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Short communication

Nicardipine in pre-eclamptic patients: placental transfer and disposition in breast milk

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To assess the safety risks to the fetus and neonate caused by maternal use of nicardipine in pre-eclamptic patients, we evaluated the placental transfer and the transfer to breast milk after maternal intravenous administration of nicardipine. In ten pre-eclamptic subjects, nicardipine concentrations of maternal blood (P) and both arterial and venous umbilical cord blood samples ($U_{arterial}$ and U_{venous}) were assessed, and the U/P ratio was calculated as an indication of placental transfer. We found a median transfer of 0.15 ($U_{arterial}$/P, range 0.05–0.22) and 0.17 (U_{venous}/P, range 0.023–0.22). The highest umbilical cord concentration found after maternal dosage of 4.5 mg/hour was 18 ng/ml, which can be considered as subtherapeutic. Therefore, adverse fetal reactions caused by a direct pharmacological effect of nicardipine are unlikely to occur. Nicardipine levels were determined in 34 breast milk samples of seven women, and were found to be undetectable in 82% of the samples. In six breast milk samples of four different women, nicardipine levels (ranging from 5.1 to 18.5 ng/ml) were detectable during maternal nicardipine dosages ranging from 1 to 6.5 mg/hour. The maximum possible exposure of a neonate to nicardipine was calculated to be less than 300 ng/day, which is an insignificant fraction of therapeutic dosages used in neonates. In conclusion, the exposure of a fetus and neonate to nicardipine through placental transfer and disposition in breast milk expression is low.

Keywords Lactation, nicardipine, placental, pre-eclampsia, transfer.

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Introduction

The main goal of treatment of severe pre-eclampsia is to lower elevated blood pressures to prevent complications to the mother and, in early-onset pre-eclampsia, to prolong the pregnancy to improve fetal outcome. The ideal antihypertensive drug for the treatment of severe hypertension in pre-eclampsia should be potent, rapidly acting, easy to titrate and does not cross the placenta. As yet no such drug is available. Intravenous administration of the calcium-channel blocker, nicardipine, has been used effectively to control blood pressure in women with pre-eclampsia.[1] The drug has shown high potency to lower maternal blood pressure, while its fast onset of action and its short elimination half-life (2–5 minute) enables accurate blood pressure control. Use of calcium-channel blocking agents with a dihydropyridine structure, e.g. nifedipine and nicardipine, has been considered hazardous in pregnant women because of studies showing fetal acidosis in pregnant rhesus monkey and sheep treated with nifedipine and nicardipine.[2,3] However, extensive experience with nifedipine as a tocolytic drug has not shown any negative effects on fetal or uteroplacental circulation.[3] There are scarce fetal and neonatal outcome data after maternal use of nicardipine, but the available data showed an outcome comparable with neonates from pre-eclamptic patients, treated with other antihypertensive drugs.[1]

Still, maternal use of nicardipine may expose the fetus to pharmacologically active concentrations of the drug, whereas postnatally, the neonate may be exposed to nicardipine during lactation. Because data regarding placental transfer and transfer into breast milk are lacking, we determined placental transfer of nicardipine and disposition of nicardipine in breast milk.

Methods

Patients with severe pre-eclampsia were treated at the Obstetric Medium Care Unit at our antenatal ward, with

intravenous nicardipine in 2004–2005 after failure to control blood pressure with intravenous ketanserin or dihydralazin (in combination with methyldopa orally). Severe pre-eclampsia was defined as the occurrence after 20 weeks of gestation of a diastolic blood pressure ≥110 mmHg and proteinuria ≥0.3 g/l in a 24-hour urine collection, or the occurrence of repetitive diastolic blood pressure >90 mmHg in combination with haemolysis, elevated liver enzymes and low platelet count (HELLP)-syndrome. HELLP syndrome was defined as alanine aminotransferase and/or aspartate aminotransferase >31 U/l, platelet count less than 100×10^9 platelets/l and haptoglobin less than 0.28 g/l. At admission, diastolic blood pressure was measured at Korotkoff phase V using mercury sphygmomanometer. During admission, intra-arterial blood pressures were measured via a radial artery catheter. Target diastolic arterial blood pressure (DAP) was <100 mm Hg (<90 mmHg for women with HELLP syndrome) measured intra-arterially. Treatment with nicardipine started with continuous intravenous infusion of 3 mg/hour, and as soon as target DAP was reached, the dose was reduced. Nicardipine doses were subsequently titrated according to the blood pressure with increments of 0.5–1 mg/hour to a maximum of 10 mg/hour.

Nicardipine was continued as long as the fetal and/or maternal condition did not warrant delivery, as judged by the attending obstetrician.

To determine the placental transfer, a maternal blood sample was drawn just before delivery, and umbilical cord blood samples, both arterial and venous, were drawn just after delivery. Both arterial and venous concentration levels were studied to obtain information with respect to fetal metabolism of nicardipine.

To determine exposure during lactation, breast milk was collected from women until 24 hours after nicardipine was stopped after delivery. None of the neonates received breast milk, while mothers were receiving, and after 24 hours nicardipine was stopped according to hospital protocol. After each breast milk collection, a maternal blood sample was drawn.

