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Pharmacokinetics of amlodipine besylate at delivery and during lactation

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ABSTRACT

Background: Amlodipine is rarely used in the treatment of pregnant hypertensive women due to limited pharmacokinetic data during pregnancy and the postpartum period.
Objective: To evaluate the pharmacokinetics of amlodipine besylate in the peri-partum period including quantities of placental passage, breast milk excretion and infant exposure.
Study design: This was a prospective study of pregnant women who were prescribed 5 mg of amlodipine daily for treatment of chronic hypertension and delivered at term. Cord and maternal blood samples were collected at delivery. On postpartum day 2, six paired maternal plasma and breast milk samples were obtained at 4, 6, 8, 12, 15 and 24 h following amlodipine dosing. Infant plasma samples were collected 24–48 h after delivery. All samples were analyzed for amlodipine concentration. A one compartment, first-order model was used to calculate pharmacokinetic estimates for maternal plasma.
Results: Of the 16 patients enrolled in the study, 11 had cord blood and maternal serum collected at delivery, of which only 6 produced sufficient breast milk for sampling. Amlodipine was detected in infant cord blood plasma with a mean concentration of 0.49 ± 0.29 ng/mL compared to mean maternal serum level of 1.27 ± 0.84 ng/mL. Amlodipine concentrations in both in breast milk and infant plasma were undetectable at the lower limit of assay detection (< 0.1 ng/mL). In the immediate postpartum period, the amlodipine elimination half-life was 13.7 ± 4.9 h, the area under the curve was 53.4 ± 19.8 ng*h/mL and the peak concentration was 2.0 ± 1.0 ng/mL.
Conclusions: Amlodipine does cross the placenta in measurable quantities, but is not detected in breast milk or infant plasma at 24–48 h of life indicating that it is likely safe to use during the peripartum period.

1. Introduction

Chronic hypertension affects approximately 7% of women of childbearing age and complicates about 5% of all pregnancies in the United States [1,2]. Although chronic hypertension is among the most common pregnancy complications, there is significant equipoise related to the clinical management of these complicated pregnancies, particularly with regard to optimal pharmacotherapy in women requiring antihypertensive treatment. While there are many well-studied, efficacious antihypertensive regimens available in the non-pregnant population, only a limited number of such drugs have been well-studied during pregnancy and lactation.

Amlodipine besylate is a long-acting dihydropyridine calcium channel blocker commonly used in the treatment of hypertension. Amlodipine selectively inhibits transmembrane influx of calcium ions into cardiac and vascular smooth muscle, leading to decreased vascular tone, reduced systemic vascular resistance, diminished afterload and coronary vasodilation [3,4]. The drug's long half-life, infrequent dosing, low cost and positive side-effect profile [5] make it an ideal candidate for treatment of chronic hypertension in pregnancy. However, there are limited data available on its use during pregnancy and lactation proscribing cautionary usage in pregnant and postpartum women. Specifically, it is not currently known whether amlodipine crosses the placenta and there are few clinical publications regarding drug levels in breast milk or potential infant side effects [6–9]. We presume that this paucity of information likely hinders widespread amlodipine use in pregnancy or in the postpartum period despite its many potential benefits.

Our objective was to evaluate the pharmacokinetics of amlodipine besylate at the time of delivery and during postpartum lactation in

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women being treated for chronic hypertension in pregnancy. Specifically, we were interested in measuring amlodipine concentrations in cord blood, maternal serum and breast milk. Secondarily, we were interested in evaluating infant drug levels as well as any neonatal side effects potentially attributable to amlodipine exposure. We hypothesized that amlodipine crosses the placenta and likely passes into the breast milk in minimal quantities based on its pharmacokinetic properties and comparability to other drugs in its class which are safely used in breastfeeding [10–12].

2. Materials and methods

Between March 2015 and January 2016, we identified and enrolled pregnant women attending the Obstetric Complications clinic at Parkland Hospital with chronic hypertension who were already taking amlodipine 5 mg daily and planned to breastfeed their infant. Additionally, the patient had to be 18 years or older at the time of enrollment with plans to deliver at Parkland Hospital. Women with preexisting kidney or liver disease were excluded. Of the eligible patients enrolled, only those women who delivered beyond 36 weeks gestation, did not require amlodipine doses in excess of 5 mg daily or additional antihypertensive medications in the peri-partum period and did not develop chorioamnionitis, endometritis or suffer postpartum hemorrhage were ultimately eligible for study inclusion. All patients eligible in the study underwent a process of informed consent prior to research participation. This study was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Research reported in the publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR001105.

