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Population pharmacokinetics of primaquine and the effect of hepatic and renal dysfunction: An exploratory approach

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Abstract:

OBJECTIVES: We attempted to develop a population pharmacokinetic model for primaquine (PQ) and evaluate the effect of renal and hepatic dysfunction on PQ pharmacokinetics.

MATERIALS AND METHODS: The data were collected from a prospective, nonrandomized clinical study in healthy volunteers and patients with mild-moderate hepatic dysfunction and renal dysfunction. Model development was conducted using NONMEM® software, and parameter estimation was conducted using first-order conditional estimation with interaction method.

RESULTS: Final data included a total of 53 study participants (13 healthy individuals, 12 with mild hepatic dysfunction, 6 with moderate hepatic dysfunction, and 22 with renal dysfunction) with 458 concentrations records. Absorption rate constant (Ka) was constrained to be higher than elimination rate constant to avoid flip-flop situation. Mild hepatic dysfunction was a significant covariate on volume of distribution, and it is approximately three folds higher compared to other subjects. Fixed effects parameter estimates of the final model – absorption rate constant (Ka), volume of distribution (V), and clearance (CL) – were 0.95/h, 498 L, and 39 L/h, respectively. Between-subject variability estimates (% CV) on Ka, V, and CL were 77, 66, and 65, respectively. Residual error was modeled as combination error model with the parameter estimates for proportion error 12% CV and additive error (standard deviation) 1.5 ng/ml.

CONCLUSION: Population pharmacokinetic modeling showed that the volume of distribution of PQ in subjects with moderate hepatic dysfunction increases approximately three folds resulting in a significantly lower plasma concentration.

Keywords:

Hepatic dysfunction, Indian patients, NONMEM, pharmacokinetics, primaquine

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Introduction

Primaquine (PQ) is the only antimalarial drug active against hypnozoites of *Plasmodium vivax* and *Plasmodium ovale* till date and is administered at the dose of 15 mg/day for 14 days as an antirelapse drug and 45 mg single dose for *Plasmodium falciparum* infestations for its gametocidal activity.[1] PQ is an ethnically insensitive, orally administered, almost completely (F = 0.96 + 0.08), and rapidly absorbed (t_{max} 2 + 1 h) drug exhibiting first-order (linear) kinetics (between 15 and 45 mg doses) with a large apparent volume of distribution (269 + 120 l). It is extensively metabolized by the liver to carboxyprimaquine.[2]

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Population pharmacokinetics is the study of sources and correlates of variability in the drug concentration among individuals administered with clinically relevant doses of the drug.[3] The traditional pharmacokinetic studies attempt to estimate the pharmacokinetic parameters for each individual, and finally, a summary of the parameters is mentioned. On the other hand, the population pharmacokinetic studies will utilize the data on drug concentrations from all the study participants and finally estimate the pharmacokinetic parameters.[4] Although traditional pharmacokinetic studies have been extensively conducted with PQ in normal healthy individuals,[5,6] malarial patients,[7] and in patients with altered renal function,[8] there is no published literature on the population pharmacokinetics of PQ, especially from Indian population. As PQ is metabolized principally by the liver, hepatic dysfunction may compromise the inactivation of the drug.[9] Similarly, renal dysfunction shall also affect the PQ pharmacokinetics.[10] Thus, our objective was to develop and qualify a population pharmacokinetic model for PQ in Indian population and evaluate the differences in pharmacokinetics due to hepatic and renal dysfunction. The present study was done as a hypothesis-generating study.

Materials and Methods

Ethics and study participants

The study was conducted between April and December 2013 after obtaining approval from the Institutional Ethics Committee (IEC), and a waiver for informed consent was obtained for this particular study. The required data for the analysis were gathered from the following three clinical studies (with their corresponding registration number with clinical trial registry of India) done at our center that evaluated the pharmacokinetics of a single-dose (15 mg) PQ administered orally in normal healthy individuals (CTRI/2011/06/001803) and patients with hepatic dysfunction (CTRI/2011/06/001794) and renal dysfunction (CTRI/2010/091/000356). All these studies were approved by the IEC, and a written informed consent was obtained from the study participants. Normal healthy individuals were defined based on history, physical examination, and laboratory investigations while the individuals with hepatic dysfunction were classified into mild or moderate degree based on Child–Pugh's criteria and patients with renal dysfunction were diagnosed according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative based on their serum creatinine levels.