Plasma samples and breast milk samples were stored at –18°C until analysis.

Nicardipine levels in plasma and breast milk were determined using a validated reversed-phase high-performance liquid chromatographic assay, with UV detection developed in our hospital pharmacy. The lower limit of quantification (LOQ) of nicardipine in plasma and in breast milk were 1.4 and 5.0 ng/ml, respectively. The inter-day variation (reproducibility) for the concentrations 10, 50 and 100 ng/ml for plasma were 4.6, 2.1 and 3.9% and for breast milk 6.5, 4.8 and 4.2%, respectively.

The concentration ratios of nicardipine in umbilical cord plasma (both arterial and venous [$U_{a,v}$]) versus maternal plasma (P) were used as a measure of placental transfer (U/P). The concentration ratios of nicardipine in breast milk (M) versus the maternal plasma (P) were used as a measure of transfer to breast milk (M/P). The daily exposure of a neonate to nicardipine during lactation was calculated by multiplying the volume by the concentration of every corresponding breast milk sample and subsequently totalling the absolute amounts of nicardipine for each day.

The differences between arterial umbilical cord concentrations and venous umbilical cord concentrations were tested using the Wilcoxon signed-rank test (P level ≤ 0.05). Correlations between placental transfer and maternal dosage at delivery and total cumulative dosage were tested using the Spearman's rank correlation test (P level ≤ 0.05).

The study protocol was reviewed and approved by the Institutional Review Board of the Erasmus MC, and all the women gave informed consent.

Results

Placental transfer

Ten patients were studied. Patient characteristics are given in Table 1.

Nicardipine dose at time of delivery ranged from 1 to 7 mg/hour. Cumulative dose until delivery ranged from 4.5

Table 1. Maternal and neonatal characteristics

	***n* (%) or median (range)**
Maternal characteristics (*n* = 10)	
Maternal age (years)	28 (17–36)
Gestational age at admission (weeks)	28 3/7 (25 5/7–32 4/7)
Gestational age at start nicardipine (weeks)	28 4/7 (26 3/7–31 4/7)
Nulliparity (*n*)	5 (50)
Systolic blood pressure at admission (mmHg)	190 (160–220)*
Diastolic blood pressure at admission (mmHg)	115 (100–130)*
HELLP at admission (*n*)	2 (20)
Caesarean deliveries	9 (90)
Vaginal deliveries	1 (10)
Indication for delivery	
Fetal distress (*n*)	6 (60)
Maternal distress (*n*)	4 (40)
Neonatal outcome (*n* = 10)	
Perinatal deaths	0 (0)
pH umbilical cord	7.29 (7.08–7.42)
Apgar <7 at 5 minute (*n*)	0 (0)
Birthweight (g)	980 (630–1660)
Admission	
Intensive care unit	9 (90)
Medium care	1 (10)
Intensive care unit stay (days)	16 (4–56)

*Measured with cuff.

to 450 mg. Median duration of treatment with nicardipine until delivery was 55 hours (range, 1.5–100 hours), and the maximum dose during treatment ranged from 1 to 9 mg/hour. Eight subjects had the same dose nicardipine for 6 hours until delivery. One woman started with nicardipine 3 mg/hour 4 hours before delivery, and after 2 hours, the dose was lowered to 1.5 mg/hour until delivery, and as a steady state should have been reached by delivery, she was included in the analysis. One woman was started on nicardipine 3 mg/hour 1.5 hours before delivery, and it was stopped just before delivery. Because of the short half-life of nicardipine, the maternal concentration dropped quickly, while the concentration in the placental compartment was still high, resulting in a high U/P ratio of 0.5. The plasma concentrations of this woman did not reflect a steady state, and she was excluded from further analysis. For one woman, arterial and venous umbilical cord blood was accidentally pooled, and for one woman, venous umbilical cord blood only was drawn. Thus, samples from nine women and their fetuses were analysed.

Nicardipine could be detected in all maternal and umbilical cord blood samples. Maternal nicardipine concentrations ranged from 9.8 to 116 ng/ml. In one umbilical cord sample, nicardipine concentration was below LOQ, and for further calculation, we assumed the concentration being 1.4 ng/nl (LOQ). Venous umbilical cord nicardipine concentrations ranged from 1.4 to 18.6 ng/ml, and arterial umbilical cord nicardipine concentrations ranged from 1.4 to 15.7 ng/ml.

The calculated median placental transfer was 0.15 ($U_{arterial}$/P, range 0.05–0.22) and 0.17 (U_{venous}/P, range 0.023–0.22). No differences could be detected between arterial and venous umbilical cord concentrations ($P = 0.15$).

There was a significant correlation between maternal dose at delivery and arterial and venous umbilical blood concentrations ($r_s = 0.857$ [$P = 0.007$] and $r_s = 0.800$ [$P = 0.005$] (Figure 1). No correlations were found between total cumulative dosage until delivery and $U_{arterial}$/P ($r_s = 0.429$ [$P = 0.169$]) and U_{venous}/P ($r_s = 0.350$ [$P = 0.178$]).

