Pharmacokinetics of Transfer of Azithromycin into the Breast Milk of African Mothers

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Azithromycin (AZI) is used for its antibiotic and antimalarial properties in pregnancy. Reported estimates of AZI breast milk transfer, based on concentrations in mostly single samples from small numbers of women, have suggested that infant intake is safe. To better characterize infant intake and the associated potential benefits and risks, AZI was measured by liquid chromatography-mass spectrometry in four breast milk samples taken over 28 days postpartum from each of 20 Gambian women given 2 g AZI during labor. A population pharmacokinetic model utilizing published parameters for AZI disposition in pregnancy, the present breast milk concentrations, and increasing/decreasing sigmoid maximum-effect (Emax) functions adequately described temporal changes in the milk/plasma ratio. The median estimated absolute and relative cumulative infant doses were 4.5 mg/kg of body weight (95% prediction interval, 0.6 to 7.0 mg/kg) and 15.7% (95% prediction interval, 2.0 to 27.8%) of the maternal dose, respectively; the latter exceeded the recommended 10% safety limit. Although some infants with bacterial infections may benefit from AZI in breast milk, there is a risk of hypertrophic pyloric stenosis with a worst-case number needed to harm of 60 based on the present and available epidemiologic data. (This study has been registered at ClinicalTrials.gov under registration no. NCT01800942.)

Azithromycin (AZI) is a macrolide antibiotic that is used in a variety of clinical situations, including young infants with pertussis (1), and in pregnancy to treat sexually transmissible and reproductive tract infections (2). It has antimalarial activity that, as part of combination therapy (3), is beneficial in pregnant women with Plasmodium infections and consequently at increased risk of anemia and obstetric complications (4). When administered at delivery, its elimination half-life of 3.3 days (5), together with high and sustained tissue concentrations relative to those in serum (6), suggest that the breastfeeding infant could ingest significant amounts of AZI. Markedly elevated AZI concentrations in maternal leukocytes, a component of breast milk (7) that can increase in response to neonatal infection (8), represent a potentially major contribution to postnatal AZI transfer.

Available data on concentrations of AZI in breast milk are sparse. In a woman with cellulitis after tubal ligation treated with 1 g AZI orally, followed 48 h later by five 500-mg daily oral doses, increasing breast milk concentrations of up to 2.8 mg/liter were present in three samples, the last taken after a cumulative dose of 2.5 g (9). Using the concentration in the last sample, the authors estimated that the infant consumed 1.3 mg/day or, after adjustment for 37% bioavailability found in healthy adults (10), 0.2 mg/kg of body weight/day. This was not considered to be a clinically significant infant dose (9). In a study of 8 women given a 500-mg intravenous (i.v.) AZI dose before cesarean section, single breast milk samples were taken from each woman between 12 and 48 h postinfusion (11). Simulations from multicompartmental pharmacokinetic (PK) modeling suggested that steady-state breast milk concentrations after 500-mg i.v. doses every 12 hours were achieved after 3 days. Under assumptions of 150 ml/kg/day milk intake and bioavailability of 38%, the comparable daily i.v. AZI dose was predicted to be 0.34 mg (0.097 mg/kg) in a 3.5-kg infant (11). This corresponds to an oral dose of 0.25 mg/kg/day, similar to the 0.2 mg/kg/day estimated in the single case report (9).

These predicted infant doses (9, 11) are based on simple PK analyses that may not adequately capture temporal changes in milk composition, volume, and AZI concentrations and, hence, infant AZI exposure. The volume of milk produced during lactation increases to a maximum at day 7 postpartum (12), when the estimated infant intake is 150 ml/kg/day (13). In addition, in the report involving 8 women (11), there was no estimate of the population variability in infant AZI intake, an important consideration in the assessment of the range of potential infant doses and thus toxicity. A key aspect of quantifying exposure is the association between macrolide therapy and infantile hypertrophic pyloric stenosis (IHPS), the risk of which appears to be highest in the first 2 weeks of life (14–16) but which is uncertain in the context of AZI-treated breastfeeding women (17).