Study design, drug administration, and laboratory analysis of primaquine concentrations

In all the above-mentioned studies, the eligible participants were admitted in the ward and were given a standardized breakfast following an overnight fast. Tablet PQ phosphate 15-mg (Batch number TB078, Bharat Parenterals, India) was administered orally under direct supervision with 200-ml water within 30 min, and a mouth check was done. Liquids were restricted for 2 h and food for 4 h postdose. The patients continued their prescribed medicines for their primary disease, and all the participants were discharged after a day's admission. Following the single-dose 15-mg PQ postbreakfast, 5-ml heparinized blood samples were collected through an indwelling forearm vein catheter at 0 h (predose) and 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postdose. A standardized, reversed-phase high-performance liquid chromatography method was used for analysis of the concentrations as described elsewhere.[8]

Data collected

The following information was collected from each of the individuals: demographic details (age, sex, and body weight) and drug concentration at each time points.

Population pharmacokinetic modeling

Population pharmacokinetic modeling was developed using NONMEM®, version 7.3 (ICON, Ellicott, City, MD, USA). One and two compartment models with first-, zero-, and mixed-order absorption were evaluated. A one-compartment model with first-order elimination and absorption was used as a previous study[11] has adequately described pharmacokinetics of PQ with the same. Log-normal distribution was assumed for modeling interindividual variability in clearance (CL) and volume of distribution (Equation 1):

$$P_j = TVP\ exp\ (\eta_i) \quad \text{(Equation 1)}$$

Where P_i is the estimate for a pharmacokinetic parameter in the i^{th} individual as predicted by the model without covariate effects; TVP is the population mean of the pharmacokinetic parameter; and η_i represents a random variable with mean 0 and variance ω^2. Absorption rate constant was constrained to be greater than elimination rate constant to avoid flip flop of rate constants.[12]

Residual variability was modeled using a combined additive and proportional error model (Equation 2):

$$C_{ij} = C'_{ij}\ (1+ \varepsilon_{add,\ j}) + \varepsilon_{prop,\ j} \quad \text{(Equation 2)}$$

Where $\varepsilon_{add,\ i}$ and $\varepsilon_{prop,\ i}$ are random variables with mean 0 and variance of σ_{add}^2 and σ_{prop}^2.

Parameter estimation was conducted using FOCEI method in NONMEM®. Volume of distribution was modeled, which was normalized to 70-kg person from in all models tested. The final covariate model was developed using stepwise forward inclusion (P = 0.05) and backward elimination (P = 0.01) approach where

NONMEM objective function value was used for hypothesis testing. Covariates tested were body weight, age, gender, hepatic dysfunction, and renal dysfunction.

Binary covariates such as gender (0 or 1) were modeled as below:

$$TVP = P \times \theta_{COV}^{Gender}$$

Where P is population parameter and θ_{COV} is the covariate effect parameter.

The covariate effect of hepatic and renal dysfunction was tested as proportional function with FLAG variables altering between different categories. The example shown below is for hepatic dysfunction.

Initially, FLAG = 0 and FLAG1 = 0,

FLAG1=0 and FLAG2=0 , if there is no hepatic dysfunction

FLAG1=0 and FLAG2=1, for mild hepatic function

FLAG1=1 and FLAG2=0, for moderate hepatic function

$$TVP = P \times (1+ \theta_{mild} \times FLAG) \times (1+ \theta_{mod} \times FLAG1)$$

Where, P, $\theta_{mild,}$ and θ_{mod} represent population parameter, covariate effect of mild hepatic dysfunction, and moderate hepatic dysfunction, respectively.

