Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man

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The effect of rifampicin and isoniazid pretreatment on the pharmacokinetics of quinine after a single oral dose (600 mg quinine sulphate) was studied in nine healthy young Thai male volunteers using a three-way randomized crossover design. Subjects were studied over three 2 day periods, during which they received no pretreatment, or pretreatment with daily 600 mg p.o. rifampicin for 2 weeks, or isoniazid 300 mg p.o. daily for 1 week, prior to quinine administration. The mean ($\pm$ s.d.) clearance (CL/F) of quinine coadministered with rifampicin (0.87 ± 0.35 l h⁻¹ kg⁻¹) was significantly greater than that of quinine alone (0.14 ± 0.05 l h⁻¹ kg⁻¹). The mean difference in clearance from the control treatment was 0.73 l h⁻¹ kg⁻¹, with 95% confidence interval (C.I.) of 0.48 to 0.98. The unbound clearance (CL_u/F) of quinine, which reflects the activity of the drug-metabolizing enzymes, was considerably greater (6.9-fold) in subjects when rifampicin was coadministered with quinine than that of quinine alone (6.9 ± 3.6 vs 1.0 ± 0.5 l h⁻¹ kg⁻¹; the 95% C.I. for the mean difference was 3.3 to 8.5). The mean elimination half-life of quinine when coadministered with rifampicin (5.5 ± 3.0 h) was significantly shorter than when quinine was given alone (11.1 ± 3.0 h; the 95% C.I. for the mean difference was -8.6 to -2.6). In contrast to rifampicin, pretreatment for 1 week with 300 mg oral isoniazid had no significant effects on the pharmacokinetics of quinine. These results indicate that rifampicin pretreatment caused a marked increase (6.2-fold) in the clearance of quinine, possibly due to enzyme induction. The extent to which the elimination of quinine is enhanced by the concomitant administration of rifampicin is likely to have important clinical consequences. Although the clinical significance of these findings is unknown, they indicate the need for caution in the administration of quinine to patients who are concurrently taking rifampicin as an anti-tuberculosis medication.

Keywords quinine pharmacokinetics rifampicin isoniazid drug interactions enzyme induction

Introduction

Quinine is widely used to treat malaria in endemic malaria areas where *Plasmodium falciparum* is resistant to chloroquine. In addition, it is commonly prescribed for the elderly to prevent nocturnal cramp. It is well recognised that the pharmacokinetics of a drug can be affected by factors such as age, genetics, disease states and coadministration with other drugs. Rifampicin is a potent enzyme inducer of hepatic drug metabolism in humans [1, 2] and is known to interact with a number of drugs such as warfarin, digitoxin, dapsone, chlorpropamide, metoprolol, theo-

phylline, antipyrine, hexobarbitone and cyclosporine [2–8]. It has been shown that rifampicin decreases the elimination half-life of quinidine, a diastereoisomer of quinine [9]. Since quinine is metabolised mainly by human CYP3A [12] and CYP3A4 is the principle isozyme induced by rifampicin [13] there is the possibility of a pharmacokinetic interaction between quinine and rifampicin.

Isoniazid, another anti-tuberculosis drug, inhibits hepatic oxidative metabolism of a number of drugs such as phenytoin (metabolised by CYP2C9), carba-

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mazepine (metabolised by CYP3A3/4), warfarin (metabolised by CYP2C9) and diazepam (metabolised by CYP3A4/2C19) [3, 14–16]. This suggests that inhibition of oxidative drug metabolism by isoniazid is not selective [17]. It has also been shown that isoniazid induces CYP2E1 in rats [18]. As isoniazid is being given to patients over a period of months for the treatment and prophylaxis of tuberculosis, quinine and isoniazid are likely to be administered together. Thus, a clinically important interaction between isoniazid and quinine could occur.

This study was conducted to determine the effects of rifampicin and isoniazid on the pharmacokinetics of quinine in healthy Thai men.