In view of these limitations, we measured AZI concentrations in breast milk collected between 3 and 28 days postpartum from 20 Gambian women given a single 2-g oral dose of AZI during labor and utilized a population PK model derived from these data to predict absolute and relative total infant dose ranges for the

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present maternal AZI regimen, as well as a higher dose (1 g daily for 3 days) that has been used as part of antimalarial therapy in pregnancy (18). In addition, we explored the association between AZI exposure through breast milk ingestion and IHPS using available data.

MATERIALS AND METHODS

Study design and participants. The women in the present study were recruited to a phase III, double-blind, placebo-controlled trial in which women in labor were randomized 1:1 to receive a single oral dose of 2 g AZI or placebo (ClinicalTrials.gov NCT01800942). The trial was conducted at the Jammeh Foundation for Peace (JFFP), a government-run health center in Western Gambia, approximately 20 km from the capital, Banjul. Women aged 18 to 45 years who gave consent during antenatal care visits and presented in labor between April 2013 and April 2014 were eligible. Exclusion criteria included known HIV infection or other clinically significant acute or chronic illness, planned cesarean section or known required referral for hospital delivery, known multiple pregnancy, known severe congenital malformation or intrauterine death, known macrolide allergy, antibiotic treatment in the week before randomization, and inability to attend all follow-up visits.

The study was approved by the joint Gambia Government-Medical Research Council (MRC) Ethics Committee. A local safety monitor and a Data Safety Monitor Board (DSMB) reviewed all the serious adverse events during the trial, and the trial was monitored by an independent clinical trials monitor.

Trial procedures. After confirmation of labor, a single 2-g oral AZI dose or placebo was administered to each woman. The date and time of dosing were recorded. Each woman was then observed closely by study nurses, who documented episodes of vomiting. A detailed clinical examination of both mother and baby was carried out by one of the study clinicians before discharge (between 6 and 24 h after delivery) and again 8 to 10 days after delivery. Additional active follow-up was conducted by study nurses and field workers daily during the first week after delivery and then weekly from week 2 to week 8.

Overall, 829 women and their 843 offspring participated in the main study. The first 40 women who took the study drug without vomiting and who were available to provide breast milk samples over 2 months participated in the presubstudy. Follow-up samples included breast milk collected by manual expression on days 3 and 6 postpartum and at 2 and 4 weeks postdelivery. The first 0.5 ml was discarded, and the next 1 to 2 ml was collected in a sterile plastic bottle, transported in a cold box within 8 h of collection, vortex mixed for 20 s, and stored at −70°C before assay.

Azithromycin assay. Breast milk AZI concentrations were measured using a validated ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC–MS–MS) method with a triple-quadrupole MS (8030 plus; Shimadzu, Kyoto, Japan) and a deuterated internal AZI standard, as described previously (5). The assays were performed without knowledge of the allocated therapy. In brief, 20-μl milk samples were spiked with internal standard and extracted based on methodology developed for plasma samples. After addition of ammonium hydroxide and methanol, vortex mixing, and freezing, the thawed sample was centrifuged, the organic supernatant was mixed with water, and an aliquot was injected onto an Agilent Eclipse Plus C18 column (Agilent Technologies, Santa Clara, CA).

Mass spectrometric quantitation was performed in multiple-reaction-monitoring mode using an electrospray ionization in positive ion mode (ESI+) ion source. AZI USP was obtained from APAC Organucytuck LLC (Ellicott City, MD) and deuterated AZI from Toronto Research Chemicals (North York, Canada). In brief, following the addition of an internal standard, AZI was extracted from 1 ml breast milk by protein precipitation. After centrifugation, supernatant (5 μl) was injected onto a 2795/Quattro Premier XE UPLC–electrospray ionization (ESI)–MS–MS (Waters Corp., MA) using a Waters BEH C18, 1.7-μm column. Matrix effect, process efficiency, and absolute recovery for AZI and deuterated AZI (AZI-D3) were within acceptable ranges (means, 92.5 to 107.9%). Intra- and interday relative standard deviations were 3.1 to 5.2% and 6.6 to 9.7% at AZI concentrations between 100 and 5,000 μg/liter, respectively. The mean accuracy was 94.5 to 103.8% over the same concentration range. The limits of quantitation and detection were 5 μg/liter and 2.5 μg/liter, respectively.

