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Pharmacokinetics and Efficacy of Piperaquine and Chloroquine in Melanesian Children with Uncomplicated Malaria▽

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The disposition of chloroquine (CQ) and the related 4-aminoquinoline, piperaquine (PQ), were compared in Papua New Guinean children with uncomplicated malaria. Twenty-two children were randomized to 3 days of PQ phosphate at 20 mg/kg/day (12 mg of PQ base/kg/day) coformulated with dihydroartemisinin (DHA-PQ), and twenty children were randomized to 3 days of CQ at 10 mg base/kg/day with a single dose of sulfadoxine-pyrimethamine (CQ-SP). After a 42-day intensive sampling protocol, PQ, CQ, and its active metabolite monodesethyl-chloroquine (DECQ) were assayed in plasma by using high-performance liquid chromatography. A two-compartment model with first-order absorption was fitted to the PQ and CQ data. There were no significant differences in age, gender, body weight, or admission parasitemia between the two groups. The PCR-corrected 42-day adequate clinical and parasitological responses were 100% for DHA-PQ and 94% for CQ-SP, but *P. falciparum* reinfections during follow-up were common (33 and 18%, respectively). For PQ, the median volume of distribution at steady state, allowing for bioavailability (V_{ss}/F), was 431 liters/kg (interquartile range [IQR], 283 to 588 liters/kg), the median clearance (CL/F) was 0.85 liters/h/kg (IQR, 0.67 to 1.06 liters/h/kg), the median distribution half-life ($t_{1/2\alpha}$) was 0.12 h (IQR, 0.05 to 0.66 h), and the median elimination half-life ($t_{1/2\beta}$) was 413 h (IQR, 318 to 516 h). For CQ, the median V_{ss}/F was 154 liters/kg (IQR, 101 to 210 liters/kg), the median CL/F was 0.80 liters/h/kg (IQR, 0.52 to 0.96 liters/h/kg), the median $t_{1/2\alpha}$ was 0.43 h (IQR, 0.05 to 1.82 h), and the median $t_{1/2\beta}$ was 233 h (IQR, 206 to 298 h). The noncompartmentally derived median DECQ $t_{1/2\beta}$ was 290 h (IQR, 236 to 368 h). Combined molar concentrations of DECQ and CQ were higher than those of PQ during the elimination phase. Although PQ has a longer $t_{1/2\beta}$ than CQ, its prompt distribution and lack of active metabolite may limit its posttreatment malaria-suppressive properties.

Piperaquine (PQ) is a 4-aminoquinoline-like antimalarial drug originally used as single-agent chemoprophylaxis and mass treatment in China but which has recently enjoyed a resurgence as a component of artemisinin combination therapy (ACT) (8). Although ACT is now recommended as first-line treatment for uncomplicated *Plasmodium falciparum* malaria by the World Health Organization (WHO) (41), only one coformulation (artemether-lumefantrine) is currently endorsed, and its relatively high cost and complex dosing may limit its widespread application (9). PQ coformulated with dihydroartemisinin (DHA-PQ) as Duo-cotecxin (formerly Artekin) represents a safe and highly effective alternative (10, 19, 23, 31, 34).

Despite its long and relatively heavy use (8), the pharmacokinetic properties of PQ have been investigated in only small numbers of healthy volunteers (28, 30, 32) and patients with malaria (17). In Papua New Guinea (PNG), DHA-PQ could replace the combination of chloroquine (CQ) and sulfadoxine-pyrimethamine (SP), which is increasingly associated with treatment failure (6). Although still widely used in the tropics because of its safety, availability, and low cost, the pharmacokinetics of CQ are also poorly characterized. Early studies involved small numbers of adults, were limited by low assay sensitivity and rudimentary modeling techniques, and revealed substantial interindividual variability in estimated pharmacokinetic parameters (20, 37).

The aim of the present study was, therefore, to characterize and compare the pharmacokinetic properties of PQ and CQ in Melanesian children with uncomplicated malaria. A secondary aim was to provide preliminary comparative efficacy data for DHA-PQ and CQ-SP in this patient group.

MATERIALS AND METHODS

Study site. The study was conducted from August 2005 to March 2006 at Alexishafen Health Centre, Madang Province, situated on the north coast of PNG. The resident population is Melanesian. *P. falciparum* is hyperendemic in this area, and most clinical disease occurs in children (7). *P. vivax*, *P. ovale*, and *P. malariae* are also endemic in this area.

