Pharmacokinetics of Piperaquine Transfer into the Breast Milk of Melanesian Mothers

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Transfer of piperaquine (PQ) into breast milk was examined in 27 Papua New Guinean women given a 3-day course of dihydroartemisinin-PQ or sulfadoxine-pyrimethamine-PQ during the second/third trimester. Breast milk was sampled on days 1, 2, 3, and 5, 7 to 11, and 14 to 17 postdelivery, a median of 70 days postdose (range, 6 to 145 days). A blood sample was taken at delivery, and additional serial samples were available from 9 women who delivered within 42 days of dosing. Milk and plasma PQ were assayed by high-performance liquid chromatography. A population-based approach was used to model the loge(plasma) and milk concentration-time data. A sigmoid $E_{\text{max}}$ model best described PQ breast milk transfer. The population average milk: plasma PQ ratio was 0.58, with a peak of 2.5 at delivery. The model-derived maximum milk intake (148 ml/kg of body weight/day) was similar to the accepted value of 150 ml/kg/day. The median estimated absolute and relative cumulative infant PQ doses were 22 µg and 0.07%, respectively, corresponding to absolute and relative daily doses of 0.41 µg/kg and 0.004%. Model-based simulations for PQ treatment regimens given at birth, 1 week postdelivery, and 6 weeks postdelivery showed that the highest median estimated relative total infant dose (0.36%; median absolute total dose of 101 µg/kg) was seen after maternal PQ treatment 6 weeks postpartum. The maximum simulated relative total daily doses from any scenario were 4.3% and 2.5%, respectively, which were lower than the recommended 10% upper limit. Piperaquine is transferred into breast milk after maternal treatment doses, but PQ exposure for suckling infants appears safe.

Women living in areas where malaria is endemic, such as coastal Papua New Guinea (PNG), are at a high risk of malaria infection during pregnancy (1, 2). Currently recommended strategies to reduce maternal and fetal risk include prompt treatment of symptomatic malaria and intermittent presumptive treatment in pregnancy (IPTp) (3–5). Given increasing parasite resistance to the conventional therapies that have been used in pregnancy, such as chloroquine (CQ) and sulfadoxine-pyrimethamine (SP), alternative regimens are needed which are safe, well tolerated, and efficacious (6). One promising candidate treatment is dihydroartemisinin-piperaquine (DHA-PQ), which has been assessed in a number of recent safety, efficacy, and pharmacokinetic studies (7–12). An alternative combination therapy for which trials have been conducted in infants as IPT is SP-PQ (13). Notwithstanding issues related to emerging SP resistance, this regimen has the advantage that the half-lives of SP are much longer than that of DHA, limiting the time between doses during which malaria parasites are exposed only to the relatively slowly eliminated PQ (14).

Although available data suggest that DHA-PQ and SP-PQ in usual adult doses have no significant maternal toxicity in the second and third trimesters of pregnancy (12), there have been no published pharmacokinetic studies of the transfer of PQ into breast milk and its subsequent ingestion by the infant (4). Since PQ is a basic compound with a $pK_a$ of 8.92 and plasma protein binding of $>99\%$, there is a high probability that the drug will readily accumulate in breast milk via a trapping effect (15). This assumption is based on previous studies which have demonstrated that the 4-aminoquinoline CQ, a weak base with a $pK_a$ of 8.4 and 10.8 for two binding sites and 61% plasma protein binding, was readily excreted in human milk at concentrations higher than in plasma (15). As breast milk contains a greater proportion of fats than protein, lipophilic drugs such as PQ readily transfer into the lipid component of milk, resulting in much higher concentrations than those of drugs with limited lipid solubility (16, 17).

The aim of the present study was, therefore, to investigate the transfer and pharmacokinetics of PQ in breast milk from PNG mothers given DHA-PQ or SP-PQ as part of a broader study of these regimens as potential IPTp (12).

MATERIALS AND METHODS

Study site, approvals, and participants. The present study was a substudy of a safety, tolerability, pharmacokinetic, and preliminary efficacy analysis of DHA-PQ and SP-PQ in pregnant and age- and community-matched nonpregnant PNG women (12). In brief, inclusion criteria were (i) >14 weeks gestation if pregnant, (ii) no treatment with any of the study drugs in the previous 28 days, (iii) no history of allergy to any of the study drugs, or any of the study drug's components.