Pharmacokinetic modeling. NONMEM (v 7.2.0; Icon Development Solutions, Ellicott City, MD, USA) (19) with an Intel Visual FORTRAN 10.0 compiler was utilized for nonlinear mixed-effects modeling of the natural logarithm (log) breast milk concentration–time data set. The first-order conditional estimates with interaction (FOCE INTER) estimation method was used, with the minimum value of the objective function value (OFV), goodness-of-fit plots, condition number (<1,000), and predictive checks used to determine suitable models. A significance level of a P value of <0.05 was set for comparison of nested models. Two structures for residual variability (RV), equivalent to proportional and combined RV structures on the normal scale, were tested using the log-transformed data.

Given that only breast milk data were available for analysis, a previously developed validated population model of AZI disposition in pregnant women was utilized (5). It comprises a linear three-compartment model with mixed zero- and first-order absorption. The structural-model parameters were as follows: k0 (rate of first-order absorption), DUR (duration of zero-order absorption), CL/F (clearance relative to bioavailability), Vc/F (central volume of distribution relative to bioavailability), Qcl/F (intercompartmental clearance for Vp/F), Vp/F (first peripheral volume of distribution relative to bioavailability), Qcl/F (second peripheral volume of distribution relative to bioavailability). As it was not possible to estimate population variability on the model parameters, the average population parameter was utilized, with a single intraindividual variability (IVIV) term estimated for bioavailability (F). This IVIV term is a scaling term encompassing variability in AZI absorption, as well as interindividual differences in the milk/plasma ratio (MP_ratio). Given that this model was developed in a different population (Melanesian women) early in pregnancy (second trimester) (5), CL/F was allowed to be estimated, while other structural-model parameters were fixed.

Breast milk concentrations were linked with the above-described model using an MP_ratio. This method has been used successfully with other antimalarial drugs (20) and pharmacotherapies for other diseases (21). Given the temporal changes in this ratio (Fig. 1) and based on prior experience (20), a sigmoid maximum effect (Emax) relationship was utilized a priori to represent these changes. In this case, positive and negative sigmoid Emax relationships were required to represent the data adequately: MP_ratio = MP_ratio[1 + SIG_neg × (Tbirth Hill neg)] and MP_ratio = MP_ratio[1 + SIG_neg × (Tbirth Hill neg/ Tbirth Hill neg + MAT_50_neg Hill neg)], where MP_ratio is the MP_ratio after consideration of the effect of time, SIG_neg is the maximum effect on MP_ratio of the positive curve, Tbirth is the time of birth, MAT_50_neg is the time to 50% of the positive curve, and Hill_neg is the Hill coefficient for the positive curve, while SIG_neg is the maximum effect on MP_ratio of the negative curve, MAT_50_neg is the time to 50% of the negative curve, and Hill_neg is the Hill coefficient for the negative curve. The lack of concurrent plasma data and the complex relationship over time did not allow informative testing of other relationships. IVIV terms were included where they could be estimated. The effects of other covariates, including maternal age, gestational age at birth, and infant birth weight, were identified by inspection of individual-parameter-versus-covariate plots and use of the generalized additive model within Xpose. Identified relationships were then tested within NONMEM using a stepwise forward (P < 0.05) and backward (P < 0.01) approach.

Model evaluation included goodness-of-fit plots with observed versus individual and population predicted values and residual plots of time from first dose. A bootstrap using Perl speaks NONMEM with 1,000 samples was performed, and the derived parameters were summarized as me-
rates and macrolide exposure (without doses) for 1,074,000 infants, was utilized, together with the present PK modeling.

RESULTS

Baseline characteristics. The 20 AZI-treated women had a mean age (± standard deviation [SD]) of 27.7 ± 6.1 years, and they weighed 68 ± 11 kg. There were 7 (35%) primigravidae (parity range, 1 to 7), and their gestational age was 38 ± 2 weeks at delivery. The mean birth weight was 3.2 ± 0.4 kg (range, 2.5 to 4.0 kg). Two of the 80 breast milk concentrations from the 20 AZI-treated women (2.5%) were below the limit of quantitation and were excluded from PK modeling. Observed breast milk concentrations plotted against the population average maternal plasma concentration curve are shown in Fig. 1. Breast milk AZI concentrations were undetectable in all 80 samples from the 20 placebo-treated women.