Methods

Subjects

Approval for this study was obtained from the Human Ethics Committee, Thammasat University, Thailand, and the Southern Regional Health Authority (Otago) Ethics Committee, Dunedin, New Zealand. All subjects gave written informed consent. Nine healthy male Thais, with a mean age of 30.3 ± 3.4 (s.d.) years, ranging from 25 to 35 years, volunteered for the study. Their mean body weight was 58.3 ± 3.7 (s.d.) kg, and ranged from 52 to 64 kg. All subjects were non-smokers, three of them drank alcohol occasionally, and none took any medication for at least 1 week before and during the study. Prior to the study, a medical history was taken and a physical examination and a full haematological and biochemical screen was performed on each individual.

Study protocol

The study was a three-way crossover design with study days separated by at least 3 weeks. In randomized fashion, subjects received no pretreatment or oral pretreatment with rifampicin (Rimactane®, Ciba-Geigy, Thailand) 600 mg daily for 2 weeks, or isoniazid (Thai Pharmaceuticals, Bangkok, Thailand) 300 mg daily for 1 week, prior to quinine administration. The 2 week pretreatment with rifampicin was to ensure maximum enzyme induction [19]. A shorter duration was decided for isoniazid pretreatment to minimise possible adverse reactions. After fasting overnight, each subject was given a single dose of 600 mg quinine sulphate (497 mg quinine base) (Quinoc®, Douglas Pharmaceuticals Ltd, New Zealand) orally with approximately 200 ml water. Rifampicin or isoniazid was also administered immediately prior to quinine dosing and then continued until the last blood sample had been taken. The subjects were allowed to eat a meal 3 h after the administration of quinine. Blood samples (4 ml each) were collected through a heparinized intravenous catheter (Venflon®) before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 30, 36 and 48 h post-dose. Urine samples were collected over the 48 h period

following administration of the drug. Plasma was separated from blood samples by centrifugation within 2 h. Aliquots of the plasma and urine samples were stored at -20°C until assayed.

Analytical procedure

Quinine concentrations in plasma and urine samples were assayed by h.p.l.c. as described previously [20]. The minimum detection limit of the assay was 0.02 mg l^{-1} . The intra-assay coefficient of variation was less than 8% over the concentration range of 0.02 to 10 mg l^{-1} . Rifampicin and isoniazid did not interfere with the quinine assay. Although metabolites of rifampicin and isoniazid were not available, chromatograms from plasma and urine samples prior to each quinine kinetic study did not show peaks that interfered with the analytes of interest. Plasma protein binding of quinine was measured by equilibrium dialysis as described previously [21].

Pharmacokinetic analysis

Plasma quinine concentration vs time data were analyzed by non-compartmental methods. The area under the plasma drug concentration-time curve from zero to infinity time (AUC) was calculated by the linear trapezoidal rule from the beginning of drug administration to the last time point and with extrapolation to infinity. The elimination half-life ($t_{1/2,z}$), renal clearance (CL_R), apparent oral clearance (i.e. CL/F) and unbound oral clearance (CL_u/F) relative to the bioavailability (F) of quinine were estimated as described previously [22]. $C_{\max}$ and $t_{\max}$ values were obtained directly from the data.

Statistical analysis

Results are expressed as mean $\pm$ s.d. Differences between means for each pharmacokinetic parameter were examined by repeated measures ANOVA followed by multiple comparison of means (Student Newman-Keuls test). This was performed by using SAS version 6.03 (SAS Institute, USA). Differences between treatment means were considered significant at $P < 0.05$.

Results

The mean plasma quinine concentration vs time profiles following quinine alone, and pretreatment with rifampicin and isoniazid are illustrated in Figure 1. A monoexponential decline in the log-plasma drug concentration curves was apparent in every subject.

