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Pharmacokinetics of chloroquine in Thais: Plasma and red-cell concentrations following an intravenous infusion to healthy subjects and patients with *Plasmodium vivax* malaria

G. EDWARDS[1,2], S. LOOAREESUWAN[4], ANGELA J. DAVIES[1], Y. WATTANAGOON[4], R. E. PHILLIPS[3,4,5] & D. A. WARRELL[3,4,5]

[1]Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool L69 3BX, [2]Departments of Parasitology and [3]Tropical Medicine and Infectious Diseases, Liverpool School of Tropical Medicine, Liverpool L3 5QA, [4]Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, 10400 Thailand and [5]Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU

1 Chloroquine diphosphate (15 mg base kg^{-1}) was given by constant rate intravenous infusion to two groups of Thai subjects. Eleven were patients with malaria (10 with *Plasmodium vivax* and one case with *Plasmodium malariae*) and 10 were healthy normal volunteers.

2 Plasma and packed red-cell concentrations of chloroquine, electrocardiographic intervals, arterial blood pressure and pulse were measured at frequent intervals.

3 Peak plasma concentrations at the end of the infusion ranged from 979 to 2,900 ng ml^{-1} in the malaria patients. In the group of healthy subjects the range was 550–2,200 ng ml^{-1}. Values for terminal elimination rate constant, (λ_z) plasma clearance (CL), initial volume of distribution (V_1) and volume of distribution at steady state (V_{ss}) were calculated. For the healthy subjects, mean estimates of these parameters were

$$\lambda_z = 0.062 \pm 0.030 \text{ day}^{-1}, \text{ CL} = 597 \pm 238 \text{ ml min}^{-1},$$
$$V_1 = 0.66 \pm 0.71 \text{ l kg}^{-1} \text{ and } V_{ss} = 132 \pm 50 \text{ l kg}^{-1}$$

For the group of malaria patients, the corresponding values were

$$\lambda_z = 0.055 \pm 0.032 \text{ day}^{-1}, \text{ CL} = 535 \pm 246 \text{ ml min}^{-1},$$
$$V_1 = 0.74 \pm 0.75 \text{ l kg}^{-1} \text{ and } V_{ss} = 136 \pm 64 \text{ l kg}^{-1}$$

There was no statistically significant difference in the estimates for any parameter between groups ($P \leq 0.05$).

4 Chloroquine concentrations in packed red blood cells consistently exceeded those in plasma and showed no consistent change with time throughout the period of study in either group. The median value for the red cell to plasma ratio was between 3 and 4 in each group. Peak red-cell concentrations were significantly higher than the equivalent plasma concentration in both groups. In the malaria patients the range of concentration was 1829–11052 ng ml^{-1}. In the healthy volunteers, the range was 2410–4570 ng ml^{-1}. These values

Dr G. Edwards, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3BX

were not statistically significant. There was no significant difference in the area under the packed red-cell concentration *vs* time curve between the malaria patients (151637 ± 85737 ng ml^{-1} h) and healthy volunteers (100053 ± 42536 ng ml^{-1} h), when measured to infinite time.

5 Various subjective side effects were reported in all participants. A small but significant fall from baseline systolic blood pressure 105 ± 6 mmHg was recorded, 2 h into the infusion (99 ± 9 mmHg), but baseline values had been regained by the end of the infusion (101 ± 10 mmHg). There was no significant rise in heart rate. However the *minimum* measured blood pressure and *maximum* recorded pulse in each subject were significantly different from the resting values.

6 Coincident with changes in blood pressure, there was, in both groups, a significant prolongation of the PR interval, QRS interval (88 ± 13 ms to 101 ± 17 ms) and an increase in T wave height (44 ± 13%).

7 These findings suggest that there are no major differences in the pharmacokinetics of chloroquine between the group of patients with vivax malaria studied here and a matched group of healthy volunteers. The cardiovascular effects of the drug are common to both groups, suggesting that the relationships between the pharmacokinetics of chloroquine are governed principally by the properties of the drug rather than the condition of the patient.

