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Effect of Rifampin on Plasma Concentrations of Mefloquine in Healthy Volunteers

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Abstract

Mefloquine is a 4-quinolinemethanol compound structurally related to quinine. Quinine is mainly metabolized by the cytochrome P450 3A4 isozyme (CYP3A4), whereas rifampin, a potent inducer of CYP3A4, is known to markedly decrease plasma quinine concentration. Our aim was to study the effect of rifampin on the pharmacokinetics of mefloquine, and explore a possible role of CYP3A4 on mefloquine metabolism.

In an open, two-phase crossover study, seven healthy Thai male volunteers received a single oral dose of 500 mg mefloquine alone, or 500 mg mefloquine plus a long-term administration of 600 mg rifampin. Blood samples were collected at specific time points over a 56-day period. Plasma mefloquine and its carboxylic acid metabolite were measured by HPLC for pharmacokinetic analysis. The results indicate that rifampin significantly decreased the area under the plasma concentration–time curve ($AUC_{0-\infty}$) of mefloquine by 68% ($P < 0{\cdot}01$), maximum plasma concentration (C_{max}) by 19% ($P < 0{\cdot}01$), and elimination half-life ($t_{½}$) by 63% ($P < 0{\cdot}01$), whereas the time to reach C_{max} (t_{max}) of mefloquine was unaffected. The apparent oral clearance (CL) of mefloquine was significantly increased by 281% ($P < 0{\cdot}01$). After administration of rifampin, the C_{max} of the carboxylic acid metabolite of mefloquine was significantly increased by 47% ($P < 0{\cdot}05$), whereas the $t_{½}$ was significantly decreased by 39% ($P < 0{\cdot}01$), and t_{max} by 76% ($P < 0{\cdot}01$). The $AUC_{0-\infty}$ and CL of the mefloquine metabolite were increased by 30% and 25%, respectively, but were not significantly different from the control phase.

The results indicate that rifampin reduces the plasma concentration of a single oral dose of 500 mg mefloquine by increasing metabolism of mefloquine in the liver and gut wall. The CYP3A4 isozyme most likely plays an important role in the enhanced metabolism of mefloquine. Simultaneous use of rifampin and mefloquine should be avoided to optimize the therapeutic efficacy of mefloquine and prevent the risk of *Plasmodium falciparum* resistance in malarial treatment.

Mefloquine (*DL*-erythro-α-(2-piperidyl)-2,8-bis (trifluoromethyl)-4-quinoline-methanol), is a 4-quinolinemethanol antimalarial drug structurally related to quinine. It is effective against all species of malarial parasites, including multidrug-resistant *Plasmodium falciparum*. It is still the treatment drug of choice in most areas with multidrug-resistant *P. falciparum* (Palmer et al 1993; Simpson et al 1999). However, mefloquine monotherapy for uncomplicated falciparum malaria was discontinued and replaced with a combination of mefloquine ($25\ mg\ kg^{-1}$) and artesunate administration ($4\ mg\ kg^{-1}$/day) for 3 days (ter Kuile et al 1992; Simpson et al 1999). Mefloquine is distributed extensively in the tissues and eliminated slowly, with considerable differences between individuals (Simpson et al 1999). The main metabolite of mefloquine is 2,8-bis (trifluoromethyl)-4-quinolinecarboxylic acid (carboxylic acid metabolite) (Bergqvist et al 1988). Quinine is a widely used antimalarial drug for the treatment of severe or multidrug-resistant *P. falciparum* malaria (White

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1996). CYP3A4 is a major cytochrome P450 involved in the metabolism of quinine both in-vitro and in-vivo (Zhao et al 1996; Mirghani et al 1999).

Rifampin is used clinically in the treatment of tuberculosis, and is usually administered for 4–12 months together with other antituberculosis agents or other medication for an accompanying disease. It is a potent inducer of CYP3A4 and other cytochrome P450 enzymes and therefore causes numerous drug interactions in man (Venkatesan 1992).

Since mefloquine is a quinolinemethanol compound structurally related to quinine, and quinine is metabolized mainly by human CYP3A4, the major isozyme induced by rifampin, there is the possibility of a pharmacokinetic interaction between mefloquine and rifampin. To our knowledge, there are no reports on the possible interaction between rifampin and mefloquine, and the possible role of CYP3A4 in the metabolism of mefloquine. We have therefore studied the effect of rifampin on the pharmacokinetics of oral mefloquine.

