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Relative bioavailability of the hydrochloride, sulphate and ethyl carbonate salts of quinine

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The hydrochloride, sulphate and ethylcarbonate salts of quinine were given in single oral doses (600 mg base equivalent) to nine healthy male subjects according to a cross-over design. No statistically significant differences were noted in the plasma drug concentration-time profiles although inter- and intra-subject variation in AUC, C_{max} and t_{max} values was appreciable. The ethylcarbonate salt may be preferred for use in paediatric patients because of its neutral taste.

Keywords quinine bioavailability

Introduction

Quinine has gained increasing importance in the management of multi-resistant infections with *Plasmodium falciparum*. For this purpose, it is usually administered orally in combination with tetracycline in order to attain acceptable cure rates. It is usually given as tablets of quinine hydrochloride or quinine sulphate. Unfortunately, these salts have a bitter taste and although this may be overcome by sugar coating it has been suggested that this may also reduce the bioavailability of the drug (Garnham *et al.*, 1976; Bruce-Chwatt *et al.*, 1981). A tasteless salt, namely quinine ethyl carbonate, has been suggested as a potential alternative, especially for paediatric practice. However, the bioavailability of this form has also been questioned and its use has remained restricted, particularly since more suitable drugs were available as alternatives while *P. falciparum* was still sensitive to 4-aminoquinolines and sulphadoxine/pyrimethamine. This situation has now changed in areas with multi-drug resistance, and a tasteless quinine formulation like the ethyl carbonate is indicated. Therefore, we have compared the bioavailability of quinine from tablets of the hydrochloride (QHC) (plain), the sulphate (QS) (sugar-coated) and the ethyl carbonate (QEC) (plain) salts after single oral doses.

Methods

Subjects

Nine healthy adult male volunteers between the ages of 20 and 35 years and weighing between 50 and 60 kg participated in the study after giving written informed consent. Each participant was subjected to physical examination, electrocardiogram, blood and urine analysis. The participants were instructed to abstain from other medications for 1 week prior to the study and from alcohol for 3 days prior to and during each treatment phase. The study protocol was approved by the Institutional Ethics Committee.

Treatment schedule

Each of the subjects received each formulation according to a randomised cross-over design. Drug administration was carried out at weekly intervals. In view of the relatively short elimination half-life of quinine an interval of 1 week between the drug doses was considered to be adequate.

Drug administration

The participants fasted overnight beginning at midnight until 3 h after the administration of the

quinine dose. Two tablets of the quinine formulation (corresponding to 600 mg quinine base) were administered in the early morning to each subject, with 250 ml water. Breakfast was served 3 h after drug administration. From then onwards food intake was not regulated.

Blood sampling

Blood (5 ml) was taken from a fore-arm vein immediately before and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 48 and 72 h after each drug administration.

The blood samples were collected into heparinized Vacutainers® using an indwelling catheter for the initial 12 h after dosing, and thereafter by venepuncture. The blood was centrifuged at 1500 rev min^{-1} for 10 min and the separated plasma coded and stored at −20° C.

Analysis of quinine in plasma

Plasma (100 μl) and the internal standard cinchocaine (aqueous solution (10 μl)) were alkalinized with 0.5 N sodium hydroxide solution. The mixture was then extracted with 5 ml of diethylether. The organic layer was separated following centrifuging at 2,500 rev min^{-1} for 10 min and absolute ethanol (100 μl) was added. The extract was dried under nitrogen and the residue reconstituted with mobile phase solvent (100 μl). 20 μl was injected into the h.p.l.c. with fluorescence detection. The retention times for quinine and the internal standard were 6.4 and 10.6 min, respectively.

Calibration plots were linear over the concentration range up to 3.0 μg ml^{-1}. The minimal detectable amount of quinine was 2.0 ng. However, starting with a 1 ml plasma sample the detection limit was 10 ng ml^{-1}. Recoveries over the concentration range of 1.0 μg ml^{-1} to 10.0 μg ml^{-1} were 99.1 to 100.0%, with coefficients of variation between 1.38% and 5.54%.

Data analysis

The time to reach peak plasma concentration (t_{max}) and the peak concentration achieved (C_{max}) were obtained from the plasma drug concentration-time curves by computer interpolation. AUC values were calculated up to 48 h using the linear trapezoidal rule. An analysis of variance was carried out to determine if there were any significant differences among the preparations for these parameters.