The improvement in model fit was assessed by change in objective function value, improvement in the goodness-of-fit plots, parameter plausibility, and test for local minimal by altering different initial estimates. A covariate was considered to be included in a model if the change in objective function value drop was at least 3.84 in forward addition and 6.63-point increase in backward elimination, based on Chi-square distribution.

Model qualification

Model evaluation was performed by visual predictive check (VPC) and bootstrap methods using PsN (Perl Speaks NONMEM) tools. VPC was stratified on hepatic dysfunction, and a total of n = 1000 simulations were conducted. The plots from VPC results were constructed using XPOSE4. The bootstrapping was conducted using PSN tools, and a total of n = 2000 resampled datasets were fit to the final model. The distribution of bootstrapped parameter estimates was used to calculate the 95% confidence interval (CI) of the parameter estimates.[13-15]

Simulations

Plasma concentrations were simulated resulting from various dosing schemes that are prescribed by the national guidelines to see the differences in the plasma concentrations between moderate hepatic dysfunction subjects to the other population in the study.

Results

A total of 53 study participants (13 healthy individuals, 12 with mild hepatic dysfunction, 6 with moderate hepatic dysfunction, and 22 with renal dysfunction) were identified, and Table 1 summarizes their demographic details and various pharmacokinetic parameters in various groups of study participants.

Model development and evaluation

One compartment model with first-order absorption best described the observed data. Goodness-of-fit plots show no major bias and were acceptable [Figure 1]. Pharmacokinetic parameters could be estimated with good precision (relative standard error [RSE] <30%]) in all parameters except the additive residual variability estimate (RSE: 116%). No between parameter correlations were >0.95 in the correlation matrix. The condition number calculated as the ratio of the highest to the lowest Eigenvalue was 10.83 showing no overparameterization

Table 1: Demographic details of the study participants (*n*=53)

	Normal healthy individuals (*n*=13)	Patients with mild hepatic dysfunction (*n*=12)	Patients with moderate hepatic dysfunction (*n*=6)	Patients with renal dysfunction (*n*=22)
Age (years), median (range)	25.5 (19-34)	45 (22-61)	50.5 (26-61)	43 (20-60)
Male: female	5:1	5:1	All are males	2:1
Body weight (kg), median (range)	66 (62-95)	65.5 (49-75)	56 (47-67)	55 (40-74)
Summary of pharmacokinetic parameters				
C_{max} (ng/ml)	29.3 (14.6-104.3)	45.6 (23.9-106)	14.4 (5.9-29.9)	45.6 (14.8-169.6)
T_{max} (h)	3.0 (1-6)	3 (1-6)	3.5 (1.5-6)	2.0 (1-8)
$AUC_{0-\infty}$ (ng-h/ml)	314.1 (86.4-685.3)	303 (246.3-1063.4)	117.2 (62.6-276.7)	261.9 (103.6-1218.2)
V_d/f (L)	300.7 (87.4-625.8)	384.49 (149.21-1503.57)	886.71 (421.08-1962.37)	275.1 (63.6-1565.7)
CL/f (L/h)	45.6 (11.6-103.3)	50.95 (25.45-60.89)	183.71 (54.64-288.41)	60.4 (12.3-144.8)
$t_{1/2}$ (h)	4.1 (1.5-6.9)	6.6 (3. -19.9)	4.3 (2.2-10.7)	3.5 (1.0-13.3)

V_d=Apparent volume of distribution, CL/f=Apparent plasma clearance, $t_{1/2}$=Half-life, T_{max}=Time for maximal concentration, $AUC_{0-\infty}$=Area under the plasma concentration-time curve, C_{max}=Maximum observed concentration

of the model. Covariate model was developed to study the impact of age and hepatic disorder on absorption (Ka), volume of distribution, and CL. Of these, the hepatic function had a significant effect on volume of distribution, and consequently, it was included in the final model. In the final model, the estimated CL was 39.1 L/h, volume of distribution (Vd) was 438 L, and Ka was 0.95/h [Table 2]. Effect of hepatic dysfunction on the volume of distribution depended on the severity of the hepatic failure. Only the moderate hepatic dysfunction showed to be significant on the volume of distribution where the parameter increased approximately three