Patient eligibility and enrolment. Children aged 5 to 10 years with an axillary temperature of >37.5°C or fever during the previous 24 h were screened with a Giemsa-stained thick blood film read by a trained microscopist. Children with monoinfections with either *P. falciparum* (>1,000 asexual parasites/μl of whole blood) or *P. vivax*, *P. ovale*, or *P. malariae* (>250 parasites/μl) were eligible for the study provided that (i) the subject had no features of severe malaria (42), (ii) the subject had not taken study drugs in the previous 14 days, (iii) there was no clinical evidence of nonmalarial infection, (iv) there were no signs of malnutrition or other comorbidity, and (v) the child's parent or guardian gave informed consent. An initial detailed clinical assessment was performed, and a 3-ml venous blood sample was obtained. Baseline tests included hemoglobin (HaemoCue, Angelholm, Sweden) and blood glucose (HaemoCue). Separated plasma was stored at lower than −20°C for subsequent drug assay, and a red cell pellet was

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TABLE 1. Details of patients at the time of admission to the study

Parameter	DHA-PQ group	CQ-SP group
No. of patients	22	20
Mean age (yr) ± SD	6.9 ± 1.4	6.7 ± 1.5
No. of male patients (%)	17 (86)	13 (65)
Mean body wt (kg) ± SD	19.1 ± 3.8	18.8 ± 3.1
Mean axillary temp (°C) ± SD	37.2 ± 1.2	38.1 ± 1.5[a]
No. of patients (%) with splenomegaly	15 (68)	10 (50)
Mean respiratory rate (per min) ± SD	27 ± 6	30 ± 12
Mean hemoglobin concn (g/dl) ± SD	8.6 ± 1.8	7.8 ± 1.2
No. of patients (%) with *P. falciparum*[b]	19 (86)	18 (90)
Mean *P. falciparum* parasitemia level per μl (range)	20,400 (3,520–191,000)	34,500 (1,640–322,000)
Mean plasma glucose (mmol/liter) ± SD	6.2 ± 1.2	5.5 ± 1.9
Mean drug dose (mg base/kg/day) ± SD	11.8 ± 1.5[c]	10.2 ± 1.3

[a] $P = 0.03$ versus DHA-PQ.
[b] A further three patients treated with DHA-PQ had monoinfections with either *P. vivax* ($n = 2$) or *P. malariae* ($n = 1$); one *P. vivax*- and two *P. malariae*-infected patients received CQ-SP.
[c] Equivalent to 20.4 ± 2.6 mg of PQ phosphate/kg/day.

retained for parasite genotyping. The study was approved by the Human Research Ethics Committee of the University of Western Australia (approval no. 1060) and the Medical Research Advisory Committee of PNG (approval no. 05.02).

Drug administration. After recruitment, an envelope labeled with a unique sequential code was opened, and a computer-generated randomized treatment was read and assigned. This process did not involve the children, parents/guardians, or ward staff. Children in treatment arm A were allocated Duo-cotecxin tablets (Beijing Holley-Cotec, Beijing, China) containing DHA and PQ (mass ratio, 1:8; 40 mg of DHA and 320 mg of PQ phosphate per tablet). A DHA dose of 2.5 mg/kg and PQ phosphate dose of 20 mg/kg (equivalent to 11.5 mg of PQ base/kg) was given daily for 3 days (at 0, 24, and 48 h; 60 mg of PQ phosphate/kg total). Children in arm B received CQ (Chlorquin; Aspen Healthcare Australia, Pty. Ltd., St. Leonards, Australia) at 10 mg base/kg daily for 3 days (at 0, 24, and 48 h; 30 mg of CQ base/kg total) and single-dose SP (Fansidar; Roche, Basel, Switzerland; 25 mg/kg [S] and 1.25 mg/kg [P]) with the first CQ dose. Dosing was directly supervised and comprised a combination of whole, half, or quarter tablets (prepared by using a tablet cutter) that best approximated the target dose. Doses were swallowed whole with water, and the administration time was recorded. Children were observed for 30 min afterward, and a repeat dose was given to those who vomited. Subjects were not required to fast. Since Duocotecxin is not produced under Good Manufacturing Practice standards, tablets from each batch were assayed for content (see below).

Monitoring and outcome assessment. All patients were admitted for 48 to 72 h for supervised drug dosing, blood sampling, and monitoring, which included a standard daily assessment of symptoms, axillary temperature, respiratory rate, blood glucose, and parasitemia. Children developing signs of severe malaria or WHO-defined early treatment failure (42) were to be withdrawn and given intramuscular quinine, as recommended for complicated malaria in PNG (3). After discharge, children were reviewed on days 7, 14, 28, and 42, at which times axillary temperatures and hemoglobin levels were measured, and a thick blood film was taken. Treatment response was assessed based on current WHO definitions (40). Children found to have late treatment failure during follow-up were retreated with quinine if symptomatic.

