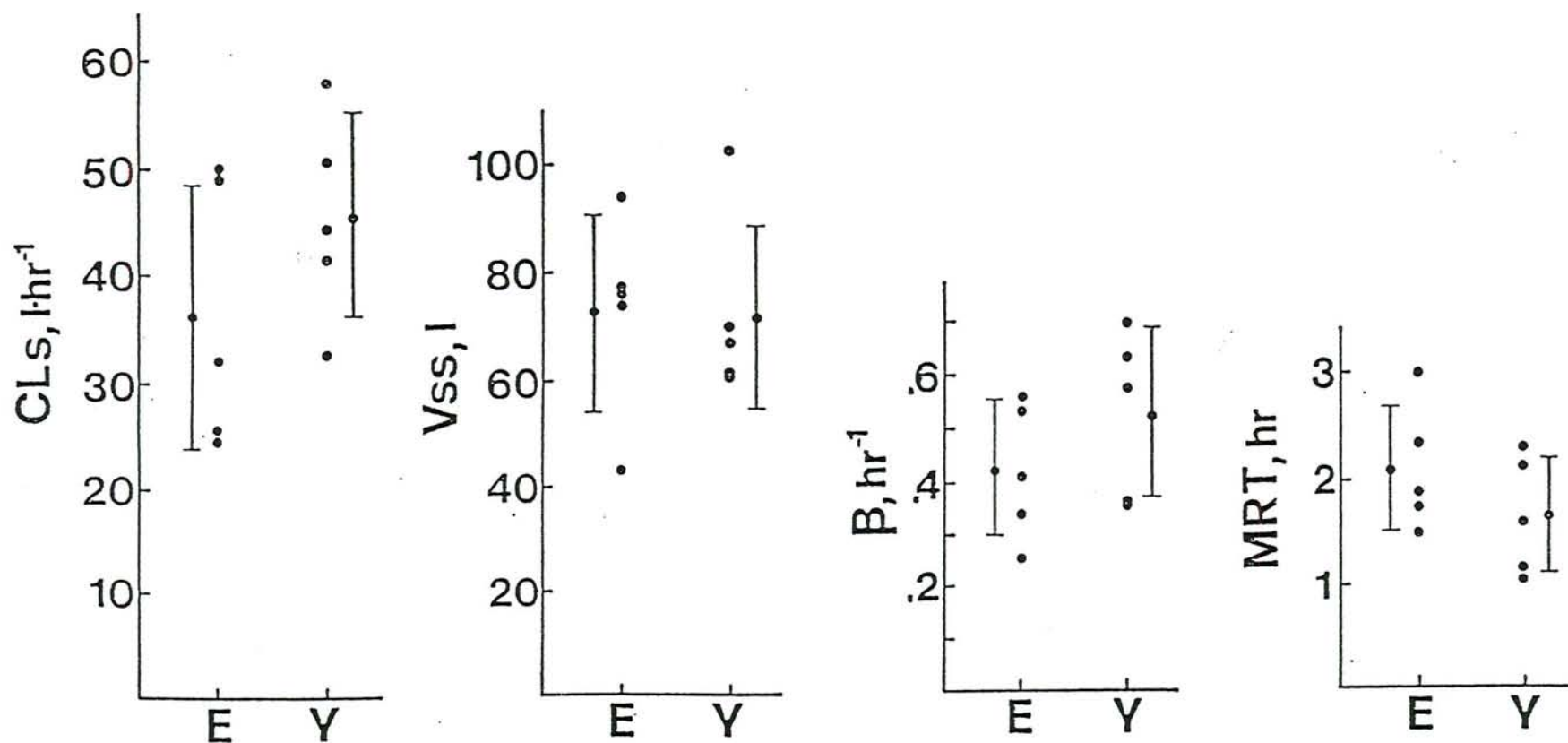


Figure 32 : Disposition parameters of moclobemide as a function of age following a 75 mg intravenous infusion. C_T is the concentration at the end of the infusion.

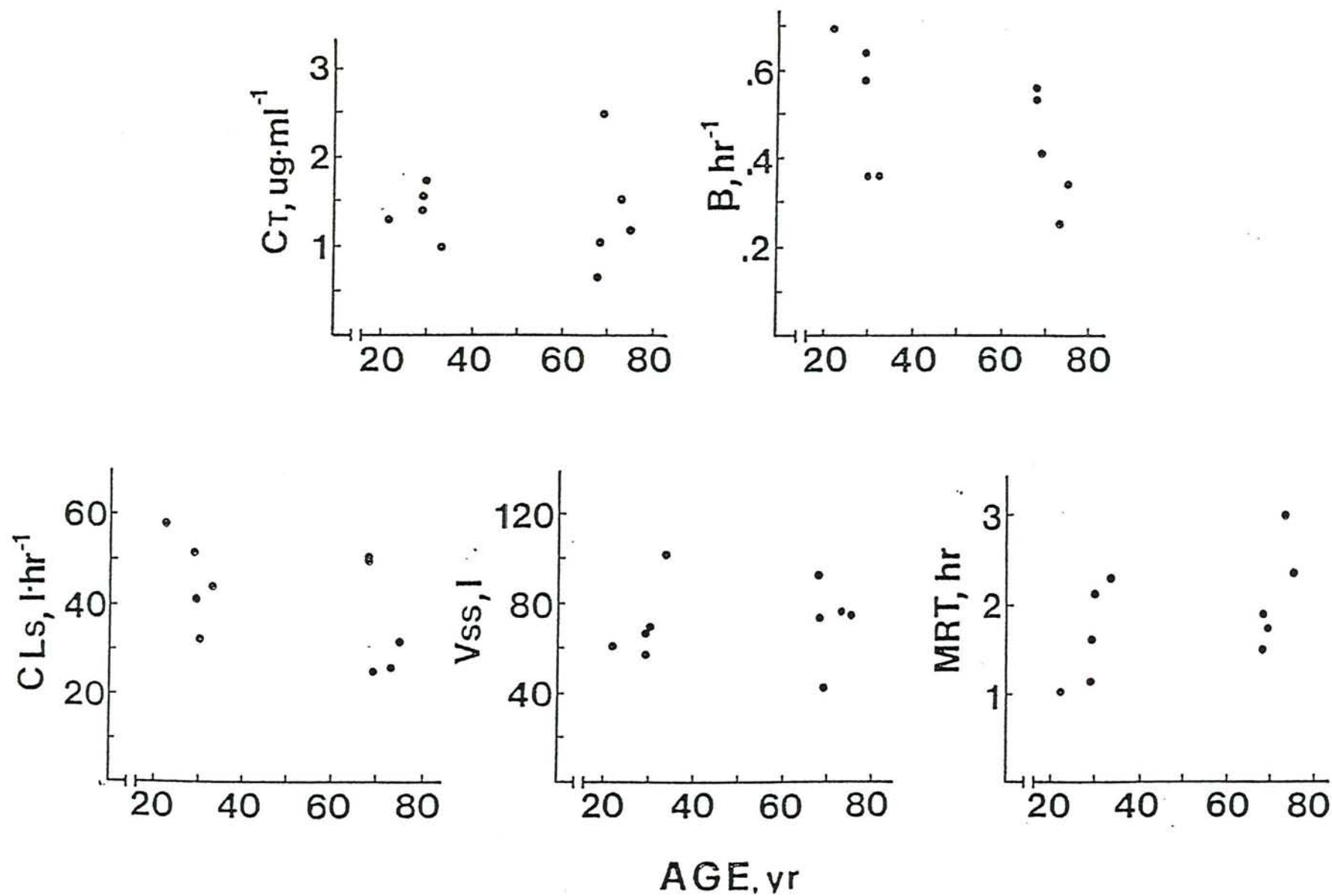


Figure 33 : The maximum plasma concentration ($C_{\max}$), terminal disposition constant (β) and mean residence time (MRT) of the metabolite, Ro 12-8095, following a 75 mg intravenous infusion of moclobemide in elderly (E) and young (Y) subjects. The cross-hatched vertical bars represent the standard deviations of the mean shown to the left and right of the individual values.

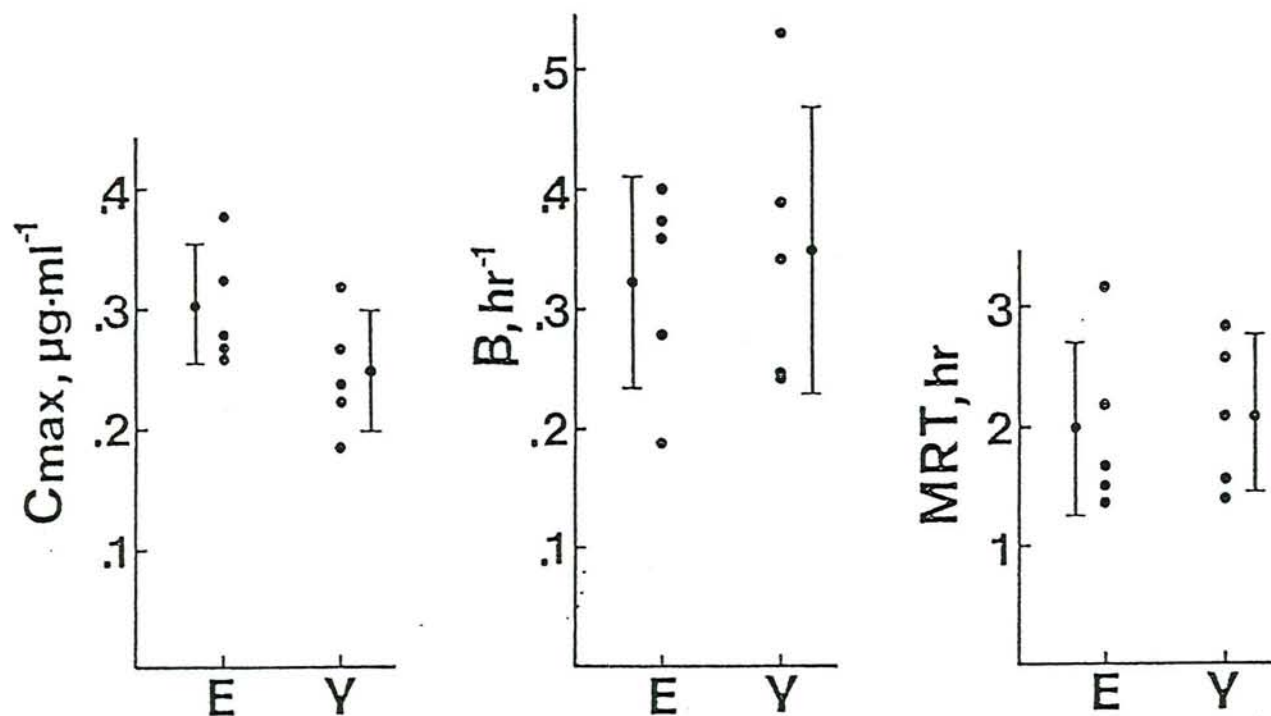


Figure 34 : The maximum plasma concentration ($C_{\max}$) and mean absorption time (MAT) of moclobemide determined after the first 100 mg dose on day 8 in elderly (E) and young (Y) subjects. The cross-hatched vertical bars represent the standard deviations of the mean shown to the left and right of the individual values.