Clinical course. None of the 40 women in the present study (20 randomized to AZI and 20 to placebo) required additional pharmacotherapy during the 28-day follow-up period. All provided four breast milk samples on days 3, 6, 14, and 28 postpartum. No serious adverse events were reported. All the infants remained well postpartum, with no cases of IHPS detected either in these 40 singleton infants or in the 419 infants whose mothers had received

![FIG 1](Top) Population average maternal plasma azithromycin concentration, based on a previously published study (5) (line), together with breast milk concentrations plotted against the population average maternal plasma concentration curve are shown in Fig. 1. Breast milk AZI concentrations were undetectable in all 80 samples from the 20 placebo-treated women.

![FIG 1](Bottom) The log_{10}(milk/plasma ratio) for azithromycin calculated using median parameters from a previously published study (5) (black line), together with the effects of the positive and negative sigmoid E_{max} relationships for the milk/plasma ratio (gray lines).

<table>
<thead>
<tr>
<th>Table 1 Final population pharmacokinetic estimates and bootstrap results for azithromycin in breast milk of lactating Gambian women</th>
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<td><strong>Parameter</strong></td>
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<td><strong>Objective-function value</strong></td>
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<td><strong>Structural-model parameters</strong></td>
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<td>CL/F AZI (liters/h/70 kg)</td>
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<td>MP_{max}</td>
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<td>DUR (h)</td>
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<td>V/F_{AZI} (liters/h/70 kg)</td>
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<td>V/F_{AZI} (liters/h/70 kg)</td>
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<td>Q_{2}/F_{AZI} (liters/h/70 kg)</td>
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<tr>
<td>V/F_{AZI} (liters/h/70 kg)</td>
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<td><strong>Variable-model parameters</strong></td>
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<td>IVF in F</td>
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<td>IVF in SIG_{pos}</td>
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<td>RV (%)</td>
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* RSE, residual standard error as a percentage of the mean.

**Simulated.** Using the method described above, simulations were performed to further define the range of expected neonatal AZI exposure. One thousand woman-neonate pairs were simulated using a 2-g Stat dose during labor and a 1-g daily dose over 3 days, as is used for intermittent preventive treatment of malaria in pregnancy (18). Absolute daily and total infant doses (in milligrams per kilogram), as well as relative daily and total infant doses (percentages of the daily and total maternal doses, respectively), were estimated for each simulated neonate to 28 days after birth.

Risk of infantile hypertrophic pyloric stenosis. For the estimated risk of IHPS in infants breastfed by an AZI-treated mother, the largest and most contemporary database available (14), which contains incidence
AZI in the main trial and who were assessed weekly for 8 weeks after delivery.

**Pharmacokinetic modeling.** Initial modeling was performed with all parameters fixed at their population means. Allowing clearance relative to bioavailability (CL/F) to be estimated resulted in significant improvement in the model (P < 0.001). Using a single sigmoid $E_{\text{max}}$ model (either positive or negative) did not adequately describe temporal changes in $\text{MP}_{\text{ratio}}$ and resulted in significant bias in the conditional weighted residual (CWRES) plots. Therefore, two linked relationships in opposite directions were utilized, with resolution of the CWRES bias and a fall in the OFV (P < 0.01). Attempts to model all parameters resulted in unstable estimates and high condition numbers (1,000). Therefore, the Hill coefficient for the positive model was fixed at 3.3, as obtained previously (20), and that of the negative model was assessed at between 2 and 20, with a final value of 10 chosen, as it best represented the data with no significant improvement in the fit of the model or in model diagnostics. IIV was estimable for bioavailability (F) and maximum effect on $\text{MP}_{\text{ratio}}$ of the positive curve (SIG$_{\text{pos}}$) at 63% and 59%, respectively. No significant covariate relationships were identified.

Final parameter estimates and bootstrap results are summarized in Table 1. Bias was <5.0% for fixed and random model parameters, with the exception of $\text{MP}_{\text{ratio}}$, where it was 14%. Goodness-of-fit plots are presented in Fig. 2 and the pcVPCs in Fig. 3. The actual 10th, 50th, and 90th percentiles were within the 95% CI of simulated data and demonstrate reasonable predictive performance of the model.