Blood sampling. Each child had a heparinized intravenous cannula inserted at enrollment. In addition to a baseline sample, 3 ml of venous blood was drawn at 1, 2, 4, 6, 12, 18, 24, 30, 48, and 72 h and by venisection at 7, 14, 28, and 42 days. The sampling protocol was identical in the two treatment arms. The exact time of each sample was recorded. Blood samples were collected into lithium heparin tubes and centrifuged at 1,800 × *g* for 5 min, and separated plasma was stored at −80°C until analyzed.

Laboratory methods. (i) Microscopy and parasite genotyping. Blood smears were examined by two skilled microscopists who were blind to treatment allocation and the other microscopist's result. At least 100 fields at ×1,000 magnification were viewed before a slide was reported as negative. Parasite density was determined from the number of asexual parasites/1,000 leukocytes and assuming a total leukocyte count of 8,000/μl. Any slide discrepant for positivity or negativity, speciation or parasite density (>10-fold difference) was read by a third microscopist, whose result was final. In cases of microscopically confirmed recrudescence or reinfection with *P. falciparum*, parasite DNA from the follow-up blood sample was compared to that of the baseline sample for MSP1, MSP2, and GLURP gene polymorphisms as described previously (6).

(ii) Drug assays. PQ tetraphosphate reference standard was obtained from Yick-Vic Chemicals and Pharmaceuticals, Ltd. (Hong Kong); CQ diphosphate was from Sigma-Aldrich (St. Louis, MO); and desethylchloroquine (DECQ) dioxalate was from Starks Associates (Buffalo, NY). All other reagents were of high-pressure liquid chromatography or analytical grade.

The methods of extraction and assay for both drugs were similar. In brief, plasma (1 ml) was spiked with either PQ or CQ as an internal standard (200 ng base) for the alternate drug assay, alkalinized with 0.1 ml of 1 M NaOH, and extracted by shaking with 8 ml of hexane-isoamyl alcohol (90:10) (PQ) or, because it improved DECQ recovery from 46 to 96%, 8 ml of *t*-butyl methyl ether (CQ). After centrifugation at 900 × *g* for 10 min, 7 ml of supernatant was back extracted into 0.1 ml of 0.05 M HCl by shaking for 5 min. The HCl layers were aspirated and recentrifuged at 900 × *g* for 20 min, after which aliquots (25 μl) were injected onto on a Chromolith Performance column (100 by 4.6 mm [inner diameter]; E. Merck GmbH, Darmstadt, Germany) at 30°C with a mobile phase of 6% (vol/vol) acetonitrile in 50 mM K_2HPO_4 buffer (pH 2.5) pumped at 2 ml/min. Retention times were 1.7, 4.9, and 6.7 min for PQ, DECQ, and CQ, respectively. Analytes were detected at 340 nm and quantified by using Chemstation Software (version 9; Agilent Technology, Waldbronn, Germany). The usual linear assay range was 3 to 1,867 nmol/liter for PQ, 6 to 6,253 nmol/liter for CQ, and 4 to 6,852 nmol/liter for DECQ. For PQ, the intraday relative standard deviations (RSDs) were 10.8, 8.2, and 9.4% ($n = 5$), and the interday RSDs were 11.6, 4.4, and 6.7% ($n = 15$) at 9, 37, and 1,867 nmol/liter, respectively. The limits of quantification and detection were 3 nmol/liter and 1.3 nmol/liter, respectively. For CQ, the intraday RSDs were 8.4, 8.6, and 2.1% ($n = 5$) and the interday RSDs were 8.6, 6.8, and 2.7% ($n = 15$) at 16, 63, and 6253 nmol/liter, respectively. For DECQ, the intraday RSDs ($n = 5$) were 8.9, 9.6, and 1.5%, and the interday RSDs were 8.2, 8.3, and 3.5 ($n = 15$) at 10, 423, and 4,230 nmol/liter, respectively. The limits of quantitation and detection were 6 and 3 nmol/liter for CQ and 4 and 2 nmol/liter for DECQ, respectively. Quality control samples (9 and 324 nmol/liter for PQ, 16 and 625 nmol/liter for CQ, and 10 and 423 nmol/liter for DECQ) were included with each analytical run. All samples were assayed within the frozen storage stability limits previously established in our laboratory of 12 months for PQ (16a) and 6 months for CQ (unpublished data).