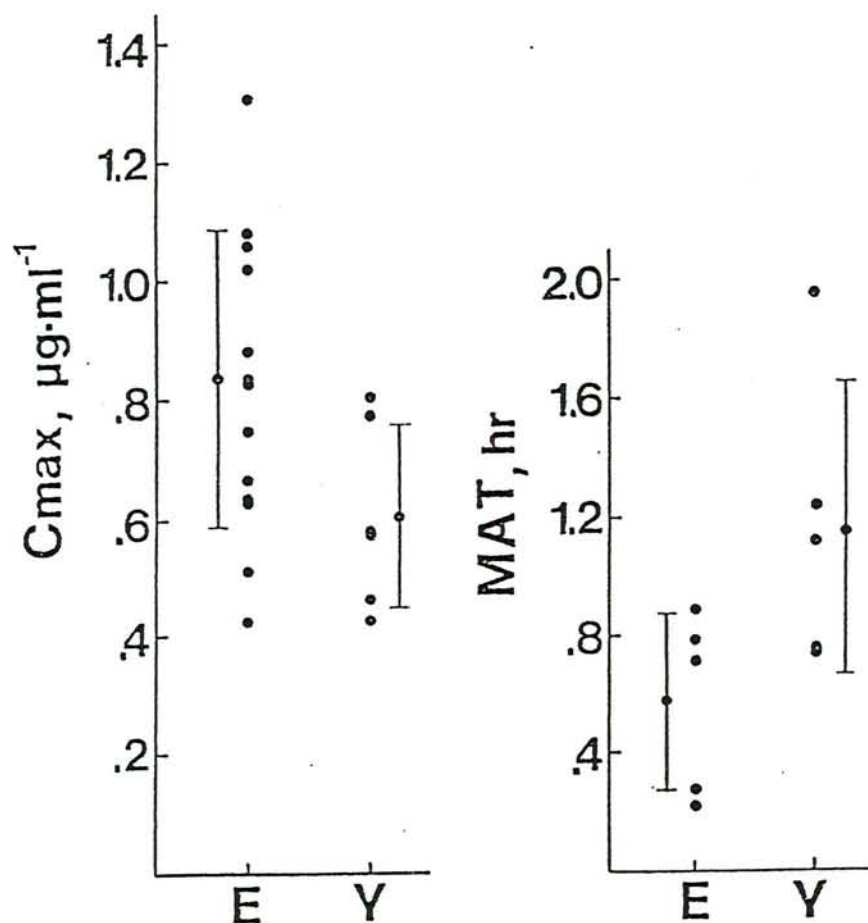


Figure 35 : Apparent oral clearance (CL_o) following the first 100 mg oral dose (d 8) and during the multiple oral dosing regimen of 100 mg three times a day (d 15,22) and the absolute oral bioavailability (F_{obs}) of moclobemide (after the first dose) in elderly (E) and young (Y) subjects. The values shown for CL_o on d 15,22 are the mean of the values determined during a dosing interval on those days. The cross-hatched vertical bars are the standard deviations of the mean shown to the left and right of the individual values.

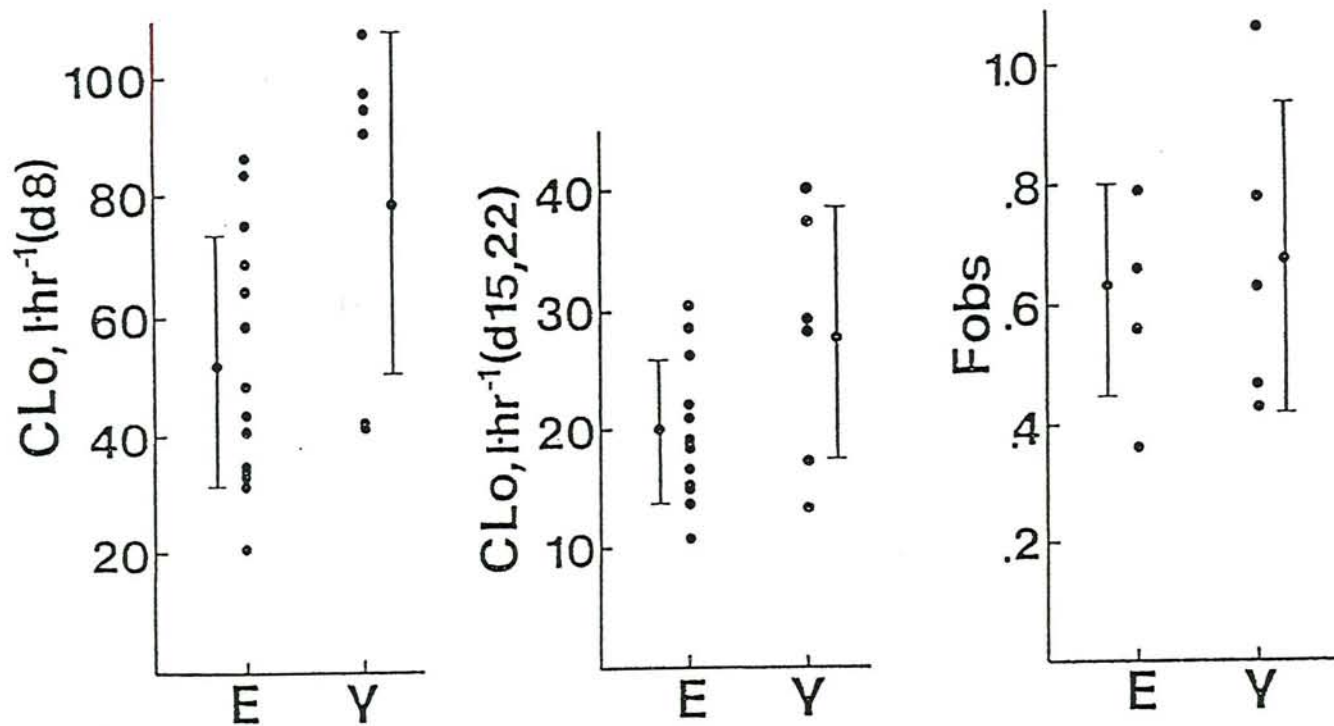


Figure 36 : Absorption parameters of moclobemide as a function of age following the first 100 mg oral dose on day 8.

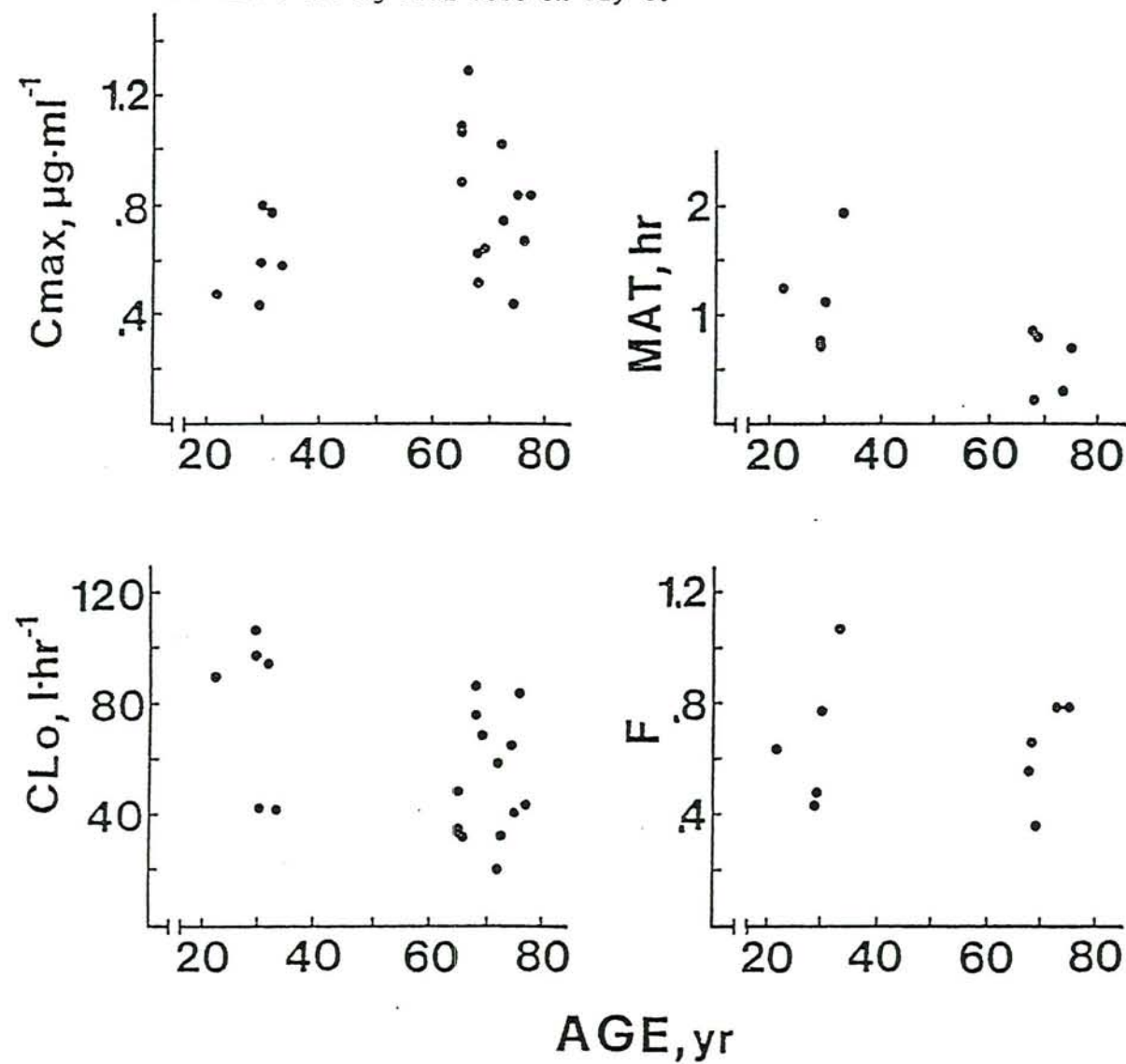


Figure 37 : Apparent oral clearance (CL_o) and terminal disposition rate constant (β) of moclobemide in elderly and young subjects following the first 100 mg oral dose (d 8) and during the multiple oral dosing regimen of 100 mg three times a day (d 15,22). The values shown for d 15,22 are the mean of the values determined during a dosing interval on those days. The cross-hatched vertical bars are the standard deviations of the mean shown to the left and right of the individual values.

