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Perinatal Pharmacokinetics of Azithromycin for Cesarean Prophylaxis

Amelia L. Sutton, M.D., Ph.D.[1], **Edward P. Acosta, PharmD.**[2], **Kajal B. Larson, Ph.D.**[2], **Corenna D. Kerstner-Wood, B.S.**[2], **Alan T. Tita, M.D., Ph.D.**[1], and **Joseph R. Biggio, M.D.**[1]

[1]Department of Obstetrics and Gynecology, Division of Maternal Fetal Medicine, University of Alabama at Birmingham, Birmingham, AL

[2]Department of Pharmacology and Toxicology, Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, AL

Abstract

Objective—Postpartum infections are polymicrobial and typically include *Ureaplasma*, an intracellular microbe treated by macrolides such as azithromycin. The aim of this study was to evaluate the perinatal pharmacokinetics of azithromycin following a single pre-incision dose prior to cesarean delivery.

Study Design—Thirty women undergoing scheduled cesarean delivery were randomized to receive 500 mg of intravenous azithromycin initiated 15, 30, or 60 minutes prior to incision and infused over one hour. Serial maternal plasma samples were drawn from the end of infusion up to 8 hours after the infusion. Samples of amniotic fluid, umbilical cord blood, placenta, myometrium, and adipose tissue were collected intraoperatively. Breast milk samples were collected 12-48 hours after the infusion in 8 women who were breastfeeding. Azithromycin was quantified using high performance liquid chromatography separation coupled with tandem mass spectrometry detection. Plasma pharmacokinetic parameters were estimated using non-compartmental analysis and compartmental modeling and simulations.

Results—The maximum maternal plasma concentration was reached within 1 hour and exceeded the *in vitro* minimum inhibitory concentration (MIC_{50}) of 250 ng/mL of *Ureaplasma* spp in all 30 patients. The concentrations were sustained with a half-life of 6.7 hours. The median concentration (C_{med}) of azithromycin in adipose was 102 ng/g, which was below the MIC_{50}. The C_{med} in myometrium was 402 ng/g, which exceeded the MIC_{50}. Azithromycin was detectable in both the umbilical cord plasma and amniotic fluid following the single pre-operative dose.

Correspondence: Amelia L. Sutton M.D., Ph.D., 1700 6th Avenue South, Birmingham, AL 35249, Phone: 205-934-5612, Fax: 205-975-9858, alsutton@uabmc.edu.

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Azithromycin concentrations in breast milk were high and sustained up to 48 hours following the single dose. Simulations demonstrated accumulation in breast milk following multiple doses.

Conclusion—A single dose of azithromycin achieves effective plasma and tissues concentrations and is rapidly transported across the placenta. The tissue concentrations achieved in the myometrium exceed the MIC_{50} for *Ureaplasma* spp

Keywords

cesarean section; endometritis; wound infection; azithromycin; pharmacokinetics; *Ureaplasma*; breast milk

Introduction

Post-cesarean infections, including endometritis and wound infections, represent a significant health and economic burden. Studies have demonstrated up to a 50% reduction in postpartum infections when cephalosporin antibiotics are administered before skin incisions with no apparent adverse effects in neonates[1, 2]. Current guidelines recommend administration of a first-generation cephalosporin within 60 minutes prior the start of cesarean delivery[3]. Despite recent advances, surgical site infections remain a significant problem. Postpartum infections are polymicrobial, and intracellular microbes such as *Ureaplasma* spp and *Mycoplasma* spp, which are not effectively treated by cephalosporins, are significant pathogens in endometritis[4, 5]. Extended-spectrum antibiotic prophylaxis with both a cephalosporin and azithromycin, which has antimicrobial activity against *Ureaplasma* spp, has been associated with a significant reduction in post-cesarean endometritis and shorter hospital stays when given after cord clamp.[6-8] An ongoing large clinical trial is investigating if the addition of azithromycin to the standard regimen of a cephalosporin prior to skin incision further decreases post-cesarean infections.

