Cardiovascular toxicity and distribution kinetics of intravenous chloroquine

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1 Chloroquine diphosphate (3 mg base kg⁻¹) was given by constant rate intravenous injection over 10 min to 12 healthy adult male volunteers. Plasma concentrations of chloroquine and the principal metabolite desethylchloroquine, electrocardiograph intervals, and arterial blood pressure were measured at frequent intervals to determine the relationship between cardiovascular effects and plasma concentrations.

2 Peak plasma concentrations ranged between 784 and 6649 (mean 2913) ng ml⁻¹. The decline in plasma concentrations was multiexponential with an initial rapid distribution phase; mean ($\pm$ s.d.) first order rate constant 0.65 ± 0.14 min⁻¹, and an estimated apparent volume of the central compartment of 0.18 ± 0.15 l kg⁻¹.

3 There was no serious toxicity, but subjective side effects were reported in all patients and there was a significant fall in systolic blood pressure (110 ± 9.5 to 101 ± 12.5 mm Hg; $P = 0.03$) and rise in heart rate which paralleled the change in plasma chloroquine concentrations.

4 Coincident with changes in blood pressure, there was a significant prolongation of the electrocardiograph QRS interval; 81 ± 15 to 92 ± 13 ms ($P < 0.01$) but no change in the QTc interval.

5 These findings suggest that the cardiovascular toxicity of parenteral chloroquine is related to transiently high plasma concentrations occurring early in the distribution phase. This results from incomplete distribution from a central compartment that is approximately one thousand times smaller than the eventual total apparent volume of distribution at steady state. Rate of administration is therefore a major determinant of toxicity.

Keywords chloroquine pharmacokinetics cardiovascular toxicity

Introduction

Chloroquine is the most widely prescribed anti-malarial in the world (WHO, 1984). It is the treatment of choice for malaria caused by *Plasmodium vivax*, *P. malariae*, *P. ovale* and sensitive

strains of *P. falciparum*. Chloroquine is well absorbed by mouth in healthy subjects (Gustafsson *et al.*, 1983) and in children with uncomplicated falciparum malaria (Adelusi *et al.*, 1982; Walker

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et al., 1983) but this route of administration is impossible in seriously ill patients who are vomiting or comatose, i.e. those in most need of urgent treatment. Parenteral chloroquine is extensively used in these circumstances in many tropical countries although there is no information on the disposition of parenteral chloroquine in severe malaria and therefore no consensus on correct dosage or route of administration. Intramuscular chloroquine has been associated with occasional deaths (Harris, 1955; Tuboku-Metzger, 1964; Williams, 1966; Geddes, 1970) and is considered dangerous. Early clinical studies in patients with falciparum malaria suggested that the principal toxicity of intravenously injected chloroquine was hypotension (Scott, 1950; Mohr, 1953; Knorr, 1953; Laing, 1955). There have been no pharmacological studies in man to define the relationship between disposition after parenteral administration and potentially dangerous toxicity. The only previous study of chloroquine pharmacokinetics after intravenous injection was not designed to address this question (Gustafsson *et al.*, 1983). Because of these uncertainties and the reports of occasional fatalities it has recently been recommended that parenteral chloroquine should no longer be used (WHO, 1984) despite the lack of parenteral alternatives in many countries. We have therefore studied the immediate disposition of intravenously administered chloroquine to investigate the relationship between blood concentrations and cardiovascular effects in order that safer regimens may be devised for the treatment of severe malaria.

Methods

Subjects

Twelve healthy adult male Thai subjects gave fully informed written consent to the procedure. They were aged between 18 and 47 years and weighed between 43 and 66 kg. Subjects who had malaria recently or had taken antimalarial prophylaxis were excluded. This study was approved by the Ethics committee of the Faculty of Tropical Medicine, Mahidol University.

Methods

All subjects were weighed and then lay on a bed. An intravenous infusion of saline was started and a sampling teflon catheter placed in the antecubital vein of the other arm. This was kept patent with heparinised saline. Chloroquine diphosphate (Resochin-Bayer) diluted to a

volume of 10 ml was given by constant rate manual injection into the side arm of the freely flowing infusion. A dose of 3 mg base kg^{-1} was given over exactly 10 min (1 ml min^{-1}). All subjects were informed that the injection could be stopped at any time if they felt unwell. Blood was sampled before then 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 30 min and then 1, 1.5, 2, 8, 24 and 168 h after the end of the injection. A 12-lead electrocardiogram was recorded before the injection. The lead giving the best complex definition was recorded at 50 mm s^{-1} paper speed and double sensitivity before, then 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 min after beginning the injection. Standard electrocardiographic intervals were recorded from the mean of five adjacent complexes. Blood pressure and pulse were measured at 2 min intervals until values had returned to baseline levels.

