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Comparison of the pharmacokinetics of chloroquine after single intravenous and intramuscular administration in healthy Africans

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1 The pharmacokinetics of chloroquine were studied after intramuscular and intravenous administration of the drug to healthy African adults.
2 Chloroquine was analysed in plasma using an h.p.l.c. method and pharmacokinetic parameters were derived from the concentration–time data using a non-linear computer programme. A two-compartment open model was assumed.
3 Chloroquine was rapidly absorbed from an intramuscular site, producing a plasma concentration-time profile similar to that obtained after a 15 min i.v. infusion of a comparable dose.
4 The pharmacokinetics of chloroquine after i.m. and i.v. administration were characterised by a long half-life and a very large volume of distribution. There was no significant difference between the values of each parameter obtained from the different routes.
5 It is suggested that the high C_{max} obtained after i.m. and i.v. administration of chloroquine might contribute to its toxicity when these routes are used in treatment.

Keywords chloroquine pharmacokinetics

Introduction

The pharmacokinetics of chloroquine (CQ) have been extensively studied in recent years in normal Caucasians (Gustafsson *et al.*, 1983), normal Africans (Walker *et al.*, 1986c) and in different diseases (Walker *et al.*, 1986a,b). CQ is normally administered orally in the treatment of malaria and as such most pharmacokinetic studies have been done after single or repeated oral dosage. However, it is sometimes necessary to use the parenteral route (in severe malaria or in those who do not tolerate the oral drug) and so it is necessary to determine the pharmacokinetic behaviour of the drug following parenteral administration. Information so obtained should provide a rational basis for the parenteral use of the drug.

The only recent comprehensive study of the pharmacokinetics of CQ after i.v. administration was that of Gustafsson *et al.* (1983) in which 200 mg CQ was administered i.v. to normal Swedes. There is no recent study of the pharmacokinetics of CQ after i.m. administration although the drug is often given by the i.m. route. We therefore studied the kinetics of the disposition of chloroquine in adult Nigerians after an i.m. dose and compared it with the kinetics after an i.v. dose in a similar group of Nigerians.

Methods

Eleven normal healthy Nigerian males were studied. They were aged 20–42 years and weighed between 45 and 65 kg. The study was clearly explained to them and they all voluntarily agreed

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to participate. None of them was on any regular drug intake. None had taken chloroquine (CQ) for at least 3 months before the study and they did not take CQ or any other drug throughout the duration of the study. The study protocol was approved by the local ethics committee. Seven subjects received CQ intramuscularly. The dose was 200 mg in 5 ml solution and it was injected deep into the gluteal muscle. The drug was given at 08.00 h (0 h) after an overnight fast. Four subjects received CQ intravenously. The dose was 3 mg kg^{-1}. It was diluted with 200 ml 0.9% saline and infused over a period of 15 min. The end of the infusion was regarded as 0 h. Blood (5 ml) was withdrawn from an antecubital vein before giving the drug and at times 0.08, 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 120, 168, 336, 504, 672 h afterwards. The blood was collected into a heparinised tube and immediately centrifuged at 1000 *g* to separate the plasma which was stored frozen at −50° C until analysed. Urine was collected for 24 h on days 1, 7, 14, 21 and 28 from the seven subjects who received CQ intramuscularly. The volume was recorded and a 10 ml aliquot stored frozen at −50° C until analysed.

Analytical technique

Chloroquine was analysed by the h.p.l.c. technique described by Alvan *et al.* (1982). The mobile phase consisted of acetonitrile, methanol and diethylamine (h.p.l.c. grade) in the ratio of 80:19.5:0.5. The stationary phase was a silica-based column (0.15 m × 4.6 mm i.d.) packed with LiChrosorb Si 60, 5 μm (Merck-Darmstadt, GFR). The internal standard used was 7-chloro-4- (4-dimethylamino -1- methyl-butylamino)-quinoline. The eluent had a flow rate of 1 ml min^{-1} and gave a good separation of chloroquine from its desethylmetabolite and from the internal standard. A fluorescence detector with excitation wavelength at 330 nm and emission at 370 nm was used. With the above conditions, the chromatograms showed retention times of 4.36, 5.34 and 6.56 min for chloroquine, internal standard and desethylchloroquine respectively. No interfering peaks were detectable in the chromatogram.