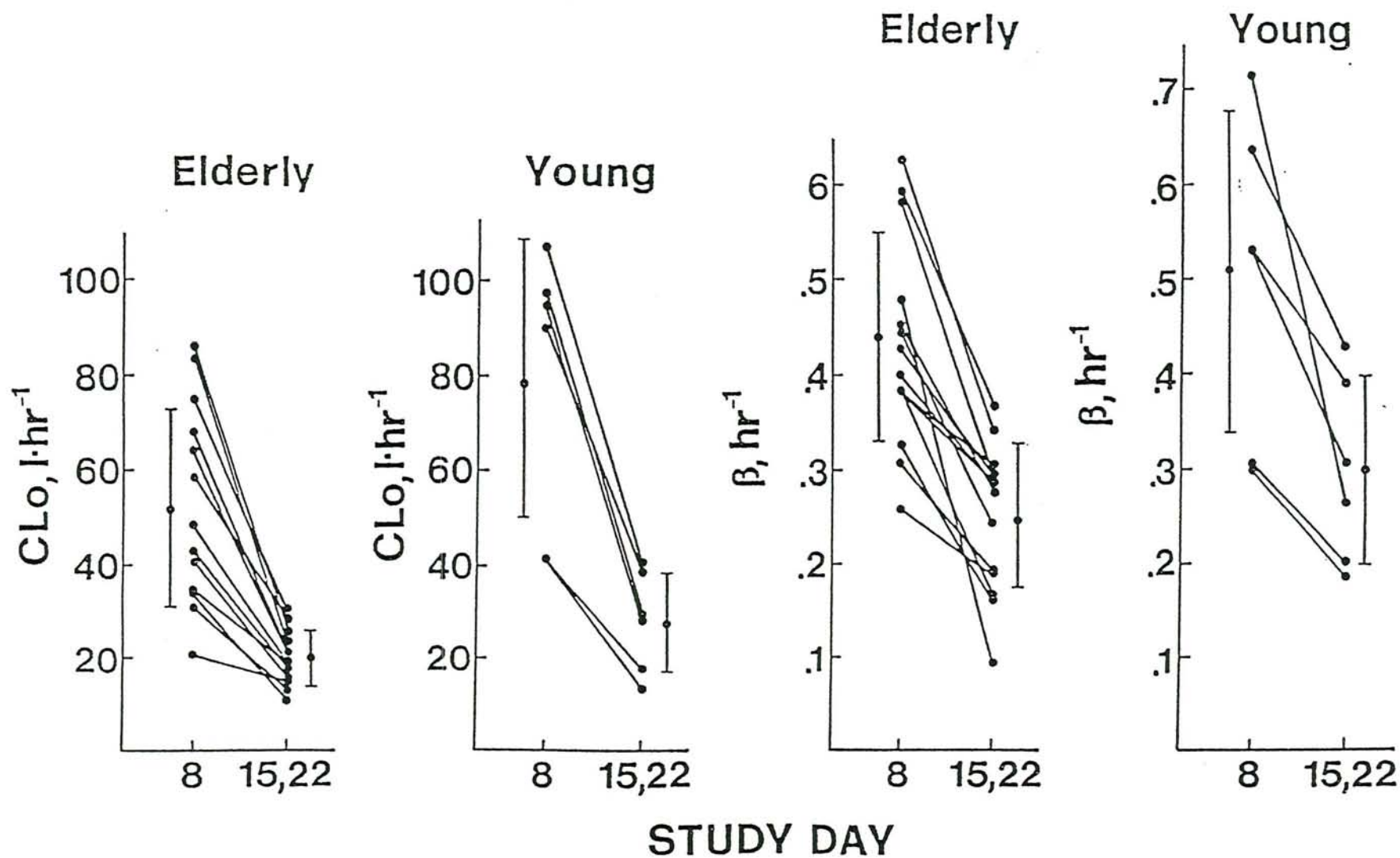


Figure 38 : The terminal disposition rate constant of the metabolite Ro 12-8095 as a function of the terminal disposition rate constant of moclobemide following a 75 mg i.v. infusion of moclobemide. The stippled line is the line of identity and the solid line is the regression fit of the data forced through the origin (slope = 0.706). Key: elderly subjects (o); young subjects (●).

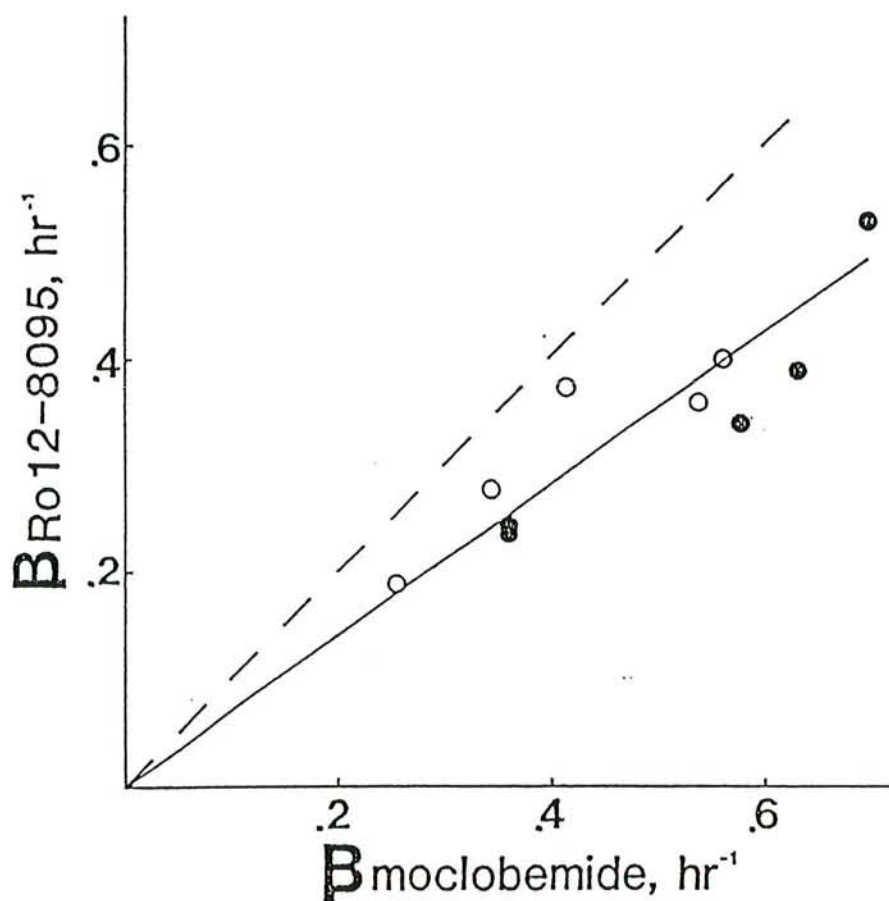
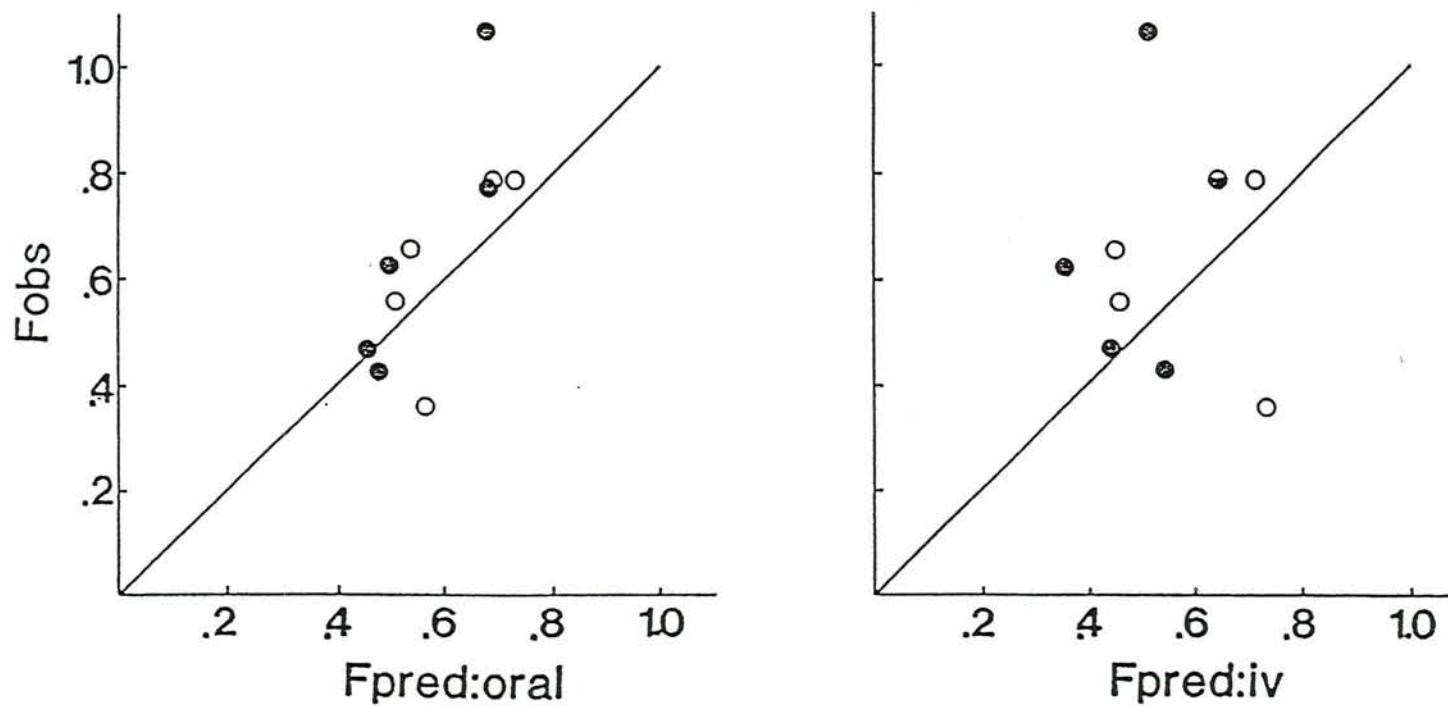


Figure 39 : The observed absolute oral bioavailability of moclobemide (F_{obs}) as a function of the predicted bioavailability based upon the oral ($F_{pred:oral}$) and iv data ($F_{pred:iv}$).
Key: elderly subjects (o); young subjects (●).



ETUDE VII

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Moclobemide excretion in human breast milk

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1 Six lactating white women, aged 24-36 years, received a single oral dose of 300 mg moclobemide, between 09.00 h and 11.00 h, 3 to 5 days after the delivery of a full term neonate.

2 Complete milk collections were obtained before, 3, 6, 9, 12 and 24 h after drug administration by means of a breast pump. Venous blood samples were drawn before, and 0.5, 1, 3, 4.5, 6, 9, 12, 24 h post-dosing.

3 Moclobemide, and its major metabolite (Ro 12-8095) were measured in milk and plasma samples using h.p.l.c. The active metabolite (Ro 12-5637) could only be detected in plasma.

4 Moclobemide and its metabolites were not detectable in 24 h plasma samples. C_{max} , t_{max} and $t_{1/2}$ for moclobemide were (mean $\pm$ s.d.) 2.70 ± 1.24 mg l⁻¹, 2.03 ± 1.19 h and 2.26 ± 0.26 h, respectively.