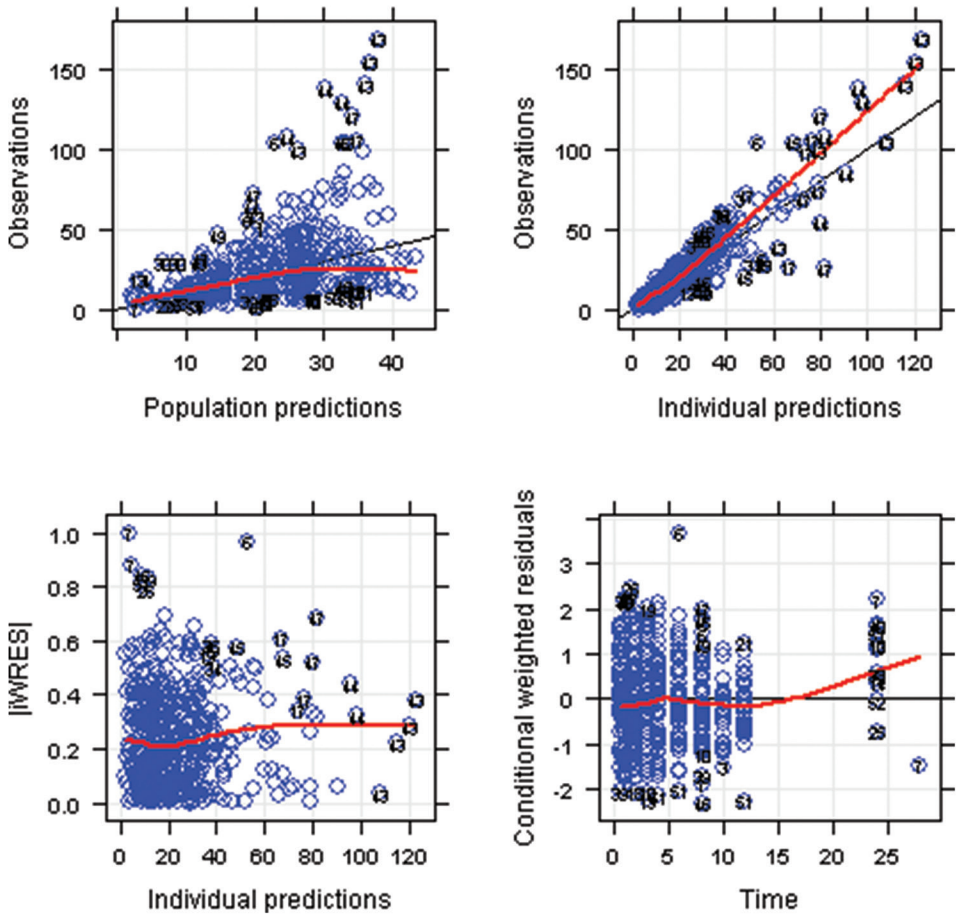

Figure 1: Basic goodness-of-fit plots for final model

Table 2: Parameter estimates of base and final model

Parameter	Population estimates		Bootstrap results	
	Population mean	RSE (%)	Medians	95% CI
OFV	2508.808		2502.1177	2334.65-2666.62
CL θ	39.14	10.34	39.175	31.36-48.30
V θ	438	11.9	439.646	345.37-550.53
Ka θ	0.9462	18.08	0.9461	0.65-1.34
Moderate HD on V θ	2.859	30.17	2.8589	1.26-5.08
Between subject variability				
BSV on CL (% CV)	65.08	19.982	64.1992	49.95-76.99
BSV on V (% CV)	66.58	19.642	64.8353	51.46-77.9
BSV on Ka (% CV)	77.44	27.44	74.5582	49.75-93.96
Residual variability				
Proportional (% CV)	32.06	12.526	31.9786	27.98-35.74
Additive (ng/ml)	1.5	102.5	1.4913	0.015-2.88

CL=Clearance, Ka=Absorption rate constant, V=Volume of distribution, CI=Confidence interval, % RSE=Relative standard error percentage, ADD-RUV=Additive residual unexplained variability, PROP-RUV=Proportional residual unexplained variability, OFV=Objective function value, HD=Hepatic dysfunction, BSV=Between subject variability

folds. There was no significant effect on absorption rate constant in the moderate hepatic failure group. The correlation between hepatic dysfunction versus eta plots in the base model vanished in the final model and the covariate explained 25% of the between-subject variability in the volume of distribution.