The lower limit of sensitivity of the method was 1 ng ml^{-1} for chloroquine and 0.5 ng ml^{-1} for desethylchloroquine. The coefficient of variation of repeated determinations of any single sample was 3.5% (n = 10) at 50 ng ml^{-1} for chloroquine and 5% (n = 10) at 25 ng ml^{-1} for desethylchloroquine. Standard curves for chloroquine and desethylchloroquine were done everyday with each set of extractions and they showed no variation from day to day. The recovery of chloroquine was 88%. At the relatively low dose of chloroquine used in this study, the values for desethylchloroquine were so low after the first few hours that the analytic method did not discriminate clearly between samples. The data for desethylchloroquine have therefore not been included in this report.

The urinary recovery of chloroquine up to 28 days after i.m. administration of 200 mg was estimated by finding the area under the curve obtained by plotting daily urinary excretion rate against time, using the trapezoidal rule. Excretion to infinite time was estimated using k-values obtained between days 14 and 28. The sum of these two gave an estimate of total urinary recovery of chloroquine.

Pharmacokinetic calculations

Concentration-time data were analysed for model-dependent pharmacokinetic parameters using a non-linear least squares regression programme (GPHARM). A two-compartment model was assumed thus:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t}$$

and the infusion period was taken into consideration when calculating the best fit parameters. The 'terminal' half-life was calculated by linear regression of the log concentration-time curve using the last four or more experimental points for such calculations. The central volume of distribution was calculated from the equation:

$$V_C = \frac{\text{Dose}}{A+B}$$

where B is the zero-time intercept of the linear terminal part of the curve and A is the zero-time intercept of the line obtained by the method of residuals (Gibaldi & Perrier, 1975) from the curve. The apparent volume of distribution (Vd) representing both the central and peripheral compartments was calculated from:

$$Vd_{ss} = \frac{\text{Dose}}{B}$$

The area under the curve (AUC) was obtained using the linear trapezoidal rule up to the last data point. The AUC beyond the last data point was estimated using the equation:

$$\int_{t_{last}}^{\infty C} C\,dt = \frac{C_{last}}{2} \cdot \frac{1}{\beta}$$

The sum of these two parameters gave the total AUC ($AUC_{0\to\infty}$) where β is the 'terminal' rate

constant. Plasma clearance, CL_p, was calculated from the model-independent equation:

$$CL_p = F \times \frac{\text{Dose}}{AUC_{o\rightarrow\infty}}$$

where $F = 1$ for both i.v. and i.m. dosing. A computer derived concentration-time curve was plotted for each subject. From these curves, the peak height concentration (C_{max}) and the time to peak height concentration (t_{max}) for each subject were read off.

Values are given in the text as mean ± s.d.

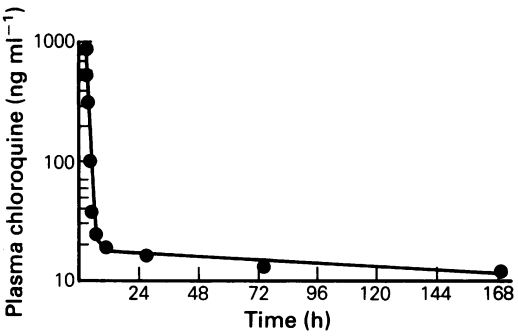

Figure 1 Computer-generated plasma chloroquine concentration-time curve in subject no. 5 after intramuscular administration of 200 mg chloroquine base.