Keywords chloroquine pharmacokinetics red-cells malaria toxicity

Introduction

Chloroquine (CQ) is the treatment of choice for malaria caused by *Plasmodium vivax, malariae, ovale* and sensitive strains of *Plasmodium falciparum*. In both healthy adults (Gustafsson *et al.*, 1983) and children with uncomplicated falciparum malaria (Adelusi *et al.*, 1982; Walker *et al.*, 1983) the drug is well absorbed after oral administration and is detectable in the plasma for up to 52 days and in the urine for up to 119 days following oral or intravenous administration of a single dose (Gustafsson *et al.*, 1983). Slow, rate-controlled intravenous infusion is an acceptable mode of administration for CQ in seriously ill patients or where oral therapy is not possible (Looareesuwan *et al.*, 1986; Edwards *et al.*, 1987). Little is known about the disposition of chloroquine in this situation (White, 1985; White *et al.*, 1987). Studies with quinine suggest that changes in clinical condition may have profound effects on drug distribution and hence plasma and red-cell concentrations in patients with malaria (White *et al.*, 1982). The present study aims to compare the pharmacokinetics of CQ, given by constant-rate intravenous infusion to healthy controls and patients with *Plasmodium vivax* malaria.

Methods

Subjects

The study took place at Pra Pokklao Hospital, Chantaburi, Eastern Thailand and a total of twenty-one subjects participated. These numbers were calculated to be sufficient to detect changes in pharmacokinetics between malaria patients and normal subjects of the same order of magnitude as those reported for quinine in subjects with *Plasmodium falciparum* malaria (White *et al.*, 1982). Pregnant women and children less than 15 years old were excluded. These studies were approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

(a) *Volunteer study:* Ten adult volunteers (eight male, two female) aged between 18 and 46 years and weighing between 44 and 66 kg and who gave fully informed consent, were studied.

(b) *Clinical study:* Eleven patients (nine male, two female) aged between 15 and 35 years and weighing between 42 and 60 kg and with a positive blood smear for *P. vivax* (one case with *P. malariae*) and who gave fully informed consent, were studied.

Drug administration

All patients and volunteers were admitted to the intensive care unit and weighed. Subjects lay supine and a Teflon catheter was inserted into a forearm vein and a sample of blood was taken for full blood count, routine biochemical tests, quantitative parasite count and baseline concentrations of plasma chloroquine. Patency of the cannula was maintained with heparinised saline. A second Teflon catheter was inserted into a large peripheral vein in the other arm and chloroquine diphosphate (15 mg base kg^{-1}; Resochin: Bayer, U.K.; 5%; 30 mg base ml^{-1}) was administered over 4 h as an infusion in 0.9% saline. Blood pressure was measured immediately before the infusion and hourly thereafter until it had been completed. Pulse was measured immediately before the infusion and after it had ceased. Standard electrocardiographic intervals were recorded from the mean of five adjacent complexes.

Sampling schedule

Samples of blood were taken at the following times: before infusion, immediately after it had ceased and at the following times post-infusion; 10, 30 and 60 min, 2, 4, 6, 8, 12, and 24 h, daily for 10 days and then for as long as possible (7–8 weeks). Where possible, blood samples were also obtained during the period of the infusion. Haemolysis was avoided by withdrawing blood very slowly through the venous cannula. Blood (5 ml) was drawn into lithium- heparin plastic tubes and then centrifuged immediately at 1,500 *g* for 10 min. Plasma was removed, the buffy coat was discarded and the packed red blood cells retained. All samples were stored at –70°C prior to transport on dry-ice to Liverpool for analysis of chloroquine.