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(iv) no significant comorbidity or clinical evidence of severe malaria, (v) availability for follow-up. Approval for the study was obtained from the PNG Institute of Medical Research Institutional Review Board and the Medical Research Advisory Committee of the PNG Health Department.

Study procedures. A detailed medical history and symptom questionnaire (including full details of recent drug treatment) were completed, and a physical examination (including body weight, height, axialillary temperature, lying and standing blood pressure and pulse rate, respiratory rate, and estimation of gestational age by fundal height in those who were pregnant) was performed. Participants were randomized by a computer-generated schedule to receive either (i) three DHA-PQP tablets (Euratressim; Simga-Tau Industrie Farmaceutici Riunite S.p.A., Italy) containing DHA at 40 mg and PQP at 320 mg, given daily for 3 days (at 0, 24, and 48 h) with water, at a total treatment DHA dose of 7 mg/kg of body weight and PQ dose of 38 mg/kg (equivalent to 33 mg/kg PQ base for a 50-kg woman), or (ii) four PQ tablets containing 320 mg (Sigma-Tau Industrie Farmaceutici Riunite S.p.A) daily for 3 days (at 0, 24, and 48 h) plus single-dose SP (25 mg/kg S, 1.25 mg/kg P) with the first PQ dose given with water. Administration of all doses was directly observed. Patients fasted for 2 h before and after dosing. Women who vomited within 30 min of drug administration were retreated.

All drugs taken over the 42 days of follow-up or up to the time of delivery were recorded. A single 3-ml blood sample was taken from the mother at delivery if possible, and breast milk samples (3 to 5 ml) were collected using manual expression by the mothers on days 1, 2, 3 to 5, 7 to 10, 11, and 14 to 17 postdelivery. In the case of women who delivered when they were within the 42-day follow-up period in the main pharmacokinetic study (12), additional serial plasma samples were available for PQ assay. The exact date and time of sampling were recorded in each case.

Piperaquine assay. Piperaquine tetraphosphate was obtained from Yick-Vic Chemicals and Pharmaceuticals Ltd. (Hong Kong). Internal standards for CQ diphosphate and amodiaquine (AQ) were purchased from Sigma-Aldrich (St. Louis, MO) and Sigma (Stockholm, Sweden), respectively. All reagents were of high-performance liquid chromatography (HPLC) grade or analytical grade. Maternal plasma PQ concentrations were determined using a validated HPLC method (18, 19). The intraday relative standard deviations (RSDs) of PQ in plasma were 8.1, 5.4, 7.4, 5.2, and 2.5 at 5, 25, 50, 200, and 500 μg/liter, respectively (n = 5), while interday RSDs were 8.4, 9.6, 6.5, 7.8, and 3.6 at 5, 25, 50, 200, and 500 μg/liter, respectively (n = 25). The limit of quantification (LOQ) and limit of detection (LOD) were 2 μg/liter and 1 μg/liter, with a signal-to-noise ratio of 3.0. Accuracy of the method was calculated from a further centrifugation at 1,500 x g, and 70-μl aliquots were analyzed by HPLC (Hewlett Packard model 1100) with a gradient pump and variable wavelength UV detector (Agilent Technology, Waldbronn, Germany). All samples with concentrations higher than the upper limit of the standard curve were diluted and reanalyzed. Separation was performed on a Gemini C8-phenyl 110A (150 by 4.6 mm, 5 μm) column connected to a Gemini C8-phenyl (4 by 30 mm) guard column (Phenomenex, Lane Cove, NSW, Australia) at 25°C. The mobile phase (11% acetonitrile in 0.1 M phosphate buffer at pH 2.5) flow rate was 1 ml/min, and analytes were detected by UV absorbance at 346 nm. The approximate retention times for PQ, CQ, and AQ were 3.4, 7.7, and 9.5 min, respectively.

The intraday RSDs of PQ were 7.5%, 6.8%, 3.8%, 4.6%, and 2.9% at 5, 25, 50, 100, and 200 μg/liter, respectively (n = 5), while interday RSDs were 9.4%, 7.3%, 7.5%, 6.4%, and 4.9% at 5, 25, 50, 100, and 200 μg/liter, respectively (n = 25). The LOQ and LOD were 2 μg/liter and 1 μg/liter, respectively, with a signal-to-noise ratio of 3.0. Accuracy of the method was calculated from quality control samples (run in parallel with the patient samples), which were 108.2 ± 9.9%, 111.4 ± 9.1%, 99.1 ± 7.2%, 98.2 ± 6.3%, and 97.1 ± 4.7% at 5, 25, 50, 100, and 200 μg/liter, respectively (n = 15). Recoveries were 90.8%, 95.3%, and 108.4% at 5, 25, and 100 μg/ml, respectively.