Ureaplasma spp has also been implicated in significant neonatal infections, such as pneumonia, meningitis, and bacteremia.[9] Multiple studies have shown that respiratory tract colonization with *Ureaplasma* spp is associated with an increased risk of bronchopulmonary dysplasia (BPD).[10] Postnatal treatment with azithromycin may prevent BPD in preterm infants with *Ureaplasma* spp colonization or infection.[11] These infections often result from perinatal transmission, as *Ureaplasma* spp are commensal organisms of the lower genital tract and are implicated in chorioamnionitis, pregnancy loss and spontaneous preterm birth.[12] Therefore, perinatal treatment of select populations with azithromycin may potentially reduce the risk of both maternal and neonatal complications caused by these organisms if transplacental transfer occurs. These benefits must be carefully weighed against the potential for antimicrobial resistance, thereby selecting for more virulent maternal and neonatal pathogens.

Depending on the clinical isolate, the *in vitro* minimal inhibitory concentration (concentration of drug required to inhibit 50% of growth, MIC_{50}) of azithromycin against *Ureaplasma* spp ranges from 250 ng/mL to 1000 ng/mL. For example, the MIC_{50} of azithromycin is 250 ng/mL for *Ureaplasma parvum* isolated from the placenta,[13] while the MIC_{50} of AZI for *Ureaplasma* spp isolated from the adult genital tract is 500 ng/mL.[14]

Neonatal isolates require higher concentrations of the antibiotic as the MIC_{50} for *Ureaplasma* spp isolated from neonatal respiratory tracts is 1000 ng/mL.[15]

There are limited data regarding the perinatal pharmacokinetics of azithromycin.[16] Given the multiple potential applications for the use of azithromycin during pregnancy, we sought to evaluate the perinatal pharmacokinetics of AZI following a single pre-incision intravenous dose. Intravenous azithromycin administration at different time points for pre-incision prophylaxis provides a model to study the maternal-fetal pharmacokinetics of intravenous azithromycin, which could enhance our understanding of appropriate dosing strategies during pregnancy.

Materials and Methods

This study was approved by the Institutional Review Board at the University of Alabama at Birmingham (F101111007) and was registered at ClinicalTrials.gov (NCT01464840). An Investigational New Drug application was approved by the Food and Drug Administration (IND 111917). Women undergoing a planned cesarean delivery at term (≥ 37 weeks) with a singleton gestation were eligible for the study. Exclusion criteria included: multiple gestation, preterm (< 37 weeks) gestation, ruptured membranes or labor, known fetal anomalies, oligo- or polyhydramnios, azithromycin exposure within 2 weeks, allergy to macrolide antibiotics, significant medical or obstetric co-morbidities, hepatic or renal impairment, concurrent treatment with medications that prolong the QT interval (such as ondansetron), concurrent treatment with nelfinavir, efavirenz, or fluconazole, structural heart defects, or known arrhythmias. Signed informed consent was obtained at least 24 hours prior to delivery. The participants were contacted and charts were reviewed 1 week and 3 months after completion of the study for any study-related maternal and fetal adverse events.

Women were randomized to receive 500 mg of azithromycin intravenously initiated 15, 30, or 60 minutes prior to the planned incision time. The infusion was given over 1 hour. Due to clinical constraints, the actual timing of the incision may have deviated from the planned interval. Each participant had a second IV line designated for phlebotomy. Maternal blood samples for azithromycin concentration determination in plasma were scheduled to be drawn prior to the infusion, at the conclusion of the infusion, at the time of incision, and 30 minutes, 1 hour, 3 hours, 5 hours, and 7 hours after the conclusion of the infusion. Amniotic fluid, umbilical cord blood, placental tissue, myometrial tissue, and adipose tissue samples were collected intraoperatively. Breast milk specimens were collected from pumped samples 12-48 hours after the infusion from breastfeeding participants. All samples were stored at -80°C until analysis.

Azithromycin and its added internal standard clarithromycin were quantified using high performance liquid chromatography (HPLC) separation coupled with tandem mass spectrometry detection. Tissue samples were weighed and homogenized in 4 volumes of 50 mM ammonium acetate. A standard curve (range 2.5 – 5000 ng/mL) was prepared in plasma, and the plasma curve was used as a surrogate for all other matrices. Quality control samples were prepared by spiking plasma with azithromycin, for final concentrations of 7, 450, and 4500 ng/mL, and the internal standard clarithromycin (250 ng/mL). Azithromycin