Chloroquine analysis

Plasma concentrations of chloroquine were measured by high performance liquid chromatography with fluorescence detection using a modification of the method of Alvan *et al.* (1982) and reported previously (Looareesuwan *et al.*, 1986). To increase sensitivity at lower concentrations, the excitation wavelength was reduced from 335nm to 247nm. Metabolites of chloroquine, commonly used antimalarials and other drugs administered routinely to the patients did not interfere with the assay. Chloroquine concentrations in packed cells were measured similarly using the following method of extraction. Cells (1.0 ml) were added to a 15 ml capacity glass culture tube. To the cells were added the internal standard, 7-chloro-4-(5-diethylamino-1-methylpentylamino)-quinoline diphosphate, a gift from the Walter Reed Army Institute of Medical Research, Washington D.C., U.S.A. (50μl, 58.5 ng) followed by acetonitrile (2.0 ml). After vortex mixing for 15s, and centrifugation (5 min; 1,500*g*) the supernatant was transferred to a second 15 ml capacity glass culture tube. Ammonia (0.88 sp. gr., 2.0 ml) and n-hexane (5.0 ml) were added and the aqueous phase extracted by mechanical tumbling for 15 min. Aqueous and organic phases were separated following centrifugation (10 min, 500 *g*) and the aqueous phase extracted a second time according to the above procedure. The organic phases were transferred to conical glass centrifuge tubes and evaporated to dryness under a stream of nitrogen at 35°C. The residues were reconstituted in methanol (50μl) and an aliquot injected into the chromatograph. All glassware was treated with dichlorodimethylsilane (5% v/v in toluene) to minimise drug absorption.

Pharmacokinetic analysis

(a) *Plasma*: Plasma chloroquine concentrations in the post-infusion period were analysed by a non-linear least-squares regression program (NONLIN; Metzler *et al.*, 1973). Equations of the general form

$$C(t) = \sum_{i=1}^{n} C_i e^{-\lambda i t}$$

where C is the concentration of chloroquine in the plasma at time = t and C_i and λ_i are the coefficients and exponents respectively of the ith exponential term were fitted to data from each subject. The expression which contained the least number of terms but adequately described the data according to the criteria of Boxenbaum *et al.* (1974) was used for the evaluation of estimates of the following pharmacokinetic parameters after applying a correction to account for the length of the infusion period (Loo & Riegelman, 1970). Terminal elimination rate constant;λ_z. Plasma clearance (CL); Initial volume of distribution (V_1); Volume of distribution at steady state (V_{ss}) (Gibaldi & Perrier, 1982).

A pharmacokinetic analysis was possible with ten of the volunteer subjects and nine of the malaria patients.

b) *Red blood cells*: The ratio of the concentration of chloroquine in packed red-cells to the equivalent plasma concentration was calculated at each time point in malaria patients and

Table 1 Admission values for biochemical, haematological and other measurements. Values are mean ± s.d.

	*Malaria patients (n = 11)	Controls (n = 10)
Age (years)	23.5 ± 7.7	28.2 ± 10.5
Sex (M,F)	9M, 2F	8M, 2F
Height (m)	1.66 ± 0.07	1.60 ± 0.07
Weight (kg)	53.0 ± 7.0	54.2 ± 6.9
Initial temperature (°C)	+38.4 ± 0.8	—
Serum creatinine (mg dl^{-1})	1.02 ± 0.34	1.03 ± 0.17
Blood urea nitrogen (mg dl^{-1})	13.6 ± 6.0	11.5 ± 3.0
Serum albumin (g dl^{-1})	3.9 ± 0.4	4.0 ± 0.4
Serum globulins (g dl^{-1})	3.1 ± 0.3	3.0 ± 0.7
Haematrocrit (%)	35 ± 7	42 ± 3
Haemoglobin (mg l^{-1})	11.8 ± 2.4	14.1 ± 1.2
White blood cells ($mm^{-3} \times 10^{-3}$)	5.2 ± 1.9	6.8 ± 1.8
Parasite count (μl^{-1}) geometric mean and range	74 (5–2013)	—

* 10 *P. vivax*; 1 *P. malariae*
+ range 37.3–40.2°C

controls. A frequency distribution plot was constructed. The area under the red-cell concentration versus time curve was calculated using the linear trapezoidal rule with an extrapolation to infinite time. An analysis of this type was possible in ten malaria patients and eight of the healthy volunteers.

