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Intravenous single administration of amiodarone and breastfeeding

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ABSTRACT

Amiodarone treatment is contraindicated during breastfeeding. As the regional pharmacovigilance center, we were contacted for information relative to the possibility of breastfeeding after single intravenous administration of 450 mg amiodarone to a breastfeeding woman.

A monitoring of amiodarone concentration in plasma and milk was performed in the mother. At day 4, milk concentration of amiodarone reached a peak (233 µg/L) and milk to plasma ratio was determined to 3.5. Milk concentration was still detectable at day 10 (132 µg/L). The maximal relative infant dose was estimated to be 0.6% of the maternal weight-adjusted dosage, corresponding to 0.18% of the usual posology used in children by parenteral route.

The review of the literature retrieved one publication suggesting that a single intravenous administration of 150 mg of amiodarone to a mother represents a negligible infant risk based on low breast milk concentration. The French National Pharmacovigilance database query did not disclose any case of side effects during breastfeeding after a single dose of amiodarone.

A very limited exposition of breastfed newborns to amiodarone, as well as a low risk of side effects, is expected after a single administration of amiodarone to their mothers.

Keywords: breast feeding, amiodarone, newborn, adverse effects

PATIENT CASE

An emergency caesarean was performed at 36 weeks of amenorrhea in a 30-year-old woman due to a retroplacental haematoma and preeclampsia. Despite a parenteral furosemide (40 mg per day) and nicardipine (4 mg per hour) therapy, the arterial hypertension remained uncontrolled during the postoperative period. Furthermore, a thrombocytopenia at 46 G/L was observed leading to administration of platelet concentrates. The day after, platelet count increased (101 G/L) and a scanner using iomeprol was performed to evaluate the presence of abdominal hematoma. No haemorrhagic focus was observed. Few minutes after this examination, an increase of the heart rate (140 bpm) occurred and led to the administration of an intravenous single dose of 450 mg of amiodarone (off-label use). Furosemide was discontinued due to polyuria. Arterial hypertension was stabilized with addition of labetalol (600 mg per day) and nicardipine was stopped two days later. Nefopam (20 mg q.i.d.) and metoclopramide (10 mg per day) were intravenously administered to manage postoperative algia, nausea and vomiting, respectively. The patient was admitted to the maternity unit for clinical monitoring. During her hospitalization, she expressed a strong desire for breastfeeding and all the medications at the exception of labetalol were stopped. By way of precaution, the patient began to discard her breast milk.

As regional pharmacovigilance centre, we were contacted to evaluate the possibility of breastfeeding with the medications (especially amiodarone) taken by the patient during her hospitalization. To answer this question, we reviewed the medical literature and performed a monitoring of amiodarone plasma and milk concentrations to evaluate the exposition to amiodarone for the newborn.

LITERATURE REVIEW

The review of the literature was based on the information available in the Summary of Product Characteristics (SmPC) [1–7] as well as in a reference book [8] and databases (lactmed [9], e-lactancia [10], MICROMEDEX® [11]) in the field of pregnancy and breastfeeding. The summary of the retrieved data is presented in Table 1.

DRUG ANALYSIS

Amiodarone and desethylamiodarone were assayed in plasma and breastmilk with Sciex QTrap® 4500 liquid chromatography tandem-mass spectrometry (LC-MS/MS) (Sciex, Villebon sur Yvette, France) using the Chromsystems commercial method for antiarrhythmic drugs (Chromsystems, Gräfelfing, Germany). Briefly, 50 µL of plasma or milk samples were added with 25 µL of extraction buffer and 250 µL of deuterated internal standard. After vortexing and centrifugation of the mixture, 10 µL of the supernatant after a 10-fold dilution were injected in the LC-MS/MS system. The quantification limits were 70 µg/L and 200 µg/L for amiodarone and desethylamiodarone, respectively.

Plasma and milk samples were collected on days 2, 3, 4 and 3, 4, 10 after amiodarone administration, respectively. Results are presented in Figure 1.

