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QUININE DISPOSITION KINETICS

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1 Intravenous quinine dihydrochloride (5 mg kg^{-1} over 5 min) was given to seven healthy male volunteers. There were minor subjective symptoms in all subjects but no significant changes in pulse or blood pressure.

2 There was significant prolongation of the electrocardiographic QRS and rate corrected QT intervals which was greatest between 1 and 4 min after completion of the quinine infusion. Values then returned towards baseline.

3 Plasma concentrations of quinine were measured spectrophotofluorimetrically after benzene extraction. Peak plasma concentrations (mean ± 1 s.d.) after the infusion were 5.1 ± 1.3 mg l^{-1}. Pharmacokinetic analysis fitted a two compartment open model in each case; distribution half-time ($t_{\frac{1}{2},\lambda_1}$) was 1.89 ± 0.54 min (mean ± 1 s.d.), elimination half-time ($t_{\frac{1}{2},z}$) 11.1 ± 2.1 h, apparent volume of the central compartment (V_1) 0.57 ± 0.32 l kg^{-1}, total apparent volume of distribution 1.80 ± 0.37 l kg^{-1} and total clearance 1.92 ± 0.45 ml min^{-1} kg^{-1}.

Keywords quinine pharmacokinetics

Introduction

Quinine is one of the oldest drugs in the pharmacopoeia and is still widely used both for the prevention of night cramps and the treatment of chloroquine-resistant falciparum malaria. Quinine is life-saving in severe falciparum malaria and it is the only available parenteral treatment for chloroquine-resistant disease. Occasional fatalities have occurred after intravenous injection of quinine to seriously ill patients (Strahan, 1948; Patrick, 1968) although this method of administration is still widely recommended (Wilcocks & Manson Bahr, 1972; Adams & Maegraith, 1980; Woodruff, 1974). This has been attributed to cardiovascular toxicity (Strahan, 1948). The disposition kinetics of quinine after intravenous injection in man have not previously been reported.

Methods

Seven healthy male volunteers aged between 18 and 35 years were studied. The nature of the investigation and the requirement for repeated blood sampling were explained in each case. The patients were studied supine. An intravenous infusion of normal (0.9%) saline was started and a teflon catheter was inserted in the antecubital vein of the opposite arm. This catheter was used for repeated blood sampling after removal of the dead space, and was maintained patent with heparinised saline. Four baseline pulse and blood pressure measurements were taken at 5 min intervals and a 12 lead electrocardiograph was recorded. The lead showing the largest TU distinction was chosen for subsequent recordings which were taken at 50 mm s^{-1} paper speed. Quinine dihydrochloride (Government Pharmaceutical Organisation, Thailand) was given by constant rate injection into the side arm of the free running intravenous infusion at a dose of 1 mg kg^{-1} min^{-1} for 5 min (total dose equivalent to 4.17 mg of base kg^{-1}). Pulse and blood pressure and ECG were recorded at 2 min intervals for 18 min. Blood was sampled before, then at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 and 30 min then at 1, 2, 4, 8, 16, 24 and 36 h after the end of the injection. Samples were taken into lithium heparin collecting tubes. Plasma was separated and stored at −40°C until analysis.

Quinine was measured by the benzene extraction fluorescence method (Cramer & Isacksson, 1963). Plasma (0.5 ml) was mixed with 1 ml of 0.1 N NaOH. Benzene (7.5 ml) was then added, and the mixture shaken vigorously for 10 min. After centrifugation at 3000 rev/min for 10 min, 4 ml of the organic phase was transferred to another tube containing 4 ml of 0.1 N H_2SO_4. This was shaken for 10 min and centrifuged. The organic layer was aspirated and discarded. The fluorescence of the acid extract was then determined at 350 mμ excitation and 450 mμ emission using an Aminco-Bowman® spectrophotofluorimeter. Appropriate standards prepared in plasma, and a blank, were analysed with the study samples. Inter-assay variation between standards did not exceed 3%. Quinine dihydrochloride used in this study was assayed and found to be within 3% of the quoted con-

centration. Plasma quinine concentrations after intravenous injection were analysed by a weighted least squares regression program, NONLIN (Metzler, 1969) run on an ICL 2988 computer.