Statistical analysis

Estimates of the pharmacokinetic parameters from the two groups were compared using a two-tailed Student's *t*-test for either paired or unpaired observations as appropriate, accepting $P \leq 0.05$ as significant.

Results

Clinical observations

There were no significant differences between the two groups of subjects in age or weight. All patients made rapid symptomatic recoveries after starting treatment. The mean (± s.d.) fever clearance time was 36.4 ± 17.2h.

Laboratory results

Admission values for biochemical, haematological and other measurements are indicated in Table 1.

Plasma chloroquine concentrations

The inter and intra co-efficients of variation for the analysis of chloroquine in plasma and packed red blood cells were each ≤ 10% and independent of drug concentration. Chloroquine concentrations at the end of the infusion varied between 979 and 2900 ng ml^{-1} in the malaria patients. In the group of healthy volunteers, the range was 550–2200 ng ml^{-1}. The mean values (± s.d.) for the two groups were 1693 ± 593 ng ml^{-1} and 939 ± 472 ng ml^{-1}. These values were significantly different. Chloroquine plasma concentrations declined in a multiexponential fashion in all subjects (Figure 1a and 1b, Figure 2a and b). There were no significant differences in the estimates of λ_z, V_1 or V_{ss} between healthy volunteers and malaria patients (Tables 2 and 3). The apparent decrease in the value for plasma clearance of chloroquine did not achieve statistical significance.

Red-cell chloroquine concentrations

Chloroquine concentrations in packed cells consistently exceeded those in plasma in both healthy volunteers and malaria patients (Figure 1a and 1b, Figure 2a and b) and showed no consistent pattern of change through the period of study in either group (Figure 3a and b). The frequency distribution curves were positively skewed with a median value between 3 and 4 in each group. Peak concentrations were significantly higher than the equivalent plasma concentrations in both groups. In the group of malaria patients, the range of values was 1829 and 11052 ng ml^{-1}. In the group of healthy volunteers, the range was 2410–4570 ng ml^{-1}.

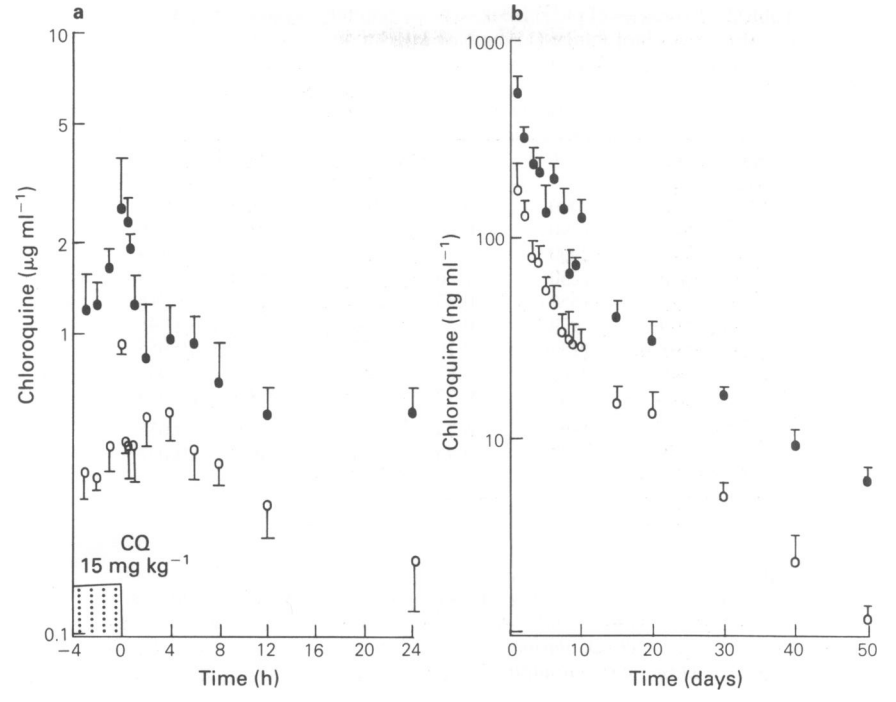

Figure 1 Plasma (○) and packed red-blood cell (●) concentrations of chloroquine (mean ± s.e. mean) (a) in the first 24 h and (b) in the complete study period following a single dose given by intravenous infusion (15 mg kg^{-1} base over 4 h) to eleven patients with *Plasmodium vivax* (n = 10) or *Plasmodium malariae* (n = 1) malaria.