Pharmacokinetic modeling. The package NONMEM (v 7.2.0, ICON Development Solutions, Ellicott City, MD, USA) with an Intel Visual Fortran 10.0 compiler was utilized for nonlinear mixed-effects modeling of the log, plasma and breast milk concentration-time PQ data. The Laplacian with interaction estimation method was used with the minimum value of the objective function value (OFV), goodness-of-fit plots, and predictive checks used to arrive at suitable models during the model-building process. A significance level of P < 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 for the log-transformed data. Given the large number of samples with concentrations below the limit of quantification (BLQ), the M3 method was utilized to avoid significant bias in the results (21). This method has previously been used successfully in the pharmacokinetic characterizations of a number of antimalarial drugs (22–24).

As breast milk samples were collected a significant period after PQ dosing, it was assumed they were from the terminal elimination phase, while plasma concentration data were included from up to 7 days prior to the first breast milk sample. Residual plots of time from first PQ dose were evaluated to assess this assumption. As such, the log-transformed data were modeled as a straight line: \( C_{PL} = INT - (SLOPE \times t) \), where \( C_{PL} \) (in micrograms per liter) is the plasma concentration at time \( t \), INT is the intercept (the loge micrograms per liter), SLOPE is the slope of the line (reported in days\(^{-1} \)), and \( t \) (in days) is the time from first dose. The relationship between plasma and milk concentrations was modeled using a milk-to-plasma ratio as follows: \( C_{ML,M} = \frac{M}{P} \times C_{PL,M} \), where \( C_{ML,M} \) (in micrograms per liter) is the breast milk concentration at time \( t \) and \( M/P \) is the milk/plasma ratio. Exponentially modeled interindividual variability (IVV) and the correlation between IVV terms were evaluated for each model parameter and included where supported by the data.

Because the initial results demonstrated a potential relationship between breast milk concentration and time after birth, with higher concentrations closer to delivery, this was investigated using linear, exponential, and sigmoid \( E_{max} \) models. For linear models, the following equation was used:

\[
\frac{C_{ML,M}}{C_{PL,M}} = \frac{INT}{INT}\times (1 + EXP\times EXP^{-INT}\times INT)\times INT\times INT
\]

where EXP is the effect on concentration at birth and EXP is the change in the effect over time. Because the initial results demonstrated a potential relationship between breast milk concentration and time after birth, with higher concentrations closer to delivery, this was investigated using linear, exponential, and sigmoid \( E_{max} \) models. For linear models, the following equation was used:

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\[
\frac{C_{ML,M}}{C_{PL,M}} = \frac{INT}{INT}\times (1 + SIG0\times SIG0^{-SIG0}\times SIG0)\times SIG0\times SIG0
\]

where SIG is the effect on concentration at birth, SIG is the time to 50% effect, and SIG is the Hill coefficient.

The effects of other covariates, including maternal age, gestation at birth, and infant birth weight were identified by inspection of individual parameters compared with covariate plots and by using the generalized additive model within Xpose. Identified relationships were then tested within NONMEM by using a stepwise forward and backwards approach (P < 0.05 for forward steps and P < 0.01 for backwards steps).

Model evaluation. Model evaluation included goodness of fit plots of observed versus individual and population predicted values, residual plots.
of time from birth, and time from first dose. A bootstrap using Perl speaks NONMEM (PSN) with 1,000 samples was performed, and the parameters derived from this analysis were summarized as median and 2.5th and 97.5th percentiles (95% empirical confidence interval [CI]) to facilitate evaluation of final model parameter estimates. In addition, visual predictive checks (VPCs) were performed for breast milk data, and numerical predictive checks (NPCs) were performed for plasma data, with 1,000 data sets simulated from the final models. The observed 10th, 50th, and 90th percentiles were plotted with their respective simulated 95% CIs to assess the predictive performance of the model and to evaluate any major bias. VPCs were plotted against time from birth as well as time from first dose. Shrinkage of population variability parameters and residual variability were incorporated to help determine whether models were overparameterized and to determine the reliability of diagnostic plots (17).