Patients who consented to study participation and met all study criteria had cord blood collected at delivery and a maternal blood sample drawn within 1 h of delivery. Patients were continued on their amlodipine dosage of 5 mg daily in the postpartum period and paired maternal blood and breast milk samples were collected on postpartum day 2 at 4, 6, 8, 12, 15 and 24 h following amlodipine administration. In addition, the infants of study patients had study blood drawn at 24–48 h of life in conjunction with the routine heel stick performed for newborn screening. All blood and breast milk samples were immediately placed on ice after collection. Serum samples were then centrifuged to separate plasma and all samples were frozen at −80 °C for batch analysis. After all samples were collected, they were transferred to the Texas Tech School of Pharmacy for further analysis.

Amlodipine was quantitated in both plasma and breast milk using an ultra-high performance liquid chromatography/mass spectrometry (LC-MS/MS) method with a Phenomenex (Luna C8, 5 μ, 50 × 2 mm) column at 40 °C. The isocratic mobile phase (0.6 mL/h) consisted of 30 mM ammonium formate/0.1% formic acid in acetonitrile (40/60). Detection was accomplished using a Sciex 5500 QTRAP that was programmed in the positive, multiple reaction mode with monitoring of transition of the mass/charge ratio from 409.095 *m/z* for the precursor ion to 238.100 *m/z* for the product ion for amlodipine and 419.149 *m/z* to 343.200 *m/z* for the internal standard (nimodipine), respectively. The total run time was 5 min. The calibration curve ranged from 0.1 to 100 ng/mL ($r^2 > 0.99$). The analytical method was demonstrated to be accurate and precise; total analytical variation (RSD%) was less than 8% for amlodipine concentrations measured throughout the range of concentrations.

Amlodipine concentrations (ng/mL) in plasma and breast milk were plotted versus time (h) for each of the respective study patients. The best fit model was selected using Phoenix® WinNonlin® (Pharsight Corporation) to determine pharmacokinetic estimates of the time to maximum concentration (T_{max}) and maximum drug concentration (C_{max}), half-life ($T_{1/2}$), clearance (Cl) and area-under-the-curve (AUC).

Table 1
Maternal and infant characteristics in 11 pregnancies complicated by chronic hypertension treated with amlodipine 5 mg daily.

Characteristic	Number (%)
Parity	
0	1 (9)
> 1	10 (91)
Race/ethnicity	
Black	3 (27)
Hispanic	8 (73)
Mode of delivery	
Vaginal	4 (36)
Cesarean	7 (64)
Severe preeclampsia*	3 (27)
Overt diabetes	2 (18)
Nursery	
NICU	0
Newborn	11 (100)
5 min Apgar	
8	1 (9)
9	10 (91)
pH	
≥7.2	10 (91)
< 7.2	1 (9)
≤7.0	0

* Severe preeclampsia defined as blood pressure elevation ≥160 systolic or ≥110 diastolic, characteristic symptoms and/or laboratory evidence indicative of severe disease including thrombocytopenia (platelets < 100,000/microliter), elevated hepatic transaminase concentrations (twice normal concentration) or increased serum creatinine levels (serum creatinine > 1.1 mg/dL in the absence of underlying renal disease).

3. Results

We enrolled 16 antepartum patients who met inclusion criteria. However, only 11 of the 16 participants had both cord blood and maternal plasma collected at the time of delivery and ultimately, only 6 of these women were able to produce sufficient breast milk to complete the study and only 8 infants had blood collected at 24–48 h of life. The mean age of the 11 study participants was 33.2 ± 5.8 years old and on average, the participants were obese with a mean body mass index of 38.5 ± 11.4 kg/m^2. The mean gestational age at delivery was 38.2 ± 0.8 weeks with the earliest delivery occurring at 37 weeks. The mean infant birth weight was 3281 ± 525 g and the average nursery stay 3.6 ± 0.5 days. Additional maternal demographics and delivery data and infant characteristics are shown in Table 1. None of the infants exposed to amlodipine required admission to the neonatal intensive care unit and none suffered major neonatal complications including intraventricular hemorrhage, apnea, seizures, periventricular leukomalacia or need for respiratory support.

Amlodipine was found in measurable quantities in cord blood with a mean level of 0.49 ± 0.29 ng/mL compared to a mean maternal serum concentration 1.27 ± 0.84 ng/mL (Fig. 1). In contrast, amlodipine concentrations in both maternal breast milk and infant plasma were undetectable at the lower limit of assay detection (< 0.1 ng/mL).

First-order pharmacokinetic parameters for amlodipine besylate in maternal plasma are shown in Table 2. However, only 4 of the 6 women who had paired milk and serum samples collected in the postpartum period has results that could be fit to a one-compartment, first-order pharmacokinetic model. For these four patients, the mean peak plasma amlodipine level was 2.0 ng/mL, which was achieved 7.5 h after dose administration (Fig. 2).