Paediatric and Perinatal Drug Therapy **Volume 4, Issue 1, 2000**

Excretion of Nicardipine in Human Milk

Pierre-Henri Jarreau
Department of Neonatal Intensive Care, Hôpital Port Royal, Paris, France

Christine Le Beller
Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Paris, France

Marianne Guillonneau
Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Paris, France

Evelyne Jacqz-Aigrain
Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, Paris, France

Abstract

*Eleven hypertensive women were treated with nicardipine orally (*n = *10) or intravenously (*n = *1) during pregnancy and treatment was maintained after birth. Breast milk was collected over a period of 24 hours at steady-state, 4–12 days after birth, and nicardipine concentrations were measured by gas chromatography–mass spectrometry in breast milk. Small amounts of the drug were found in the milk and we conclude that breast-feeding under nicardipine at the usual doses is permissible.*

Key words: Breast milk – Nicardipine

Introduction

Calcium channel blockers have potential advantages over other drugs in the treatment of hypertension, particularly during pregnancy. They cause vasorelaxation and lower peripheral vascular resistance, and diminish vascular sensitivity to vasopressive hormones. Among them, nicardipine, which acts more selectively than nifedipine on blood vessels, is prescribed increasingly for the treatment of hypertension during pregnancy[1]. It has been reported to be safe and effective for mothers at the usual doses with no evident adverse effects on foetuses and neonates[2,3]. It may be continued after delivery to control maternal blood pressure. Because it is not known whether nicardipine is excreted in human milk, we cannot make a clear recommendation on whether breast feeding should be discouraged. This study was therefore undertaken to quantify the excretion of nicardipine in human milk.

Methods

Subjects

Eleven women requiring antihypertensive treatment received nicardipine and were included in the study, after informed consent. Five had gestational hypertension, three had pre-eclampsia and three had essential hypertension prior to pregnancy. They were aged 34 ± 7 years. Caesarean delivery was performed on six patients and the other five delivered spontaneously. At birth, the babies weighed 2.2 ± 0.5 kg and had a gestational age of 36.5 ± 2.6 weeks. Clinical examination at birth was normal for all infants.

Sample Collection and Analysis

Samples were collected for 24 hours, between day 2 and day 14 after birth. On the day of sample collection, mothers were treated with nicardipine

in the standard oral tablet form (40–80 mg/24 h, $n = 4$), with the slow release oral form (100–150 mg/24 h, $n = 6$) or with the intravenous form (120 mg/24 h, $n = 1$). They agreed to collect all of the milk with a breast pump for 24 hours. The total milk volume was measured and aliquots were kept for the determination of nicardipine concentrations. In addition, a maternal blood sample (drawn from an antecubital vein) and a milk sample were collected simultaneously 3 h after oral dosing. Nicardipine concentrations in plasma and milk were measured by gas chromatography–mass spectrometry, using a method adapted from Higuchi[4]. The sensitivity limit was 5 ng/ml and recovery from the plasma was 92.5 ± 5.3% ($n = 6$).

Analysis of Data

Data analysis was performed following the guidelines for studies of the passage of drugs into breast milk[5]. The milk to plasma ratio was determined from paired data obtained under intravenous treatment ($n = 1$) or 3 h after drug intake in patients treated orally ($n = 7$). The maximum milk concentration was the maximum concentration observed in milk samples over the period of collection. The maximum dose that the infant would ingest was calculated assuming a rate of ingestion of 150 ml/kg/day. The result is given in absolute amounts per kilogram and day, and also expressed as a percentage of the weight-adjusted maternal daily dose. Results are expressed as mean ± standard deviation. Individual data are presented in Table 1.

Results

Eleven mothers took part in the study while undergoing treatment with nicardipine. They collected 4 ± 2 milk samples per patient, 4–14 days after delivery. The milk to plasma ratio, measured 3 h after dosing, was 0.25 ± 0.23 (range 0.08–0.75) ($n = 8$). The maximum milk concentration was 7.3 ± 4.9 ng/ml (range: 1.9–18.8, $n = 11$). The mean milk concentration was 4.4 ± 4.0 ng/ml (range: 1.3–13.8, $n = 11$).

The maximum dose to the infant was 1.1 ± 0.7 mg/kg/day (range: 0.3–2.8, $n = 11$). Therefore the amount of nicardipine that a suckling infant would ingest in a day is at a maximum of 0.07 ± 0.04% of the weight-adjusted maternal daily dose (range: 0.03–0.14, $n = 11$). The highest values (2.8 mg/kg and 0.14%) corresponded to the patient's receiving intravenous nicardipine. If the neonatal oral dose of nicardipine, extrapolated for doses used in children, is assumed to be 1 mg/kg/day, then an infant would ingest on average a maximum of 0.3% of this dose.

