Pharmacokinetics of intravenous amodiaquine

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1   Amodiaquine hydrochloride (3 mg base kg^{-1}) was given by constant rate intravenous injection over 10 min to seven healthy adult male volunteers, and by constant rate infusion (10 mg base kg^{-1}) over 4 h to 10 adult patients admitted to hospital with falciparum malaria.

2   After intravenous injection in volunteers there was considerable variation in plasma concentration profiles between subjects; peak plasma concentrations ranged between 65 and 1921 ng ml^{-1}. A biexponential equation was fitted to the plasma concentration time data and the following estimated pharmacokinetic parameters (geometric mean; range) were derived; λ_1 = 24.4 (7.6–95.0) h^{-1}, λ_2 = 0.33 (0.12–0.79) h^{-1}, V_1:1.1 (0.3–3.6) l kg^{-1}, V_{ss}: 17.4 (2.3–95.9) l kg^{-1} and systemic clearance 13.0 (4.7–56.6) l kg^{-1} h^{-1}.

3   After intravenous infusion there was also considerable variability between patients with post-infusion plasma concentrations ranging between 82 and 836 ng ml^{-1}. The plasma concentration-time profiles were biphasic with the following estimated pharmacokinetic parameters (geometric mean; range) α = 1.87 (0.60–8.52) h^{-1}, β = 0.069 (0.021–0.265) h^{-1}, V_1: 4.6 (0.5–29.3) l kg^{-1}, V_{ss}: 38.3 (3.7–127.9) l kg^{-1} and systemic clearance CL (1.6–17.3) l kg^{-1} h^{-1}.

4   There was no measurable long terminal elimination phase, and the principal metabolite desethyl amodiaquine was not detected in the plasma samples.

5   There was no serious toxicity in either group. During intravenous injection there was a significant fall in systolic blood pressure in four subjects (mean fall 16 mm Hg) but there was no significant change in heart rate. There was a slight increase in the electrocardiograph QRS interval in six subjects (mean increase 6.5 ms) but no other electrocardiographic changes were noted.

6   Modelled plasma drug concentration profiles based on the derived pharmacokinetic parameters in the patients with falciparum malaria accurately predicted those measured after subsequent doses. These data were therefore used to model alternative intravenous treatment regimens designed to reduce the large peak to trough fluctuations in plasma drug concentrations and therefore limit toxicity.

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7   Although there are important differences between the pharmacokinetic properties of amodiaquine and the related 4-aminoquinoline antimalarial chloroquine, both drugs are distributed from a relatively small central compartment following intravenous administration. Intravenous amodiaquine should not be administered by intravenous injection, but by slow rate-controlled infusion.

Keywords   amodiaquine   malaria   pharmacokinetics

Introduction

The 4-aminoquinoline amodiaquine has generally been considered equal in antimalarial activity to the more widely used chloroquine. However, recent studies have suggested that amodiaquine is more effective than chloroquine for the treatment of drug resistant falciparum malaria (Watkins *et al.*, 1984; Looareesuwan *et al.*, 1985). For nearly forty years both drugs have been used extensively although very little was known about their disposition in man. Dose recommendations are still largely empirical. Although parenteral amodiaquine was used in the early 1950s, a similar compound (amopyroquine) superseded amodiaquine for intramuscular use and this preparation is the form currently commercially available. However, recent studies in Thailand showed that intravenous amodiaquine was effective and well tolerated in the treatment of chloroquine resistant falciparum malaria (Looareesuwan *et al.*, 1985). There is no pharmacokinetic information on either parenteral amodiaquine or amopyroquine.

The antimalarial activity of amodiaquine is greater than that of its principal biologically active metabolite desethylamodiaquine (Churchill *et al.*, 1985; Childs *et al.*, 1987). As very little of the parent compound escapes first pass metabolism after oral administration (Churchill *et al.*, 1985; Pussard *et al.*, 1985; Salako & Idowu, 1985; Winstanley *et al.*, 1986), parenteral amodiaquine may have particular advantages as an antimalarial. We report the plasma pharmacokinetics of amodiaquine in man following intravenous administration to both normal volunteers and patients during treatment of chloroquine-resistant *P. falciparum* malaria.