The pharmacokinetic parameters of quinine obtained in this study (Table 1) were comparable with those previously reported [22–26]. Results from ANOVA revealed that there were no period effects among the three treatments studied. $C_{\max}$ was significantly lower in subjects during pretreatment with rifampicin ($P < 0.005$) compared with the control

phase. Both total AUC and AUC (unbound) were significantly less in subjects during pretreatment with rifampicin when compared with the controls ($P < 0.001$). The oral clearance (CL/F) and unbound oral clearance (CL_u/F) of quinine were significantly greater (6.2 and 6.9 fold, respectively) ($P < 0.001$)

Figure 1 Mean plasma quinine concentrations after a single oral dose of 600 mg quinine sulphate in nine healthy male subjects pretreated with rifampicin (■-----■); isoniazid (▲-----▲); or no pretreatment (control, ○—○).

when the drug was coadministered with rifampicin, than when quinine was given alone (Table 1). The mean $t_{1/2,z}$ of quinine in subjects during the rifampicin treatment period was significantly shorter than that during the control treatment ($P < 0.005$). Rifampicin caused a 5-fold decrease in the amount of unchanged quinine excreted in the urine.

In contrast, the results for isoniazid show no significant differences in C_{max} , t_{max} , oral clearance (CL/F) and renal clearance of quinine between the treatment and control periods. However, the mean $t_{1/2,z}$ of quinine in subjects during pretreatment with isoniazid was slightly but, significantly, longer than that during the control period ($P < 0.05$).

Discussion

Our results have shown that the clearance of quinine is dramatically increased (6.2-fold) in subjects during concomitant administration with rifampicin. Although the increase in clearance was somewhat variable, ranging from 3.6-fold to 8.9-fold, it occurred in every subject. There was no significant correlation ($r = -0.125$, $P > 0.5$) between baseline clearance (i.e. when quinine was given alone) and the magnitude

Table 1 Pharmacokinetic measurements after a single oral dose of 600 mg quinine sulphate during three treatment periods: control (i.e. quinine alone); rifampicin pretreatment; and isoniazid pretreatment

Quinine pharmacokinetic parameters	Control	Rifampicin pretreatment	Isoniazid pretreatment	95% C.I. of difference	
				Rifampicin vs control	Isoniazid vs control
C_{max} (mg l ⁻¹)	4.6 ± 1.0a (2.9–6.4) ^b	2.2 ± 1.1* (1.3–4.6) ^b	4.4 ± 1.6 (2.8–8.4) ^b	–2.4 (–3.5 to –1.4)	–0.2 (–1.5 to 1.1)
t_{max} (h)	2.5 ^c (1.5–10)	2.5 ^c (0.7–4)	3.0 ^c (2.0–6.0)		
$t_{1/2,z}$ (h)	11.1 ± 3.0 (6.6–16.3)	5.5 ± 3.0* (2.1–10.8)	14.2 ± 2.9 [‡] (9.5–19.0)	–5.6 (–8.6 to –2.6)	3.1 (0.15 to 6.1)
CL/F (l h ⁻¹ kg ⁻¹)	0.14 ± 0.05 (0.08–0.25)	0.87 ± 0.35** (0.62–1.6)	0.16 ± 0.04 (0.1–0.2)	0.73 (0.48 to 0.98)	0.02 (–0.03 to 0.07)
CL_u/F (l h ⁻¹ kg ⁻¹)	1.00 ± 0.45 (0.51–2.10)	6.87 ± 3.64** (2.7–14.5)	1.22 ± 0.34 (0.72–1.90)	5.9 (3.3 to 8.5)	0.22 (–0.18 to 0.6)
AUC (mg l ⁻¹ h)	66 ± 20 (32–105)	11 ± 4** (5–19)	56 ± 13 (39–79)	–55 (–69 to –41)	–10 (–27 to 7)
AUC (unbound) (mg l ⁻¹ h)	9.8 ± 3.5 (3.8–16.9)	1.6 ± 0.8** (0.6–3.2)	7.5 ± 2.1 (5–5.1)	–8.2 (–10.7 to –5.7)	–2.3 (–5.2 to 0.6)
% Unbound	14.8 ± 1.2 (12.6–16.3)	13.8 ± 2.7 (11.0–17.5)	13.9 ± 2.1 (11.9–16.5)	–1.0 (–3.1 to 1.1)	–0.9 (–2.6 to 0.8)
% dose excreted as unchanged quinine in the urine (0–48 h)	7.9 ± 6.5 (2.0–22.2)	1.7 ± 1.8 [‡] (0.5–6.3)	5.4 ± 3.1 (1.6–10.0)	–6.2 (–11 to –1.5)	–2.5 (–7.6 to 2.5)
CL_R (l h ⁻¹ kg ⁻¹)	0.011 ± 0.009 (0.003–0.029)	0.014 ± 0.017 (0.002–0.055)	0.009 ± 0.006 (0.002–0.013)	0.003 (–0.018 to 0.007)	–0.002 (–0.009 to 0.006)