and the internal standard were extracted from all unknown samples, standards, and quality control samples by addition of 50 μL of sample to 500 μL of acetonitrile in microcentrifuge tubes. The tubes were centrifuged and the supernatant was diluted (1:2 dilution) in a mixture of 50 mM ammonium acetate and methanol (1:1). Reversed phase chromatographic separation of azithromycin and the internal standard was performed on a XTerra® MS C8 column (5 urn, 2.1 × 100mm, Waters Corp, Milford, MA) under isocratic conditions. A binary mobile phase consisting of 50 mM ammonium acetate, acetonitrile, and methanol (50:31:19) was used. The detection and quantitation was achieved for azithromycin and the internal standard by multiple reaction monitoring (MRM). The de-protonated molecular ions $[M-H]^-$were monitored at *m/z* 749.6 > 573.2 for AZI, and *m/z* 748.5 >157.9 for clarithromycin. These provided adequate sensitivity with minimal interference from endogenous matrix components. Plasma pharmacokinetic parameters were estimated using noncompartmental methods (Phoenix WinNonlin, Certara USA, Inc., St. Louis, MO). Modeling and simulations of plasma and breast milk data were performed using ADAPT 5.[17]

Results

Thirty women undergoing scheduled cesarean deliveries completed the study. The baseline characteristics of the participants are shown in Table 1. The median time between initiation of the infusion and the skin incision was 51 minutes with a range of 10-219 minutes. The incision time was within 15 minutes or less of the planned interval in 20 of the 30 patients. There were no significant adverse events related to azithromycin exposure reported in the women or infants.

Maternal serum concentrations peaked within 1 hour and were sustained over the study period (Fig.1) with a half-life of 6.7 hours (Table 2). Pharmacokinetic parameters (Table 2) were estimated using a 2-compartment plasma model linked to a 1-compartment breast milk model with an intermediate delay compartment between the plasma and breast milk. The last plasma sample collection in our dataset was at approximately 8 hours, thus a 2 compartment model adequately fit the data in this case as no points in the terminal elimination phase were collected. Figure 1 depicts the raw AZI plasma and breast milk concentrations and the best model fit for each. The mean (standard deviation) plasma area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), minimum concentration (C_{min}), and maximum concentration (C_{max}) were 6030 (2170) ng × hr/mL, 147 (43) ng/mL, and 4500 (2430) ng/mL, respectively. Azithromycin was rapidly distributed into tissues (Fig. 2). The median concentrations (C_{med}) of AZI in adipose, placental, and myometrial tissue were 102, 221, and 402 ng/g, respectively (Fig. 2). The highest concentration of AZI was achieved in myometrial tissue, with a C_{max} of 7774 ng/g. The C_{max} in adipose and placental tissue were 717 and 961 ng/g, respectively.

AZI was transported across the placenta with concentrations detectable in fetal compartments within 30 minutes (Fig. 3). The C_{med} in amniotic fluid was 33 ng/mL at a median time of 0.92 hours post-dose. The C_{med} in venous umbilical cord plasma was 150 ng/mL at a median time of 0.95 hours post-dose.

AZI achieved sustained concentrations in breast milk up to 48 hours after the single dose (Fig. 4). At a median of 30.7 hours post-dose, the median breast milk concentration was 1713 ng/mL. The model used to fit the concentration-time data was also used to simulate plasma and breast milk concentrations following multiple IV doses of 500 mg every 12 hours (Fig 4). Simulations predicted accumulation in breast milk following 3 doses with steady-state achieved at approximately 3 days. Assuming an intake of 150 mL/kg/day and bioavailability of 38%, the daily AZI dose of a 3.5 kg exclusively-breast fed infant is estimated to be 340 μg (~0.1 mg/kg).

Comment

A single intravenous dose of 500 mg of azithromycin administered just prior to skin incision achieved effective maternal plasma concentrations that exceeded the MIC_{50} for most *Ureaplasma* spp isolates. Assuming an average tissue density of 1 g/mL, the C_{med} of azithromycin in myometrium of approximately 402 ng/mL exceeded the MIC_{50} (250 mg/mL) of *Ureaplasma parvum* isolated from the reproductive tract.[13] However, the C_{med} of all tissues was below the MIC_{50} (1000 mg/mL) for *Ureaplasma* spp derived from neonatal tracheal aspirates.[15] Azithromycin was rapidly transferred across the placenta, with concentrations detectable in the umbilical cord plasma and amniotic fluid within approximately 20-30 minutes. However, these median concentrations following this single dose were well below the MIC_{50} for *Ureaplasma* spp. In breast milk, azithromycin exhibited high and sustained concentrations over the sampling period.

