PHARMACOKINETICS OF QUININE, QUINIDINE AND CINCHONINE WHEN GIVEN AS COMBINATION

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Abstract. Pharmacokinetics of quinine, quinidine and cinchonine when given as a combination were evaluated in Thai patients with falciparum malaria during acute infection and convalescence. The combination of quinine, quinidine and cinchonine was randomly given to thirteen patients at 400 mg or 600 mg (consisting of one-third of each component; 7 patients were enrolled in 400 mg regimen and 6 in 600 mg regimen) intravenously every 8 hours for 7 days. The drug combination was given again at day 35 to define the pharmacokinetics of each drug during convalescence.

All patients with the 600 mg regimen had good response with 100% cure rate while patients with the 400 mg regimen had a good initial response but one patient recrudesed on day 46. This particular patient had plasma concentrations of all three drugs lower than the mean values of patients with sensitive responses.

The plasma levels of quinine and quinidine obtained from the present study were higher than that expected from one-third of the conventional dose (600 mg) when given alone, suggesting drug combination interaction. The terminal half-lives of each of the three components were prolonged during acute malaria when compared to those obtained during convalescence.

INTRODUCTION

Plasmodium falciparum in Thailand is highly resistant to chloroquine and sulfadoxine/pyrimethamine (Harinasuta *et al,* 1965; Reacher *et al,* 1980) and there is increasing resistance to the alternative antimalarials: quinine (Bunnag *et al,* 1986; Suntharasamai *et al,* 1984) and mefloquine (Boudreau *et al,* 1982).

Alternative more potent antimalarial drugs are urgently needed. There is some evidence that quinidine is more effective than quinine but the cardiotoxicity of quinidine is also greater (Sanders and Dawson 1932; Sander 1935; Taggart *et al,* 1984). The cardiovascular effects of quinidine remain the most important concern regarding the use of quinidine in falciparum malaria, as the dose is higher than that required for antiarrhythmic effects. Recently, cinchonine has been tested *in vitro* against *P. falciparum* and was found to be more active than either quinine or quinidine (Brandicourt *et al,* 1986).

To conceive the best therapeutic response and least toxicity, the combination of quinine, quinidine and cinchonine was proposed (consisting of one-third of each compound). *In vitro,* it has been shown to be more active than the individual compound with no evidence of cross-resistance between the combination and the three individual alkaloids (Druilhe *et al,* 1986). In man, 13 patients who were treated with a dose of 600 mg base of the combination threetimes daily for 7 days were all cured (Bunnag and Harinasuta, 1986). We have investigated the pharmacokinetic properties of this combination in patients with falciparum malaria during acute infection and convalescence.

MATERIALS AND METHODS

Patients

Thirteen Thai male patients with uncomplicated falciparum malaria, aged between 18-40 years included into the study. Informed consent was obtained from all patients. The patients were excluded from the study if there was liver, kidney dysfunction or cerebral complication, patients had history of recent antimalarial treatment or

patients presented with positive urine test for sulphonamide or 4-aminoquinolines. The study was approved by the Ethical Committee, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Methods

Ten ml of blood were taken from venous site on day 0, before infusion, end of infusion and at 0.5, 1, 2, 4, 6 hours after infusion, then after the first infusion on days 1, 2, 3, 4, 5 and 6. On day 7 and day 35, frequent blood samples were obtained at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours after infusion. The blood was centrifuged, plasma was removed and stored at -20°C until analysis.

Blood samples were taken before treatment for both the Jensen and Trager technique and the Rieckmen "microtechnique" for parasite culture and determination of the minimum inhibitory concentration (MIC) for mefloquine, chloroquine, quinine, quinidine, cinchonine and the combination of quinine, quinidine and cinchonine (results are presented elsewhere).