Results

Intramuscular administration

Chloroquine was rapidly absorbed after intramuscular administration, peak concentration being reached in all subjects by the time the second blood sample was taken 15 min after giving the drug. The peak plasma concentration varied between 365 and 900 ng ml^{-1} (mean, 548 ± 189.5 ng ml^{-1}). The concentration fell rapidly within the first 8 h to a value usually between 10 and 20 ng ml^{-1}. Concentration then declined very slowly with the concentration-time curve being almost flat so that chloroquine was still detectable in the blood 28 days after giving the drug. Figure 1 shows the log concentration-time curve for one of the subjects (No. 5) which is typical for the group. The calculated pharmacokinetic parameters for the group are summarised in Table 1. The 'terminal' half-life varied between 58 and 364 h with a mean of 216.8 ± 95.9 h. The central volume of distribution was 6.0–16.6 l kg^{-1} (mean 10.2 ± 3.3 l kg^{-1}), and the 'steady state' volume of distribution (Vd_{ss}) was 118–275 l kg^{-1} (mean 181 ± 48.6 l kg^{-1}). Total AUC was 2062–7304 ng ml^{-1} h (mean 6077 ± 1859 ng ml^{-1} h) but in view of the relative flatness of the 'terminal' concentration-time line the extrapolated AUC was more than 20% of the total AUC. This can be expected to increase the margin of error of this parameter. As with the volume of distribution, the total clearance was calculated from the intramuscular data on the assumption that absorption from the intramuscular site was rapid (supported by the concentration-time data) and complete. The total clearance varied from 450–1616 ml min^{-1} (mean 657 ± 425 ml min^{-1}). The renal clearance was 145 ± 93.7 ml min^{-1}.

Intravenous administration

Four subjects received CQ i.v. The concentration of chloroquine reached its peak within 15 min of starting the infusion, with the peak concentration ranging between 250 and 1250 ng ml^{-1}. The concentration then fell rapidly reaching a concentration of between 15 and 27 ng ml^{-1} at 24 h. Thereafter the concentration fell very slowly and the drug was still detectable in the blood 21 days after its administration. Figure 2 shows the log concentration-time curve for subject No. 2 which is typical for the group and Table 2 shows a summary of the pharmacokinetic parameters

Table 1 Pharmacokinetic parameters for chloroquine after intramuscular injection of a single dose of 200 mg in normal African adults

Subject	*Weight (kg)*	C_{max} *(ng ml⁻¹)*	t_{max} *(min)*	$t_{½}$ *(h)*	V_c *(l kg⁻¹)*	V_{ss} *(l kg⁻¹)*	CL_p *(ml min⁻¹)*	CL_R *(ml min⁻¹)*
1	61	600	15	219	10.7	164	567	196
2	66.2	390	15	364	16.6	275	533	50
3	56	365	5	58	8.1	162	1616	313
4	59	640	15	243	10.9	188	517	190
5	56	540	15	216	8.5	162	450	89
6	56	900	5	270	10.5	198	450	62
7	53	400	15	148	6.0	118	467	118
Mean	58.2	547.9	12.1	216.9	10.2	181	657.1	145
s.d.	4.4	189.5	4.9	95.9	3.3	48.6	425.2	93.7

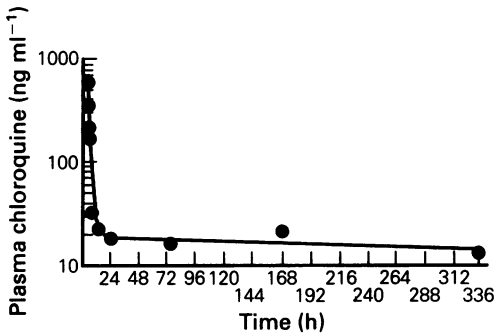

Figure 2 Computer-generated plasma chloroquine concentration-time curve in subject no. 2 after slow intravenous injection of 3 mg kg^{-1} chloroquine base.