Data for each patient were fitted to an equation of the form

$$C = Ae^{-\lambda t} + Be^{-zt}$$

using a weighting factor equivalent to the reciprocal of the concentration at each data point. This equation is consistent with a standard two compartment pharmacokinetic model. C represents the plasma quinine concentration at time t after the end of the injection. A and B are hybrid intercept terms and λ and z are the hybrid rate constants (Greenblatt & Koch-Weser, 1976). Initial estimates for each of the parameters A, λ, B, z, were obtained using an automated curve stripping procedure (Sedman & Wagner, 1977), and the final 'best fit' parameters were corrected for infusion time (Loo & Riegelman, 1970), and used to generate standard pharmacokinetic parameters. Paired two tailed Student's t-tests were used for comparison of clinical and electrocardiographic data.

Results

Subjective effects

All subjects felt light headed and slightly dizzy towards the end of the injection, but this resolved within 5 min. Five subjects complained of tinnitus and one felt slightly nauseated. There were no other auditory or visual symptoms.

Clinical effects

There were no consistent changes in pulse or blood pressure. Heart rate rose in four subjects, returning to baseline values by 6 min, there was no change in one, and a fall in the other two. These changes did not exceed 12 beats min^{-1}. Blood pressure was reduced in five subjects but the fall was less than 10 mm Hg (systolic) in each case.

ECG effects

There were no significant changes in the PR interval. The QRS interval was lengthened significantly in all subjects; baseline 87.5 ± 3.3 ms (mean ± 1 s.d.) to 95.6 ± 5.1 ms at 10 min ($P = < 0.001$).

Prolongation of the rate corrected QT interval $\left(\frac{QT}{\sqrt{R\text{–}R}}\right)$ was more variable with maximum values between 6 and 10 min after starting the quinine injection. Both intervals had returned towards baseline values by 15 min (Figure 1). There was a significant reduction in the height of the T wave in all cases. The overall reduction was 30 ± 18% (mean ± 1 s.d.) of the baseline value with lowest values occurring between 6 and 14 min after starting the quinine injection.

Pharmacokinetics

In each patient data points obtained during the first 1–2 min following completion of the infusion showed an increase in drug concentration with time, with peak concentrations occurring at 0.5 min in two instances, 1.0 min in three instances and 1.5 min and 2 min each in the other two cases. Although a fairly good fit could be obtained to the biexponential function when these earlier points were included, a considerably improved fit was obtained by their exclusion. The mean (± 1 s.d.) peak concentration was 5.1 ± 1.3 $mg\ l^{-1}$. The disappearance of quinine from the plasma had two exponential phases in each patient; r^2 values for fitting the biexponential function exceeded 0.99 in all cases. The 'distribution' phase was short having a mean apparent half-time of 1.89 ± 0.54 min (mean ± 1 s.d.) (Figure 2). The mean coefficient of variation for these estimates was 16%. The mean apparent volume of the central compartment was 0.57 ± 0.32 1 kg^{-1} (Table 1), and mean total apparent volume of distribution was 1.8 ± 0.37 1 kg^{-1}. Total clearance was 1.92 ± 0.45 ml min^{-1} kg^{-1}. The elimination half-time of quinine ($t_{½,z}$) was 11.1 ± 2.1 h with a mean coefficient of variation for the estimates of 7.4%.

Discussion

The use of intravenous quinine is increasing as chloroquine resistant *P. falciparum* spreads in South East Asia and South America. Recommendations for the optimum method of parenteral quinine administration vary widely. Many textbooks still recommend that quinine should be given by slow intravenous injection although this method has been associated with fatalities in seriously ill patients (Strahan, 1948; Patrick, 1968). These deaths have been attributed to hypotension or 'cardiac depression' occurring early in the distribution phase, and possibly associated with transiently high plasma concentrations of quinine, although these have never been measured. Slow infusions of quinine at therapeutic doses do not have a measurable distribution phase and are not associated with adverse cardiovascular effects even in severe malaria (Hall, 1977; White *et al.*, 1982).

