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The pharmacokinetics of quinine in patients with hepatitis

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The pharmacokinetics of quinine were studied in six patients with hepatitis B infection (during acute and convalescent periods) and six healthy subjects. A single 10 mg kg^{-1} dose of quinine was given intravenously over 2 h. Pharmacokinetic parameters of quinine during the acute phase of the infection were not different from those during the recovery phase. However, when compared with those obtained from healthy subjects, significant changes were found. The terminal elimination half-life was prolonged (17 and 15 *vs* 10 h) and clearance was lower (2.9 and 2.3 *vs* 3.5 ml min^{-1} kg^{-1}). Unbound quinine concentration in plasma at 2 h was approximately 10% of the total concentration in all subjects in the three study groups. A prolonged QTc interval (<25%) was observed in all groups. The present data suggest that current dosage regimens of quinine used in the treatment of falciparum malaria may not be suitable for malaria patients with acute hepatitis or those who have had hepatitis within the past 3 months.

Keywords pharmacokinetics quinine hepatitis

Introduction

The pharmacokinetics of quinine are altered (slower clearance and prolonged elimination half-life) during acute falciparum malaria compared with the convalescent period or in healthy subjects (White *et al.*, 1982). Hepatic dysfunction during acute infection may be responsible for these changes.

Approximately 20,000–25,000 of the Thai population suffer from acute hepatitis each year (Annual report of Ministry of Public Health, Thailand). These patients may also have malaria and may be receiving treatment with quinine. Since acute falciparum malaria is described with altered disposition of quinine, it is possible that hepatic dysfunction due to hepatitis may contribute to these changes. Therefore, we have investigated the pharmacokinetics of quinine in patients with acute hepatitis, convalescent hepatitis and in healthy subjects.

Methods

Healthy subjects

Six Thai male adults aged between 19 to 25 years and weighing 45 to 50 kg with no history of liver or kidney diseases and normal results for haematological and biochemical tests were included in the study. Written informed consent was obtained from all subjects and they were admitted to the Bangkok Hospital for Tropical Diseases for 2 days.

Patients

Six Thai male patients, aged between 24 to 30 years and weighing 49–59 kg with acute hepatitis B infection, with no alteration of renal function were included in the study. They had total plasma bilirubin levels greater than 3 mg% and/or SGOT/SGPT of greater than 120 iu ml^{-1}.

All patients were admitted to the ward at the Bangkok Hospital for Tropical Diseases during the acute phase of the infection where they stayed until the results of liver function tests returned to normal (at least 3 months). The patients received vitamin B complex 1 tablet three times daily during the admission period.

Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok.

Drug administration

Healthy subjects: quinine (10 mg base kg^{-1}) was given by i.v. infusion over 2 h.

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Patients: quinine (10 mg base kg^{-1}) was given by i.v. infusion over 2 h on two occasions. The first occasion was during the acute stage of hepatitis and the second was during convalescence.

Electrocardiographic monitoring and analysis

ECG monitoring was performed prior to administration of quinine and at hours 2, 4, 6, 12, 24 and 48 after dosing using a simultaneous 12-lead computerized recorder and analyser (Siemen, Sicard P).

The pulse rate and blood pressure were measured at the same time as ECG recordings.

Laboratory investigations

Laboratory investigations including CBC and biochemistry were repeated weekly until the patients were discharged from the hospital.

Blood collection

Blood samples (2 ml) were taken through a Teflon catheter inserted into an antecubital vein, into lithium-heparinized tubes at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h (sampling was up to 48 h only in healthy subjects). The blood was centrifuged at 3000 rev min^{-1} within 30 min and plasma was stored at −20° C until analysis.

Drug analysis

To assay plasma unbound quinine concentrations (at 2 h) a 1 ml plasma sample was subjected to ultracentrifugation at 25° C using the Amicon YMT system (Amicon Corporation, Danver, Massachussets, U.S.A.; Silamut *et al.*, 1985). The ultrafiltrate contained less than 0.1% w/v protein. Concentrations of unbound and total quinine were assayed using the methods previously described by Karbwang *et al.* (1989). The limit of quantitation was 4 ng ml^{-1} using a 0.25 ml specimen. Calibration curves were linear (r = 1.0) in the range 0–8000 ng ml^{-1}. Interassay coefficients of variation were 6.8%, 0.3% and 1.2% at concentrations of 1, 16 and 32 ng ml^{-1}, respectively.

Data analysis

A two compartment model was fitted to the unweighted data using the PC-NONLIN program. Although plasma samples in patients were collected up to 72 h, the last point was not included in the pharmacokinetic analysis in order to make it consistent with the analysis of data from healthy subjects. The percentage of AUC extrapolated from 48 h to infinity was between 5–12% in all groups. Pharmacokinetic parameters were compared between groups using the Mann Whitney U-test (unpaired data) and the Wilcoxon Rank Sign test (paired data).