5 The concentrations of moclobemide and Ro 12-8095 in milk were highest at 3 h after drug administration and the drug and metabolite were not detectable after 12 h. Ro 12-5637 was not detected in any milk sample. The percentages of the dose excreted as moclobemide and Ro 12-8095 were (mean $\pm$ s.d.) $0.057 \pm 0.020\%$ and $0.031 \pm 0.011\%$, respectively. An average 3.5 kg breast-fed neonate would therefore be exposed to only a 0.05 mg kg⁻¹ moclobemide dose (approximately 1% of the maternal dose on the mg kg⁻¹ basis). The low amount of moclobemide excreted into breast milk is unlikely to be hazardous to suckling infants.

Keywords breast milk antidepressant monoamine oxidase inhibitor moclobemide

Introduction

Moclobemide, a benzamide derivative, is a new reversible monoamine oxidase-A inhibitor (Keller *et al.*, 1987). It possesses an antidepressant efficacy comparable with that of clomipramine, amitriptyline and imipramine (Larsen *et al.*, 1984; Norman *et al.*, 1985; Stabl *et al.*, 1989) and superior to that of placebo (Casacchia *et al.*, 1984; Stabl *et al.*, 1989). Most patients tolerate moclobemide better than tricyclic antidepressants (Larsen *et al.*, 1984; Stabl *et al.*, 1989). Moclobemide might be useful in the

management of postnatal depression. The advantages of breast feeding in this condition are well recognized and physicians are often reluctant to advise discontinuation of breast feeding because of potential risks to the infant posed by the presence of an antidepressant drug in mother's milk. The purpose of this study was to measure the time course of moclobemide and its metabolites in human milk and to determine the exposure of breast-fed neonates after a single 300 mg oral dose.

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Moclobemide is a weak base (pKa 6.3) with an *n*-octanol/water distribution coefficient of 62 at a pH of 7.4 and a molecular weight of 269. It is 50% bound to plasma proteins (Schoerlin *et al.*, 1989). Data in normal healthy volunteers indicate a short terminal half life (1 to 2 h), an intermediate clearance (39 l h^{-1}) and a large volume of distribution ($1 \text{ to } 1.5 \text{ l kg}^{-1}$) after a 150 mg intravenous dose. The drug is eliminated primarily by metabolism and exhibits non linear kinetics. The absolute bioavailability averages about 60% after a 100 mg oral dose (Schoerlin *et al.*, 1987).

Ro 12-8095, the main metabolite, produced by hydroxylation of the morpholine ring, is inactive while Ro 12-5637 produced by *N*-oxidation of the same ring is active.

Methods

Six lactating white women, ranging in age from 24 to 36 years, in height from 158 to 172 cm and in weight from 48 to 63 kg were recruited to the study. Each subject was in good health as assessed by medical history, physical examination and routine laboratory tests. The study was performed on day 3 to 5 after delivery of a full term neonate. Mothers nursing twins were excluded. The subjects had not used any medication known to induce or inhibit drug metabolism, for at least 2 weeks before drug administration and during the study. Written informed consent was obtained from all subjects prior to the study. The protocol was approved by the UER Cochon Port-Royal Ethics Committee. Before the study each mother agreed to stop nursing her infant for 24 h after drug administration.

Each mother received a single oral dose of 300 mg moclobemide as three 100 mg tablets with 120 ml of water between 09.00 h and 11.00 h after a low-fat breakfast. A lunch was served 4 h after drug intake. During the entire blood sampling period, the subjects were allowed light meals which were low in fat. Breast milk was collected using an Egnell SMB breast electric pump (AMEDA AG, Zug, Switzerland). The working cycle of the breast pump is divided into three phases: a short suction phase, during which the pressure decreases from atmospheric pressure to 520 mm Hg (negative pressure of 240 mm Hg); a short relief phase, back to atmosphere pressure; a resting phase under slight overpressure of about 10 mm Hg. The suction rhythm is of 48 periods min^{-1} . Milk samples were collected immediately before dosing and 3, 6, 9, 12, 24 h after drug administration. Available milk was collected as completely as possible

from each breast. Blood samples were drawn, immediately before, 0.5, 1, 3, 4.5, 6 and 9 h after drug administration in the first two patients. Two additional blood samples were taken, 12 and 24 h post-dosing in the remaining four. Plasma and milk samples were stored at -20°C until analysis.

The concentrations of moclobemide and its metabolites (Ro 12-5637) and (Ro 12-8095) in plasma were measured by h.p.l.c. (Geschke *et al.* 1987). Moclobemide and Ro 12-8095 were measured in milk using the same h.p.l.c. method after a two step extraction with butylchloride and an acetonitrile/hexane (1 : 1 v/v) mixture. The detection limits were as follows: 20, 30 and 30 ng ml^{-1} in 0.5 ml of plasma for moclobemide, Ro 12-5637 and Ro 12-8095; and 0.025 and 0.030 mg l^{-1} in 0.5 ml of milk for moclobemide and Ro 12-8095, respectively. The interassay reproducibility was as follows: 1.8 to 7.9% and 3.3 to 9.0% for moclobemide and Ro 12-8095 over the concentration range in plasma ($0.15 \text{ to } 2.50 \text{ mg l}^{-1}$) and in milk ($0.035 \text{ to } 0.700 \text{ mg l}^{-1}$), respectively. The apparent elimination half-life ($t_{1/2}$) was calculated by linear regression from the slope of the log linear decay of the 4.5 to 12 h concentration-time points. The area under the moclobemide plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to infinity using the ratio of the concentration calculated at the last time point divided by the terminal elimination rate constant. The oral clearance (CL_0) was calculated as the ratio of the oral dose/AUC.

The results are expressed as means and standard deviations (s.d.). For $t_{1/2}$, values of the mean and s.d. are the harmonic mean and the 'pseudo' standard deviation (Lam *et al.*, 1985).

Results

Milk yield was $440 \pm 103 \text{ ml } 24 \text{ h}^{-1}$ and $82.6 \pm 37.5 \text{ ml/time-point}$.

Mean plasma moclobemide and metabolite plasma concentration-time curves are shown in Figure 1a. Moclobemide, Ro 12-5637, Ro 12-8095 were not detectable in 24 h plasma samples. The maximum plasma concentration of moclobemide (C_{max}) was observed between 0.58 and 3.17 h after drug administration (t_{max}) and ranged from $1.47 \text{ to } 4.93 \text{ mg l}^{-1}$ (Table 1). The mean $t_{1/2}$, AUC and oral plasma clearance (CL_0) values of moclobemide were $2.27 \pm 0.26 \text{ h}$, $11.66 \pm 3.30 \text{ mg l}^{-1} \text{ h}$ and $27.61 \pm 8.28 \text{ l h}^{-1}$, respectively (Table 1).

The concentrations of moclobemide and its main metabolite Ro 12-8095 excreted in breast

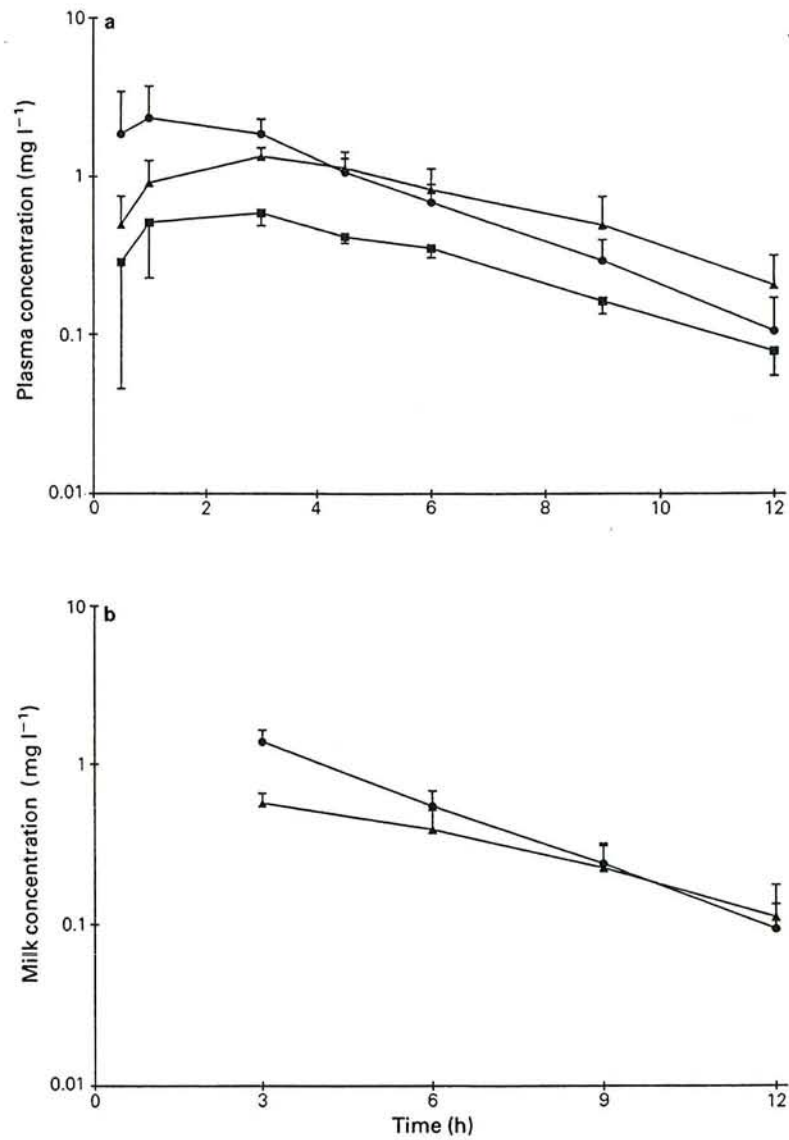


Figure 1 a) Plasma concentration-time profiles (mean $\pm$ s.d.) of moclobemide (●), Ro 12-8095 (▲) and Ro 12-5637 (■) following a 300 mg oral dose of moclobemide in six lactating mothers. b) The mean ($\pm$ s.d.) concentration of moclobemide (●) and Ro 12-8095 (▲) in breast milk as a function of time following a 300 mg oral dose of moclobemide in six lactating mothers.