In this study quinine was measured by the benzene extraction fluorescence method. This assay gives identical results for quinine and the diastereomer quinidine. Dihydroquinine and dihydroquinidine are quantitated in this method, but the polar metabolites

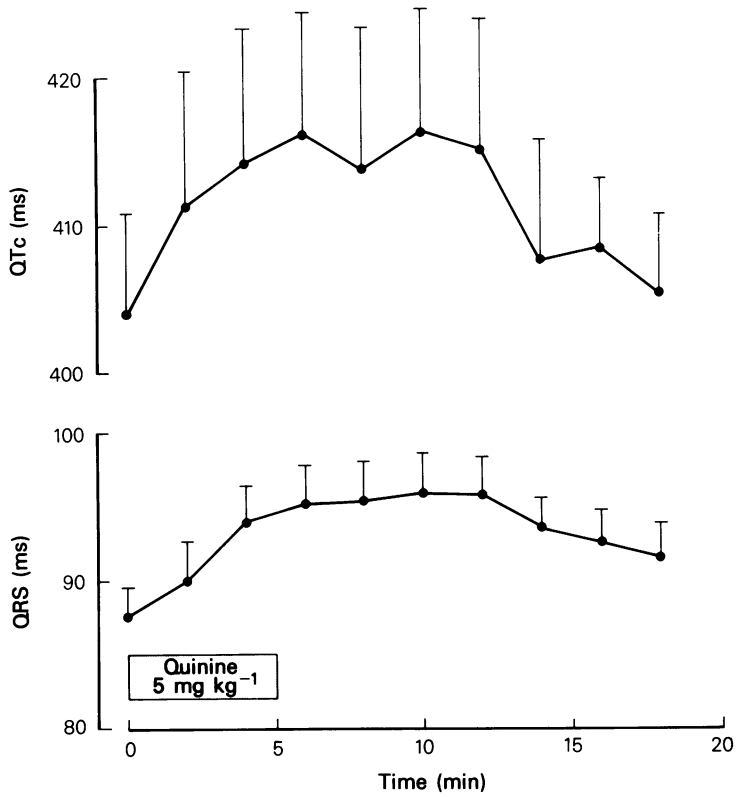

Figure 1 Changes in electrocardiographic indices (mean + 1 s.e. mean) associated with quinine infusion.

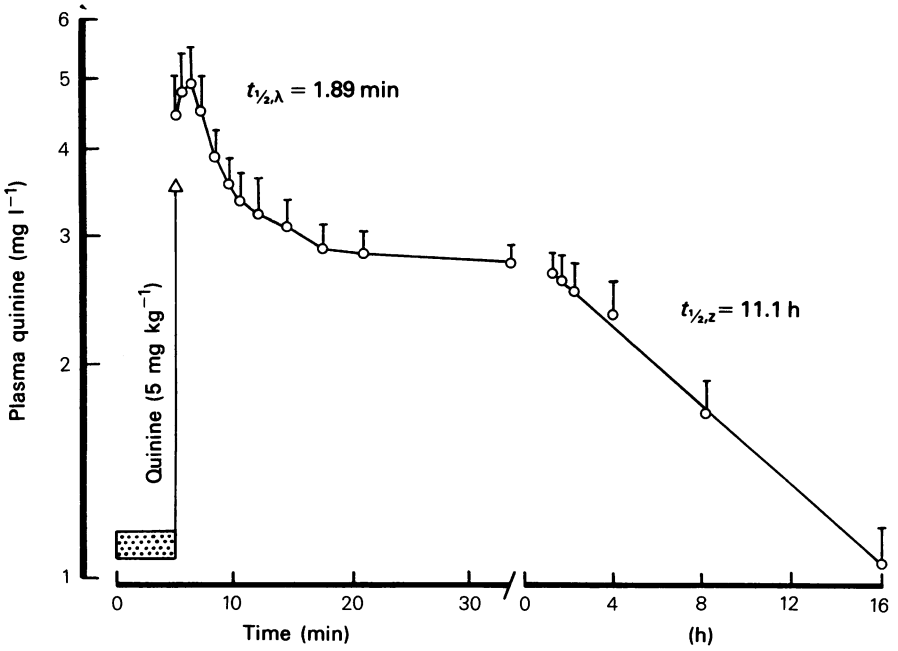

Figure 2 Plasma quinine concentrations (mean + 1 s.e. mean) following a 5 min infusion of quinine dihydrochloride. Distribution (λ) phase on left, elimination (z) phase on the right.