Methods

Drug formulation

Amodiaquine dihydrochloride was obtained as pure salt from the manufacturer (Parke-Davis). This was dissolved and dispensed in 10 ml glass ampoules containing 300 mg base by the Pharmacy Department, John Radcliffe Hospital, Oxford. These were stored in darkness until used.
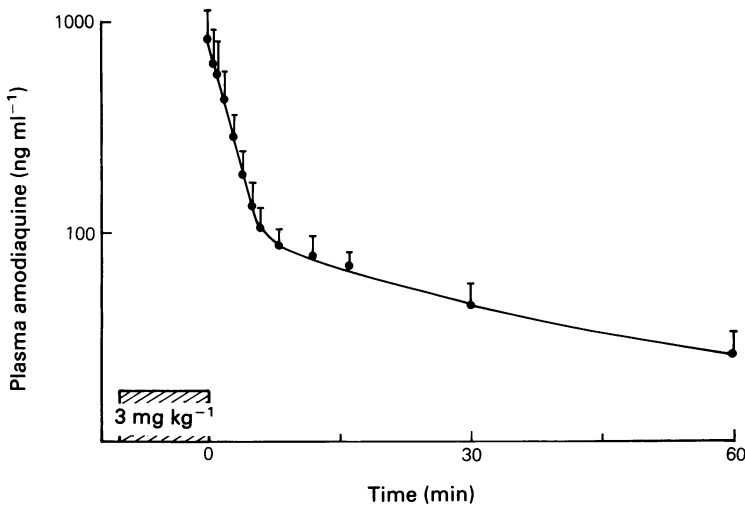
Volunteer study: Slow intravenous injection

Seven healthy adult male Thai subjects aged between 21 and 35 years and weighing between 41 and 59 kg gave fully informed consent to the study. Subjects lay supine and a Teflon catheter was inserted into a forearm vein and kept patent with heparinised saline while an infusion of 0.9% saline was given intravenously into the other arm. Baseline pulse and blood pressure measurements were recorded at 2 min intervals for 10 min and a baseline electrocardiographic recording was made. Amodiaquine dihydrochloride 3 mg kg^{-1} base was then injected at constant rate over 10 min into the free flowing infusion. Pulse and blood pressure recordings were then made at 2 min intervals for 20 min and ECG rhythm strips were obtained at a paper speed of 50 mm s^{-1} at 3 min intervals during and after the injection. Blood samples (5 ml) were drawn through the indwelling cannula after removal of the dead space, then at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 30 min then 1, 2, 5, 8, 12, 24, 36, 48, and 168 h after the injection was completed. The blood was taken into lithium heparin containers and immediately centrifuged (1200 *g* for 10 min). Separated plasma was stored at −20 °C until it was analysed.

Clinical study: Intravenous infusion

Patients admitted to Pra Pokklao hospital, Chantaburi, Eastern Thailand, who had asexual forms of *P. falciparum* in a peripheral blood smear, denied taking previous antimalarials, and who gave informed consent were included in the study. Those with severe or complicated malaria, a positive urine test for aminoquinolines (Wilson-Edeson test) or sulphonamides (lignin test), children (under 15 years), and pregnant women were excluded. Clinical and laboratory details of these patients have been published elsewhere (Looareesuwan *et al.*, 1985).

Figure 1 Mean (s.e. mean) plasma amodiaquine concentrations following an intravenous injection of 3 mg base kg^{-1} over 10 min to seven healthy adult male volunteers.

Amodiaquine dihydrochloride (10 mg base kg^{-1}) was diluted in 500 ml of normal (0.9%) saline in glass bottles and infused at a constant rate over 4 h. Subsequent infusions (5 mg base kg^{-1} over 4 h) were given at 24 h intervals for 3 days. Pulse and blood pressure were measured hourly during the initial infusion and then 4 hourly. Temperature was measured 4 hourly. Blood samples were drawn through an indwelling venous cannula, separated and stored as described above. Samples were taken before, then 0, 10 and 30 min, then 2, 6, 12 and 20 h after the end of the infusion. Samples were taken before and after the end of the subsequent three infusions, then daily until discharge, and finally on days 15 and 32.

These studies were approved by the Ethics committee of the Faculty of Tropical Medicine, Mahidol University.