Chloroquine assay

Blood was taken into plastic lithium heparin bottles, centrifuged immediately at 1500 g for 10 min and the plasma stored at -20°C for up to 2 weeks, then at -70°C until analysed. Chloroquine and the principal biologically active metabolite monodesethyl chloroquine were measured by high performance liquid chromatography according to the method of Alvan *et al.* (1982) with modifications. To plasma, or urine (0.5 ml) contained in 15 ml capacity screw-capped tubes was added, as an aqueous solution of the salt, the internal standard, 7-chloro-4-(5-diethylamino-1-methylpentyl-amino)-quinoline diphosphate, a gift from the Walter Reed Army Institute of Research, Washington D.C., U.S.A. ($25 \mu\text{l } 25 \text{ ng}^{-1}$ for plasma, $300 \mu\text{l } 300 \text{ ng}^{-1}$ for urine) ammonia (sp.gr. 0.88 (1.0 ml), and n-hexane (5.0 ml). Following mechanical tumbling for 15 min the tubes were centrifuged (500 g, 5 min) and the organic phase removed and transferred to a tapered glass centrifuge tube. The extraction was repeated and the combined organic phase evaporated to dryness under a stream of nitrogen gas at 35°C . The residue was redissolved in acetonitrile (50 μl) and 30 μl injected into the chromatograph. Concentrations of chloroquine and monodesethyl chloroquine were quantified by relating peak height ratios of drug and metabolite to internal standard in chromatograms of samples, to peak height ratios obtained from authentic standards.

The chromatography system consisted of a Spectra-Physics SP 8770 pump and SP 8750 organiser equipped with a Rheodyne injector and a Schoeffel FS 970 fluorescence detector. Excitation wavelength was 335 nm and a 370 nm emission filter was used. The column ($0.25 \text{ m} \times$

4.6 mm i.d.) was packed with Spherisorb silica (5 μm particles; Technicol, Stockport, U.K.) and eluted with a mobile phase of methanol: acetonitrile: diethylamine: dichloromethane (80:18.5:0.5:1.0) flowing at 1.5 ml min⁻¹. Under these conditions the typical retention times for chloroquine, the internal standard and desethyl chloroquine were 5 min 6 s, 6 min 15 s and 7 min 23 s respectively. The limit of detection for chloroquine in plasma was 1.0 ng ml⁻¹ and the coefficient of variation for the determination of chloroquine in plasma and urine was 3.5% at 50 ng ml⁻¹. All glassware was treated with dichlorodimethylsilane (5% v/v in toluene) to minimise drug absorption.

Data analysis

Plasma chloroquine 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 standard pharmacokinetic equations after correction for infusion time using a weighting factor equivalent to the reciprocal of the concentration at each data point. Estimates for the hybrid rate constants were obtained using an automated curve stripping procedure (Sedman & Wagner, 1977). Paired two tailed Student's *t*-tests were used for comparison of clinical and electrocardiographic data.

Results

Plasma chloroquine concentrations

Chloroquine concentrations at the end of the 10 min injection varied between 784 and 6649 ng ml⁻¹. In some patients plasma concentrations continued to rise within the first 90 s following the end of the injection suggesting incomplete equilibration, but then fell rapidly. Peak plasma concentrations were 2913 ± 1434 ng ml⁻¹ (mean $\pm$ s.d.) with a range of 784 to 6649 ng ml⁻¹ but by 4 min after the end of the injection had fallen to a mean value of 785 ± 310 ng ml⁻¹ (Figure 1). A full kinetic analysis of these data is not appropriate because of the extremely long terminal elimination phase which was not defined, however, analysis of the initial phase suggested a multi-exponential decline in plasma concentrations. A biexponential function was adequate to describe the plasma concentrations in two subjects, but a significantly better fit was obtained with a tri-exponential function in the remaining eight sub-

Figure 1 Plasma chloroquine concentrations (mean $\pm$ s.e. mean) in 12 subjects following intravenous injection (3 mg base kg⁻¹ over 10 min).

jects. The estimated first order rate constant of the first phase was 0.65 ± 0.14 min⁻¹ ($t_{1/2} = 1.1 \pm 0.24$ min). The second (intermediate) phase rate constant ranged from 0.133 to 0.003 min⁻¹ ($t_{1/2}$ 5.2 to 231 min) and the final phase rate constant ranged from 0.93 to 0.029 day⁻¹ ($t_{1/2}$ 0.75 to 23 days). The second phase in the two patients' series fitting biexponential functions had rate constants of 13.0 and 2.1 day⁻¹ ($t_{1/2}$ 1.3 and 7.9 h). The estimated mean ($\pm$ s.d.) apparent volume of the central compartment derived from these data and the infusion time corrected intercept values was 0.184 ± 0.145 l kg⁻¹. Mean plasma concentrations of desethylchloroquine at the end of the injection were 88 ± 41 ng ml⁻¹. These then fluctuated between 105 and 275 ng ml⁻¹ over the subsequent 8 min before declining in parallel with the chloroquine concentrations. The mean chloroquine:desethyl chloroquine ratio at 1 h was 3.6:1.