(iii) Pharmacokinetic analysis. For both PQ and CQ, individual two- or three-compartment models with a lag time and using weighting of $1/y$ or $1/y^2$ were fitted to individual patient concentration (y)-time (x) data (16). Discrimination between models was based on the overall model goodness-of-fit criterion (B^2), visual inspection of the distribution of residuals, and the Akaike Information Criterion value. Derived parameters of interest included half-lives for absorption ($t_{1/2abs}$), distribution ($t_{1/2\alpha}$), and elimination ($t_{1/2\beta}$); the volume of distribution at steady-state relative to bioavailability (V_{ss}/F); the clearance relative to bioavailability (CL/F); and areas under the concentration-time curve (AUC) to 42 days ($AUC_{0\text{-}42}$) and infinity ($AUC_{0\text{-}\infty}$). For DECQ, the $AUC_{0\text{-}42}$ (log-linear trapezoidal rule), $AUC_{42\text{-}\infty}$ (C_{42}/terminal elimination rate constant), $AUC_{0\text{-}\infty}$ ($AUC_{0\text{-}42}$ plus $AUC_{42\text{-}\infty}$), and $t_{1/2\beta}$ (log-linear regression of last three to four data pairs) were estimated by noncompartmental analysis (33). Drug concentrations and AUC measurements are expressed as molar concentrations.

TABLE 2. Treatment outcomes as determined by microscopy at days 28 and 42 in children with *P. falciparum* monoinfection at baseline ($n = 35$)[a]

Outcome	No. of patients (%) with the indicated outcome at:			
	Day 28		Day 42	
	DHA-PQ ($n = 18$)	CQ-SP ($n = 17$)	DHA-PQ ($n = 18$)	CQ-SP ($n = 17$)
P. falciparum parasitemia	0	2 (12)	6 (33)	4 (24)
Reinfection	0	1 (6)	6 (33)	3 (18)
Recrudescence	0	1 (6)	0 (0)	1 (6)
P. vivax parasitemia	0	6 (35)*	1 (5.6)	6 (35)*

[a] Recurrent infections during follow-up were differentiated as either reinfection or recrudescence by genotyping (see the text). *, $P < 0.05$ for the differences between treatment groups.

Statistical analysis. Student *t* test (for normally distributed data) or the Mann-Whitney U test (for non-normally distributed data) was used for between-group comparisons of admission characteristics, pharmacokinetic parameters, and outcomes. Categorical data were compared by using the Pearson chi-squared or Fisher exact test where appropriate. A two-tailed level of significance of $P < 0.05$ was used (v9.0; SPSS, Chicago, IL).

RESULTS

Patient characteristics. A total of 101 febrile children aged 5 to 10 were screened, 35 of whom were ineligible due to a negative blood slide or a parasitemia of <1,000 asexual parasites/μl. A further 12 declined consent, and 12 were excluded due to recent treatment ($n = 2$), inability to attend for follow-up ($n = 9$), concomitant illness ($n = 3$), and/or signs of severe malaria ($n = 2$). Of the remaining 42 children, 36 had falciparum, 3 had vivax, and 3 had malariae malaria. Their baseline characteristics by allocated treatment are summarized in Table 1. There were no statistically significant differences between the two treatment groups, except that children treated with CQ had a higher mean axillary temperature. Only one child vomited during the 30-min postdose. This was the first dose of CQ and SP that was readministered promptly without further incident. No children were known to have vomited subsequent to the 30-min observation period.

Response to treatment. The treatment outcomes in the 35 falciparum patients are summarized in Table 2. Parasite clearance (the number of days taken to a negative blood slide) was faster in the DHA-PQ group (median, 2 versus 3 days in CQ-SP group [$P = 0.001$]). A higher number of CQ-SP patients (8 of 17) were gametocytemic at day 14 compared to DHA-PQ patients (1 of 18 [$P = 0.007$]). According to WHO definitions, all 18 DHA-PQ-treated patients achieved an adequate clinical and parasitological response (ACPR) of 100% at 28 days. For CQ-SP-treated patients, only one recrudescence occurred (PCR-corrected ACPR of 94%). By day 42, a further six DHA-PQ-treated patients and two other CQ-SP-treated patients had developed reinfections with *P. falciparum*, but there were no further recrudescences. Thus, the PCR-corrected ACPRs at day 42 were unchanged (100% for DHA-PQ and 94% for CQ-SP). There were no statistically significant differences between treatment arms for *P. falciparum* reinfections, recrudescences, or ACPR at days 28 or 42.

A significantly higher number of those in the CQ-SP group developed *P. vivax* infections during follow-up (Table 2). Of four patients with *P. vivax*, one treated with CQ-SP was lost to follow up, two treated with DHA-PQ had ACPR, and one treated with DHA-PQ showed a reappearance of *P. vivax* on day 42. All three patients with *P. malariae* (two treated with CQ-SP and one treated with DHA-PQ) made a full recovery without relapse.