Assay methods

Amodiaquine concentrations in plasma were measured by the method of Mihaly *et al.* (1985). Chloroquine does not interfere with the assay of amodiaquine in this method. A slight modification of the method was used for the analysis of urine samples. This is described elsewhere (Winstanley *et al.*, 1986). The limit of detection for amodiaquine and desethylamodiaquine was 5 ng ml^{-1}.

Pharmacokinetic analysis

The plasma concentration profiles obtained after intravenous injection in volunteers were analysed

by a weighted non-linear least squares regression programme, NONLIN (Metzler, 1969) run on a SAGE IV microcomputer under the version i.v. 13 P-system. Equations fitted to the data for each patient were of the general form.

$$C = \sum_{i=1}^{n} \frac{\lambda_i C_i e^{-\lambda_i t}}{1-e^{-\lambda_i \tau}}$$

where C_i = zero time intercept, λ_i = first order rate constant, t = time, τ = duration of infusion, C = plasma concentration at time t, n = number of exponentials. Using initial parameters obtained from the automated curve stripping programme N. AUTOAN (Sedman & Wagner, 1977) two, three and four exponential functions were fitted to each set of data. Standard pharmacokinetic parameters were then generated.

A biexponential function was fitted to the intravenous infusion plasma concentration profiles after weighting, using a standard curve fitting programme (Yamaoka *et al.*, 1979) with Simplex analysis run on an IBM PC computer. The pharmacokinetic parameters derived from these data after correction for infusion time were then used to model concentration profiles that would be expected to follow other infusion regimens. These were modelled graphically using a microprocessor adapted programme (Koup & Benjamin, 1983).

Statistical analysis

The pharmacokinetic parameters from the two groups were compared using a two tailed Student's *t*-test after logarithmic transformation.

Results

(a) Slow intravenous injection in healthy volunteers

Peak plasma amodiaquine concentrations at the end of the 10 min injection varied between 65 and 1921 (geometric mean 415 ng ml^{-1}). Desethyl-amodiaquine was not detected at this point. In some patients plasma amodiaquine concentrations fluctuated within the first 90 s after completion of the injection suggesting incomplete equilibration within the circulation. There was then a rapid fall in plasma concentration which was adequately described by a biexponential function (r^2 for the fits > 0.933). In one patient an improved fit was obtained with a triexponential function, but in the remainder the addition of exponential terms conferred little or no advantage. The pharmacokinetic parameters derived from the biexponential functions are given in Table 1. There was considerable variation between individuals and logarithmic transformation was used to normalise the group data. The mean coefficient of variation for the individual estimates of the first order rate constants λ_1 and λ_2 were 20.5 and 58.5%, respectively, and for the intercept terms C_1 and C_2 were 26.9 and 32.1%, respectively. The geometric mean of the estimated distribution phase half times ($t_{\frac{1}{2}, \alpha}$) was 1.7 (range 0.4–5.5) min and the geometric mean of the estimated elimination phase half times ($t_{\frac{1}{2},z}$) was 2.1 (range 0.5–5.7) h. The apparent volume of the central compartment (V_1) comprised 8.4 ± 7.1% (mean ± s.d.) of the estimated total apparent volume of distribution (V_{ss}).
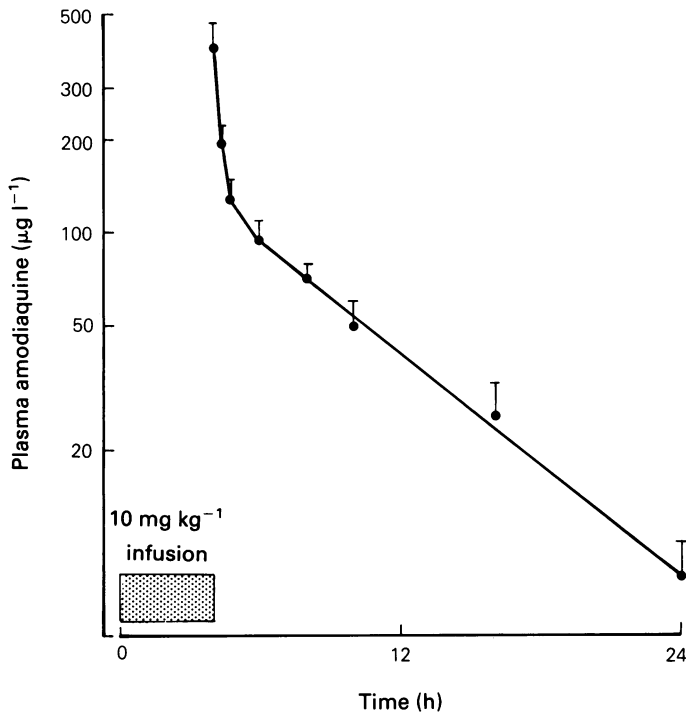
(b) Intravenous infusions in falciparum malaria