derived from the concentration-time data. The 'terminal' half-life showed a wide interindividual variation, the estimated values in the four subjects being 168, 415, 821 and 871 h. The total AUC was between 6655 and 22,031 ng ml^{-1} h. The extrapolated AUC from the last sampling points to infinity was more than 20% of the total thus increasing the margin of error inherent in the calculation of the total AUC. There was also a wide interindividual variation in the total clearance with values of 133, 133, 150 and 483 ml min^{-1} being obtained in the four subjects. The distribution of CQ from the central compartment to the peripheral compartments was rapid with a half-life of 0.61–2.08 h. The volume of distribution of the central compartment (V_c) was 5.47–10.1 l kg^{-1} (mean 7.5 ± 2.1 l kg^{-1}) while that of the steady state compartment (Vd_{ss}) was 100–188 l kg^{-1} (mean 141.9 ± 36.7 l kg^{-1}).

Urinary excretion

The amount of unchanged chloroquine excreted in the first 24 h after intramuscular injection of 200 mg chloroquine was 18.02 ± 5.7 mg which was approximately 9% of the administered dose. The daily excretion rate diminished rapidly at first and subsequently slowly and a plot of the daily excretion of unchanged chloroquine against time gave an exponential type of curve (Figure 3). The total urinary recovery of unchanged chloroquine estimated from the area under the excretion rate versus time curve extrapolated to infinity was 82.0 ± 9.3 mg giving a mean percentage recovery rate of 41%.

Chloroquine metabolites

Desethylchloroquine (DEC) was detectable following administration by the two routes. However, the values of DEC were so low that discrimination between samples was very little indeed. It was therefore decided to leave out the DEC results.

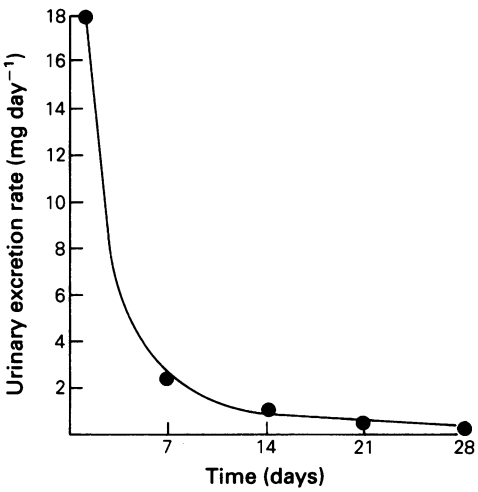

Figure 3 Plot of rate of excretion of chloroquine per day (in mg) against time. Each point represents the mean for seven subjects given one intramuscular dose of 200 mg chloroquine base.

Table 2 Pharmacokinetic parameters of CQ after i.v. infusion of 3 mg kg^{-1} over 15 min in four normal African subjects

Subject	*Weight (kg)*	*Total dose (mg)*	C_{max} *(ng ml^{-1})*	t_{max} *(min)*	$t_{1/2}$ *(h)*	V_c *(l kg^{-1})*	V_{ss} *(l kg^{-1})*	CL_p *(ml min^{-1})*
1	55	165	260	15	871	10.1	188	133
2	56	168	600	15	821	8.3	150	133
3	62	186	1250	15	415	5.5	100	150
4	64	192	800	15	168	6.2	130	483
Mean	59.2	177.8	727.5	15	568.7	7.5	142	224.7
s.d.	4.4	13.3	413.6	0	336.3	2.1	36.7	172.4

Side effects

All the patients who received i.m. CQ had side effects. The subjects were all ambulant and the most prominent side effect was dizziness. This was most severe 5–30 min after the injection. Other side effects complained of were blurring of vision, abdominal discomfort with or without nausea, weakness and unsteadiness of gait. The side effects almost always passed off within 1 h of the injection. The patients who received the i.v. CQ did not complain of any side effects. However, the subjects were all confined to bed for a few hours before and after the injection.