Materials and Methods

Subjects

Seven healthy non-smoking Thai male volunteers (24–35 years; 57–72 kg) participated in the study. All subjects were informed of the objectives of the study and gave their written consent. The study protocol was approved by the Ethics Committee of the Faculty of Science, Prince of Songkla University. A medical history, physical examination, and essential laboratory tests were carried out on all the volunteers before they were enrolled in the study. The subjects were not allowed to take any medications for one week before or during the study period.

Study protocol

An open, two-phase crossover study design was used. The phases were separated by a two-month washout period. A single oral dose of 500 mg mefloquine (two 250 mg tablets; Larium, F-Hoffmann-La Roche Ltd, Bangkok, Thailand) was given during the two study phases.

Phase one. Mefloquine alone. On the study days, each subject ingested only 500 mg mefloquine with 200 mL water.

Phase two. Mefloquine plus 600 mg rifampin (two 300 mg capsules; Rifagen, General Drug House Ltd, Bangkok, Thailand). All subjects ingested 600 mg rifampin once daily for pretreatment at 0700 h before breakfast for 7 days, and on Days 1 through 7 after rifampin pretreatment, 600 mg rifampin was orally administered once daily, then 600 mg rifampin twice weekly on Days 8 through 56. On the study Day 7, 500 mg mefloquine was ingested with 200 mL water 3 h after rifampin administration.

All subjects fasted overnight before mefloquine administration and received regular meals 3 h after mefloquine. The subjects were not allowed to smoke or have coffee, tea, alcohol or cola on the test days.

Determination of plasma mefloquine and its carboxylic acid metabolite

A forearm vein was cannulated with a sterile catheter kept patent with heparinized saline solution. Blood samples were collected in heparinized tubes before mefloquine intake and at 0·5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24 h, and on Day 2, 3, 4, 7, 14, 21, 28, 35, 42, 49 and 56 after mefloquine administration. Blood samples were centrifuged at 2500 *g* for 15 min, and plasma was separated within 30 min and kept at −20°C until analysed. Plasma mefloquine and its carboxylic acid metabolite concentration were determined by HPLC (Bergqvist et al 1988; Crevoisier et al 1997). The lower detection limit of mefloquine and its carboxylic acid metabolite was 50 ng mL^{-1}. The intra-day coefficient of variation of both mefloquine and its carboxylic acid metabolite was less than 6%, whereas the inter-day coefficient of variation did not exceed 9 and 8%, respectively. The relative recovery of standard mefloquine and its carboxylic acid metabolite in human plasma was 99–111% and 95–105%, respectively.

Pharmacokinetic calculations

Plasma mefloquine and its carboxylic acid metabolite concentrations were analysed by one-compartment methods. Maximum plasma mefloquine concentration (C_{max}) and time to reach C_{max} (t_{max}) were read directly from the original data. The elimination rate constant (k_{el}) was determined by a linear regression analysis of the terminal phase of the plasma concentration–time profile. The elimination half-life ($t_{½}$) was calculated as $0{\cdot}693/k_{el}$. The area under the plasma concentration–time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated by the trapezoidal rule from the start of the drug administration to the last data point with extrapolation to infinity. The area from the last data point (C_t) to infinity was obtained as C_t/k_{el}. Since

there is no parenteral formulation of mefloquine used in man, the apparent oral clearance (CL) was approximately calculated as dose/$AUC_{0-\infty}$, assuming complete bioavailability of mefloquine and, that rifampin does not alter the bioavailability of mefloquine.

Statistical analysis

All results are expressed as mean ± s.d. Pharmacokinetic variables between the groups were compared by Student's *t*-test for paired data. $P < 0.05$ was considered to be statistically significant. Data were analysed with CLR ANOVA, analysis of variance statistical program for the Apple Macintosh (Clear lake research, Houston, TX).

Results

All seven subjects completed the study. The mean plasma concentration–time profile of mefloquine and its carboxylic acid metabolite after mefloquine administration alone, and during rifampin phase are shown in Figure 1. The pharmacokinetic data are summarized in Table 1.