Treatment

Drug administration was randomly given to patients in two different dosages, 400 mg (7 patients) or 600 mg (6 patients) of the combination (1/3 to each component) per dose by intravenous infusion over two hours, every 8 hours for 7 days. No other antimalarial drugs were given during the 35 days of study. Additional dose of 400 or 600 mg (base) of the combination was given to patients on day 35 to define the pharmacokinetics of quinine, quinidine and cinchonine during convalescence.

Drug analysis

Quinine, quinidine and cinchonine concentrations were simultaneously analysed by HPLC.

Data analysis

Maximum concentration (C_{max}) and time to maximum concentration (T_{max}) were the observed values. Terminal elimination half-lives of the three drugs were analysed by conventional methods.

Statistical analysis

Wilcoxon Matched-pairs Signed-rank Test was used.

RESULTS

Therapeutic response

All patients responded to the treatment with at least a 36-day follow-up period. However, one patient who received the dose of 400 mg recrudesced on day 46.

In vitro sensitivity tests showed the MIC of quinine, quinidine and cinchonine to be lower when the combination (ratio of 1/3:1/3:1/3 for quinine:quinidine:cinchonine) was used.

Concentrations of quinine, quinidine and cinchonine after the end of infusion of 400 mg and 600 mg doses are shown in Fig 1, 2 and 3. At a dose of 400 mg, mean values of C_{max} were found to be 7,843, 4,025 and 1,794 ng/ml at day 2, day 3 and day 3 for quinine, quinidine and cinchonine, respectively. At a dose of 600 mg, the values were 10,584, 6,186 and 3,199 ng/ml on day 1 for quinine, quinidine and cinchonine, respectively. The concentrations of quinine, quinidine and cinchonine in the patient with recrudescence on day 46 were lower than the mean concentrations of those with sensitive response (Fig 1, 2 and 3).

The mean values of C_{max} (during frequent blood sampling) of quinine, quinidine and cinchonine are presented in Table 1. The maximum concentrations of quinine and quinidine were similar on day 0 and day 7 but much lower on day 35. However, the maximum cinchonine concentrations were found to be at the same levels for all occasions (*ie* day 0, day 7 and day 35).

Terminal half-lives of quinine, quinidine and cinchonine are presented in Table 2. The half-lives of each component on day 0 were not reliable as there was limited blood sampling due to the subsequent dosing (*ie* at 8 hours). Terminal half-lives of quinine, quinidine and cinchonine on day 7 were found to be significantly longer than on day 35.

DISCUSSION

The increase of chloroquine-resistant falciparum malaria has led to the search for the new antimalarial drug and reevaluation of the previously used drugs for malaria. Mefloquine and halofantrine are two new effective antimalarials but both

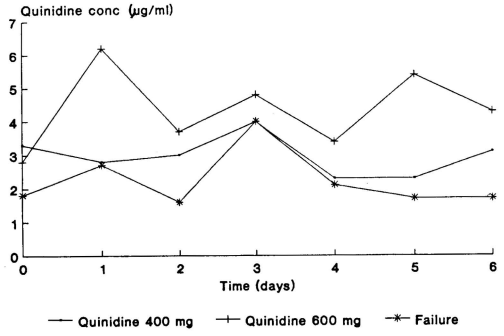

Fig 1—Plasma concentration of quinine.

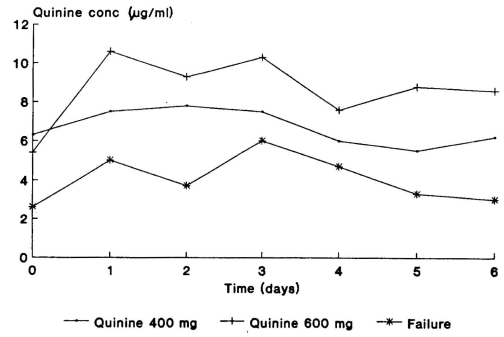

Fig 2—Plasma concentration of quinidine.