One child in the DHA-PQ group developed a painful foot and malaise 7 days after treatment in association with a painful, indurated intravenous cannula site. Her symptoms were consistent with disseminated bacterial sepsis secondary to thrombophlebitis. She made an uneventful recovery with a course of antibacterial therapy (flucloxacillin). No other significant adverse effects were observed in either treatment arm.

Drug assays and pharmacokinetic analysis. The mean drug contents of the Duo-cotecxin tablets were 109% ± 7% for PQ and 106% ± 4% for DHA. In the development of pharmacokinetic models for both CQ and PQ datasets, a two-compartment model with $1/y^2$ weighting gave the best fit. The pharmacokinetic parameters for CQ and PQ are summarized in Table 3. Noncompartmental analysis derived $t_{1/2\beta}$ values for PQ and CQ were similar to those derived from compartmental methods: the noncompartmental $t_{1/2\beta}$ values were 431 h (interquartile range [IQR], 322 to 531 h) for PQ and 235 h (IQR, 212 to 298 h) for CQ ($P < 0.001$). Plasma concentration profiles of PQ, CQ, and DECQ are presented as spaghetti plots in Fig. 1 and 2. The similarity of $t_{1/2\beta}$ values for DECQ (290 h [IQR, 236 to 368 h]) to those for CQ suggests that DECQ $t_{1/2\beta}$ may be formation rate limited. In DHA-PQ-treated patients on day 7, the median concentrations of PQ (78 nM) were lower than the median concentrations of CQ (223 nM) and DECQ (167 nM)

TABLE 3. Pharmacokinetic parameters for PQ, CQ, and DECQ in children with malaria

Parameter[a]	Median (IQR)		
	PQ ($n = 22$)	CQ ($n = 20$)	DECQ ($n = 20$)
$t_{1/2\alpha}$ (h)	0.12 (0.05–0.66)	0.43 (0.05–1.82)	
$t_{1/2\beta}$ (h)*	413 (328–515)	233 (206–298)	290 (236–368)
$t_{1/2abs}$ (h)	8.3 (6.2–11.8)	12.8 (7.1–19.4)	
t_{lag} (h)	0.89 (0.03–1.02)	0.55 (0.01–0.86)	
V_{ss}/F (liters/kg)*	431 (283–588)	154 (101–210)	
CL/F (liters/h/kg)	0.85 (0.67–1.06)	0.80 (0.52–0.96)	
$AUC_{0\text{-}42}$ (μmol · h/liter)	76.4 (51.9–84.7)	117.2 (98.7–153.0)	83.6 (58.1–127.4)
$AUC_{0\text{-}\infty}$ (μmol · h/liter)	87.4 (63.3–113.1)	122.5 (101.1–165.8)	98.5 (69.5–133.8

[a] *, $P < 0.001$ for PQ versus CQ.

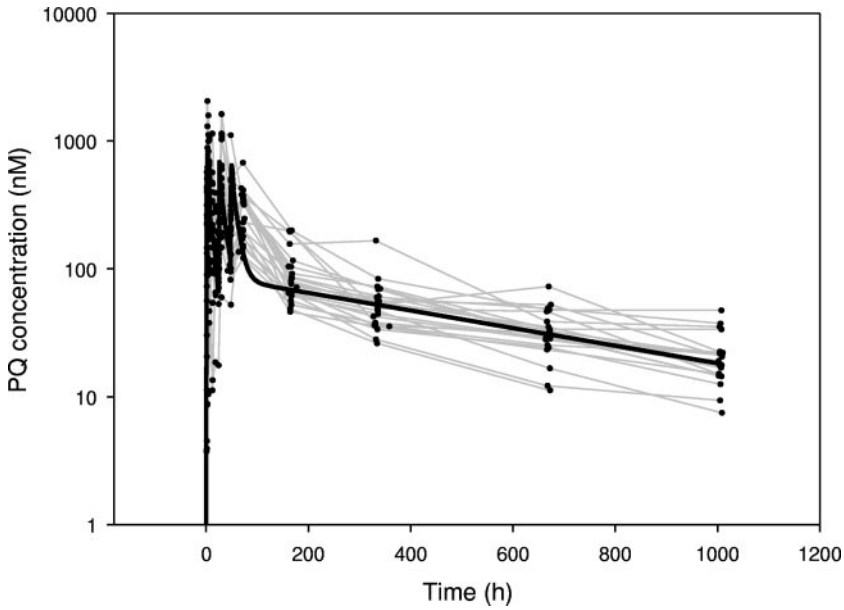

FIG. 1. Plot of measured (closed circles) and predicted (solid line) plasma piperaquine concentrations against time. The predicted concentrations were derived from geometric mean parameters for the pharmacokinetic model.

seen in CQ-SP-treated patients, a finding consistent with the significantly larger V_{ss}/F for PQ. This was also the case at day 28 (median concentrations of 30 nM [PQ], 28 nM [CQ], and 35 nM [DECQ]).