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Table 1 Parameters describing the pharmacokinetics of moclobemide following a 300 mg oral dose in six lactating mothers

Subject	t_{max} (h)	C_{max} (mg l ⁻¹)	$t_{1/2}$ (h)	AUC (mg l ⁻¹ h)	CL ₀ (l h ⁻¹)
1	3.17	1.88	2.43	9.66	31.05
2	1.10	3.14	2.42	13.39	22.41
3	3.08	1.47	1.98	7.40	40.56
4	0.58	4.93	2.28	16.33	18.37
5	1.20	2.14	2.00	9.66	31.06
6	3.03	2.63	2.63	13.49	22.25
Mean	2.03	2.70	2.27	11.66	27.62
s.d.	1.19	1.24	0.26	3.30	8.16

Table 2 Breast milk excretion of moclobemide and Ro 12-8095 following a 300 mg oral dose in six lactating mothers

Subject	Moclobemide			Ro 12-8095	
	Cumulative amount excreted in milk (0-24 h) (mg)	% of dose excreted in milk (%)	Cumulative amount/ plasma AUC ratio (l h ⁻¹)	Cumulative amount excreted in milk (0-24 h) (mg)	% of dose excreted in milk (%)
1	0.1059	0.035	0.01096	0.0500	0.106
2	0.1948	0.065	0.01455	0.1285	0.041
3	0.1483	0.049	0.02005	0.0950	0.030
4	0.1408	0.047	0.00862	0.0772	0.024
5	0.1576	0.053	0.01631	0.1445	0.046
6	0.2833	0.094	0.02101	0.0841	0.027
Mean	0.1718	0.057	0.01525	0.0966	0.031
s.d.	0.0617	0.020	0.0049	0.0347	0.011

milk were highest 3 h after drug administration and were no longer measurable after 12 h. The milk concentration-time curves paralleled the plasma concentration-time curves (Figure 1b). The concentration of moclobemide in milk correlated with its plasma concentration ($y = 45.118 + 0.71892x$; $r = 0.986$): the slope of this equation indicates that the concentration of drug in milk is, on average, 72% of that in plasma. The percentage of the administered dose excreted in 24 h was 0.057 ± 0.020 and $0.031 \pm 0.011\%$ for moclobemide and Ro 12-8095, respectively (Table 2). Ro 12-5637, an active metabolite, was not detected in breast milk.

Discussion

The experimental design took into consideration the significant changes, previously described (Wilson *et al.*, 1980), in milk composition and

yield, which depend on the time of sampling during a feeding, the side of collection, the time of the day, the stage of lactation and the nutritional state. The sampling protocol was standardized to allow interpatient comparisons and also for the measurement to be relevant to clinical practice. Milk was sampled from each breast as completely as possible in order to obtain samples representative of a complete feed. The time interval between consecutive milk collections was similar to that of a regular schedule of breast feeding. In all patients the study was performed during the fourth to the sixth days postpartum and at the same time of the day. All of the lactating mothers were well nourished and had given birth to a full term neonate.

Drug excretion in breast milk is primarily by passive diffusion across the mammary membranes leading to rapid equilibration of drug between plasma and milk (Wilson *et al.*, 1980). Breast milk can, therefore, be considered as a

compartment with bidirectional transfer across a blood-milk barrier rather than a bladder with milk accumulation between two consecutive collections. We thus chose to consider each milk sample as instantaneous, at the mid-point of the milk collection interval, rather than to consider the amount of drug recovered as the result of drug accumulation in breast during the time elapsed since the previous milk collection. The parallel decline of milk and plasma moclobemide concentrations (Figure 1a and 1b) support the hypothesis of rapid equilibration of drug between plasma and milk. The kinetic parameters describing the time course of moclobemide in plasma in the lactating mothers following a 300 mg dose are consistent with those observed in previous studies in healthy male volunteers (Data on file Hoffmann La Roche).

We have shown that breast-fed neonates from mothers treated with a single 300 mg oral dose of moclobemide would be exposed to only a small amount of the drug and its major and inactive metabolite Ro 12-8095 when fed as early as 3 h after drug administration. Using the total amounts of compounds recovered in breast milk over the period of the study, a child weighing 3.5 kg is estimated to receive, on average, about 0.050 mg kg^{-1} moclobemide (approximately 1% of the maternal dose on the mg kg^{-1} basis) and 0.028 mg kg^{-1} Ro 12-8095, assuming that such a 3-5 day old infant would be able to ingest the

relatively large amount of milk collected. The amount of moclobemide transferred into milk is not expected to be very much higher after the 6th day post-delivery due to changes in milk yield and composition which occur during maturation.

During multiple dosing, accumulation of the compounds in plasma and breast milk may occur. Accumulation in plasma has been demonstrated in healthy volunteers. Furthermore, moclobemide exhibits non linear kinetics when given as a 100 mg dose three times daily for 15 days, the steady-state area under the plasma drug concentration-time curve being two times higher than after a single 100 mg dose (Schoerlin *et al.*, 1987). The dosage used in the present study is two to three times higher than a single therapeutic dose. Thus, the AUC obtained in the present study in lactating mothers receiving a single 300 mg dose was similar to that, at steady-state, in healthy volunteers receiving 150 mg three times daily (Data on file Hoffmann La Roche). The dosage used in the present study might, therefore, be considered as representative of steady-state conditions, suggesting that exposure of breast-fed neonates during a dosing interval of a 150 mg three times daily therapeutic chronic dose is not expected to be different to that following a single 300 mg dose. The low amount of moclobemide excreted into breast milk is unlikely to be hazardous to suckling infants.

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ETUDE VIII

Comparison of the pharmacokinetics of moclobemide in poor and efficient metabolizers of debrisoquine

Schoerlin MP, Blouin RA, Pfefen JP, Guentert TW. Comparison of the pharmacokinetics of moclobemide in poor and efficient metabolizers of debrisoquine.

Acta Psychiatr Scand 1990; Suppl 360: 98-100.

A number of pharmacokinetics studies in which patients had been phenotyped and poor metabolizers for moclobemide found were analysed retrospectively. There were 27 subjects in all, aged between 19 and 75 years, and 5 of these were classified as poor debrisoquine metabolizers. Although there was a wide variability in the pharmacokinetic parameters observed, no consistent relationship was found between these and debrisoquine phenotype. Poor debrisoquine metabolizers all had values within the extremes for the efficient metabolism. This was true for both single and multiple dosing. This analysis is limited by the small number of subjects as well as its retrospective nature. Nevertheless, the data suggest that no deviations of moclobemide pharmacokinetics should be expected in poor metabolizers of debrisoquine compared with normal metabolizers.

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Key words: antidepressant; moclobemide; metabolism; pharmacokinetics; phenotype; debrisoquine

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In several pharmacokinetic studies involving healthy volunteers, a few individuals were observed for whom moclobemide half-life was considerably longer than the average of approximately 1.5 h and in whom the oral bioavailability appeared uncharacteristically high. This was not age-related. The observations might simply be an expression of interindividual variability. Nevertheless, it cannot be excluded that a genetically controlled polymorphism in enzymatic activity may also play a role in this variability. Because participating subjects had been phenotyped with the model drug debrisoquine in some studies, a retrospective analysis was performed comparing pharmacokinetic parameters for moclobemide in extensive and poor metabolizers of debrisoquine after single and/or multiple doses of the monoamine oxidase (MAO) inhibitor. All pharmacokinetic studies were included in this comparison in which subjects had been phenotyped and poor metabolizers were found.

Material and methods

Subjects

A compilation of all phenotyped subjects included in previous pharmacokinetic trials was made. Twenty-seven phenotyped subjects with ages between 19 and 75 years were included who had participated in 3 different studies. Informed written

consent was obtained from all subjects prior to the different studies. Prior to enrolment and after completion of the studies, a physical examination and a series of laboratory tests (haematology, blood chemistry and urinalysis) was performed, including phenotyping with 10 mg debrisoquine. The debrisoquine hydroxylation ratio was assessed using the method of Mahgoub et al. (1). Volunteers were excluded from the studies if they had any recent drug exposure or history of drug intolerance or any clinically significant deviation from normal in physical examination or laboratory tests.

Study procedures

Subjects had abstained from ethanol for 24 h before the study and did not smoke during the study. After an overnight fast each subject received 1-2 single intravenous (i.v.) infusions of moclobemide (75-150 mg over 20 min) and a single oral 100- or 150-mg dose of the drug on different occasions. Additionally, 14 subjects received multiple oral doses of the drug (150 mg 3 times daily) during 14 days. Blood was collected before and at several times until 24 h after each dosing. Plasma was separated and stored at -20°C until assayed. Moclobemide in these samples was determined by a published high-pressure liquid chromatography method with ultraviolet light detection (2).

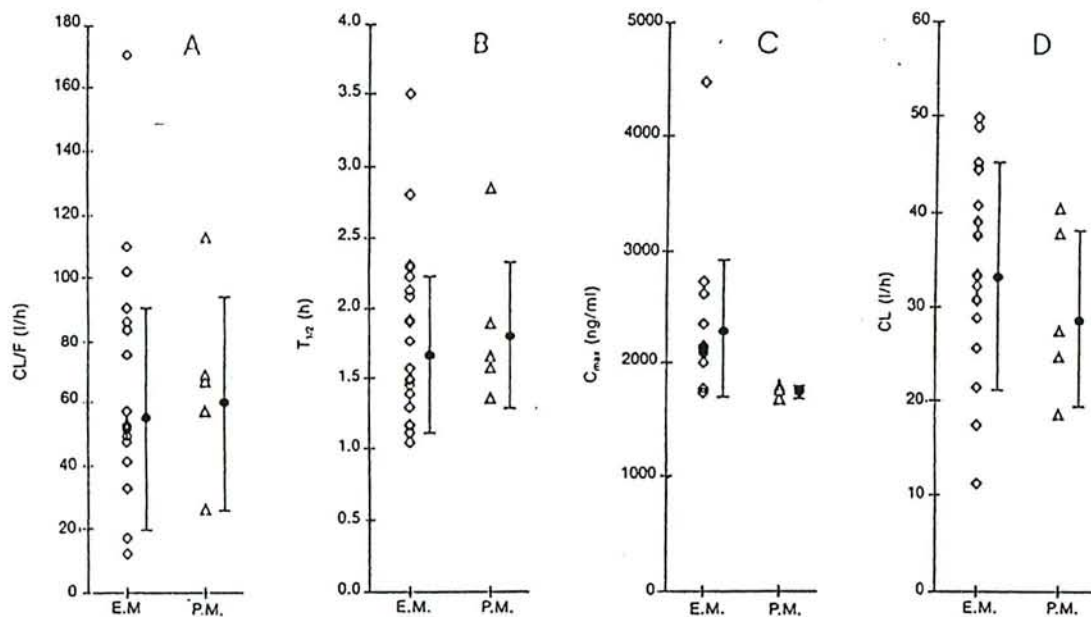


Fig. 1. Comparison of pharmacokinetic parameters of moclobemide (oral clearance, CL/F ; elimination half-life, $t_{1/2}$; maximum plasma concentration, C_{max} ; systemic clearance, CL) in poor and extensive debrisoquine metabolizers. Panel A, B: single oral doses, 100 mg; Panel C: multiple oral doses, 150 mg 3 times daily; Panel D: single i.v. doses, 75–150 mg/20 min. Bar denotes geometric mean $\pm$ SD.

Analysis of moclobemide pharmacokinetics

Moclobemide plasma concentration-time (C, t) data were analysed by model-independent methods to determine, after oral dosing, the half-life of the terminal slope ($t_{1/2\beta}$), area under the concentration-time curve (AUC) and clearance (CL/F); maximum plasma concentrations (C_{max}) were directly read from the C, t data. Whenever i.v. data were available, systemic clearance (CL), steady-state volume of distribution (V_{ss}) and absolute oral bioavailability were determined.