Sixteen patients were treated with intravenous amodiaquine. Clinical details of these have been published elsewhere (Looareesuwan et al., 1985).

Concurrent administration of antiemetic (metoclopramide) and antipyretic agents (dipyrone, paracetamol) resulted in a series of co-eluted peaks on some patients' chromatograms which precluded amodiaquine measurement under the assay conditions employed. Pharmacokinetic analysis was possible in data from 10 patients. As in the volunteer study, there was considerable variation between individuals in the plasma drug concentration versus time profiles with peak plasma concentrations of amodiaquine varying between 82 and 820 ng ml^{-1} (geometric mean 322 ng ml^{-1}). Desethyl-amodiaquine was not detected in these plasma samples. The mean plasma amodiaquine concentration – time profile after the initial infusion is shown in Figure 2 and the derived pharmacokinetic parameters in Table 2. There was a significant difference between the estimated systemic clearance (geometric mean 5.5, range 1.6–17.3 l kg^{-1} h^{-1}) in this group and that in the previous volunteer study (geometric mean 13.0, range 4.7 to 56.6 l kg^{-1} h^{-1}), $P = 0.04$. After the end of the slow intravenous infusion there was a rapid initial decline in plasma concentrations with an estimated distribution phase half time ($t_{\frac{1}{2},\alpha}$) of 22 (geometric mean: range 5–126) min and a terminal elimination half time ($t_{\frac{1}{2},z}$) of 10.1 (2.6–33) h. There was no evidence of a long terminal elimination phase as seen with chloroquine. The plasma concentrations measured before and after subsequent doses of amodiaquine were then compared in each case with those predicted from the kinetic parameters derived from the initial infusion data. As can be seen from Figure 3 there was good overall agreement between observed and predicted values. These parameters were therefore used to model a series of alternative profiles predicted to follow other regimens and designed to reduce differences between peak and trough concentrations (Figure 4).

Table 1 Amodiaquine pharmacokinetics: intravenous injection in healthy volunteers

Patient	Peak plasma concentration (ng ml^{-1})	λ_1 (h^{-1})	λ_2 (h^{-1})	V_1 (l kg^{-1})	V_{ss} (l kg^{-1})	CL (l kg^{-1} h^{-1})
A	106	22.1	0.211	3.6	59.8	15.5
B	687	35.3	0.203	0.3	12.7	4.7
C	463	13.4	0.122	2.7	95.9	11.0
D	1,929	26.4	0.789	0.3	2.3	6.8
E	397	95.0	0.567	0.9	26.5	19.9
F	65	7.6	0.139	3.1	34.6	56.6
Geometric mean	415	24.4	0.33	1.1	17.4	13.0

Figure 2 Mean (s.e. mean) plasma amodiaquine concentrations following the initial 4 h intravenous infusion of amodiaquine (10 mg base kg^{-1}) given to ten adult patients with acute falciparum malaria.

Table 2 Amodiaquine pharmacokinetics: intravenous infusion in falciparum malaria

| Patient	Peak plasma concentration (ng ml^{-1})	λ_1 (h^{-1})	λ_2 (h^{-1})	V_1 (l kg^{-1})	V_{ss} (l kg^{-1})	CL (l kg^{-1} h^{-1})
1	204	2.28	0.108	7.0	39.3	9.9
2	82	1.26	0.077	27.9	127.8	17.3
3	559	1.38	0.021	3.9	55.2	1.6
4	268	0.60	0.064	29.3	76.8	7.0
5	334	0.33	0.082	3.0	28.6	6.5
6	405	7.32	0.099	1.2	22.1	3.8
7	836	7.92	0.082	0.5	10.0	2.7
8	286	1.92	0.041	9.5	108.0	11.7
9	810	8.52	0.265	0.5	3.7	2.7
10	183	0.72	0.029	20.8	127.9	5.8
Geometric mean	322	1.87	0.069	4.6	38.3	5.5