The association between drug exposure and suppression of infection was assessed by comparing the PQ and CQ $AUC_{0\text{-}42}$s in patients with a relapse of *P. falciparum* (including all reinfections and one recrudescence in the CQ-SP group) during the 42-day follow-up period to those in patients without evidence of relapse. There was a lower PQ $AUC_{0\text{-}42}$ (median, 59.3 μmol · h/liter [IQR, 43.1 to 76.4 μmol · h/liter]) for patients treated with DHA-PQ who experienced relapse than in those who did not (median, 79.0 μmol · h/liter [IQR, 36.7 to 147.0 μmol · h/liter]; $P = 0.036$). However, there was no such relationship in the case of CQ-SP whether the $AUC_{0\text{-}42}$ was that for CQ alone or for the composite of CQ and DECQ ($P > 0.6$ in each case).

DISCUSSION

The present study adds to the limited knowledge of the pharmacokinetic properties of two widely used and chemically related long half-life antimalarial agents. One (PQ) is likely to see increased use as part of ACT, while the other (CQ) is becoming ineffective in many areas of the tropics despite coadministration with other drugs. The disposition of PQ and CQ in Melanesian children with uncomplicated malaria is broadly consistent with available data from other studies in different contexts. However, the prompt distribution phase of PQ may limit its posttreatment suppressive properties in areas of high transmission such as PNG. In contrast, the long terminal elimination phase of its active metabolite DECQ may explain why the decline of CQ effectiveness as monotherapy has been slower than that of other quinoline drugs such as mefloquine.

In a population PQ pharmacokinetic analysis of Cambodian children with malaria (17), the median $t_{1/2abs}$ (9.3 h), $t_{1/2\beta}$ (13.5 days), and V_{ss}/F (614 liters/kg) values were similar to those in our 22 DHA-PQ-treated patients (8.3 h, 17.2 days, and 431 liters/kg, respectively), although the CL/F (1.85 liters/h/kg) was higher than in the present study (0.85 liters/h/kg). Although our children were of similar age to the Cambodian patients (6.9 ± 1.4 versus 7 ± 2 years) (17), they tended to be heavier (19.1 ± 3.8 versus 16 ± 4 kg), to be more often male (86% versus 55%), and to have higher parasitemias (range, 3,520 to 191,000/μl versus 3,100 to 33,342/μl), and they were not (unlike the Cambodian patients) required to fast. These differences may also have contributed to the shorter median $t_{1/2\alpha}$ in the present study (0.12 h) than in Cambodian children (1.7 h) (17), but this discrepancy might also reflect the relatively rich sampling and consequently better characterization of the distribution phase in our children.

A study of PQ in healthy young adults using noncompartmental analysis (30) derived mean values for $t_{1/2\beta}$ (20.3 and 20.9 days after fasting and a high fat meal, respectively), V_{ss}/F (716 and 365 liters/kg), and CL/F (1.14 and 0.6 liters/h/kg) similar to those in the present study. Röshamaar et al. (28) also demonstrated similar $t_{1/2\beta}$ (11.7 days using a two-compartment and 19 days using a three-compartment model) and CL/F (0.97 liters/h/kg) values in healthy Vietnamese adults but a lower V_{ss}/F (103 liters/kg). The present study used PQ coformulated with DHA, trimethoprim, and primaquine, and the lower V_{ss}/F could have been a consequence of drug interactions or other pharmaceutical factors. In addition, Röshamaar et al. (28) demonstrated multiple absorption peaks and used a dual pathway first-order absorption model to improve the goodness-of-fit, which may also have contributed to the lower calculated V_{ss}/F.

Although the median $t_{1/2\beta}$ of 17 days in the present study was within the range of those from the three previous PQ pharmacokinetic studies (17, 28, 30), a study of a single Caucasian