Results and discussion

According to the criteria accepted for categorization of phenotypes, a total of 5 poor debrisoquine metabolizers (PM) were identified among 27 phenotyped subjects in the 3 different studies. Since subjects with known PM phenotype were encouraged to participate in these studies, the PM frequency in the study population does not reflect the incidence of deficient debrisoquine metabolizers in the general population.

The pharmacokinetics of moclobemide in efficient debrisoquine metabolizers (EM) following single-dose administration compared favourably between studies and was consistent with earlier reports (3, 4). The data are characterized by wide intersubject variability in the pharmacokinetic parameters observed.

When absorption and disposition parameters of moclobemide in subjects characterized as PM were compared with those in subjects characterized as EM, no consistent relationship between moclobemide pharmacokinetics and debrisoquine phenotype was found. The parameter values in subjects with deficient hydroxylation capacity for debrisoquine were all encompassed in the range of values seen in EM (Fig. 1). This was true for parameters determined after single doses (CL/F , $t_{1/2\beta}$, CL) as well as for maximum concentrations observed after multiple dosing when steady-state conditions had been achieved. Therefore, no different accumulation characteristics of the drug under chronic dosing conditions than have been described in previous reports (3, 4) are to be expected in PM.

This analysis of a possible co-segregation of debrisoquine and moclobemide metabolism has its limitations not only because of the small number of poor metabolizers included in the studies but also because of its retrospective nature. Furthermore, inclusion of moclobemide metabolites might have strengthened the analysis. Nevertheless, the data suggest that no gross deviations are to be expected between the pharmacokinetic characteristics of moclobemide in poor metabolizers of debrisoquine and those seen in subjects with extensive hydroxylation capacity.

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Pharmakokinetik und Metabolismus reversibler MAO-A-Hemmer beim Menschen

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Pharmacokinetics and Metabolism of Reversible MAO-A Inhibitors in Man

Monoamine oxidase (MAO) type A inhibitors are used as antidepressants. A number of drug candidates in this therapeutic class are currently being evaluated clinically.

The objective of the present review is to evaluate the pharmacokinetics of five MAO-A inhibitors (moclobemide, toloxatone, brofaromine, cimoxatone, amiflamine). Differences between these drugs exist in their absorption and disposition characteristics. However, a detailed comparison reveals a strong similarity between moclobemide and toloxatone (high hepatic extraction ratio; reduced oral bioavailability due to first-pass metabolism; similar binding to plasma proteins, $f_b \approx 0.23$).

Elimination half-lives of 1–3 h for moclobemide and toloxatone contrast with the higher values for amiflamine (5–12 h), cimoxatone (9–16 h) and brofaromine (12–15 h). All five MAO-A inhibitors undergo complete hepatic elimination, and only a negligible fraction of the dose (< 1%) is excreted unchanged in the urine. Oxidation represents the major degradation pathway.

Results from studies in populations with increased risk factors are scarce for the discussed MAO-A inhibitors except for moclobemide. For this drug it has been shown that neither age nor reduced kidney function influence plasma levels significantly. Liver insufficiency reduces the body's elimination capacity for moclobemide. As a consequence similar doses result in higher plasma concentrations in liver impaired patients than subjects with normal hepatic function and a dose adjustment may therefore become necessary.

Zusammenfassung

Monoamino-Oxidase-Hemmer vom Typ A (MAO-A-Hemmer) werden spezifisch als Antidepressiva eingesetzt. Verschiedene Vertreter dieser therapeutischen Klasse befinden sich derzeit in klinischer Prüfung. In der vorliegenden Arbeit werden verfügbare pharmakokinetische Daten von fünf MAO-A-Hemmern (Moclobemid, Toloxaton, Brofaromin, Cimoxaton, Amiflamin) miteinander verglichen. Da sich die einzelnen Vertreter sowohl in ihren Absorptions- wie Dispositionseigenschaften und Verfügbarkeit unterscheiden, führen ähnliche Dosierungen zu unterschiedlichen Plasmakonzentrations-Zeit-Profilen. Bei einem detaillierten Vergleich zeigt sich jedoch eine starke Ähnlichkeit zwischen Moclobemid und Toloxaton. Beide Verbindungen werden rascher absorbiert als Brofaromin, Cimoxaton oder Amiflamin, und zeigen außerdem eine hohe hepatische Extraktionsrate. Dies führt bei oraler Verabreichung zu einer erheblichen Reduktion der Bioverfügbarkeit während des ersten Leberdurchgangs (F nach Einfachdosierung $\approx 60\%$).

Die Plasmaproteinbindung ergibt bei den verglichenen Pharmaka sehr unterschiedliche Werte. Wiederum sind Moclobemid und Toloxaton einander sehr ähnlich (gebundene Fraktion $f_b \approx 0,5$), während Cimoxaton und Brofaromin stärker ($f_b 0,95-0,98$) und Amiflamin schwächer ($f_b 0,23$) an Plasmaproteine gebunden werden.

Zuverlässige Zahlenwerte für das Verteilungsvolumen sind nur für Moclobemid und Toloxaton erhältlich ($\approx 1,3 \text{ l/kg}$).

Die Plasmakonzentrationen fallen im Körper nach der Verabreichung der einzelnen MAO-A-Hemmer mit unterschiedlicher Geschwindigkeit ab. Dabei findet man für Moclobemid und Toloxaton mit 1–3 h die niedrigsten Halbwertszeiten im Gegensatz zu höheren Werten bei Amiflamin (5–12 h), Cimoxaton (9–16 h) und Brofaromin (12–15 h). Die Ausscheidung aller fünf hier besprochenen Vertreter erfolgt fast ausschließlich über metabolische Veränderungen in der Leber. Nur eine verschwindend kleine Dosisfraktion dieser Substanzen (< 1%) wird unverändert über die Niere ausgeschieden. Beim Metabolismus spielen Oxidationsreaktionen eine entscheidende Rolle. Infolge einer gegenüber der Muttersubstanz verlängerten Halbwertszeit (36 h) wird die Wirkung der MAO-A-Hemmer besonders bei Cimoxaton, durch aktive Metaboliten mitbestimmt. Amiflamin unterliegt einem genetisch bestimmten Polymorphismus vom Debrisoquin-Typ.

-Untersuchungen an Populationen mit erhöhten Risikofaktoren sind, mit Ausnahme von Moclobemid, für die hier verglichenen MAO-A-Hemmer kaum bekannt. Bei Moclobemid zeigte sich, daß weder fortgeschrittenes Alter noch eingeschränkte Nierenfunktion nach Standard-dosen klinisch relevante Änderungen im Plasmakonzentrations-Zeit-Profil bewirken. Aus pharmakokinetischer Sicht ist daher bei diesen Patienten keine Dosisanpassung nötig. Leberschädigungen reduzieren dagegen die Eliminationskapazität für Moclobemid beträchtlich. Bei eingeschränkter Leberfunktion sind deshalb höhere Plasmaspiegel als bei Patienten mit normaler hepatischer Funktion zu erwarten und entsprechende Dosierungsanpassungen vorzusehen.

Einleitung

Monoamino-Oxidasen (MAO) sind mitochondriale Enzyme, die sowohl Aminotransmitter im Nervensystem als auch biogene Amine im Körper abbauen. Bisher wurden zwei verschiedene MAO-Aktivitäten (Typ A und B) nachgewiesen, die sich hinsichtlich ihrer Substratspezifität und Empfindlichkeit gegenüber Inhibitoren (1) unterscheiden. Die neue Generation von MAO-Hemmern zeigt bezüglich Reversibilität und Spezifität der induzierten Inhibitoren unterschiedliche Eigenschaften. Therapeutisch zeigen MAO-Hemmer vom Typ A antidepressive und MAO-Hemmer vom Typ B Antiparkinson-Eigenschaften. Die Ausgangsstruktur der älteren, nichtselektiven und teilweise irreversiblen MAO-Hemmer basiert auf Hydrazin-, Hydrazid- oder Aminstrukturen (Abb. 1), während die neueren reversiblen MAO-A-Hemmer Oxazolidinon-, Benzamid- und Benzofuranderivate sind oder sich von Harmala-Alkaloiden ableiten (Abb. 2). Sämtliche MAO-Hemmer weisen eine von den trizyklischen Antidepressiva unterschiedliche Struktur auf.

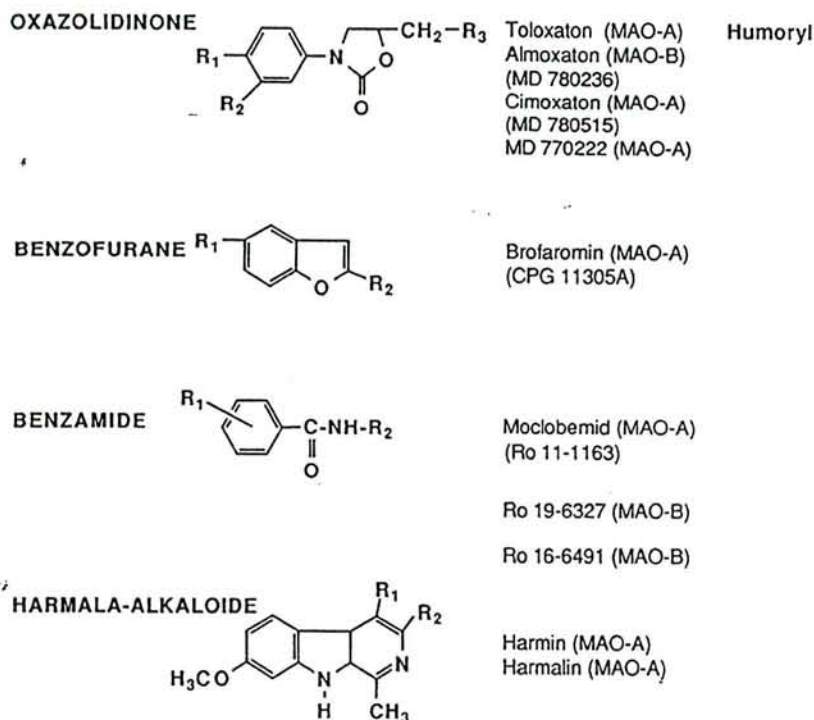
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HYDRAZIDE $\begin{array}{c} R_1-C-NH-NH-CH \\ \quad \quad \quad \\ O \quad \quad \quad R_2 \\ \quad \quad \quad R_3 \end{array}$	Benmoxin Iproniazid Iproclozid Isocarboxazid Nialamid Pivalylbenzhy IH-3	Neuralex Marsilid Sursum Marplan Nlamide Tersavid
HYDRAZINE $\begin{array}{c} R_1-CH_2-CH-NH-NH_2 \\ \\ R_2 \end{array}$	Phenelzin Pheniprazin Phenoxypipazin Octamoxin	Nardelzine ,Nardil Catron Drazine Ximaol ,Nimaol
AMINE Propargylamine $\begin{array}{c} R_1 \\ \\ R_2-CH-N-CH_2-C \equiv CH \\ \\ CH_3 \end{array}$	SU 11-739/5-508/ AGN-1133 Dinitranil Clorgylin Abbott 21,855 L-Deprenyl, Selegilin* Pargylin*	Eldepryl Eutonyl ,Euditron
Cyclopropylamine $R_1-\triangle-NHR_2$	Tranylcypromin AGN-1135* Lilly 49393 Lilly 51641** Lilly 54761* PCO	Tylciprine ,Parnate
Indolethylamine $\begin{array}{c} \text{Indol-Ring} \\ \\ CH_2-CH-NH_2 \\ \\ R_1 \end{array}$	Etryptamin	Monase
Phenylethylamine $\begin{array}{c} R_2 \\ \\ R_1-\text{C}_6\text{H}_4-CH_2-CH-NH_2 \\ \\ R_3 \end{array}$	Amiflamin** (FLA 336)	

* Vorzugsweise MAO-B Hemmer

** Vorzugsweise MAO-A Hemmer

Abb. 1 Chemische Grundstrukturen nicht selektiver MAO-Hemmer

Markennamen [®] Abb. 2 Chemische Grundstrukturen selektiver MAO-Hemmer



Die Kenntnis der pharmakokinetischen Eigenschaften der verschiedenen MAO-Hemmer könnte mithelfen, die therapielevanten Unterschiede zwischen den einzelnen Vertretern zu definieren und die Dosierungsempfehlungen auf eine rationale Grundlage zu stellen. Die vorliegende Übersicht bezweckt daher, die neueren reversiblen MAO-A-Hemmer pharmakokinetisch zu bewerten. Zu diesem Zweck wird die Pharmakokinetik von Moclobemid (2–6), mit der von Toloxaton (7–9), Brofaromin (10–12), Cimoxaton (13–14) und Amiflamin (15) verglichen.