Despite the inclusion of only severe, early-onset pre-eclamptic patients with preterm deliveries, there were no perinatal deaths in our study. All infants had umbilical cord pH and Apgar scores in the normal range (see Table 1). Therefore, maternal use of nicardipine does not appear to compromise the safety of the fetus or neonate, although the number of neonates is too small for valid conclusions.

Transfer in breast milk

A total of 34 breast milk samples were obtained from seven woman who used nicardipine postpartum. Median gestational age at delivery was 28 6/7 weeks (26 1/7–33). After delivery, intravenous nicardipine was continued for a median of 1.9 days (range 0.8–4.6 days). The maximum dose of intravenous nicardipine during lactation was 6.5 mg/hour.

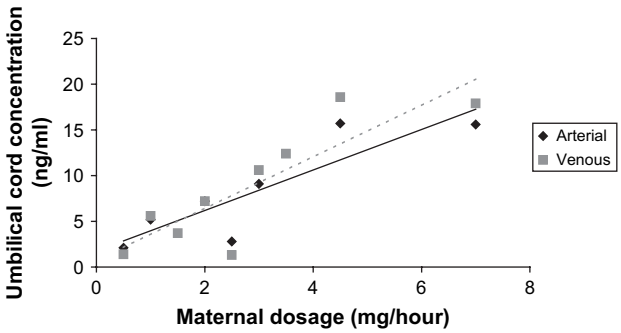

Figure 1. Maternal nicardipine dosage at delivery versus umbilical cord nicardipine concentration, both arterial and venous. The correlation between maternal nicardipine dosage and umbilical cord concentration and arterial and venous umbilical blood concentration was found to be $r_s = 0.857$ ($P = 0.007$) and $r_s = 0.800$ ($P = 0.005$), respectively.

In 82% of the breast milk samples, no nicardipine could be detected and therefore, the median M/P ratio could not be determined. In six breast milk samples from four women, nicardipine levels (range 5.1–18.5 ng/ml) were detectable with maternal nicardipine dose of 1–6.5 mg/hour. Because of the limited data, no analysis could be performed to investigate the influence of maternal drug dose and breast milk concentrations.

The highest concentration of nicardipine determined in breast milk was 18.5 ng/ml, with a maternal dose of 5.5 mg/hour.

The maximum possible exposure of a neonate to nicardipine during lactation was calculated to be less than 300 ng/day. In comparison, intravenous doses of nicardipine used for treating preterm neonates with hypertension were reported to be 0.72–2.9 mg/kg/day, which corresponds to an oral dose of 2–8.3 mg/kg/day, assuming an oral bioavailability of 35%. The possible exposure of 300 ng/day from breast milk corresponds, therefore, to 0.015–0.004% of a therapeutic dose of nicardipine in a 1-kg neonate.

Discussion

When using drugs in pregnant women, data about placental transfer are essential to assess the risk of adverse effects on fetus and neonate. In this study, placental transfer and levels of nicardipine in breast milk were assessed after mothers were treated with nicardipine intravenously for treatment of pre-eclampsia. Our study shows that placental transfer of nicardipine is low, leading to low umbilical cord blood concentrations. Carbonne *et al.* have described the use of nicardipine in pre-eclamptic women.[4] Using their data, we calculated placental transfer for two individual women of 0.17 and 0.11, respectively, which are comparable with our results. Studying the extent of placental transfer of drugs by comparing umbilical cord blood concentrations with

maternal blood concentrations is a well-established approach. A limitation of this method is that only a single set of data is available for each woman, but the results do yield important information regarding *in vivo* transfer of a drug to, and elimination, from the fetus.

Passive diffusion is the main mechanism of placental transfer of drugs. Key factors in this mechanism are physiochemical properties of the drug such as protein binding.[5] Because only the unbound fraction of nicardipine is available for placental transfer, the high protein binding (98%) of nicardipine is probably the main cause of the low placental transfer.

The low placental transfer of nicardipine contrasts with that of other antihypertensive drugs used in pre-eclampsia such as hydralazine, nifedipine, methyldopa and labetalol, which are known to cross the placenta extensively.[6,7]

We found no correlation between total cumulative dose until delivery and placental transfer, suggesting that nicardipine does not accumulate in the fetus. No difference in arterial and venous umbilical cord concentrations was found. This may be related to the relatively immature fetal hepatic metabolising capacity. For adults, nicardipine levels of 70–100 ng/ml are considered therapeutic.[8] The highest umbilical cord nicardipine level found was 18 ng/ml, indicating a low risk for a direct pharmacological effect on the human fetus.

Our data showing absence of nicardipine into the majority of breast milk samples indicate low transfer into breast milk. Nifedipine, structurally similar to nicardipine, also has a low rate of transfer into breast milk.[9] The limited transfer into breast milk in combination with an oral bioavailability of 35% of nicardipine indicate that exposure of the neonate to nicardipine during lactation will be low.

Our results showing limited transfer across the placenta and low concentrations in breast milk support the use of nicardipine as antihypertensive drug in pre-eclampsia. ■

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