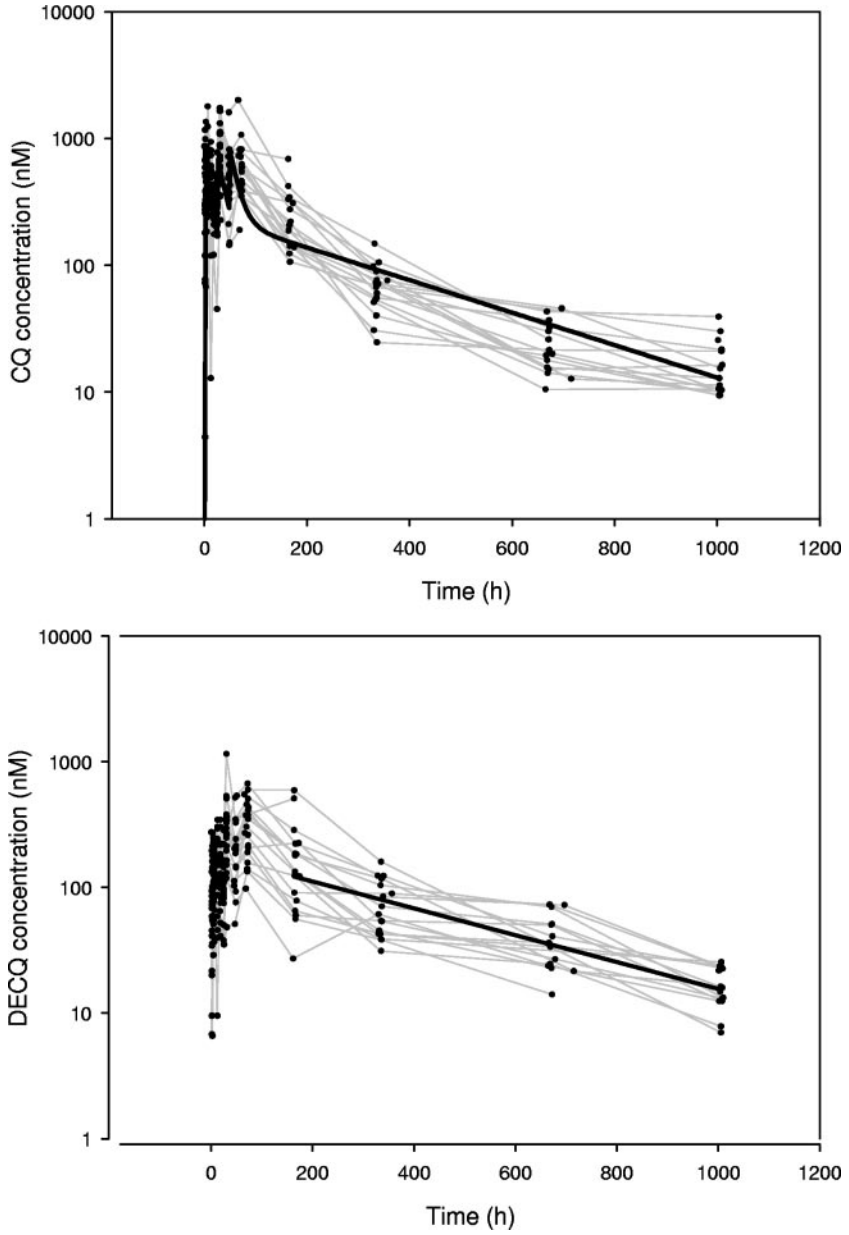

FIG. 2. (Upper panel) Plot of measured (closed circles) and predicted (solid line) plasma chloroquine concentrations against time. The predicted concentrations were derived from geometric mean parameters for the pharmacokinetic model. (Lower panel) Plot of plasma DECQ concentrations (open circles) against time. The solid line represents the terminal elimination phase, based on linear regression of the final four data points (at 7, 14, 28, and 42 days).

volunteer used a 93-day sampling duration that suggested prolonged multiphasic elimination (32). The authors of that study calculated a $t_{1/2\beta}$ of 33 days but, based on linear regression of the final three data points, the real $t_{1/2\beta}$ may have been 80 days (32). Because of difficulties in monitoring patients in remote settings and ethical constraints on repeated blood sampling in children, our study was not of sufficient duration to confirm these findings. However, our two-compartment model generated a curve whose log-linear elimination phase fitted the last four data points (from 7 to 42 days) well (see Fig. 1). Whereas we cannot exclude a longer elimination phase, drug concentrations beyond 42 days are likely to be well below the *P. falciparum* MIC. Such concentrations should not influence recrudescence but may have implications for the selection of resistant parasites if reinfection occurs (8).

Despite extensive use of CQ for >50 years, CQ pharmacokinetics remain poorly defined and have been determined mainly in adult patients (20, 37). However, consistent with the present study, all have shown large volumes of distributions (ranging from 59 to 882 liters/kg) and multiexponential pharmacokinetic profile (2, 13, 20, 37) and, when reported, a rapid distribution phase with initial half-lives of 0.16 to 1.07 h (13, 21, 39). Our median $t_{1/2\beta}$ of 9.7 days is consistent with values of 5.8 to 20.0 days generated from studies with sampling over 28 to 56

days (1, 2, 5, 12, 14, 24, 35, 36). One 6-month study generated a $t_{1/2\beta}$ of 42 days (13). However, as with PQ, a prolonged CQ elimination phase is unlikely to be of clinical significance if plasma concentrations have fallen to well below the parasite MIC. Values for CL/F for CQ in the present study (0.80 liters/h/kg) are similar to those reported previously in generally older patients with or without malaria (range, 0.13 to 1.1 liters/h/kg) (1, 2, 5, 12, 14, 24, 35, 36). Many of these previous studies have relied on noncompartmental methods, and none has determined a value for CQ clearance in children, nor an absorption rate constant or half-life in adults or children.