Infant dose was estimated from the final model by using previously published data on breast milk transfer in the first week of life (25). A sigmoid $E_{\max}$ model was fitted to the mean amount (milliliters per kilogram) of milk transfer for women with normal vaginal delivery from this study. This was incorporated into the NONMEM control file to provide an estimate of the total infant PQ dose as a continuous function. For the purposes of estimation, discrete feeds were not modeled, given the long half-life of PQ in comparison to the short time between infant feeds. Absolute daily and total infant dose (in milligrams per kilogram) of milk transfer for women with normal vaginal delivery from this study were used to simulate the infant exposure in different dosing situations. Maternal plasma concentrations and weights were simulated from birth, were used to simulate the infant exposure in different dosing situations. Maternal plasma concentration and weight were simulated from birth, and all were reported to be feeding within 12 h of delivery, at which time all were reported to be feeding successfully with good sucking reflexes.

Simulations. The results of the final model, specifically, the milk-to-plasma ratio and the relationship of breast milk concentration and time from birth, were used to simulate the infant exposure in different dosing situations. Maternal plasma concentrations and weights were simulated from a population pharmacokinetic model of nonpregnant and pregnant women (12). Where the simulations included the first week of life, the sigmoid $E_{\max}$ model for increasing breast milk intake fit to published data, as described above, was used (25). For other situations, an average daily milk intake of 150 ml/kg/day was used (26). All simulations were for a full treatment course of PQ of three doses, 24 h apart. One thousand woman-infant pairs were simulated for each of the following three scenarios: (i) PQ dose at birth, (ii) PQ dosing 1 week after birth (i.e., when breast milk intake is established), and (iii) PQ dosing >6 weeks after birth. The first two scenarios assumed the pharmacokinetic properties of PQ in the mothers to be those seen in pregnant women, while the third scenario assumed a return to nonpregnant disposition. Absolute daily and total infant dose (mg/kg) as well as relative daily and total infant dose (as the percentage of daily and total maternal dose, respectively) were calculated for each participant to 42 days after the first PQ dose.

RESULTS
Breast milk samples were successfully collected from 27 (84%) of the 32 pregnant women recruited into the main trial (Table 1). All these women delivered healthy full-term babies between 6 and 124 days after DHA-PQ or SP-PQ treatment. The majority of deliveries (78%) were supervised at the Alexishafen Health Center labor ward, with the remainder occurring in the participant’s village. The average neonatal weight was 2.9 ± 0.6 kg (mean ± standard deviation; $n = 27$), and 57% of babies were males. All neonates were examined by study staff within 12 h of delivery, at which time all were reported to be feeding successfully with good sucking reflexes.

Pharmacokinetic modeling. There were 135 breast milk concentration measurements from 24 women, of which 32 samples (24%) were below the limit of quantification (BLQ). There were three women in whom all breast milk concentrations were BLQ, and these women were excluded from the analysis. The time to birth (and therefore breast milk sampling) was significantly later in these three women than the remainder (124 versus 63 days; $P < 0.05$). Given difficulties in obtaining maternal blood samples from community-based deliveries and when women delivered outside of the open hours at the Alexishafen Health Center, nine women had a blood sample drawn for PQ assay at delivery while a total of 22 serial plasma PQ concentrations from six women, all above the LOQ, were available for pharmacokinetic analysis.

Initial modeling demonstrated that a single straight line for log-transformed concentrations was suitable in modeling the data...
with no bias in the time-since-first-dose residual plots. When re-
sidual plots of time from birth were examined, a pattern was noted
with underestimation of earlier samples and overestimation of later
samples. A sigmoid $E_{\text{max}}$ model was superior to both exponential
and linear models in describing this pattern with a significantly lower
OFV ($P < 0.01$), and no trend was seen in residual plots. IIV was
estimable for MPRATIO, MAT50, and SIG0 with estimates of 52%,
26%, and 90%, respectively, and a full covariate matrix. No other
significant covariate relationships were identified.