Discussion

One of the remaining problems in the use of chloroquine is the controversy over its parenteral use. In severe and complicated malaria in areas of resistance to chloroquine, i.v. quinine is clearly the drug of choice. Quinine has also been recommended as the drug of choice in areas of full CQ-sensitivity in consideration of the possible severe toxicity following i.v. chloroquine (World Health Organisation, 1984). This fear of severe toxicity following i.v. CQ is justified by the data in the study by Gustafsson *et al.* (1983). These workers gave 300 mg CQ i.v. (about 4.5–5 mg kg^{-1}) to normal adult volunteers in an infusion over 25 min. The plasma level rose rapidly to values of 1000 ng ml^{-1} and above and every volunteer developed side effects which included dizziness, diplopia, difficulty in swallowing, muscle weakness, nausea and tiredness. In the study reported here we gave 3 mg kg^{-1} CQ i.v. to normal adult volunteers by slow infusion over 15 min and obtained in three out of four subjects high peak values which in one subject reached 1250 ng ml^{-1} (the usual mean peak concentration after 10 mg kg^{-1} CQ orally is 250 ng ml^{-1} or less (Adelusi *et al.*, 1982). Since acute side effects to CQ are concentration-related and appear to coincide with plasma concentrations higher than 250 ng ml^{-1} (Gustafsson *et al.*, 1983), it is obvious from this study and that of Gustafsson *et al.* (1983) that administering chloroquine i.v., even at a dose as low as 3 mg kg^{-1} given over a period less than 30 min, is fraught with the danger of toxic effects which might not be well tolerated by a patient already debilitated by acute malaria.

However, chloroquine may very well be the only potent antimalarial available in a country where *P. falciparum* is still fully sensitive to CQ, and treatment of cerebral malaria for which oral CQ is not feasible then poses a problem. One approach recently suggested without any pharmacokinetic backing (World Health Organisation, 1985) was an initial slow intravenous infusion of 10 mg kg^{-1} CQ i.v. over at least 4 h followed by a maintenance dose of 5 mg kg^{-1} i.v. over 2–4 h at 12-hourly intervals. This seems logical but requires further study.

The question of intramuscular CQ has even been more controversial since this route is often used in patients who are able to receive the drug orally. The danger of i.m. CQ has been underscored by reports of sudden death, especially in children, after giving the drug by this route (Tuboku-Metzger, 1964; Olatunde, 1970). In spite of these reports, CQ continues to be given i.m. to adults and children. Since in most countries in which this practice is common, adverse drug reactions are poorly monitored and records poorly kept it is not possible to estimate the danger to health or life that the practice constitutes and many authorities have accordingly advocated avoidance of this route as much as possible until further information is available (World Health Organisation, 1984, 1985; Trigg *et al.*, 1984). In the study reported here we administered 200 mg CQ i.m. to normal adult volunteers 200 mg was chosen because this is the standard adult i.m. dose used in this country. Our results showed a very rapid absorption of CQ with peak concentrations well above 250 ng ml^{-1} similar to the observation after i.v. administration in this study and in the study by Gustafsson *et al.* (1983). This study thus confirms the danger inherent in the i.m. administration of chloroquine and strengthens the view which has been expressed on clinical grounds that this route should not be used in uncomplicated malaria where, with a little clinical care, the drug can be successfully administered orally. Where it becomes impossible to give the drug orally, then in the present state of knowledge of the pharmacokinetics of CQ a slow i.v. infusion of 5 mg kg^{-1} over 2–4 h seems the next logical mode of administration.

The other pharmacokinetic parameters obtained in this study ($t_{½}$, Vd_{ss}, CL_p) did not differ from data from earlier studies in which the drug was given i.v. (Gustafsson *et al.*, 1983) or orally (Walker *et al.*, 1986c). Hence, it can be concluded that, by whatever route the drug is given, its pharmacokinetics are characterised by a long half-life, a very large volume of distribution and a predominantly renal route of excretion via which approximately 10% of the administered drug is excreted in the first 24 h.

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