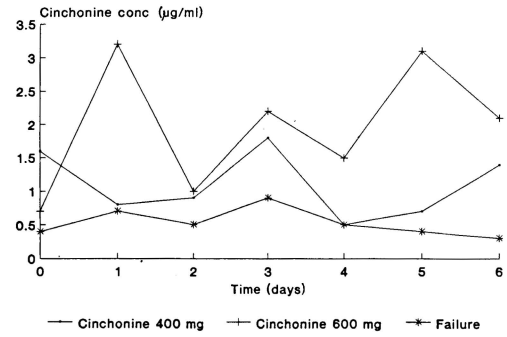

Fig 3—Plasma concentration of cinchonine.

have no parenteral preparation. This limits their use in patients who can not take the drug orally. Quinine or quinidine is now the drug of choice for treatment of severe chloroquine-resistant falciparum malaria in Thailand. The therapeutic concentration of quinine to treat falciparum malaria in Thailand is expected to be over 10 µg/ml (White *et al,* 1983); with this level cinchonism could be very common. Quinidine has major adverse effects on the heart, particularly when a large rapid dose is administered. The dose for the treatment of falciparum malaria is three times higher than that required for antiarrhythmic effects.

Table 1

Mean values of C_{max} of quinine, quinidine and cinchonine when given as a combination on days 0, 7 and 35.

	Dose = 400 mg		
	Day 0	Day 7	Day 35
Quinine (ng/ml)	6,395	6,477	1,973
Quinidine (ng/ml)	2,486	2,516	1,208
Cinchonine (ng/ml)	443	420	400
	Dose = 600 mg		
	Day 0	Day 7	Day 35
Quinine (ng/ml)	5,555	13,348	7,918
Quinidine (ng/ml)	2,824	9,551	7,248
Cinchonine (ng/ml)	706	2,120	2,184

Table 2

Terminal half-lives of quinine, quinidine and cinchonine when given as combination on days 0, 7 and 35.

	Day 0	Day 7	Day 35
Quinine (hours)	12.8±6.0	22.3±10.4	13.1±5.2
Quinidine (hours)	6.0±1.5	11.5±4.8	8.4±2.1
Cinchonine (hours)	1.9±0.8	3.8±1.4	1.7±0.8

In the present study, we have decreased the dose of each component to be one-third of the conventional dosage regimen in the treatment of chloroquine resistant falciparum malaria. The therapeutic response was satisfactory. The favorable therapeutic responses were obtained despite lowering the dose to one-third (600 mg of the mixture, 100% cured) and to lesser than one-third (400 mg of the mixture, 6 out of 7 cured).

Plasma quinine and quinidine concentrations from this study are of interest when compared to other studies (White, 1987). Doses of quinine, quinidine have been decreased to one-third but plasma concentrations had not fallen to one-third as would be expected. Drug interaction between the three compounds should be considered since

quinine and quinidine has been shown to have potential to inhibit microsomal enzymes *in vitro* and *in vivo* (Riviere and Back, 1986; Murray 1984). The study of the drug combination interaction is needed.

The terminal half-lives of each of the three components were prolonged during acute infection of malaria when compared to those obtained during convalescent period (day 35, Table 2). This is consistent with the study of White *et al* (1982) where they found the half-life of quinine in patients with uncomplicated malaria to be longer than in healthy volunteers and longest in cerebral malaria.

Lower MIC of each component of the combination at a ratio of 1/3:1/3:1/3 of quinine, quinidine and cinchonine support the idea that the use of the combination is better than a single compound as far as resistant strains of falciparum malaria are concerned. Additional studies were carried out by Bunnag *et al* (1987), who found significantly lower concentrations for MIC when the drugs were used in combination. Whether this is true *in vivo* requires further studies.

One patient with recrudescence was clearly shown to have lower plasma concentrations of the three components. The dose of 600 mg may be a better choice than 400 mg for chloroquine-resistant falciparum malaria, as we can assure adequate plasma concentrations. This is supported by the study of Bunnag *et al* (1987) where the cure rate in 400 mg was only 67% while it was 100% with 600 mg.

ACKNOWLEDGEMENTS

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