Final parameter estimates and bootstrap results are summa-
rized in Table 2. Bias was $<6\%$ for all fixed and random model
parameters. Goodness-of-fit plots for PQ in breast milk are pre-
sented in Fig. 1. VPCs for the breast milk data are presented in Fig.
2, with the actual 10th, 50th, and 90th percentiles within the 95%
CI of simulated data. NPC of the plasma demonstrated the ex-
pected percentage of the data within, below, and above the 80%
prediction interval, specifically, 77%, 14%, and 9%, respectively.

The slope of the straight line was $0.0131 \text{ days}^{-1}$, corresponding
to a half-life of 52.8 days or 1,270 h. The population average milk:
plasma ratio was 0.58. The relationship between breast milk con-
centration and time from birth indicated concentrations were on
average 3.3 times higher at birth (resulting in a milk:plasma ratio
of 2.5 at birth), with a half-time of reduction at this ratio to a stable
level of 49 h and a Hill coefficient of 3.3.

FIG 1 Goodness-of-fit plots for piperaquine in breast milk. The observed breast milk concentration was plotted against population (A) and individual (B)
predicted breast milk concentrations, and also the weighted residuals against time from the first dose (C) and time from birth (D). Observations that were BLQ
have been separated to assist with visual interpretation. The solid lines in the upper two graphs represent the lines of identity, and the dashed lines are the
least-squares regression lines.

The sigmoid $E_{\text{max}}$ equation used to fit daily breast milk con-
sumption (in milliliters per kilogram per day) from previously
published data in women after normal vaginal delivery (25) re-
vealed an initial intake of 5.3 mg/kg/day, a time to reach 50% of
maximum intake of 67 h, a Hill coefficient of 3.05, and a maxi-
mum intake of 148 ml/kg/day. This maximum value is close to the
accepted daily breast milk intake of 150 ml/kg/day (26). Using this
model for breast milk intake, the estimated absolute and relative
cumulative infant dose was calculated, with median values of 22
$\mu$g and 0.07%, respectively. From this, the estimated absolute and relative daily infant doses were 0.41 $\mu$g/kg/day and 0.004%, re-
spectively (Table 3).

Simulation results. The results from the simulation study are
presented in Table 3 and Fig. 3. The highest median estimated
relative total dose (0.36%) was seen with dosing of piperaquine for
more than 6 weeks after birth, corresponding to a median absolute
total dose of 101 $\mu$g/kg. The median estimated total relative dose
was slightly lower for dosing 1 week after birth at 0.31% and was
lowest for dosing at birth, at 0.29%. The highest median relative
infant daily dose was similar in all scenarios, at 0.11 to 0.12% (10.0
to 10.9 $\mu$g/kg/day) occurring on day 3 after first PQ dose (i.e., after
the third and final PQ dose). The maximum simulated relative
total and daily dose from any scenario were 4.3% and 2.5%, re-
spectively, each lower than the suggested 10% safety limit (26).
DISCUSSION

This is the first study to have examined the transfer of PQ into breast milk after conventional adult doses of DHA-PQ or SP-PQ given over 3 days in pregnant PNG women attending their first antenatal visit. Given the length of time between dosing and delivery, it was not surprising that both maternal and breast milk concentrations were low postpartum. However, despite PQ being given up to 124 days before delivery, it was readily transferred into breast milk with a median (interquartile range) concentration of 27.5 (13.3 to 46.7) μg/liter. This was substantially higher than maternal plasma PQ concentrations at day 42 (5.5 [4.7 to 9.6] μg/liter) and reflected the milk:plasma ratio of 2.5 at birth. Simulations involving PQ administration between birth and 6 weeks postpartum suggested that the maximum total dose of PQ delivered to the suckling infant in breast milk was 101 μg/kg, or 4.3% of the maternal dose, which was below the 10% level at which safety concerns emerge (26). The disposition of PQ in a young breast-fed infant in whom drug-metabolizing enzyme systems are immature is, however, unknown. Although most unlikely to be a significant risk to the young infant, it is possible that PQ ingestion through breast milk may contribute to protection from malaria in early life. It is also possible that prolonged subtherapeutic PQ concentrations in the infant could facilitate the development of parasite resistance.