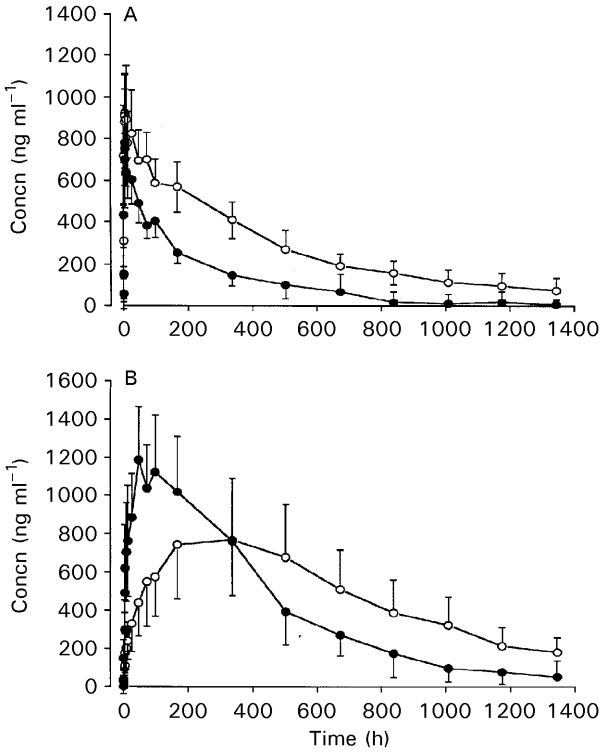

Figure 1. The plasma concentration–time profiles of mefloquine (A) and its carboxylic acid metabolite (B) in seven healthy subjects after a single oral dose of 500 mg mefloquine alone (○) or during rifampin phase (●). Data are mean ± s.d.

The mean C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ of mefloquine significantly decreased by 19% (from 855·6 ± 168·0 to 695·7 ± 56·6 ng mL^{-1}; $P < 0.01$), 68% (from 373·7 ± 57·5 to 119·8 ± 54·9 mg h L^{-1}; $P < 0.01$), and 63% (from 305·3 ± 47·2 to 113·4 ± 49·7 h; $P < 0.01$), respectively, during the rifampin phase compared with control. The mean t_{max} of mefloquine was unaffected by rifampin. The mean CL of mefloquine was fourfold increased (from 0·021 ± 0·004 to 0·08 ± 0·03 L h^{-1} kg^{-1}; $P < 0.01$) during the rifampin phase (Figure 1; Table 1).

After administration of rifampin, the mean C_{max} of the mefloquine metabolite increased by 47% (from 813·2 ± 298·0 to 1194·5 ± 249·1 ng mL^{-1}; $P < 0.05$), and the elimination $t_{1/2}$ and t_{max} decreased by 39% (from 506·66 ± 127·6 to 307·45 ± 28·8 h; $P < 0.05$) and 76% (from 220·62 ± 69·8 to 52·5 ± 28·8 h; $P < 0.05$), respectively. Although the mean $AUC_{0-\infty}$ and CL of the mefloquine metabolite increased by 30 and 25%, respectively, these were not significant changes compared with the control phase (Figure 1; Table 1).

Discussion

The results indicate a significant interaction between rifampin and mefloquine, resulting in a significant reduction in plasma mefloquine concentrations. After administration of rifampin, the mean $AUC_{0-\infty}$, C_{max}, $t_{1/2}$, and CL of oral mefloquine were 32, 81, 37 and 381% of the respective values in the control phase (Table 1). A smaller $AUC_{0-\infty}$ and lower C_{max} of mefloquine during the rifampin phase compared with the respective values for the control phase (decreased by 68 and 19%, respectively) is likely explained by an enhanced presystemic elimination of mefloquine. The reduction in the elimination $t_{1/2}$ of mefloquine caused by rifampin, indicated that systemic clearance of mefloquine was increased. Our results, however, showed that the $t_{1/2}$ obtained in the control phase (305 h or 12·7 days) was rather short as values in the range 13·8 to 40·9 days (median 20 days) have been reported (Karbwang & White 1990). These results could be explained by the inter-individual variations with respect to age-, sex- and race-related changes (Shimada et al 1994).

In this study, although the $AUC_{0-\infty}$ of the major mefloquine metabolite (carboxylic acid metabolite) was not significantly reduced with rifampin treatment, the C_{max} of the carboxylic acid metabolite was moderately higher and occurred sooner after rifampin treatment than in the control phase. These

Table 1. Pharmacokinetic parameters of mefloquine and its carboxylic acid metabolite in seven healthy volunteers administered single oral doses of 500 mg mefloquine alone and during rifampin phase.