There are limited data regarding the pharmacokinetics of azithromycin during pregnancy and lactation. In one study of oral azithromycin administered 6 to 72 hours prior to cesarean delivery in humans, drug concentrations in myometrium, adipose tissue, and placenta were 900-2100 ng/mL,[16] thus exceeding the MIC_{50} for most *Ureaplasma* spp. Maternal serum, amniotic fluid, and umbilical cord blood levels were 19-311 ng/mL. In a primate model of intra-amniotic *Ureaplasma* infection, multiple doses of AZI, administered every 12 hours intravenously for 10 days, resulted in a prolonged plasma half-life of 66 hours and accumulation of the drug in the amniotic fluid with a half-life of 129 hours.[18] Importantly, this multi-dose regimen resulted in eradication of *Ureaplasma* with a 95% effective concentration of 39 ng/mL. Also, there is currently only one case report of a single patient which analyzed the transfer of AZI into breast milk.[19]

This pharmacokinetic study has some strengths and limitations. The dose timing, administered just prior to delivery, is clinically relevant, mirroring real-world dosing of prophylactic antibiotics for cesarean. Multiple maternal and fetal compartments were sampled in this study. Although many of the measured concentrations were below the MIC_{50} for *Ureaplasma* spp, the *in vitro* MIC may not correlate with the *in vivo* microbial activity of azithromycin in this setting. Additionally, the single early time points of tissue concentrations are not reflective of the continued tissue uptake of azithromycin, which was demonstrated in a previous study of oral azithromycin.[16] In addition to the higher tissue concentrations of azithromycin attained in the previous study, the cost of oral azithromycin is significantly less than the intravenous formulation. However, administration of prophylactic antibiotics several hours to several days prior to cesarean delivery is not

practical, especially for non-scheduled deliveries with the highest risk of infection. As this was designed as a pharmacokinetic study, we did not assess the clinical or microbial efficacy of azithromycin in post-surgical infections. Primate models of intra-amniotic *Ureaplasma* infection have indicated that multiple doses of azithromycin leads to eradication of the infection with drug concentrations below 100 ng/mL.[18, 20] These amniotic fluid concentrations are similar to those in the current study (C_{med} of 33 ng/mL).

This study also represents the first report of breast milk concentrations of azithromycin measured in multiple patients. Following a single dose, azithromycin exhibited high and sustained concentrations in breast milk. Pharmacokinetic simulations showed that multiple doses of azithromycin would result in further accumulation with higher concentrations during the treatment period. The estimated daily neonatal exposure following a single dose was calculated at approximately 340 μg. Although this is below the treatment dose recommended for neonates at 10 mg/kg/day, this dose would be additive to the transplacental exposure of azithromycin.

This study shows that a single intravenous dose of 500 mg of azithromycin prior to cesarean delivery results in adequate plasma and myometrium concentrations to for prophylaxis against *Ureaplasma* spp. Administration of azithromycin 1 hour or greater prior to the surgery appears to be optimal given the continued tissue uptake of the drug. Although azithromycin concentrations are lower in the adipose tissue, they still may be adequate for wound infection prophylaxis, especially considering the accumulation of azithromycin in tissue over time. In fact, an ongoing multicenter trial is assessing the clinical efficacy of extended-spectrum prophylaxis including azithromycin for post-cesarean infections. Further understanding of the transplacental pharmacokinetics of multiple doses of azithromycin over a longer sampling period will provide guidance in determining the optimal dose and timing of the drug for other indications, such as preterm premature rupture of membranes or perinatal treatment of syphilis. Additionally, such studies may set the stage for perinatal treatment of fetal and neonatal infections with *Ureaplasma* associated with bronchopulmonary dysplasia.