Pharmakokinetische Eigenschaften verschiedener MAO-A-Hemmer

Ähnliche Dosierungen der MAO-Hemmer Moclobemid, Toloxaton, Cimoxaton, Brofaromin und Amiflamin führen zu recht unterschiedlichen Plasmakonzentrationen. Abb. 3 zeigt das unterschiedliche pharmakokinetische Verhalten dieser Substanzen nach einer Einfachdosierung.

Absorption

Nach oraler Verabreichung werden Moclobemid (16–17) und Toloxaton (18) verhältnismäßig rasch absorbiert. Die Zeit für das Erreichen des Konzentrationsmaximums im Plasma t_{max} liegt zwischen 0,5 und 2 h. Die Absorption von Brofaromin (19), Amiflamin (20–21) und Cimoxaton (22–23) verläuft langsamer. Bei diesen Substanzen werden maximale Plasmaspiegel zwischen 1,5 und 4 h erreicht. Die Dosisfraktion, die den systemischen Kreislauf in unveränderter Form erreicht (Bioverfügbarkeit F), ist für Toloxaton und Moclobemid unvollständig. Eine hohe Leberextraktionsrate bewirkt, daß lediglich zwei Drittel der jeweiligen Einfachdosis

den systemischen Kreislauf in unveränderter Form erreichen. Bei den anderen hier angesprochenen Substanzen sind diese Angaben nicht bekannt.

Verteilung und Bindung an Plasmaproteine

Die Verteilung eines Pharmakons im Körper wird durch seine lipophilen Eigenschaften und die Stärke seiner Bindung an Blut- und Gewebe-Makromoleküle bestimmt. Lipophiliewerte ergeben für die in dieser Übersicht verglichenen Substanzen keine Korrelation zwischen den Oktanol-Wasser-Verteilungskoeffizienten und einem anderen der bekannten pharmakokinetischen Parameter (Tab. 1). Das Plasmaproteinbindungsverhalten der verglichenen Substanzen zeigt sehr unterschiedliche Charakteristika (Tab. 1). Amiflamin wird nur unbedeutend (23 %), Cimoxaton und Brofaromin dagegen praktisch vollständig (95–98 %) an Plasmaproteine gebunden; Moclobemid und Toloxaton nehmen in diesem Vergleich eine Mittelstellung (50 %) ein. Für Substanzen mit niedriger Proteinbindung sind Interaktionen mit anderen, gleichzeitig verabreichten Pharmaka zumindest auf der Bindungsebene nicht zu erwarten.

Zur Beschreibung des Ausmaßes einer Verteilung wird oft das scheinbare Verteilungsvolumen herangezogen. Dieses kann jedoch nur nach systemischer Verabreichung bestimmt werden und ist aus der derzeit verfügbaren Literatur lediglich für Moclobemid (0,63–1,6 l/kg) und Toloxaton (1,1–1,6 l/kg) bekannt. Die Größe dieses Verteilungsraumes, der mit dem der Benzodiazepine vergleichbar ist (25), weist darauf hin, daß sich das Pharmakon überwiegend im extravaskulären Raum aufhält. Der rasche Plasmakonzentrationsabfall von Moclobemid und Toloxaton während der ersten

Tab. 1 Pharmakokinetische Parameter reversibler MAO-A-Hemmer¹⁾

Pharmakon	Absorption F	t _{max} h	V l/kg	Verteilung P	f _b %	T _{1/2} h	Ausscheidung Cl l/h/kg	f _e
Moclobemid	0,5–0,8	0,5–2,0	0,63–1,6	40,7	50	1–3	0,2–1,0	< 0,01
Toloxaton	0,5–0,6	0,5–1,0	1,1–1,6	11 ²⁾	50	0,9–2,5	0,46–0,86	< 0,01
Brofaromin		1,8–4,0	4,3–6,0	15,5	98	12–15	0,26–0,29	< 0,01
Cimoxaton		1,0–5,0	0,46–0,69	257	95	8,9–16	0,023–0,045	n. d.
Amiflamin		2	4,2–8,4	0,5	23	4,9–12	0,42–0,83	0,002

¹⁾t_{max}: Zeit der maximalen Konzentration nach Einfachdosierung, f_e: renal ausgeschiedene Dosisfraktion (unveränderte Substanz), f_b: gebundene Fraktion der Substanz im Plasma, V: scheinbares Verteilungsvolumen, F: Bioverfügbarkeit, P: Verteilungskoeffizient in Oktanol/Wasser, Cl: Clearance, n. d.: nicht detektierbar, ²⁾Berechnet nach Hansch und Leo (24)

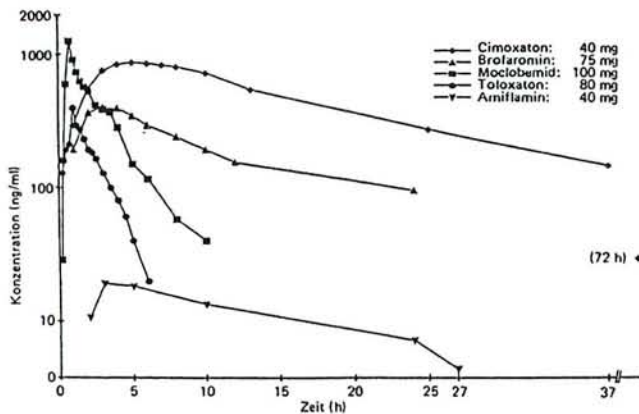


Abb. 3 Plasmakonzentrations-Zeit-Profile von fünf reversiblen MAO-A-Hemmern

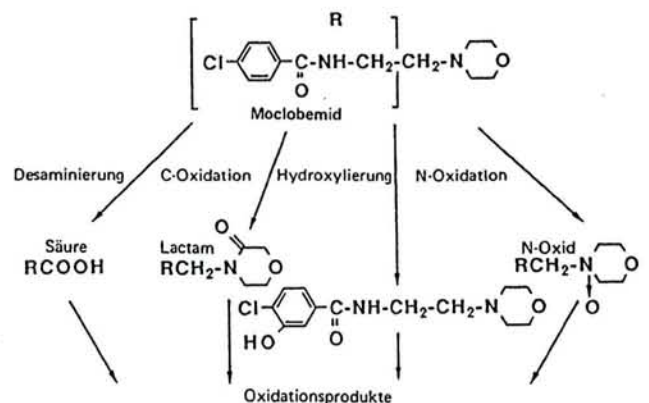


Abb. 4 Metabolismus von Moclobemid beim Menschen

Stunden nach intravenöser Injektion ist eine Folge dieser ausgeprägten extravaskulären Verteilung.

Biotransformation und Ausscheidung

Der markanteste Unterschied zwischen den Konzentrations-Zeit-Profilen der hier verglichenen MAO-Hemmer besteht im unterschiedlich raschen Absinken der Plasmakonzentrationen nach dem Erreichen der Maximalwerte. Die Eliminationshalbwertszeit reicht von wenigen Stunden (Moclobemid, Toloxaton) bis weit über 10 Stunden (Brofaromin, Cimoxaton).

Den wichtigsten Ausscheidungsweg für die fünf MAO-A-Hemmer stellt der Metabolismus in der Leber dar. Nur ein verschwindend kleiner Anteil einer absorbierten Dosis wird in unveränderter Form über die Niere ausgeschieden (Tab. 1). Bei Moclobemid, Toloxaton und Amiflamin verläuft die hepatische Elimination extrem rasch und wird teilweise nur durch den Blutfluß zur Leber begrenzt. Aus diesem Grund wird bei oraler Darreichung ein signifikanter Teil der Dosis während der ersten Leberpassage eliminiert.

Oxidationsreaktionen wie Hydroxylierung und oxidative Desalkylierung/Deaminierung spielen beim Metabolismus der MAO-Hemmer eine wichtige Rolle. Der Metabolismus von Moclobemid ist komplex (Abb. 4). Vier Gruppen von Metaboliten wurden im Urin des Menschen nach Einzeldosen gefunden: saure (49% der Dosis), neutrale (8%) und basische (2%) Metaboliten sowie N-oxide (4,5%).

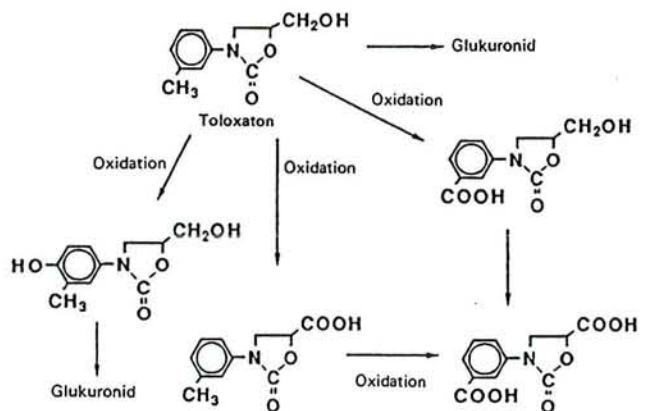


Abb. 5 Metabolismus von Toloxaton beim Menschen

Die metabolische Kaskade wird durch vier primäre Oxidationsreaktionen initiiert: Morpholin-C-Oxidation, Desaminierung, Morpholin-N-Oxidation, aromatische Hydroxylierung (Abb. 5). Oxidationsprodukte des Morpholinrings sind besonders häufig. Sie können alle als Abkömmlinge eines einzigen Oxidationsproduktes betrachtet werden, bei dem der Morpholinring eine zusätzliche Sauerstofffunktion trägt. Als Endprodukte sind die daraus resultierenden Metabolite quantitativ nicht bedeutend, da sie weiteren Abbaureaktionen unterliegen. Im Plasma findet sich der Lactam-Metabolit als eines der Hauptabbauprodukte (inaktiv), da Folgeprodukte

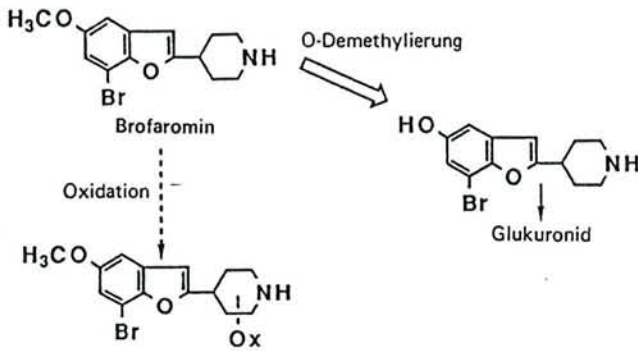


Abb. 6 Metabolismus von Brofaromin beim Menschen

durch ihre Polarität rasch über die Niere ausgeschieden werden können. Der einzige MAO-A-aktive Metabolit, ein N-Oxid, ist im Plasma nur in sehr geringen Mengen meßbar.