Urinary elimination

Urine collections were made in four patients over the 3 days of treatment. Urinary elimination was relatively small comprising less than 2% of the administered dose in each 24 h period. The ratio of desethylamodiaquine to parent compound varied between 0.27 and 14.1 (mean 3.6).
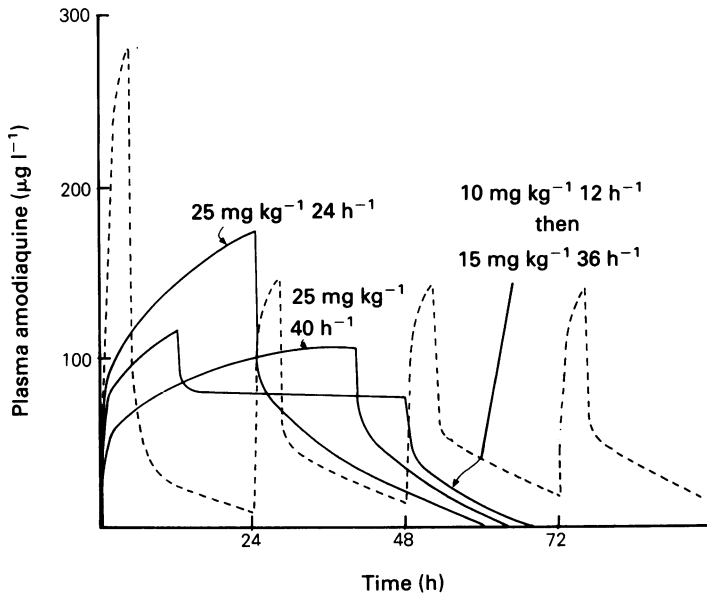
Toxicity

(a) *Intravenous injection* Two patients felt dizzy during the study. In both cases this began as the
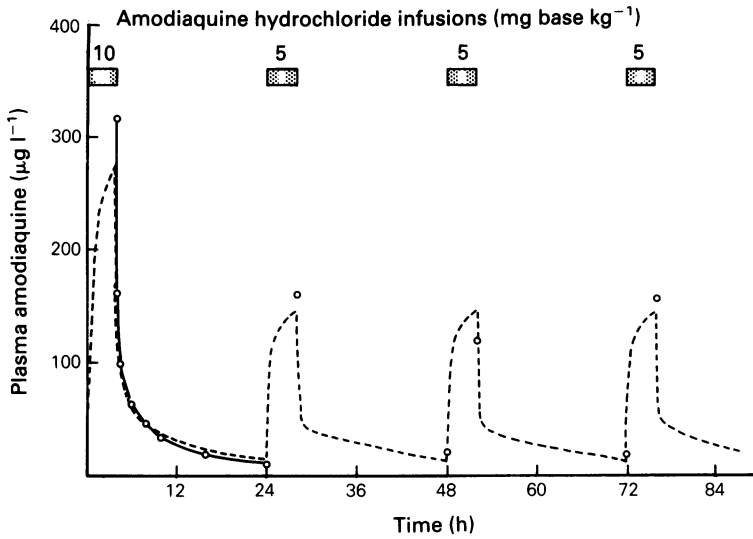
Figure 3 Observed mean plasma amodiaquine concentration profile in falciparum malaria (○), compared with the profile predicted from the admission pharmacokinetic parameters (-----) which were derived from the initial slope (○———○).

Figure 4 The amodiaquine plasma concentration profile from Figure 3 (-----) is compared with profiles predicted to follow other intravenous regimens.

injection ended and persisted for 10 and 8 min. In the first patient there was a significant fall in blood pressure from a mean baseline value of 106/71 to 91/58 mm Hg at the end of the injection . There was no change in pulse rate or rate corrected QT interval on the electrocardiogram but there was a

30 ms prolongation of the QRS interval, maximal at 2 min after the end of the injection. These abnormalities disappeared rapidly over 5 min. Peak plasma amodiaquine concentration was 106 ng ml^{-1}. In the second patient there was a slight (10 mm Hg) fall in systolic blood pressure but no

change in diastolic pressure or pulse rate, and a 10 ms prolongation of the QRS interval. Peak plasma amodiaquine was 687 ng ml^{-1}. Overall four patients had a fall in systolic blood pressure (mean fall 16 mmHg) but in only the patient mentioned was a diastolic fall recorded. There was no significant overall change in heart rate, or electrocardiographic PR or QTc intervals but in six patients there was a small increase in the QRS duration (overall 86.3 ± 7.9 ms increasing to 93.8 ± 11.9 ms).