Parameters	Mefloquine alone (control phase)		Mefloquine + rifampin	
	Mefloquine	Metabolite	Mefloquine	Metabolite
C_{max} (ng mL^{-1})	855·6 ± 168·0	813·2 ± 298·0	695·7 ± 56·6**	1194·5 ± 249·1*
% of control (range)	100	100	81 (73–88)	147 (119–181)
t_{max} (h)	8·2 ± 2·9	220·6 ± 69·8	8·7 ± 3·9	52·5 ± 28·8**
% of control (range)	100	100	106 (55–204)	24 (11–50)
$t_{½}$ (h)	305·3 ± 47·2	506·7 ± 127·6	113·4 ± 49·7**	307·5 ± 28·8**
% of control (range)	100	100	37 (21–71)	61 (47–72)
$AUC_{0-\infty}$ (mg h L^{-1})	373·7 ± 57·5	786·4 ± 285·4	119·8 ± 54·9**	549·9 ± 170·3
% of control (range)	100	100	32 (18–64)	70 (41–113)
CL (L h^{-1} kg^{-1})	0·021 ± 0·004	0·012 ± 0·005	0·08 ± 0·03**	0·015 ± 0·006
% of control (range)	100	100	381 (148–619)	125 (67–208)

C_{max}, maximum plasma concentration; t_{max}, time to reach C_{max}; $t_{½}$, elimination half-life; AUC, area under the plasma concentration–time curve; CL, apparent oral clearance. Data are mean ± s.d. *$P < 0·05$, **$P < 0·01$ significantly different compared with control phase (paired Student's *t*-test).

changes probably indicate the enhanced presystemic elimination of mefloquine and reflect an increased rate of metabolite formation. The $t_{½}$ of the carboxylic acid metabolite of mefloquine was significantly decreased, suggesting that metabolism of the carboxylic acid metabolite was increased during the rifampin phase. The higher clearance in subjects with rifampin treatment indicated enhanced hepatic metabolism of mefloquine. This suggests that rifampin induces the hepatic metabolism of mefloquine.

Rifampin is a potent inducer of CYP3A4 not only in the liver but also in the intestine (Kolars et al 1992), and several studies have shown drug interactions between rifampin and other drugs including quinine (Venkatesan 1992; Wanwimolruk et al 1995). Rifampin has been shown to markedly increase the elimination of quinine (Wanwimolruk et al 1995). The doses and duration of rifampin used in this study were chosen on the basis of the initial treatment of tuberculosis as recommended by the Centers for Disease Control of the USA (Stauffer 1996). We chose this regimen because it is a short-course therapy for tuberculosis in patients and provided the minimum amount of rifampin to the volunteers compared with other regimens.

Our results showed that rifampin enhanced the metabolism of mefloquine during both presystemic and elimination phases (decreased C_{max} and shorter $t_{½}$ values for mefloquine in rifampin phase). The liver and intestine play an important role in the presystemic metabolism of many CYP3A4 substrates, and rifampin is a potent inducer of CYP3A4 in both these organs. However, the decrease in mefloquine concentrations after rifampin treatment is probably due to enhanced metabolism in the liver rather than in the gut wall, as the t_{max} of mefloquine was unaffected by rifampin. We previously found that cimetidine, a potent CYP3A4 inhibitor, reduces the clearance and prolongs the elimination $t_{½}$ of mefoquine in a similar manner to quinine (Sunbhanich et al 1997). Plasma mefloquine concentrations in blood samples from volunteers experiencing prophylaxis failure were all less than 400 ng mL^{-1}, suggesting that higher mefloquine concentrations are necessary to suppress *P. falciparum* parasitaemia (Crevoisier et al 1997). It has been estimated that 99 and 95% prophylactic efficacy can be achieved at mefloquine blood concentrations of 915 and 620 ng mL^{-1}, respectively (Lobel et al 1991, 1993). It is therefore important to investigate and avoid possible causes of decreased plasma levels of mefloquine. In this study, plasma mefloquine concentrations after oral administration of 500 mg mefloquine during rifampin phase were 695·67 ± 56·63 ng mL^{-1} which is just over 95% prophylactic efficacy.

In conclusion, this study shows that the long-term use of rifampin considerably reduces plasma concentrations of mefloquine by inducing its metabolism. Enzyme induction, probably involved in CYP3A4-mediated metabolism, is a possible explanation for the interaction between rifampin and mefloquine in this study. Although the clinical significance of this interaction is not clear, it is reasonable to assume that rifampin and other potent inducers of CYP3A4 may reduce the therapeutic efficacy of mefloquine in the treatment of *P. falciparum* malaria. Simultaneous use of rifampin and mefloquine should be avoided to prevent treatment

failure and decrease the risk of *P. falciparum* resistance to mefloquine.

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