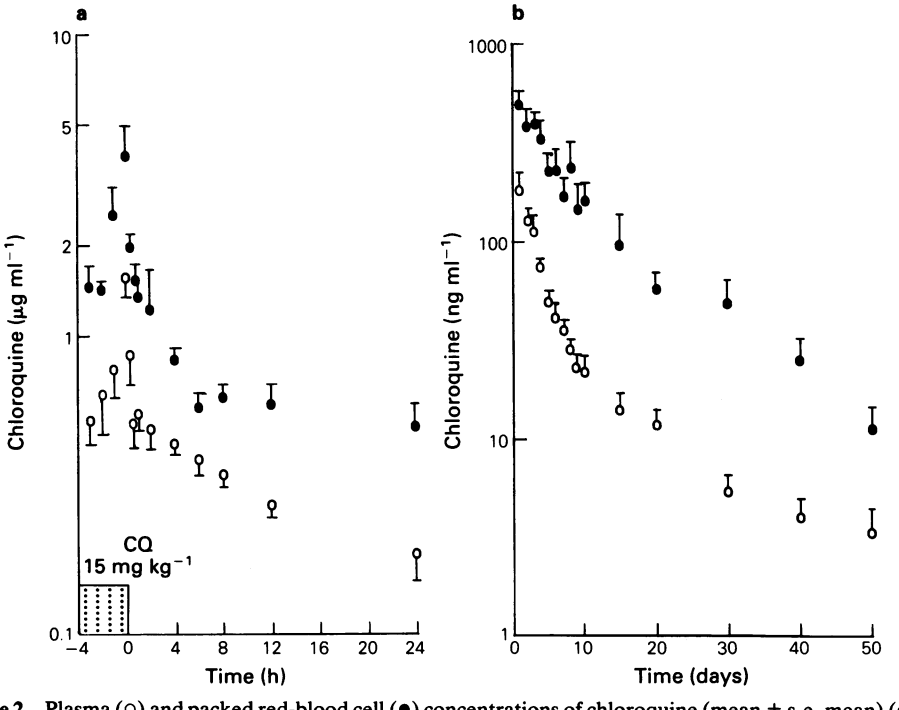

Figure 2 Plasma (○) and packed red-blood cell (●) concentrations of chloroquine (mean ± s.e. mean) (a) in the first 24 h and (b) in the complete study period following intravenous infusion (15 mg base kg^{-1} base over 4 h) to ten healthy Thai volunteers.

Table 2 Estimates of pharmacokinetic parameters obtained following an infusion of chloroquine (15 mg base kg^{-1}) to nine patients with *Plasmodium vivax* malaria.

Patient	Dose (mg)	Peak plasma concentration (ng ml^{-1})	V_1 (l kg^{-1})	V_{ss} (l kg^{-1})	CL (ml min^{-1})	λ_z (day^{-1})
1	840	2000	0.22	179	231	0.017
2	840	1290	0.66	76	467	0.086
3	870	2900	0.38	53	399	0.114
4	630	1250	1.26	75	283	0.069
5	630	1650	0.33	224	362	0.018
6	900	979	0.22	179	663	0.048
7	705	1237	0.10	123	666	0.055
8	885	2103	0.87	213	776	0.034
*9	855	1829	0.72	99	964	0.053
Mean	798	1693	0.74	136	535	0.055
s.d.	111	593	0.75	64	246	0.032

* *Plasmodium malariae*

Table 3 Estimates of pharmacokinetic parameters obtained following an infusion of chloroquine (15 mg base kg^{-1}) to 10 healthy Thai volunteers.