Although the present study was not powered to assess efficacy, it is encouraging that the 42-day PCR-corrected ACPR was 100% for the 18 *P. falciparum* patients treated with DHA-PQ. However, the ACPR was 94% in the CQ-SP group, suggesting that CQ-SP retains some efficacy in this semi-immune pediatric population despite a high local prevalence of genotypic CQ and SP resistance markers (6). The rate of *P. falciparum* reinfection seen in both groups confirms local endemicity but also suggests that, for both drug combinations, plasma concentrations had fallen to below the parasite MIC well before 42 days posttreatment. The preliminary observation that a higher PQ AUC was associated with a better treatment response is consistent with a Cambodian study in which the patients with recrudescent infections were those given the lowest mg/kg doses (10). However, larger-scale pharmacokinetic-pharmacodynamic studies are needed to explore this association further. In the case of PQ, the apparently short-duration posttreatment chemoprophylactic effect is surprising given its long $t_{1/2\beta}$. However, its short $t_{1/2\alpha}$ means that plasma PQ concentrations have fallen precipitously by day 7. At the doses used, the combined plasma concentrations of CQ and DECQ were almost five times higher at day 7, and twice as high at day 28, than those of PQ.

The curative and suppressive effects of CQ and PQ will depend on the susceptibility of local parasite strains, as well as drug elimination kinetics. An in vitro study of Cameroonian *P. falciparum* field isolates demonstrated that, for CQ-sensitive strains, the mean 50% inhibitory concentrations (IC_{50}) for CQ (41.6 nM), DECQ (17.8 nM), and PQ (35.5 nM) were similar (4). For CQ-resistant strains (mean CQ IC_{50} of 201 nM), PQ and DECQ sensitivity were preserved (40.7 and 37.4 nM, respectively). Such assays are unreliable predictors of therapeutic response. In addition, both CQ and DECQ exist as entaniomers with stereospecific differences in protein binding, pharmacokinetics, and intrinsic potency (11). Nonetheless, IC_{50}s can be useful for comparing geographic and temporal trends in drug resistance and in characterizing local resistance patterns. Therefore, the plasma DECQ concentrations similar to those of PQ and CQ between days 7 and 42 in our patients may be clinically significant, with DECQ contributing more than CQ to posttreatment prophylaxis. The greater parasite susceptibility to PQ may have been counterbalanced by the higher levels of CQ and its more potent active metabolite during the elimination phase. No active metabolite has been described for PQ, and it seems unlikely based on our pharmacodynamic data.

The emergence of *P. vivax* infections during follow-up has been well described (22), even in ACT-treated patients (18), and represents either suppression of *P. vivax* to a submicroscopic level by a dominant *P. falciparum* coinfection at presentation, relapses from hypnozoites, or newly acquired infections. If the antimalarial therapy used is more effective against *P. falciparum* than *P. vivax*, eradication of *P. falciparum* will allow *P. vivax* parasitemia to emerge. The pattern seen in the present study could reflect the known high level of *P. vivax* resistance to CQ in PNG (27, 29) and suggests that PQ has greater activity than CQ against local strains. Parallel data have been reported recently in the nearby West Papua Province of Indonesia (26). The more rapid reduction in *P. falciparum* gametocytemia seen in the DHA-PQ arm primarily reflects the well-described potent gametocidal activity of the artemisinin component (25).

Characterization of the elimination kinetics of long-acting antimalarial drugs is of particular importance to the effectiveness of malaria control strategies such as ACT and intermittent presumptive treatment in pregnancy and infancy. Short-course ACT requires that the nonartemisinin partner drug achieve parasiticidal concentrations for several parasite life cycles in order to eliminate the submicroscopic parasite residuum (9). The effectiveness of intermittent presumptive treatment strategies may also rest on the duration of posttreatment prophylaxis (38). Elimination kinetics may have implications for future development and the spread of parasite drug resistance (15). However, the present study demonstrates that drug elimination must be considered in association with distribution kinetics, parasite susceptibility, and the role of active metabolites. Because drug disposition can vary according to age and with pregnancy, strategies for deploying drugs such as PQ in pregnant women and infants should include careful pharmacokinetic evaluation.

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