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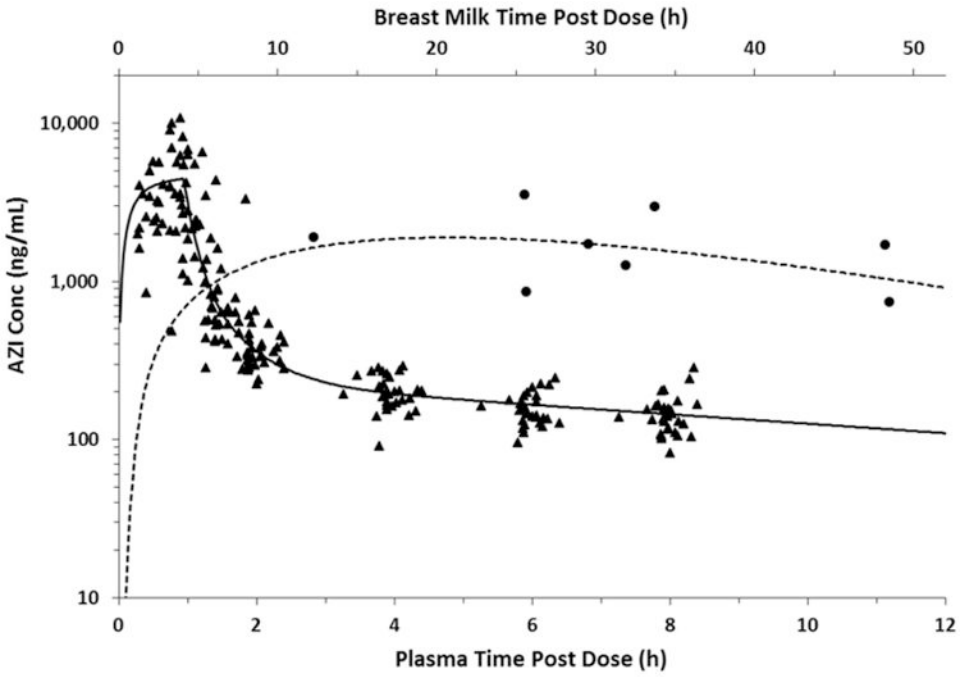

Figure 1.

Concentration-time profile of maternal plasma AZI (triangles) and breast milk (circles) following a single intravenous dose. Solid line represents the best model fit of plasma data and dashed line is the best model fit of breast milk data.

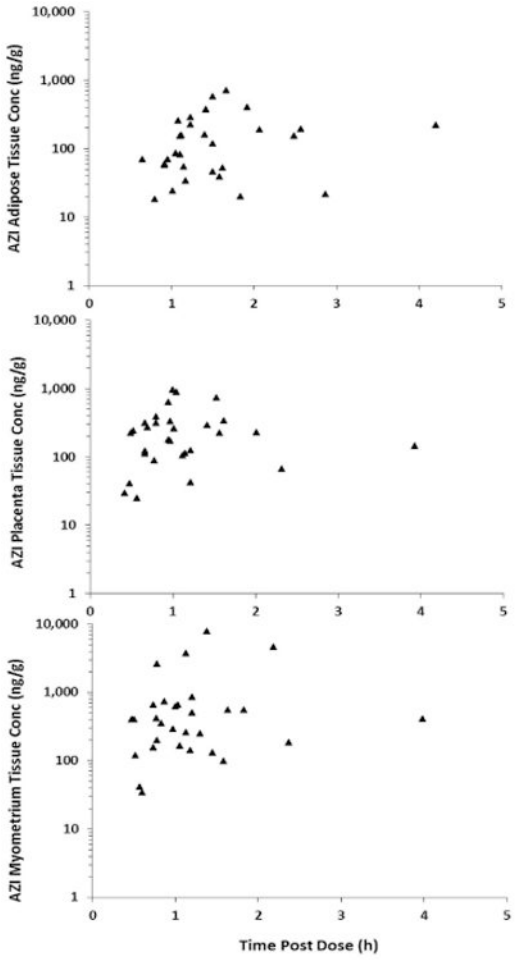

Figure 2.
AZI concentrations (triangles) in a) adipose, b) placental, and c) myometrial tissues.

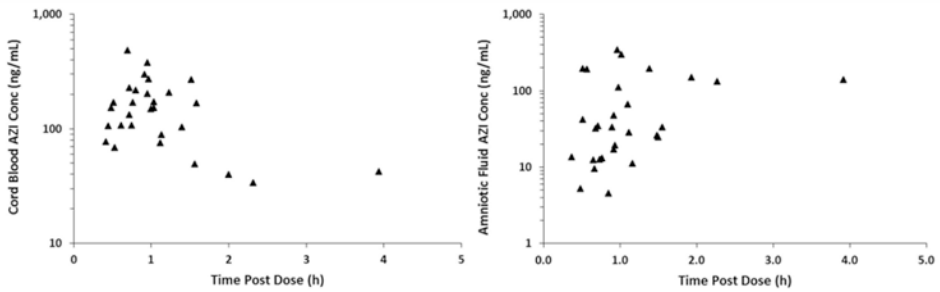

Figure 3.