The estimated absolute and relative cumulative infant doses were calculated with median values of 4.5 mg/kg and 15.7%, respectively (Table 2). From this, the estimated absolute and relative daily infant doses were then calculated, with a median maximum daily intake of 0.7 mg/kg/day and 2.5%, respectively. The maximum estimated cumulative infant dose was 27.8% (8.0 mg/kg), while the maximum estimated relative daily infant dose was 4.5% (1.3 mg/kg/day).

**Simulations.** The results of simulations are presented in Table 2 and Fig. 4. The median estimated relative total dose was 13.7% (95% prediction interval [PI], 3.5 to 64.7%) for 2 g maternal oral

![FIG 2 Goodness-of-fit plots for azithromycin in breast milk. (A and B) Observed breast milk concentration plotted against population (A) and individual (B) predicted breast milk concentrations. (C and D) Weighted residuals against time from first dose (C) and time from birth (D).](http://aac.asm.org/)

![FIG 3 Prediction-corrected visual predictive check for azithromycin in breast milk. Observed 50th (solid line) and 10th and 90th (dashed lines) percentiles are shown within their simulated 95% CIs (gray shaded areas) with overlying data points (○).](http://aac.asm.org/)
AZI, corresponding to a median absolute total dose of 3.9 mg/kg (95% PI, 1.0 to 18.5 mg/kg). The highest median relative infant daily dose was 2.2% (95% PI, 0.6 to 10.7%) or 0.6 mg/kg/day (95% PI, 0.2 to 3.1 mg/kg/day) on day 6. This value was higher for the daily 1-g dose over 3 days, with a median relative total dose of 18.2% (95% PI, 4.6 to 63.9%) or 7.8 mg/kg (95% PI, 2.0 to 35.9 mg/kg) and highest median relative daily dose of 2.9% (95% PI, 0.8 to 13.8%) or 1.2 mg/kg/day (95% PI, 0.3 to 4.0 mg/kg/day).

The maximum simulated relative total and daily doses (in only 1 in 1,000 simulations) were 104% and 18%, respectively, for the 2-g Stat dose and 169% and 29%, respectively, for 1 g daily for 3 days. These estimates are close to, or exceed, the suggested 10% safety limit (13). Neonatal infections, such as pertussis, Ureaplasma, and chlamydial conjunctivitis are treated with 10 and 20 mg/kg AZI daily for 5 or 3 days, respectively (total, 50 to 60 mg/kg) (1, 22). Based on the present data, we estimate that the maximum simulated total AZI doses in infants breastfed by mothers given 2 g AZI during labor or 1 g daily for 3 days are 32 mg/kg and 63 mg/kg, respectively, over 14 days, corresponding to doses that are 36% lower and 5% higher, respectively, than the total neonatal treatment range (50 to 60 mg/kg).

**Risk of infantile hypertrophic pyloric stenosis.** The overall IHPS rate in the large published database was 2.3/1,000, which compares with 20.3/1,000 in infants given AZI between 0 and 14 days postpartum, with an adjusted odds ratio and 95% CI of 8.26 (2.62 to 26.0) (14). Based on these data, the number needed to harm (NNH) is approximately 60. Assuming a dose-dependent risk during the first 14 days of life, the additional cases of IHPS and NNH by threshold cumulative dose (in milligrams per kilogram) for both maternal AZI dose regimens (2 g Stat and 1 g daily for 3 days) were estimated.

**TABLE 2 Estimated infant doses of azithromycin to 28 days**

<table>
<thead>
<tr>
<th>Source</th>
<th>Infant doseb</th>
<th>Highest daily</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total Absolute (mg/kg)</td>
<td>Relative (%)</td>
</tr>
<tr>
<td>Measured breast milk concn</td>
<td>4.5 (0.6–8.0)</td>
<td>15.7 (2.0–27.8)</td>
</tr>
<tr>
<td>Simulation for 2-g dose during labor</td>
<td>3.9 (1.0–18.5)</td>
<td>13.7 (3.5–64.7)</td>
</tr>
<tr>
<td>Simulation for three 1-g daily doses from labor</td>
<td>7.8 (2.0–35.9)</td>
<td>18.2 (4.6–83.9)</td>
</tr>
</tbody>
</table>

*a* Derived from breast milk concentrations and from simulations and assuming 100% bioavailability.