Bei Toloxaton (7, 26) führt die Oxidation der primären alkoholischen Gruppe zur Bildung eines inaktiven sauren Metaboliten, der zu 50% für die mit dem Urin ausgeschiedene Dosis verantwortlich ist (Abb. 5). Saure Nebenmetabolite – gebildet durch aromatische Hydroxylierung oder Oxidation der aromatischen Methylgruppe – sind ebenfalls identifiziert worden. Toloxaton selbst und das Phenolderivat werden ausschließlich nach erfolgter Konjugation mit Glukuronsäure im Urin ausgeschieden.

Brofaromin (27) wird hauptsächlich durch O-Desmethylierung der aromatischen Methoxygruppe abgebaut, wodurch ein Glukuronidderivat entsteht (Abb. 6). Nebenmetabolite, die durch Oxidation des Piperidinrings entstanden sind, wurden ebenfalls gefunden.

Der Umbau von Cimoxaton wird durch O-Desmethylierung (Abb. 7) bestimmt (23, 28); dieser Schritt führt zum stärker aktiven Metaboliten MD 770222. Die freigelegte primäre Hydroxylgruppe wird entweder oxidiert oder konjugiert (Glukuronidierung, Sulfatierung). Hydroxylierung des Oxazolidinonrings oder Debenzylierung sind weitere alternative Abbauschritte. Der Oxazolidinonring selbst scheint metabolisch stabil zu sein. Eine Ringöffnung wird, ebenso wie bei anderen Derivaten, nicht beobachtet (Toloxaton, ref. 29–30; Metaxalon, ref. 31; Mephinoxalon, ref. 32). Die Biotransformation von Amiflamin wird durch N-Desmethylierung des tertiären Amins bestimmt (Abb. 8). Diese Reaktion unterliegt einem genetisch determinierten Polymorphismus vom Debrisoquin-Typ (33–34). Dabei können langsame und schnelle Metabolisierer unterschieden werden. Bei Patienten mit defizientem Metabolismus können Nebenwirkungen schon bei sonst gut verträglichen normalen klinischen Dosen auftreten. Bei Moclobemid ergab eine retrospektive Beurteilung sämtlicher phänotypisierter Probanden aus pharmakokinetischen Studien kein Zusammenfallen der metabolischen Abbaugeschwindigkeit mit den Debrisoquin-Phänotypen.

Mehrfachdosierung

Aufgrund von pharmakokinetischen Überlegungen gilt, daß nach Mehrfachdosierung eines Pharmakons die Höhe der mittleren Fließgeschwindigkeitskonzentration

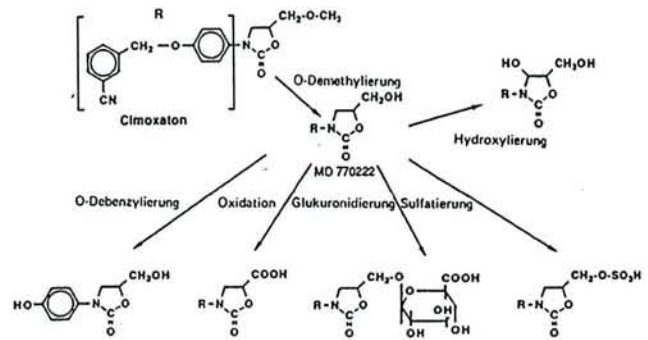


Abb. 7 Metabolismus von Cimoxaton beim Menschen

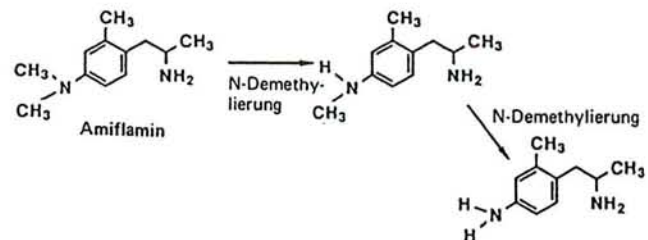


Abb. 8 Metabolismus von Amiflamin beim Menschen

nen durch Dosierung, Einnahmefrequenz und Clearance bestimmt wird. Die Halbwertszeit gibt Hinweise auf die Zeitdauer, die bei Dosierungsänderungen bis zur Einstellung neuer Gleichgewichtsbedingungen benötigt werden. Außerdem bestimmt dieser Term die Differenz zwischen den höchsten und tiefsten Konzentrationswerten während eines Dosierungsintervalls. Substanzen wie Moclobemid und Toloxaton werden deshalb stärkere Konzentrationsschwankungen innerhalb eines gewählten Dosierungsintervalls (τ 8–12 h) zeigen als die drei übrigen MAO-A-Hemmer (τ 24 h). Andererseits wird der Konzentrationsunterschied nach Einfach- und Mehrfachdosierung bei den Substanzen mit längeren Halbwertszeiten größer als bei den Vertretern mit kürzeren Halbwertszeiten. Solche Voraussagen basieren auf der Annahme einer dosisunabhängigen Kinetik. Im Fall von Moclobemid wurde allerdings gezeigt, daß Mehrfachdosierung vermutlich infolge Hemmung des metabolischen Abbaus durch ein Zwischen- oder metabolisches Endprodukt zu höheren Plasmaspiegeln als erwartet führt. Steady-state-Konzentrationen werden deshalb mit Moclobemid erst nach einer einwöchigen Therapie erreicht.

Für Cimoxaton mit einer Halbwertszeit zwischen 9 und 16 h ist zu erwarten, daß ein Fließgleichgewicht innerhalb von drei bis vier Tagen erreicht ist. Diese Schätzung ist durch Versuchsdaten bestätigt worden. Allerdings ist die Halbwertszeit für den aktiven Metaboliten bedeutend länger ($\approx$ 36 h), weshalb ein Fließgleichgewicht unter Einschluß dieses Metaboliten erst nach 8 bis 11 Tagen erreicht wird.

Pharmakokinetik von Moclobemid bei Risikopopulationen

Moclobemid scheint heute der am besten pharmakokinetisch charakterisierte MAO-A-Hemmer zu sein. Nur für diese Substanz sind Absorptions- und Dispositionsverhalten bei Patienten mit erhöhten Risikofaktoren (Alter, Nieren, Leberinsuffizienz), bekannt (35–37).

Risikofaktor Alter

Bei älteren Patienten ergaben sich nach oraler Verabreichung einer Einzeldosis von 100 mg Moclobemid nach subchronischer Verabreichung über 14 Tage (100 mg t. i. d.) hinsichtlich der Bioverfügbarkeit, wie auch der Halbwertszeit und des Akkumulationsverhaltens ähnliche Werte wie bei einer Vergleichsgruppe junger Probanden. Demgemäß braucht die Dosierungsweise für Moclobemid mit dem Alter nicht geändert zu werden.

Reduzierte Nierenfunktion

Nachdem Moclobemid hauptsächlich über metabolische Wege eliminiert und außerdem nicht intensiv an Plasmaproteine gebunden wird, ist nicht zu erwarten, daß Patienten mit Niereninsuffizienz eine wesentlich veränderte Ausscheidungskinetik zeigen. Diese Voraussage wurde in einer kürzlich durchgeführten Studie (36) bestätigt. Eine Anpassung der Dosis ist demzufolge bei Patienten mit reduzierter Nierenfunktion nicht erforderlich.

Reduzierte Leberfunktion

Leberschädigungen reduzieren die Eliminationskapazität des Körpers für Moclobemid drastisch (37). Nach intravenöser Dosierung ist die systemische Clearance bei Patienten mit schwerer chronischer Leberinsuffizienz, gegenüber einer gesunden Vergleichspopulation stark reduziert (14,6 vs. 37,7 l/h). Da die Verteilungscharakteristik unverändert ist (V_{ss} 75,7 l), resultiert daraus eine entsprechende Verlängerung der Eliminationshalbwertszeit (3,9 vs. 1,7 h). Nach oraler Verabreichung einer Einzeldosis von 100 mg ist bei diesen Patienten der Leber-first-pass-Effekt merklich reduziert (F 0,84 vs. 0,56) und die maximale Plasmakonzentration stark erhöht (1607 vs. 582 ng/ml).

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Résumé

La résorption du moclobémide à partir du tractus gastro-intestinal est rapide et complète et n'est pas influencée par la prise de repas. Un taux d'extraction hépatique élevé conduit à un effet de premier passage hépatique important. Une dose orale de 100 mg donne une biodisponibilité orale absolue de 60 %. En augmentant les doses, apparaît une saturation du métabolisme hépatique durant l'effet de premier passage hépatique conduisant à une augmentation de la biodisponibilité, surtout avec des doses ≥ 400 mg. Le moclobémide est entièrement éliminé de l'organisme par métabolisme hépatique. Le temps de demi-vie d'élimination est court. Des quantités négligeables sont excrétées dans le lait maternel. Après traitement chronique, la clairance orale varie durant la première semaine, puis les concentrations plasmatiques restent constantes avec des valeurs doubles de celles prédites à partir d'une prise orale. Les concentrations plasmatiques à l'état d'équilibre augmentent de façon non-proportionnelle en augmentant les doses orales de 100 à 150 mg 3 x/jour, due à une inhibition du métabolite affectant l'élimination par premier passage et disposition. Ni l'âge avancé, ni l'insuffisance rénale n'affectent les concentrations plasmatiques après prise de moclobémide, par contre l'insuffisance hépatique réduit la clairance hépatique du moclobémide ainsi la posologie doit être diminuée chez l'insuffisant hépatique pour obtenir des concentrations semblables à celles des sujets sains.

Mots clés

Pharmacocinétique - Moclobémide - IMAO-A - Dose unique - Dose multiple - Insuffisance rénale - Insuffisance hépatique - Gériatrie - Nouveau-né - Polymorphisme génétique.