(b) *Slow intravenous infusion*   Information on therapeutic efficacy and toxicity of amodiaquine in falciparum malaria has been presented already (Looareesuwan *et al.*, 1985). Essentially there were no adverse cardiovascular effects. Two patients vomited but this could not be clearly attributed to the timing of drug administration or the plasma concentration of amodiaquine.

Discussion

The pharmacokinetic properties of amodiaquine differ from those of chloroquine. Amodiaquine is cleared rapidly and apparently completely from the plasma after intravenous administration, ($t_{\frac{1}{2},z}$) after intravenous injection was between 30 min and 5.7 h, whereas chloroquine exhibits complex pharmacokinetic properties with a multiphasic decline in plasma concentrations and an extremely long terminal elimination phase (Gustafsson *et al.*, 1983; Looareesuwan *et al.*, 1986). Recent estimates of the terminal elimination half time of chloroquine vary between 1 and 2 months (Frisk-Holmberg *et al.*, 1984) with a total apparent volume of distribution (V_{ss}) for plasma chloroquine of between 100 and 1000 l kg^{-1}, whereas in this study V_{ss} for plasma amodiaquine was estimated as being between 2.3 and 59.8 (geometric mean 17.4) l kg^{-1} in healthy subjects, 4 and 128 (geometric mean 38.3) l kg^{-1} in malaria. It is possible that very low plasma drug concentrations (i.e. below the assay's level of detection; < 5 ng ml^{-1}) persist for long periods in plasma but this would not significantly alter predictions about treatment regimens based on the present data. When amodiaquine is given by mouth relatively little of the parent compound is present in the blood (Churchill *et al.*, 1985; Pussard *et al.*, 1985; Salako & Idowu, 1985; Winstanley *et al.*, 1986). However, orally administered amodiaquine is undoubtedly an effective antimalarial. Churchill *et al.* (1985) have identified monodesethylamodiaquine as the principal biologically active metabolite after oral administration and this appears to be eliminated slowly

(Pussard *et al.*, 1985). These observations suggest that hepatic biotransformation to desethylamodiaquine is the predominant route of amodiaquine clearance with such a considerable first pass effect that very little orally administered amodiaquine escapes untransformed into the systemic circulation (Winstanley *et al.*, 1985). This is also the principal metabolic pathway for chloroquine, but it must be considerably less active as the bioavailability of oral chloroquine is approximately 85 per cent (Gustafsson *et al.*, 1983). Furthermore, over half of the chloroquine taken appears unchanged in the urine whereas urinary concentrations of unchanged amodiaquine are low; less than 2% of the administered dose per day.

Having emphasized the differences in pharmacokinetic properties between chloroquine and amodiaquine, it is important to note the similarities in immediate disposition after intravenous administration as these are relevant to toxicity. Both drugs are distributed from a relatively small central compartment at similar rates (rate: constants: amodiaquine 0.41 min^{-1}, chloroquine 0.65 min^{-1}), although the apparent volume of the central compartment for chloroquine (approximately 0.18 l kg^{-1}; Looareesuwan *et al.*, 1986) is some six times smaller than that estimated for amodiaquine (1.1 l kg^{-1}) in healthy subjects. Immediately following intravenous injection there are transiently high plasma concentrations of both drugs. The profile of plasma amodiaquine concentrations following intravenous infusion in falciparum malaria is also similar to that observed after intravenous chloroquine (White *et al.*, in press). A significant distribution phase is evident even with a four hour infusion. Despite considerable variation between patients the individually derived amodiaquine pharmacokinetic parameters accurately predicted subsequent pre- and post- dose plasma drug concentrations. This justified their use in modelling alternative and possibly better tolerated regimens. Clearly slower rates of infusion will give a smoother plasma drug concentration profile and would be preferable if high concentrations were responsible for adverse effects.