^aData shown are means ± s.d. ($n = 9$).

^bRange of the values.

^cMedian values are given (range).

* $P < 0.005$ compared with control.

** $P < 0.001$ compared with control.

[‡] $P < 0.05$ compared with control.

of rifampicin-induced enhancement of quinine clearance. The higher clearance in subjects with rifampicin pretreatment indicates enhanced hepatic metabolism of quinine since the renal clearance of quinine was not affected by the coadministration of rifampicin. Furthermore, the unbound clearance (CL_u/F) of quinine which reflects activity of drug-metabolizing enzymes, was increased by 6.9-fold in subjects during the pretreatment period with rifampicin. This suggests that rifampicin induces the hepatic metabolism of quinine. Consistent with this enzyme induction effect, the % dose excreted as unchanged quinine in the urine was much less during the rifampicin treatment period. A smaller AUC and less C_{max} during the rifampicin treatment period compared with that when quinine was given alone, is most likely explained by an enhanced presystemic elimination of quinine despite the fact that quinine is a high bioavailability drug [27] with low hepatic clearance. Enhanced systemic elimination of quinine is likely to result from induction of CYP3A in the liver and possibly the gut wall [28].

Rifampicin induces certain liver cytochrome P450 isoenzymes, notably CYP3A and CYP2C8-10 in humans [13, 29]. Induction of CYP3A4 is responsible for the rifampicin-oral contraceptive interaction [10, 13, 30, 31]. Our recent observations using *in vitro* human liver microsomal preparations suggest that the formation of the major quinine metabolite, 3-hydroxy-quinine, is catalysed by CYP3A [12]. The increased elimination of quinine in subjects receiving rifampicin is consistent with induction of CYP3A-mediated metabolism. Similar findings have been reported for quinidine [9], and cyclosporine [8], also metabolised by CYP3A.

Isoniazid inhibits the oxidative metabolism of a number of drugs. However, a lack of selectivity for the different forms of cytochrome P450 has been suggested, since isoniazid has been shown to inhibit the metabolism of phenytoin and warfarin (CYP2C9),

carbamazepine (CYP3A) and the activation of paracetamol (partly CYP2E1) [14–16, 18]. In the present study the pharmacokinetics of quinine were not appreciably affected by coadministration with isoniazid. It is possible that isoniazid may alter the pharmacokinetics of quinine at a higher dose. We have shown that isoniazid (50 μ M) is a weak inhibitor of quinine metabolism by human liver microsomes (Wanwimolruk *et al.*, unpublished data).

In conclusion, our study has shown that the elimination of quinine when coadministered with rifampicin is dramatically increased. This could result in sub-therapeutic plasma quinine concentrations if the maintenance dose of quinine is not increased. For the treatment of falciparum malaria, low plasma concentrations may result in parasitic survival and development of resistance. A recent study in Thailand showed that coadministration of quinine and rifampicin led to malaria treatment failure due to development of type R-II resistance (Dr Sasithon Pukrittayakamee, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, personal communication). This interaction may also render quinine ineffective for the prophylaxis of night cramps in the elderly. It is not known whether any of the metabolites of quinine possesses significant antimalarial activity. The induction by rifampicin of pathways leading to active metabolite formation would make the clinical implications of our findings more complex. The lack of effect of isoniazid on the pharmacokinetics of quinine may suggest that isoniazid is preferred to rifampicin in patients receiving concomitant quinine therapy.

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