Subject	Dose (mg)	Peak plasma concentration (ng ml^{-1})	V_1 (l kg^{-1})	V_{ss} (l kg^{-1})	CL (ml min^{-1})	λ_z (day^{-1})
1	759	654	2.20	128	789	0.053
2	735	732	0.39	109	803	0.108
3	780	840	0.13	102	651	0.051
4	915	940	0.20	182	753	0.071
5	825	940	0.05	157	413	0.023
6	780	615	1.14	227	664	0.064
7	825	550	0.09	164	891	0.044
8	707	1066	1.09	87	480	0.107
9	660	2200	0.24	95	115	0.024
10	945	850	0.21	67	412	0.075
Mean	793	939	0.66	132	597	0.062
s.d.	88	472	0.71	50	238	0.030

The mean values (± s.d.) were 3752 ± 2589 (n = 11) and 3276 ± 706 (n = 9) respectively. These values were not statistically significant. The areas (mean ± s.d.) under the packed-cell concentration *vs* time curves for malaria patients and healthy volunteers were 151637 ± 85737 ng ml^{-1} h (n = 10) and 100053 ± 42536 ng ml^{-1} h (n = 8) respectively and were not significantly different.

Toxicity

Subjective effects Seven of the patients with malaria and six of the volunteers complained of dizziness. Three patients and seven of the volunteers reported blurred vision during the infusion. All except one patient complained of headache, five patients and one volunteer felt nauseous, one volunteer and one patient vomited and one volunteer complained of itching.

Cardiovascular effects Data from each group were pooled as information from a total of only fourteen subjects was available. There was a small but significant fall in systolic blood pressure, from a resting value of 105 ± 6mm Hg to a value of 99 ± 9 mmHg 2 h after the infusion. Systolic blood pressure had regained pre-infusion values by the time the infusion was completed (101 ± 10 mmHg; not significantly different from the resting value). There was no significant change in measured pulse rates when baseline values (77 ± 11 beats min^{-1}) and those at the end of the infusion (82 ± 10 beats min^{-1}) were

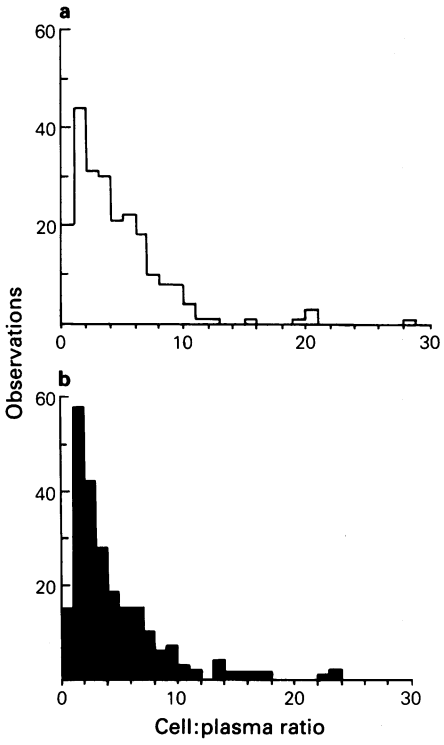

Figure 3 Number of observations of ratios between chloroquine concentrations in erythrocytes (packed red-blood cells) and plasma after administration of chloroquine as an intravenous infusion (15 mg kg^{-1} base over 4 h) (a) 224 observations in 10 healthy volunteers and (b) 227 observations in 11 malaria patients.

compared. When the *minimum* value for systolic blood pressure obtained during the infusion was compared with the baseline value for each patient using the paired *t*-test the differences were highly significant ($P \leq 0.0001$). Likewise, if the maximum pulse measurement was compared with the resting value, a highly significant increase ($P \leq 0.01$) was observed.

Electrocardiographic effects

There was a small but significant increase (9%) in PR interval when the value at the end of the infusion, 173 ± 24 ms was compared with the baseline value (158 ± 25 ms). The mean baseline QRS interval (88 ± 13 ms) increased to a mean value at the end of the infusion of 101 ± 17 ms. Similarly the mean baseline QTC interval (409 ± 15 ms) increased to a mean value at the end of the infusion of 477 ± 26 ms. These increases were statistically significant. The T wave height measured at the end of the infusion was 1.58 ± 0.29 mm compared with a baseline value of 2.71 ± 0.72 mm. This represented a mean, statistically significant, reduction of 44 ± 13%. In all comparisons, $n = 12$.