DISCUSSION

According to summaries of product characteristics, labetalol, nicardipine, metoclopramide, nefopam, iomeprol and furosemide are not contraindicated during lactation.

Furthermore, according to the lactation reference databases, publications or books, the newborn was exposed to a dose of labetalol, nicardipine or nefopam estimated to represent less than 3% of

the weight-adjusted maternal dose allowing to consider maternal breastfeeding (Table 1). For iomeprol, only limited data are available but the summary of product characteristics specifies that breastfeeding is possible after a single dose of this medication. Considering diuretics, hydrochlorothiazide at the lowest effective dose is generally preferred to furosemide which is responsible of an intense diuresis decreasing lactation. However, furosemide is considered as probably compatible with breastfeeding. Finally, if some infants could be exposed to pharmacologically active serum levels of metoclopramide during breastfeeding, most of them would receive less than 10% of the maternal weight-adjusted dosage. Thus, metoclopramide should be discontinued during lactation.

Contrary to other administered drugs, amiodarone is contraindicated during breastfeeding as mentioned in the summary of product characteristics. Indeed, this class III antiarrhythmic drug (Vaughan Williams' classification) is known to display high lipophilicity and high distribution volume of 65.8 L/kg [12] resulting to its passage into milk. In our case, concentration of amiodarone measured in plasma and milk of the mother ranged from 67 to 94 µg/L and from 132 to 233 µg/L, respectively. These determined plasma concentrations were about 5-fold less than the lowest concentration described as therapeutic (N: 500-2500 µg/L – [13]) and were undetectable 4 days after the single administration of amiodarone. Amiodarone reached a peak concentration of 233 µg/L in milk at day 4, which was similar to the concentration reported by Khurana *et al.* of 190 µg/L observed 4 days after a single amiodarone IV administration of 150 mg [14]. The observed delay between the plasma and the milk concentrations is illustrated by the value of milk to plasma ratio (M/P), described from 2.3 to 9.1 [12]. In our case, this ratio was determined according to Chaves and Lamounier and was equal to 2.2 and 3.5 at day 3 and 4, respectively [15]. This calculation method, based on single paired maternal milk and plasma concentrations, is not recommended by the “Clinical Lactation Studies” FDA guidance [16]. It is advocated to use the ratio of AUC_{milk} to AUC_{plasma} . However, in the present clinical case, the number of collected samples was driven by real

life conditions and it was not possible to perform relevant AUC determination since this determination needs at least 5 to 6 samples [17].

However, if the M/P ratio is of primary interest in understanding the mechanisms of drug transfer, it is sometimes erroneously considered as a predictor risk to the infant [17]. Thus, the assessment of exposure risk of newborn requires the determination of milk concentrations, allowing the calculation of the absolute (AID) and/or the relative infant dose (RID) [17] as follow:

$$\text{AID } (\mu\text{g/kg/day}) = (\text{Drug concentration in milk } (\mu\text{g/L}) \times \text{Volume of ingested milk } (\text{L/kg/day}))$$

$$\text{RID } (\%) = (\text{AID } (\mu\text{g/kg/day}) \times 100) / \text{Maternal dose } (\mu\text{g/kg/day})$$

Based on a mean volume of ingested milk of 0.150 L/kg/day [15] for a newborn, AID was at most 35 $\mu\text{g/kg/day}$ corresponding to an RID of 0.6% of the maternal dose. This RID is similar to the value of 1% previously reported by Khurana *et al.* [14]. In addition, the amiodarone posology generally described for arrhythmias in children consists in an IV bolus of 5mg/kg followed by a 10 to 15 mg/kg/day maintenance infusion (ie 15-20 mg/kg/day) [6]. The AID of 35 $\mu\text{g/kg/day}$ would correspond to 0.18 % of this posology, if an oral bioavailability of 100% was considered. However, since the oral amiodarone bioavailability ranges usually between 22 to 86% [12], the dose ingested by the newborn would be probably lower. This very poor exposition of the newborn to amiodarone after a single administration suggests a very low risk of side effects during breastfeeding. Despite this theoretical low risk, breastfeeding was delayed for 3 weeks after delivery as a precaution since amiodarone was still detectable in milk at 10 days after amiodarone administration.