The median total PQ dose through breast milk in the simulations was 2.9% for maternal PQ-containing treatment at birth. This is similar to the 3.2% for the combination of CQ and desethyl chloroquine, a CQ metabolite with antimalarial activity (27), that was included in a previous study of PNG women given a treatment dose of CQ at delivery (20). Whether PQ also has an active metabolite is unknown and, despite the possibility of cytochrome P450 (CYP) enzyme involvement (28), there is chromatographic evidence that PQ is not extensively metabolized in adults and older children (29). Since the activities of prominent drug-metabolizing enzymes such as CYP3A develop slowly after birth (30), it is likely that maternally administered PQ is transferred mostly unmetabolized into breast milk, and it persists unmetabolized for many weeks in the circulation of young breastfed infants.

The equation used to model breast milk intake after birth from previous data facilitated the estimation and simulation of PQ exposure in the infant. Given that the estimated maximum value in the equation (148 ml/kg/day) was similar to the accepted established breast milk intake of 150 ml/kg/day (26), the modeling appears robust. It would, however, be informative to measure

![Graph A](image1)

**![Graph B](image2)**

**FIG 2** Visual predictive check for piperquine in breast milk, presented as both time from first dose (A) and time from birth (B) (in micrograms per liter, on a log10 scale). Observed 50th (solid line) and 10th and 90th (dotted lines) percentiles are shown within their simulated 95% CI (gray shaded areas), overlying the data points (○) as well as the observed fraction of BLQ data (▲ and dashed black line) with its simulated median and 95% CI (gray solid lines).

### TABLE 3

Estimated infant doses in the study sample and from simulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Absolute total infant dose (μg/kg)</th>
<th>Relative total infant dose (%)</th>
<th>Highest absolute daily infant dose (μg/kg/day)</th>
<th>Highest relative daily infant dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study patients</td>
<td>22 (18–56)</td>
<td>0.07 (0.06–0.18)</td>
<td>0.4 (0.3–0.8)</td>
<td>0.004 (0.003–0.007)</td>
</tr>
<tr>
<td>Simulation results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First dose at birth</td>
<td>81 (18–473)</td>
<td>0.29 (0.07–1.75)</td>
<td>10 (2–57)</td>
<td>0.11 (0.02–0.61)</td>
</tr>
<tr>
<td>First dose 1 wk after birth</td>
<td>88 (18–522)</td>
<td>0.31 (0.07–1.8)</td>
<td>11 (2–66)</td>
<td>0.12 (0.03–0.76)</td>
</tr>
<tr>
<td>First dose &gt;6 wks after birth</td>
<td>101 (27–409)</td>
<td>0.36 (0.10–1.42)</td>
<td>10 (3–44)</td>
<td>0.11 (0.03–0.43)</td>
</tr>
</tbody>
</table>

*Data presented are medians (with interquartile ranges in parentheses) for study participant data and medians (with 95% prediction intervals) for simulation data.*
plasma PQ concentrations in infants to further validate the model and to examine the pharmacokinetic properties of PQ in infancy. This would indirectly assist in formulating DHA-PQ dosing schedules in young children with acute malaria.

A limitation of the present study was the variability in breast milk concentrations, which may have been attenuated had we been able to measure milk crematocrit, a significant determinant of drug transfer between the plasma and milk compartments in other contexts (31). The present study was opportunistic, and a more definitive pharmacokinetic characterization would be facilitated by standardizing the time of dosing (such as at delivery, as in the CQ study [20]) and optimizing the sampling schedule based on the current relatively sparse data. Collection of fore- and hind-milk samples with measurement of crematocrit may also facilitate understanding of transfer processes. Because of location and logistics, we had few maternal plasma samples at time of delivery (n = 9), and a larger number would allow a more robust estimation of the PQ milk:plasma ratio.

The present study has provided novel data and valuable insights relating to the transfer of PQ into breast milk in the context of an IPTp study. The pharmacokinetic model describing the accumulation of PQ in breast milk appeared valid, and model-based simulations suggested that the amounts of PQ ingested by the breastfed infant are within established safety limits. Whether plasma PQ concentrations in the infant have any effect on malaria infection and whether they could contribute to the development of parasite resistance are unknown, but a formal pharmacokinetic evaluation would help to resolve these questions.

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![Simulation results demonstrating the median (black solid line) and 95% prediction interval (gray shaded area) for absolute (in micrograms per milliliter) and percent relative total infant dose (A, C, and E) and absolute and percent relative daily infant dose (B, D, and F) from time of first dose for treatment doses of piperaquine given at birth (A and B), 1 week after birth (C and D), and more than 6 weeks after birth (E and F).](http://aac.asm.org/\#)
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