Discussion

For decades chloroquine has been the mainstay of treatment for malaria throughout the world. It remains the most widely used antimalarial agent although there is considerable concern surrounding its safety when given parenterally (WHO, 1984). Preliminary studies in volunteers (Gustafsson *et al.*, 1983; Looareesuwan *et al.*, 1986) showed that intravenous injection of chloroquine was potentially dangerous because of transient but very high, plasma chloroquine concentrations. It seemed likely that slow intravenous infusion of chloroquine would be safer. Until recently, the acute pharmacokinetics of intravenous chloroquine had not been investigated (White, 1985). Before rational and safe regimens for the use of intravenous chloroquine

could be devised it was essential to know the pharmacokinetics of the drug when given by slow intravenous infusion to patients with malaria. Studies had shown that malaria altered the acute pharmacokinetics of quinine so tending to increase drug concentrations even when slow intravenous infusion was used (White *et al.*, 1982). If disease also altered the handling of chloroquine, regimens might have to be altered to take this into account. Intramuscular injection of chloroquine to patients with malaria, although widely practised, was considered by some to be dangerous whereas slow intravenous infusion of chloroquine has generally been thought safe. Our preliminary studies in patients with falciparum malaria confirmed this but the plasma concentration profiles obtained were variable (Edwards *et al.*, 1987). Recently White *et al.* (1987) showed that slow infusion of chloroquine in Zambian patients with malaria produced therapeutic drug concentrations without serious toxicity. However, it was not clear from this work whether malaria itself altered the pharmacokinetics of the drug.

The present study shows that acute *Plasmodium vivax* or *Plasmodium malariae* malaria does not alter appreciably the plasma pharmacokinetics even when the drug is given in a relatively high therapeutic dose. Drug concentrations at the end of the 4 h infusion were above the level where toxicity might be expected and most subjects complained of some side effects. At the end of the infusion chloroquine concentrations initially declined rapidly but the drug remained detectable in plasma and packed red cells for more than 50 days. This slower decline, which reflects the large volume of distribution of chloroquine at steady state and its long elimination half-life, was not different in malaria patients as compared with controls. These findings are relevant to the optimal use of the drug in man.

When chloroquine in a dose of 3 mg of base per kg body weight was injected intravenously over 10 min to healthy volunteers, plasma drug concentrations of up to 6649 ng ml^{-1} were achieved. Although there was no serious toxicity, all patients noticed side effects and there was a significant fall in blood pressure (Looareesuwan *et al.*, 1986). The apparent initial volume of distribution (V_1) derived from data obtained in that study was 0.184 ± 0.145 1 kg^{-1} compared with a steady state value (V_{ss}) obtained in our subjects of approximately 134 1 kg^{-1}. This discrepancy explains the unsatisfactory plasma concentration profiles usually obtained with intravenous use in that rate of administration rather than dose size largely determines plasma concentration. Although intravenous infusion is relatively safe, (Edwards *et al.*, 1987; White *et al.*, 1987) our work and that of others (White *et al.*, 1987) shows that distribution is incomplete after 4 h. Longer infusion times or even continuous infusion should produce a more satisfactory profile but these would be impracticable in many hospitals in the tropics.

Acute *P. vivax* malaria did not appreciably alter the plasma pharmacokinetics of chloroquine or the red cell: plasma ratio but other studies suggest that pregnancy and the more severe grades of falciparum malaria could conceivably alter chloroquine handling (White *et al.*, 1982; Phillips *et al.*, 1986) to a degree where regimens should be modified. Doses as high as that used in the present study are unnecessary; 5 mg of base kg^{-1} infused so that plasma concentrations do not exceed 500 ng ml^{-1} should be safe and effective (White *et al.*, 1987). Infusion times for this dose (5 mg kg^{-1}) should be 6-8 h although this regimen should be evaluated in patients of all ages and grades of disease severity before it is accepted for routine use.