Model qualification

VPC [Figure 2] shows reasonable agreement between the distributions of observed and predicted data. The 95% CI of prediction intervals were well separated, and the respective quartiles fell within those intervals. Nonparametric bootstrap estimated the 95% CI of the model estimates. The estimates were well within the CI range [Table 2]. Total 98% of the bootstrap runs were successful in minimization, and the remaining was terminated due to rounding errors. All the runs were included in the calculation of bootstrap 95% CIs of the parameters. The simulations of various dosing regimens of PQ as per national guidelines show [Figure 3] significantly different plasma concentration versus time profiles for subjects with moderate hepatic dysfunction.

Discussion

The present study was conducted to evaluate the population pharmacokinetics of PQ in Indian patients and evaluate the effect of hepatic dysfunction on pharmacokinetic parameters. We found that the final model that was developed had better estimates of the parameters and was within the criteria of changes in objective function values during the forward inclusion and backward elimination procedures. We also found that hepatic dysfunction increases the volume of distribution of PQ significantly.

To the best of our knowledge, this study is the first attempt to evaluate the population pharmacokinetic parameters of PQ using nonlinear mixed-effects modeling approach. CL and volume of distribution were found to be in agreement to the traditional pharmacokinetic studies from various other populations[5,16] including the previous one from the same center.[17]

PQ is extensively metabolized by the liver.[2] In general, bioavailability of the drugs that are mainly metabolized by liver increases following a decrease in the hepatic