*b* The data are presented as median (range) for PK modeling based on measured concentrations and median (95% prediction interval) for simulations.

![Simulation results demonstrating the median (solid black lines), maximum (dashed black lines), and 95% prediction intervals (gray-shaded areas) for absolute (in milligrams per kilogram) and percent relative total infant doses (A and C) and absolute (in milligrams per kilogram per day) and percent relative daily infant doses (B and D) from time of dose for 2 g Stat (A and B) and 1 g daily over 3 days (C and D). The cross-hatched areas during the first 3 days represent the lack of data during this period.](http://aac.asm.org/)

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...exposed children. The maximum NNH of 60 (14) applies if the... increase in gastric pH during the first few weeks of life may not influence AZI bioavailability in the suckling... and ion trapping alone (25). Although concentration-dependent migration of maternal leukocytes with high AZI concentrations from ingested breast milk into the neonatal circulation (7, 32). In the absence of a formal PK evaluation of the net effect of these factors on the neonatal plasma AZI concentrations from breast milk versus oral treatment, we assumed that bioavailabilities were equivalent.

The median total infant dose was 3.9 mg/kg for 2 g AZI given to pregnant women during labor and approximately double that for 1 g daily for 3 days. The highest median absolute daily infant doses (on day 6) for the two maternal AZI regimens were 0.6 and 1.2 mg/kg/day, respectively, comparable to the 0.25 to 0.5 mg/kg/day derived from simpler PK models after 0.5 g i.v. Stat and 2.5 g in divided oral doses (9, 11). However, our PK modeling was also able to investigate the total infant dose over longer periods, and this suggested that some infants receive significantly more than this, specifically, >70% of an infant oral AZI treatment course (1) over 28 days in up to 2.5% of children whose mothers were given 1 g daily over 3 days. This percentage may be greater with neonatal infection and thus a stimulus to increased numbers of AZI-rich maternal leukocytes in breast milk (8), a potential benefit.

There is, however, also concern regarding an association between macrolides and IHPS in neonates. Based on available data (14) and the present PK modeling, the NNH for African infants breastfed by a mother treated with 2 g AZI is, at worst (based on the upper 95% CI), 111. Although this should be interpreted against the possibility of higher maternal doses given for malaria treatment/prevention (3 g [18] or even 4 g [33] total), the true risk is likely to be much smaller than this and only estimable from larger-scale intervention trials. This potential adverse effect needs to be considered against AZI benefits for neonatal infections and complications, such as bronchopulmonary dysplasia (34). In addition, there is some evidence that the incidence of IHPS may be relatively low in developing countries, including those in sub-Saharan Africa (35).

The present study had limitations. The MP_{ratio} although providing an adequate characterization of the present data, was not based on plasma AZI concentrations in the African women in the present study. Although (and importantly) these data would not affect the infant dose estimates, the true MP_{ratio} may be different from the model-derived value. Alternative dynamic models of AZI breast milk transfer may have been possible, but their complexity would be limited by the numbers of available samples. Nevertheless, the present model fit the data well between 3 and 28 days. From simulations, the extrapolated data between delivery and day 3 account for only 8 to 16% of the estimated total infant dose.
consistent with the fact that infant milk consumption during the first 3 days is relatively low (36). Variations in milk creatocrit could help explain some of the between-subject variability (37), although the effect of coadministrated fat on bioavailability appears limited (10, 28). Measurement of AZI concentrations in maternal and neonatal blood, as well as breast milk, from birth would provide the most robust data on which to base an integrated PK model and thus recommendations regarding safety.

The present study represents the most comprehensive evaluation of the transfer of AZI into breast milk performed to date. It shows that infant versus maternal AZI dosing through lactation may exceed the suggested 10% safety limit in a relatively large proportion of neonates even if only a single dose is given at the time of labor (13). There may be advantages for the infant in reducing the risk of respiratory tract and other infections in the small proportion of infants with high levels of exposure, but the association with IHPS needs further evaluation in larger trials.

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