Table 1 Pharmacokinetics of intravenous quinine

Subject	*Infusion time* (*min*)	$t_{½,\lambda}$ (*min*)	V_1 (1 kg^{-1})	$t_{½,z}$ (*h*)	V_d area (1 kg^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})	k_{el} ($min^{-1} \times 10^{-3}$)	*Clearance* (*ml* kg^{-1} min^{-1})
1	4	2.07	0.34	11.13	2.01	0.273	0.056	6.15	2.09
2	5	1.50	0.68	9.02	1.48	0.250	0.210	2.81	1.91
3	5	1.21	0.21	14.93	2.01	0.521	0.062	7.33	1.54
4	5	2.06	0.73	10.68	2.36	0.244	0.110	3.51	2.56
5	5	2.77	0.59	8.96	1.42	0.145	0.104	3.11	1.83
6	5	1.45	0.29	10.33	1.92	0.400	0.073	7.33	2.12
7	5	2.16	1.14	12.61	1.43	0.064	0.257	1.14	1.30
Mean		1.89	0.57	11.09	1.80	0.271	0.125	4.48	1.92
s.d.		0.54	0.32	2.11	0.37	0.152	0.078	2.44	0.45

All subjects were given 5 mg kg^{-1} of quinine dihydrochloride. $t_{½,\lambda}$ is the half-time of the distribution phase. V_1 is the apparent volume of the central compartment. $t_{½,z}$ is the half-time of the terminal (elimination) phase. V_d area is the total apparent volume of distribution. k_{12} is the first order rate constant of transfer between the 'central' and the 'peripheral' compartment, and k_{21} the first order rate constant of transfer in the opposite direction. k_{el} is the first order rate constant for elimination from the central compartment.

are largely excluded (Cramer & Isaksson, 1963). Comparisons between the extraction fluorescence method and more specific methods including gas chromatography (GC), GC combined with mass spectroscopy, and high pressure liquid chromatography indicated a high degree of comparability: the slopes of the method-comparison regression lines were usually 0.9 or higher (Ochs *et al.*, 1980).

The pattern of quinine disappearance from the plasma closely fitted a two compartment open model. In these healthy subjects distribution to the tissues was rapid (mean apparent half-time $t_{½,\lambda}$ of 1.9 min) and extensive. Biological activity as evidenced by prolongation of electrocardiographic indices of depolarisation and repolarisation followed almost immediately. The mean total apparent volume of distribution was 1.8 1 kg^{-1} which is slightly less than that of patients convalescing from falciparum malaria (White *et al.*, 1982), and also that reported in healthy subjects for the diastereomer quinidine (Ochs *et al.*, 1980). As quinine is extensively bound to plasma proteins, the distribution of the free (unbound) component must be considerably greater than that of the total drug. The mean apparent elimination half-time was 11.1 h which is similar to that reported elsewhere (Hall 1977; White *et al.*, 1982), but is longer than that of quinidine (Ochs *et al.*, 1980). Mean total clearance was 1.92 ml min^{-1} kg^{-1}. These data suggest that a slow intravenous injection will not produce toxic plasma concentrations in normal subjects. However, patients with severe falciparum malaria have a contracted total apparent volume of distribution (V_d) of quinine and considerably reduced total clearance when compared with patients who have uncomplicated infections, who in turn have smaller V_d and lower total clearance than during convalescence (White *et al.*, 1982). The apparent volume of the central compartment was approximately one third of the total V_d in the healthy subjects in this study. In severe malaria it is likely that the volumes of both compartments would be contracted, and in addition distribution might be delayed.

In the rural setting it is common for parenteral antimalarials to be given in a fixed dose rather than adjusted for body weight. In Thailand a standard dose of 600 mg quinine dihydrochloride is usually given, although average body weights are nearer 50 kg. In these circumstances toxic plasma quinine concentrations might well result after intravenous injection, particularly if the injection were given rapidly. The clinical relevance of the distribution phase may be appreciated from the electrocardiographic changes that followed slow injection of a low dose of quinine in these healthy subjects. There was consistent prolongation of the QRS interval and a more variable prolongation of the QT interval both of which were transient and synchronous with the distribution phase. This may explain the adverse cardiovascular effects reported after quinine injection. Slow infusion is not

associated with a measurable distribution phase or adverse cardiovascular effects and is therefore a preferable method of administration.

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