The dangers of intravenous chloroquine have been exaggerated. There is a strong suggestion in the older literature that chloroquine is superior to quinine in severe falciparum malaria (Wilson & Edeson, 1958; Scott, 1950). It should not be abandoned where *P. falciparum* remains fully sensitive to this drug and may still achieve clinical cure in areas of RI and RII resistance.

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References

Adelusi, S. A., Dawodu, A. H. & Salako, L. A. (1982). Kinetics of the uptake and elimination of chloroquine in children with malaria. *Br. J. clin. Pharmac.*, **14**, 483–487.

Alvan, G., Ekman, L. & Lindström, B. (1982). Determination of chloroquine and its desethyl metabolite in plasma, red blood cells and urine by liquid chromatography. *J. Chromatogr.*, **229**, 241–247.

Boxenbaum, H. G., Riegelman, S. & Elashoff, R. M.

(1974). Statistical estimations in pharmacokinetics. *J. Pharmacokin Biopharm.*, **2**, 123–148.

Edwards, G., Davies, A. J., Phillips, R. E., Looareesuwan, S., Karbwang, J., White, N. J. & Warrell, D. A. (1987). Plasma concentrations and toxicity of chloroquine after slow intravenous infusion in patients with falciparum malaria. *Ann. Trop. Med. Parasitol.*, **81**, 79–84.

Gibaldi, M. & Perrier, D. G. (1982). *Pharmacokinetics*, 2nd edition. New York and Basel: Marcel Dekker.

Gustafsson, L. L., Walker, O., Alván, G., Beerman, B. Estevez, F., Gleisner, L., Lindström, B. & Sjöqvist, F. (1983). Disposition of chloroquine in man after single intravenous and oral doses. *Br. J. clin. Pharmac.*, **15**, 471–479.

Loo, J. C. K. & Riegelman, S. (1970). Assessment of pharmacokinetic constants from post infusion blood curves obtained after i.v. infusion. *J. pharm. Sci.*, **59**, 53–55.

Looareesuwan, S., White, N. J., Chanthavanich, P., Edwards, G., Nicholl, D. D., Bunch, C. & Warrell, D. A. (1986). Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br. J. clin. Pharmac.*, **22**, 31–36.

Metzler, C. M., Elfring, G. L. & McEwen, A. J. (1973). *A users manual for NONLIN* Kalamazoo, Michigan, U.S.A: Upjohn Co.

Phillips, R. E., Looareesuwan, S., White, N. J., Silamut, K., Kietinun, S. & Warrell, D. A. (1986). Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. *Br. J. clin. Pharmac.*, **21**, 677–683.

Scott, V. (1950). Single intravenous injection of chloroquine in the treatment of falciparum malaria: toxic and immediate therapeutic effects in 110 cases. *Am. J. trop. Med. Hyg.*, **30**, 503–509.

Walker, O., Dawodu, A. H., Adeyokunnu, A. A., Salako, L. A. & Alvan, G. (1983). Plasma chloroquine and desethylchloroquine concentrations in children during and after chloroquine treatment for malaria. *Br. J. clin. Pharmac.*, **16**, 701–705.

White, N. J. (1985). Clinical pharmacokinetics of antimalarial drugs. *Clin. Pharmacokin.*, **10**, 187–215.

White, N. J., Looareesuwan, S., Warrell, D. A., Warrell, M. J., Bunnag, D. & Harinasuta, T. (1982). Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am. J. Med.*, **73**, 564–571.

White, N. J., Watt, G., Bergqvist, Y. & Njelesani, E. K. (1987). Parenteral chloroquine for treating falciparum malaria. *J. infect. Dis.*, **155**, 192–201.

Wilson, T. & Edeson, J. F. B. (1958). Studies on the chemotherapy of malaria. VII The treatment of acute malaria in Malaya. *Med. J. Malaya*, **12**, 477–499.

World Health Organisation (1984). *Advances in malaria chemotherapy*. Technical Report Series 711.

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