Urinary chloroquine excretion

Twenty-four hour urinary chloroquine excretion ranged between 5.7 and 33 mg of free base (mean 13.5 mg) equivalent to 4.5% of the administered dose.

Subjective effects

All subjects complained of feeling light headed but none asked for the injection to be stopped. Eight subjects said their eyes felt heavy and vision was temporarily unclear. Three subjects felt transiently faint. None vomited, but three felt nauseated. These symptoms had resolved within 8 min of completing the injection.

Cardiovascular effects

There was a small but significant fall in systolic blood pressure during the injection (Figure 2); resting systolic pressure 110 ± 9.5 mm Hg (mean $\pm$ s.d.), falling to 101 ± 12.5 mm Hg at the end of the injection ($P = 0.03$). There was no correlation within the group between the fall in systolic blood pressure and the peak plasma chloroquine concentration. There was no significant change in diastolic blood pressure. Systolic blood pressure had regained pre-injection values by the eighth minute after the injection was completed. Heart rate rose significantly from a baseline value of 69 ± 9.2 beats min^{-1} to 82 ± 6.5 beats min^{-1} ($P < 0.001$) at the end of the injection, and returned to baseline values between 4 and 12 min after completion of the injection.

Electrocardiographic effects

There were no changes in PR interval. The QRS interval was prolonged in all but one patient with maximum prolongation either at the end of the injection or in the subsequent (2 min) recording (Figure 2); overall the mean baseline QRS interval 81 ± 15 ms, increased to a mean value at the end of injection of 92 ± 13 ms ($P < 0.01$). There was no correlation between QRS prolongation and log plasma chloroquine concentration at the end of the injection. The QRS interval returned to baseline values in all subjects within 12 min of completing the injection. There was no consistent change in the rate corrected QT interval

$$\left(\frac{\text{QT}}{\sqrt{\text{R-R}}} \right)$$

or the ST segment but there was a reduction in T wave height in all but one subject. The overall mean reduction in T wave height was $27 \pm 17\%$ of baseline value ($P < 0.01$) with a time course which paralleled that of the QRS prolongation.

Discussion

The pharmacokinetic properties of chloroquine are complex (White, 1985). The decline in plasma concentrations after a single dose is multiphasic with an extremely long terminal elimination phase during which plasma concentrations are measurable for up to three months (Gustafsson *et al.*, 1983; Frisk-Holmberg *et al.*, 1984). Tissue distribution is extensive and there is concentration in the blood cells. The total apparent volume of distribution is consequently enormous—for

Figure 2 Changes in systolic blood pressure and electrocardiographic QRS interval during and immediately following intravenous chloroquine injection.

plasma chloroquine this has been estimated to be in the order of 1000 l kg^{-1} (Frisk-Holmberg *et al.*, 1984). The relatively low plasma chloroquine concentrations observed in steady state conditions with daily dosing in rheumatoid arthritis (usually under 200 ng ml^{-1}) or weekly anti-malarial prophylaxis (usually under 80 ng ml^{-1}) sharply contrast with the transiently high concentrations (peak values up to 6649 ng ml^{-1}) measured in this study, in which a relatively small dose ($3 \text{ mg base kg}^{-1}$) was given by intravenous injection over ten minutes to healthy volunteers. This reflects incomplete distribution from a central compartment (0.18 l kg^{-1}) that is approximately three orders of magnitude smaller than the eventual total apparent volume of distribution at steady state (V_{ss} ; $100\text{--}1000 \text{ l kg}^{-1}$). The enormous differences between these values, and between the distribution and elimination phase rate constants mean that the plasma concentration profile and toxicity of parenteral chloroquine during the usual 3 day treatment course in falciparum malaria, would be determined largely by distribution rather than elimination processes.

In this study transiently high plasma chloroquine concentrations produced reversible haemodynamic and electrocardiographic changes and transiently unpleasant subjective effects.