Results

Mean plasma drug concentrations after administration of the different preparations are shown in Figure 1 and individual AUC, C_{max} and t_{max} values are shown in Table 1.

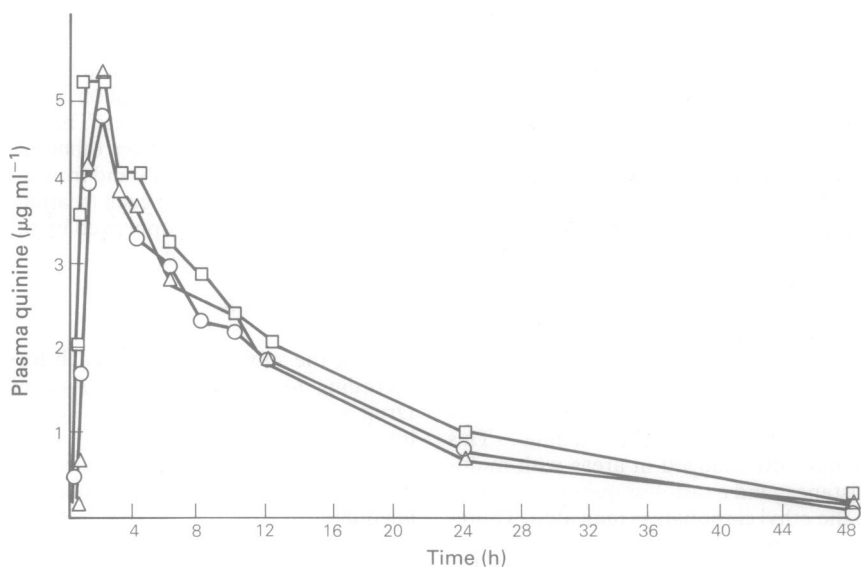

Figure 1 Average plasma concentrations of quinine after oral administration of single doses of three salt forms (600 mg base equivalent) to healthy adult males (○ quinine ethyl carbonate, □ quinine hydrochloride and △ quinine sulphate).

Table 1 Area under plasma drug concentration-time curve (AUC), time to reach maximum plasma drug concentration (t_{max}) and maximum plasma concentration (C_{max}) in individual subjects following oral administration of 600 mg base equivalent of quinine in three different salt tablet formulations

	AUC ($\mu g\ ml^{-1}\ h$)			t_{max} (*h*)			C_{max} ($\mu g\ ml^{-1}$)		
				Formulations					
Subject	*QEC*	*QHC*	*QS*	*QEC*	*QHC*	*QS*	*QEC*	*QHC*	*QS*
1	54.2	46.2	39.3	1.4	1.9	3.4	4.9	3.3	3.2
2	45.8	60.0	61.0	2.2	1.1	2.8	3.1	5.0	4.2
3	56.2	54.7	59.4	2.7	0.5	2.4	5.1	5.0	5.8
4	81.2	93.0	64.3	2.1	1.0	2.1	5.7	6.3	4.0
5	73.6	135.7	89.2	4.0	2.3	2.9	3.0	7.6	4.6
6	92.3	70.8	73.8	1.9	2.3	1.9	4.4	4.5	5.1
7	40.0	49.6	69.8	4.3	3.6	2.4	2.4	4.2	4.7
8	64.2	46.7	41.5	1.8	1.1	3.9	5.3	6.0	3.2
9	43.1	54.5	73.4	2.6	1.8	1.8	3.4	4.5	3.3
Mean	61.2	67.9	63.5	2.5	1.7	2.6	4.1	5.1	4.2
s.d.	18.1	29.4	15.8	1.0	0.9	0.7	1.2	1.3	0.9
CV %	29.6	43.3	24.9	40.0	52.9	26.9	29.3	25.5	21.4

No statistically significant differences were noted in any of these parameters for the three preparations, although inter- and intra-individual variation in the values was large.

Discussion

The results suggested no significant differences in the rate or extent of absorption of quinine from the three preparations studied. These findings are of interest with regard to quinine ethyl carbonate (QEC) since this salt is preferable in paediatric patients because of its neutral taste. Extensive inter- and intra-subject variability in the plasma concentration-time profiles of quinine indicates that the monitoring of plasma quinine concentrations may be required to optimise treatment.

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