To the best of our knowledge, the review of the literature found only one reported case of hypothyroidism in a newborn exposed to amiodarone during the last 6 weeks of pregnancy and during 5 weeks of lactation. However, amiodarone was discontinued 1 week after delivery [18].

Since amiodarone contains two iodine atoms per molecule, the intake of an AID of 35 $\mu\text{g/kg/day}$ leads to an iodine exposition of 14 $\mu\text{g/kg/day}$. It corresponds to 34 $\mu\text{g/day}$ in the present case (baby weight of 2.46 kg). This amount is smaller than the iodine daily intake recommendations for newborn of 90 $\mu\text{g/day}$ and 110 $\mu\text{g/day}$ defined by the WHO and the National Institutes of Health of United States, respectively [19,20]. Thus, the risk of thyroid dysfunction of a breastfed infant after a single intravenous dose of 450 mg to his mother appears as negligible.

The query within the French National Pharmacovigilance database retrieved no reported case of side effects after an amiodarone exposition during breastfeeding.

In conclusion, excretion of amiodarone in milk was showed in a woman who received a single intravenous dose of 450 mg of amiodarone. Peak milk concentration was observed at day 4 and amiodarone concentration was still detectable at day 10. The exposure risk for the newborn was low since the absolute infant dose represented only 0.18 % of the amiodarone dosage generally used for arrhythmias in children. Furthermore, it was estimated that the iodine exposition was about 3 times lower than the recommended iodine daily intake, suggesting a negligible risk of thyroid dysfunction.

Finally, it is possible to consider that a single administration of amiodarone to a mother is poorly associated with a risk of side effects for the breastfed newborn.

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Table 1: Summary of data about breastfeeding during treatment with labetalol, furosemide, nicardipine, nefopam, metoclopramide and amiodarone according to summary of product characteristics (SmPC) and references book and databases.

| International Non-proprietary Name (INN) | Labetalol | Furosemide | Nicardipine | Nefopam | Metoclopramide | Iomeprol | Amiodarone |
|--|--|---|--|---|--|---|--|
| Example of one SmPC | TRANDATE [2] | DIURESAL [3] | NICARDIPINE MERCURY [4] | ACUPAN [1] | METOCLOPRAMIDE TEVA [5] | IOMERON [7] | CORDARONE X [6] |
| SmPC - Contraindications during breastfeeding (section 4.3) | Not contraindicated | No | No | No | No | No | Yes |
| SmPC – other relevant information related to breastfeeding (section 4.6) | Excreted in breast milk. Breast-feeding not recommended | Excreted in breast milk. Breast-feeding not recommended. May inhibit lactation. | Excreted in breast milk (at very low concentrations) Breast-feeding not recommended. Insufficient information in newborns/infants. | Excreted in breast milk Insufficient information in newborns/infants | Excreted in breast milk (at low concentrations). Breast-feeding not recommended or should be discontinued Adverse reactions in the breast-fed baby cannot be excluded. | No data about excretion in human breast milk. Stopping breastfeeding is unnecessary. Minimal absorption by the gastrointestinal tract of the young. Adverse effects on the infant are unlikely to occur. | Excreted into the breast milk in significant quantities. |
| E-lactancia [10] | Very low risk | Low risk probable | Very low risk | Absence of monograph | Very low risk | Absence of monograph | High risk probable |
| Lactmed [9] | | | | | | | |
| Levels in milk | Low | Little available information | Low (indetectable till 18,5 µg/L) | Small (6 to 299 mcg/L) | Variable amount | Absence of monograph | Unpredictable but can be high |