The toxic threshold for serum chloroquine concentrations in patients with rheumatoid arthritis on chronic treatment has been estimated as between 200 and 400 ng ml⁻¹ (Frisk-Holmberg *et al.*, 1979a,b) but serum concentrations are generally much higher than plasma concentrations because of release of platelet bound chloroquine during clotting (Bergqvist & Domeij-Nyberg, 1983). Gustafsson *et al.* (1983) in a detailed study of chloroquine disposition after oral and intravenous administration gave a single dose of 300 mg base intravenously over 12 min to two subjects and the same dose over 23.5 min to a further nine subjects. Similar subjective side effects to those observed in the present study were reported by all subjects but cardiovascular effects were not observed. These subjective effects disappeared when plasma concentrations fell below 145–370 ng ml⁻¹. Although distribution phase kinetics were not analysed in that study, plasma chloroquine concentrations after intravenous injection were approximately ten times higher than produced by the same dose given orally with peak concentrations of between 478 and 1200 ng ml⁻¹ (mean 837 ng ml⁻¹). This compares with peak concentrations in the present study of between 784 and 6649 ng ml⁻¹ (mean 2913 ng ml⁻¹) with a shorter injection time but a smaller dose. In the present study the initial distribution phase following slow (10 min) intravenous injection was rapid; the first exponential term had a rate constant of 0.65 min⁻¹ (half-time 1.1 min) but initial plasma concentrations were approximately fifty times higher than those measured 8 h later. A complete definition of chloroquine pharmacokinetics after intravenous injection is not possible in man because doses sufficiently large to produce measurable blood levels 1 month later, and therefore to define the terminal elimination phase, cannot be administered safely. Although chloroquine is well absorbed after oral administration the initial distribution phase is not measurable and peak plasma concentrations are much lower than those recorded after parenteral administration. Clearly, slow intravenous infusion would also allow more complete distribution and therefore avoid the transiently high blood concentrations associated with this potentially toxic initial phase. Modes of administration in which chloroquine is absorbed more rapidly than by mouth may also risk toxicity. Rapid absorption also occurs after intramuscular administration (White *et al.*, in preparation) and may account for the sudden deaths that have been reported in children treated for falciparum malaria. Pharmacokinetic studies of parenteral chloroquine in malaria are urgently needed to resolve these questions.

Fatal chloroquine intoxication is associated with shock and central nervous system toxicity (Good & Shader, 1982). Whole blood chloroquine concentrations of 3,000 ng ml⁻¹ (corresponding to an approximate plasma concentration of 400 ng ml⁻¹) were recorded in a healthy girl who survived an overdose of 82 mg kg⁻¹ base (Frisk-Holmberg *et al.*, 1979). Convulsions, and respiratory and cardiac arrest occurred initially and the electrocardiogram showed widened QRS complexes with ST segment depression. Plasma concentrations considerably higher than this were briefly recorded in the present study and that of Gustafsson *et al.* (1983). Similar electrocardiographic findings were reported following chloroquine overdose (Don-Michael & Aiawzadeh, 1970) and were confirmed in experiments on dogs (Lansimies *et al.*, 1971). With increasing intravenous doses there was progressive hypotension with broadening and flattening of the QRS complex. Electrocardiographic changes have not previously been documented with administration of therapeutic doses of parenteral chloroquine. In the present study there was progressive QRS complex widening and T wave flattening which paralleled the profile of plasma concentrations and was associated with a fall in systolic blood pressure. In contrast to the predominant effects of the cinchona alkaloids on ventricular repolarisation (White *et al.*, 1983), QTc interval prolongation was not observed with intravenous chloroquine.

Parenteral chloroquine was extensively evaluated after its introduction in the late 1940s; Scott (1950) gave intravenous injections of between 5.7 and 14.9 mg base kg⁻¹ body weight to 110 patients with falciparum malaria. Rapid intravenous injection (130 mg min⁻¹) was associated with adverse effects in all patients; systolic blood pressure fell by an average of 26 mm Hg whereas diastolic blood pressure remained unchanged. Chloroquine infusion (400 mg base over 1 h) was without complications. Mohr (1953) treated 15 adults and Knorr (1953) 92 cases of falciparum malaria with parenteral chloroquine and confirmed the predictable hypotensive effects of rapid injection. These clinical observations and the present investigation all suggest that the cardiovascular toxicity of chloroquine after intravenous injection is associated with incomplete distribution of the drug from a relatively small central compartment. The plasma concentration threshold for this is probably over 1000 ng ml⁻¹. With currently employed intravenous doses, rate of administration rather than dose is therefore the principal determinant of toxicity. Slow intravenous infusion of chloroquine should allow sufficient time for adequate distribution, although

pharmacokinetic studies in malaria are needed to determine the optimum rate of administration. Following the present study we have now treated over 50 patients with intravenous chloroquine infusions (10 mg base kg⁻¹) over 4 h and observed no adverse cardiovascular effects. If parenteral chloroquine is required and the facilities are available then slow rate controlled intravenous infusion is the best method of administration. Chloroquine should not be given by intravenous injection.

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