Discussion

Data on excretion in breast milk are available for nifedipine[6]. This study included 11 pregnant women studied in the early puerperium and demonstrated that excretion of nicardipine through breast milk was limited. There is very little data available for verapamil[7] and diltiazem[8] and there is no data available for nicardipine.

Table 1. Individual data of nicardipine-passage into breast milk in 11 patients

	Maternal dosage (mg)	Milk/plasma ratio*	Maximum milk concentration (ng/ml)	Maximum dose ingested by the infant (ng/kg/day)*	Maximum dose ingested by the infant (as a percentage of the weight-adjusted maternal daily dose)
1	20 × 3 S	0.25	1.9	285	0.03
2	20 × 2 S	0.40	5.2	780	0.12
3	20 × 4 S	0.75	9.7	1455	0.11
4	20 × 2 S	0.12	5.9	885	0.13
5	50 × 2 SL	0.09	1.8	273	0.02
6	50 × 3 SL	0.13	4.3	640	0.03
7	50 × 2 SL	–	4.1	612	0.04
8	50 × 2 SL	–	9.8	1468	0.09
9	50 × 2 SL	–	10.3	1545	0.09
10	50 × 2 SL	0.17	8.2	1230	0.07
11	120 IV	0.08	18.8	2823	0.14

Maternal treatment: Standard (S), SL (slow release) or intravenous (IV) forms of nicardipine.
*The milk to plasma ratio was determined 3 h after maternal dosing.

Nicardipine administered orally has a low systemic availability. The drug is more than 95% protein bound. It undergoes oxidative metabolism, the major metabolites excreted in urine being inactive. The extent of drug excretion in human breast milk is, as yet, unknown, but animal studies indicate that nicardipine is excreted in maternal milk. In our study, the maximum nifedipine concentration in milk after oral dosing ranged from 1.8 ng/ml to 10.3 ng/ml and was 18.8 ng/ml during continuous intravenous administration of 120 mg/day.

The maximum amount of drug that a suckling baby would ingest can be calculated and compared with the weight-adjusted maternal daily dose and/or to the therapeutic neonatal dose. Therefore the amount of nicardipine that a suckling infant would ingest in a day is at a maximum of 0.07 ± 0.04% of the weight-adjusted maternal daily dose. If the neonatal oral dose of nicardipine, extrapolated for doses used in children, is assumed to be 1 mg/kg/day, then an infant would ingest on average a maximum of 0.3% of this dose.

As expected from high-protein binding to plasma proteins, the quantity of drug that passes into milk is small and exposure to nicardipine through breast-milk is minor. Therefore the risk to the suckling infant of administering nicardipine to the mother is very limited and breast-feeding is permissible. Because data are limited, we would advise careful observation of the baby, especially if premature and/or small for its gestational age.

References

1. Carbonne B, Jeannet D, Touboul C, Khelifati Y, Milliez J. Nicardipine treatment of hypertension during pregnancy. Obstet Gynecol 1993; 81: 908–914.
2. Jannet D, Carbonne B, Sebban E, Milliez J. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. Obstet Gynecol 1994; 84: 354–359.
3. Magee LA, Schick B, Donnenfeld AE, Sage SR, Conover B, Cook L, McElhatton PR, Schmidt MA, Koren G. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. Am J Obstet Gynecol 1996; 174: 823–828.
4. Higuchi S, Kawamura S. Specific determination of plasma nicardipine hydrochloride levels by gas chromatography–mass spectrometry. J Chromatogr 1981; 223: 341–349.
5. Guidelines for studies on the passage of drugs into breast milk – WHO Working Group; pp. 59–64.
6. Mannine AK, Juhakoski A. Nifedipine concentrations in maternal and umbilical serum, amniotic fluid, breast milk and urine of mother and offspring. Int J Clin Pharm Res 1991; 11: 231–236.
7. Saulnier JL. Medicaments et allaitement. Encycl Med Chir Pédiatrie 1997; Elsevier Eds, Paris, pp. 4002-X-50.
8. Okada M, Inoue H, Nakamura Y, Kishimoto M. Excretion of diltiazem in breast milk. N Eng J Med 1984; 312: 992.