The distribution phase half times observed after intravenous injection to healthy volunteers (geometric mean 1.7; range 0.4–5.5 min) were significantly faster than those observed after intravenous infusion to patients with malaria (geometric mean 22.2; range 5–126 min). In addition the apparent volume of the central compartment (1.1; range 0.3–3.6 l kg^{-1}) was one quarter of that estimated after the infusion (4.6; range 0.5–29.3 l kg^{-1}). These observations suggest that there is probably an additional distri-

bution phase in the malaria patients obscured by the slower rate of infusion and therefore that conclusions should not be based in these comparisons. It is possible that with more data points and a larger initial injection to provide higher plasma concentrations in the terminal elimination phase, a triphasic elimination profile would have been more prominent in the volunteers but it was considered unsafe to give a larger dose by intravenous injection. The importance of the distribution phase has become apparent in studies with the other quinoline antimalarials, quinine (White *et al.*, 1983), and chloroquine (Looareesuwan *et al.*, 1986) as transient and reversible, but potentially dangerous, cardiovascular effects occur synchronously with the temporarily high plasma concentrations that follow intravenous injection.

Systemic clearance values in falciparum malaria (5.5; range 1.6–17.3 $l kg^{-1} h^{-1}$) were significantly lower than those estimated in healthy volunteers (13.0; range 4.7–56.6 $l kg^{-1} h^{-1}$, $P = 0.04$). As the predominant route of elimination is hepatic biotransformation this difference suggests an impairment of hepatic metabolising capacity or a reduction in liver blood flow in acute malaria. The clearance of other quinoline antimalarials is reduced in malaria (White, 1985), with the degree of impairment related to the severity of the infection. However, because of the wide variation in amodiaquine pharmacokinetic parameters between individuals more information will be necessary to provide conclusive information on this point.

Despite the relatively high post-infusion plasma drug concentrations slow intravenous infusion of amodiaquine was well tolerated. No local or systemic toxicity other than nausea and occasional vomiting was observed in the patients with falciparum malaria despite relatively high plasma concentrations. Intravenous injection of a small dose was associated with a fall in systolic blood pressure in four patients and a subjective sensation of dizziness in two patients. There was no significant change in pulse rate. There was also slight prolongation of the electrocardiographic QRS interval in four of the seven volunteers but no change in QTc interval. In earlier studies with intravenous amodiaquine it was also observed that following intravenous injection there was a 'small fall in blood pressure, not more than 10 at 15 mmHg continuing no longer than

20 to 30 min' (Payne *et al.*, 1951). Although the authors of that study concluded that amodiaquine did not produce toxic effects when administered intravenously, the hypotensive potential should not be underestimated. A similar pattern of transient hypotension following slow intravenous injection of the same dose of chloroquine (3 mg base kg^{-1} over 10 min) has recently been observed (Looareesuwan *et al.*, 1986). After intravenous chloroquine the fall in blood pressure was greater and peak plasma concentrations were higher (748–6649; mean 2913 ng ml^{-1}) than in the present study with the same dose of amodiaquine. In both studies hypotension was synchronous with the early distribution phase when plasma concentrations were transiently high. The hypotensive potential of chloroquine is probably greater than that of amodiaquine because of its relatively smaller central distribution volume but potentially lethal hypotension could result from rapid intravenous injection of either drug. Cardiovascular toxicity is prominent in animals given high doses of intravenous amodiaquine (Bertagna, 1951). It has been argued that transiently toxic chloroquine concentrations resulting from rapid absorption and inadequate distribution may occur in some children with malaria given parenteral chloroquine (White *et al.*, 1987). This may explain the occasional reports of sudden death. Similar caution should be applied to the rate at which parenteral amodiaquine is administered.

The modelled profiles derived from this study suggest that parenteral amodiaquine should be given by constant rate intravenous infusion and predict that administration of 5 mg base kg^{-1} every 8 h (i.e. 25 mg kg^{-1} total dose infused over 40 h) would be safe and effective. It remains to be seen whether short term treatment of acute malaria with intravenous amodiaquine carries the same risks of neutropaenia (Hatton *et al.*, 1986) as does use of oral amodiaquine as an antimalarial prophylactic.

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