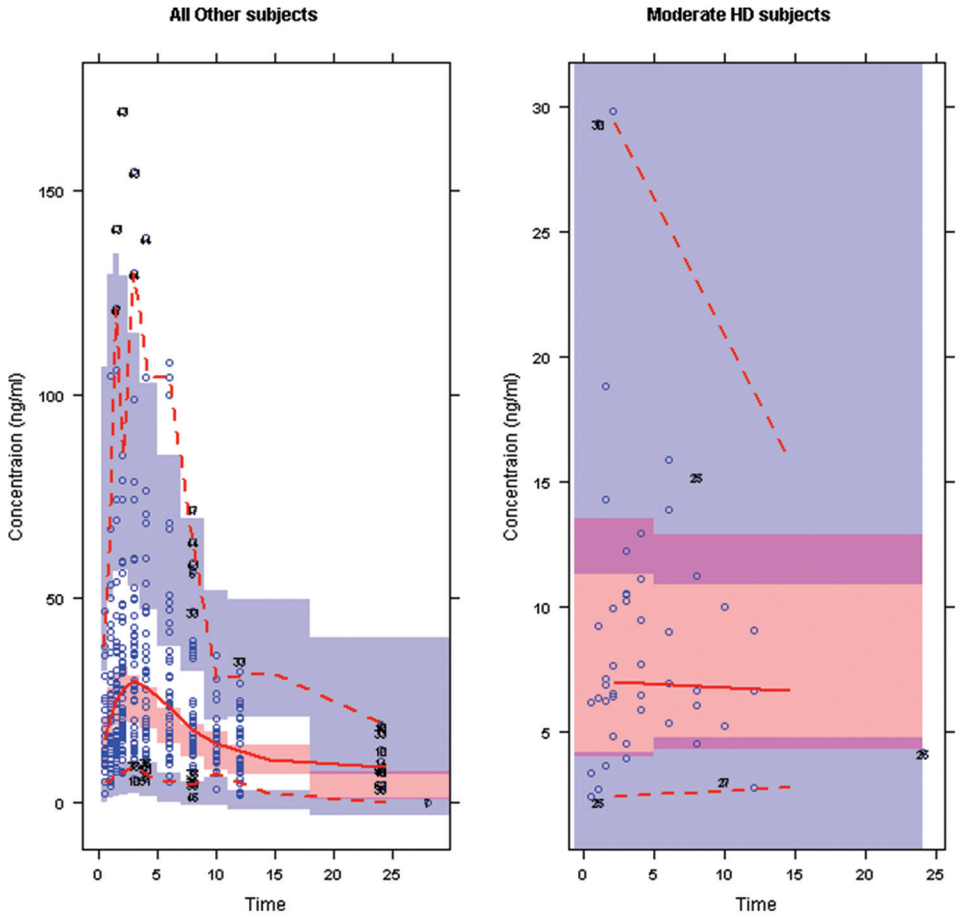

Figure 2: Visual predictive check plots for the final model

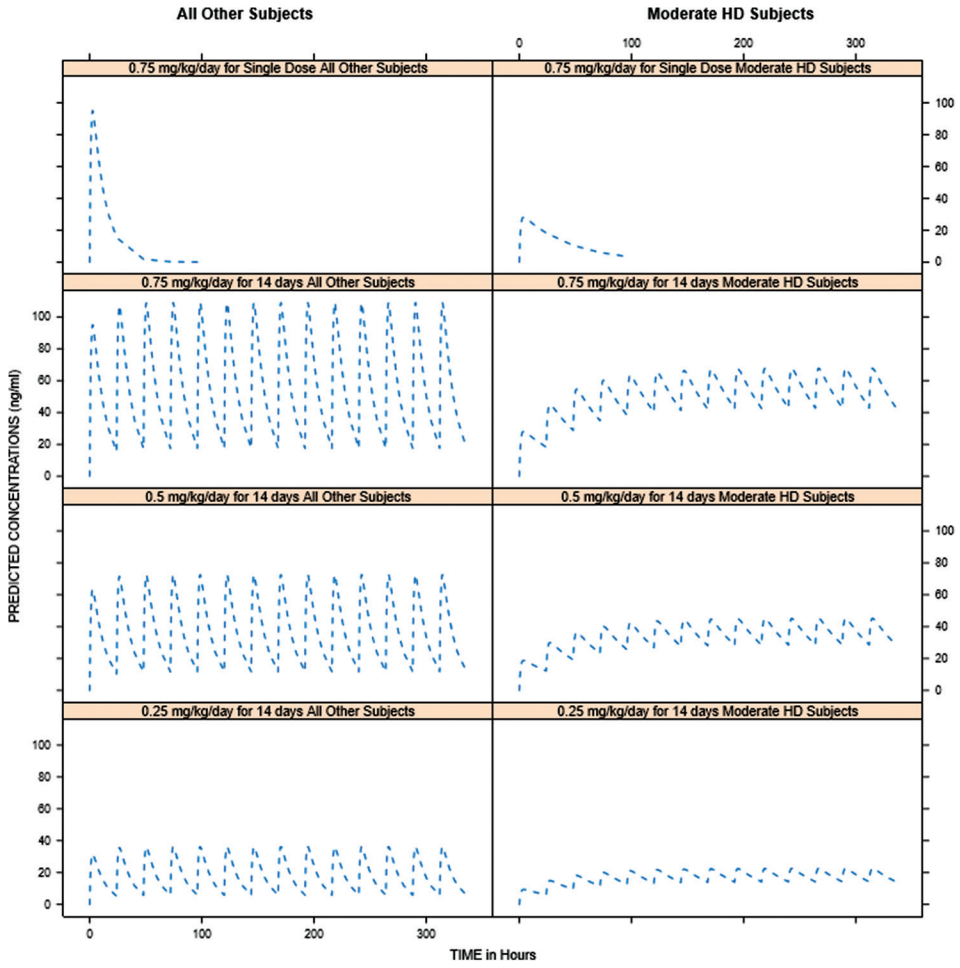

Figure 3: Simulation of plasma concentrations from different regiments recommended by the national guideline