Results

Mean plasma quinine concentrations in the three groups are shown in Figure 1 and derived pharmacokinetic parameters are presented in Table 1. There were no differences in C_{max} and t_{max} values among the three groups. Values of AUC were significantly higher,

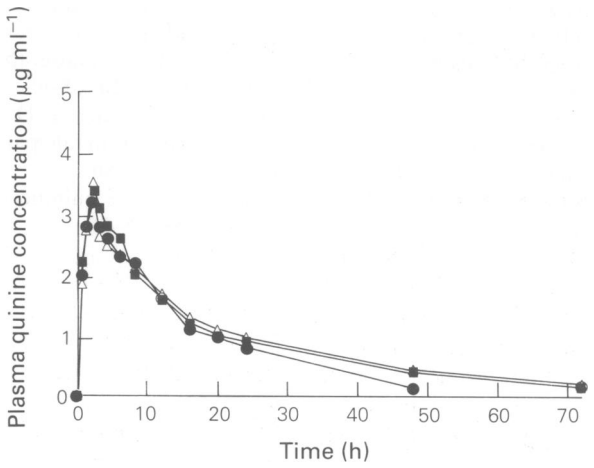

Figure 1 Mean plasma quinine concentrations in healthy subjects (●) and in patients with hepatitis during acute (△) and convalescent (■) periods.

Table 1 Mean pharmacokinetic parameters of quinine in healthy subjects and patients with hepatitis during acute infection and convalescence (numbers in brackets refer to ranges of values) (i.v. infusion of 10 mg kg^{-1} quinine base over 2 h)

	Acute hepatitis	*Recovery*	*Healthy*
C_{max} (μg ml^{-1})	3.5 (2.1–5.3)	3.4 (2.8–4.5)	3.2 (2.1–3.8)
t_{max} (h)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.0
$t_{1/2,z}$ (h)	17 (11–26)	15 (11–19)	10 (9–14)[a]
AUC (μg ml^{-1} h)	70.2 (49–115)	69.1 (56–85)	47.6 (36–72)[b]
CL_0 (ml min^{-1} kg^{-1})	2.9 (1.7–4.0)	2.3 (1.0.3.4)	3.9 (1.3–4.6)[c]
Unbound quinine at 2 h (%)	10.1 (7.4–14.0)	9.8 (8.1–11.3)	10.3 (7.6–15.0)

[a]significantly different from acute hepatitis (P = 0.003; C.I. −12.4 to −4.5) and convalescence (P = 0.008; C.I. 1.65 to 8.04).
[b]significantly different from acute hepatitis (P = 0.004; C.I. 5.7 to 35.5) and convalescence (P = 0.01; C.I. 3.3 to 35.91).
[c]significantly different from acute hepatitis (P = 0.02; C.I. 0.09 to 2.23) and convalescence (P = 0.03; C.I. 0.12 to 2.14).

clearances lower and terminal $t_{1/2}$ values were longer in the patients with hepatitis relative to normal controls. However, no differences were apparent between the acute and convalensence phases in the patients. The percentage of unbound quinine in plasma was about 10% in all three groups.

The only ECG change was a prolongation of the QTc interval and this change was similar and less than 25% in all groups.

Discussion

Maximum plasma concentrations of quinine and changes in QTc interval were similar in all groups after administration of a single i.v. infusion dose of quinine. Therefore, a greater incidence of side-effects would not be anticipated in patients with hepatitis compared with those with normal liver function. However, on continuous dosage the differences in AUC suggest that drug accumulation may be greater in patients with hepatitis. This would apply to unbound as well as total plasma drug concentrations since the extent of plasma binding was similar in all three groups. In contrast, malaria infection is associated with an increased plasma binding of quinine such that total drug concentrations are elevated but unbound concentrations remain the same (White, 1985). Despite a return of liver function tests to normal during convalescence after hepatitis, the clearance of quinine remained impaired. The combined effects of acute hepatitis and malaria on the kinetics of quinine suggest caution with its dosage in patients with both conditions.

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References

Karbwang, J., Na Bangchang, K., Molunto, P. & Bunnag, D. (1989). Determination of quinine and quinidine in biological fluids by high performance liquid chromatography. *Southeast Asian J. Trop. Med. Publ. Hlth.*, **20**, 65–69.

Silamut, K., White, N. J., Looareesuwan & Warrell, D. A. (1985). Binding of quinine to plasma proteins in falciparum malaria. *Am. J. Trop. Med. Hyg.*, **34**, 681–686.

White, N. J. (1985). The pharmacokinetics of quinine and quinidine in malaria. *Acta Leidensia*, **55**, 65–76.

White, N. J., Looareesuwan, S., Warrell, D. A., Warrell, M. J., Bunnag, D. & Harinasuta, T. (1982). Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am. J. Med.*, **73**, 567–572.

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