AZI concentrations (triangles) in a) venous umbilical cord plasma and b) and amniotic fluid.

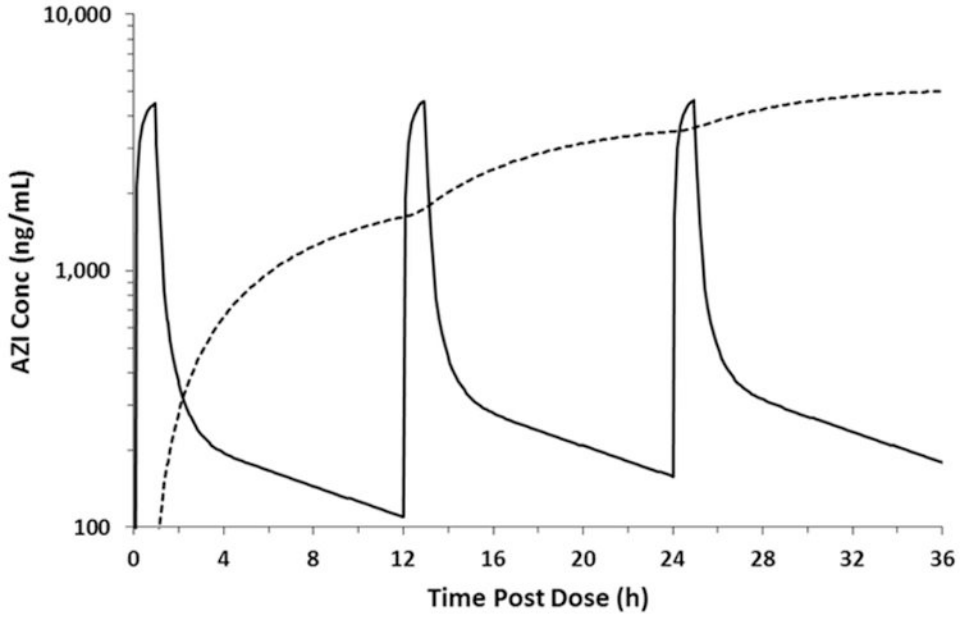

Figure 4.
Simulated plasma and breast milk concentration-time curves following 3 IV doses.

Table 1

Baseline demographics of the study population.

Characteristic	Result
Maternal age, years – mean ± SD (range)	28.1 ± 5.4 (20-41)
Parity – median (interquartile range; range)	2 (1-2; 0-6)
Race – no. (%)	
African-American	17 (56.7%)
Hispanic	8 (26.7%)
Caucasian	4 (13.3%)
Asian	1 (3.3%)
Pre Preg Body mass index, kg/m – mean ± SD (range)	30.1 ± 6.0 (19.8-43.1)
Body mass index, kg/m^2 – mean ± SD (range)	36.6 ± 7.0 (26.5-59.3)
Indication for cesarean delivery – no. (%)	
Elective repeat cesarean	27 (90%)
Malpresentation	1 (3.3%)
Prior classical, vertical, T or J	1 (3.3%)
Other	1 (3.3%)
Gestational age at delivery, weeks – mean ± SD (range)	39.1 ± 0.3 (39-40)
Birthweight, grams – mean ± SD (range)	3318 ± 359 (2800-4290)
Dose timing*, min – mean, range	51 (10-219)

* time between initiation of infusion and skin incision

SD, standard deviation

Table 2

Plasma and breast milk (BM) pharmacokinetic parameters of AZI for cesarean prophylaxis.

Parameter	Median (range)
$T_{1/2}$ – plasma half-life (hr)	6.7 (6.4-7.6)
CL - plasma clearance (L/hr)	73.2 (59.0-87.1)
V_c – central volume of distribution in plasma (L)	27.7 (24.0-35.0)
V_p – peripheral volume of distribution in plasma (L)	290 (286-292)
CL_d – intercompartmental clearance (L/hr)	51.0 (43.9-56.0)
Tau – rate constant for delay compartment (hr^{-1})	0.096 (0.06-0.22)
$T_{1/2bm}$ – BM half-life (hr)	15.6 (15.5-15.8)
CL_{bm} – BM clearance (L/hr)	0.17 (0.17-0.17)
V_{bm} – BM distribution volume (L)	3.87 (3.85-3.88)