CL.[18] PQ is highly plasma protein bound (mainly to alpha-1-acid glycoprotein [AAG-1] protein), and Vd of such high protein-bound drugs has been reported to be high in patients with hepatic dysfunction[2,18] and it is in agreement with our finding. The reduction in the production of AAG-1 in hepatic dysfunction could result in lower protein binding and higher volume of distribution. It is interesting in our study that there was no effect of mild hepatic dysfunction on the volume of distribution and could possibly that the protein binding differences may not be apparent until moderate dysfunction develops. In the present study, volume of distribution was found to be significantly altered (approximately three folds higher) as the patients with moderate hepatic dysfunction groups. The absorption rate constant was not significantly different in patients with moderate hepatic dysfunction patients. Similarly, area under the curve (AUC) has also not found to be significantly changed except for a trend of decrease in patients with moderate hepatic dysfunction in comparison to healthy participants. We hypothesize that presence of a gut wall edema may hamper the absorption of the drug in these patients leading to reduced bioavailability. Future studies are required to find the presence and extent of effect of gut wall edema in patients with moderate and severe hepatic dysfunction on the pharmacokinetics of PQ using contrast-enhanced computed tomography. In addition, we did not see a difference in CL for renal and hepatic dysfunction subjects. It was apparent that the drug may not have significant impact of renal dysfunction as the major elimination pathway was metabolic CL and in agreement with our previous report.[8] The reason for no significant impact of hepatic dysfunction (mild and moderate) on CL parameter could possibly be that the liver still retains the metabolic capacity for PQ. The impact of severe hepatic dysfunction may need to be evaluated to confirm this hypothesis where potentially differences in CL may be seen. Initial model attempts that did not constrain the parameters to avoid flip-flop phenomenon showed differences in absorption parameters. It could potentially due to the differences in the elimination rate constant that reflected in absorption due to flip-flop phenomenon. Given the short half-life (3–4 h) and rapid absorption, it is important that we avoid flip-flop situation to correctly model this

compound. The current model is parameterized in the CL and volume terms with a constraint to avoid flip-flop phenomenon.

Interpreting clinical implications of safety and efficacy of the lower concentrations due to higher volume of distribution in moderate hepatic dysfunction is not straight forward. The simulations show that the AUC and T_{max} parameters are not affected by the increase in volume of distribution, but C_{max} will be approximately three folds lower in moderate hepatic dysfunction subjects. PQ's efficacy has been reported to be driven by the total dose administered rather than regimen for the treatment of *P. vivax* and *P. ovale* infestations. It was reported that total dose of 360 mg (45 mg once/week for 8 weeks) was as effective as total dose of 420 mg (either 30 mg daily for 14 days or 60 mg daily for 7 days) and was also more effective than a total dose of 210 mg (15 mg daily for 14 days).[19,20] As AUC has not been found to be a significant parameter affected in the modeling in the present study even in patients with moderate hepatic dysfunction, there may not be any need to change the dosing regimen for treating *P. vivax* and *P. ovale* infestations. Controversies still exist in the most appropriate dose of PQ for its gametocidal activity for *P. falciparum* malaria.[21] The reported *in vitro* EC_{50} and EC_{90} for PQ were 181 and 543 ng/ml, respectively, for transmission-blocking activity for *P. falciparum*; the values are much greater than the average C_{max} obtained in the present study.[22] Even the concentration achieved in patients as reported in other studies was of similar range as that of our study.[23] Stepniewska *et al*. also had evaluated the dose-response assessment of *P. falciparum* and found ED 90 of approximately 0.06 mg base/kg.[24] More studies evaluating the dose-response relationships for PQ for its transmission-blocking activity in *P. falciparum* malaria are the need of the hour to assess the appropriate gametocidal dose of PQ.

Conclusion

The population CL and volume of distribution in Indian population were similar to other populations, and a significant increase in the volume of distribution of PQ was observed in patients with moderate hepatic dysfunction which results lower plasma concentrations.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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