| | | | | | | | | |
|-----------------------------------|---------------------------------------|---|---------------------------------|--|---|---|----------------------|---|
| | Ingested amount by the infants | Small (between 0.004% and 0.07% of the maternal dose) | | Small (between 0.006% to 0.33% of the maternal dose) | < 3% of the maternal dose | < 10% of the maternal dose but could achieve pharmacological active serum levels | | Unpredictable but can be high with a dose of amiodarone + desethylamiodarone between 3.5 and 45% of the maternal dose (median 11%) |
| | Expected adverse reactions | Not be expected in fullterm infants | | Not be expected to cause any adverse effects | No influence of neurobehavioral scores of neonates. | | | Thyroid dysfunction (n=1) and possibility of cardiac effects |
| | Special precaution in infants | No, except in preterm infant (preferred other agents) | Yes, prefer an alternate drug | No | Breastfeeding is acceptable | | | Controversy about the possibility of administration : monitoring of infant cardiac and thyroid function status especially if only a single dose is given. |
| Micromedex (Reprotox) [11] | | | | | | | | |
| | Levels in milk | Very Low | Excreted (levels not specified) | Small amount (levels not specified) | Not specified | Excreted in unknown levels | Absence of monograph | Concentrations from 0.5 to 14.4 mg/L for amiodarone and from 0.4 to 5.7 mg/L for desethylamiodarone. |
| | Ingested amount by the infants | 0.3% of the maternal dose | Not specified | Less than 0.3% of the usual infant dose | Not specified | Unknown but presence of detectable serum concentrations (M/P = 2) | | Not specified |
| | Expected adverse reactions | Bradycardia (n=1) | Not specified | Not specified | Not specified | Mild intestinal discomfort (n=2) and possibility of elevation of prolactin concentrations | | Yes, but not specified |
| | Special | Not specified | Not specified | Not specified | Not specified | Not specified | | Contreversy about the |

| | | | | | | | | |
|------------|--|--|-------------------------------------|----------------------|---|----------------------|-----------------|---|
| | precaution in infants | | | | | | | possibility of administration : keep the dose as low as possible and observe neonate carefully for disturbances of thyroid function |
| Briggs [8] | Limited Human data – Probably Compatible | Limited Human data – Probably Compatible | No human data – Probably Compatible | Absence of monograph | Limited human data – Potential Toxicity | absence of monograph | Contraindicated | |

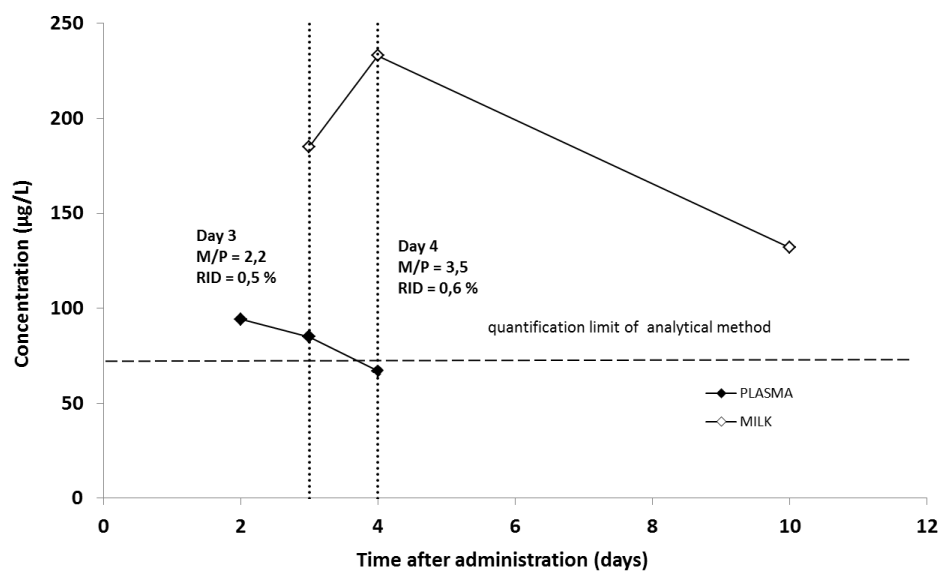


Figure 1: Evolution of amiodarone concentration in plasma and breast milk. Milk to plasma ratio (M/P) and relative infant dose (RID) were determined at day 3 and day 4 (vertical dashed line). Desethylamiodarone was below the quantification limit over the whole period (data not shown).