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Bioavailability of hydroxychloroquine tablets in healthy volunteers

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1 Five healthy volunteers received, in a randomised crossover design study, a 155 mg oral tablet and an intravenous infusion of 155 mg racemic hydroxychloroquine (200 mg hydroxychloroquine sulphate) to assess the bioavailability of the commercially available tablet (Plaquenil, Winthrop Laboratories, Australia).

2 The terminal elimination half-life of hydroxychloroquine is more than 40 days, thus blood and urine samples were collected for 5 months following each dose to characterise adequately the terminal elimination phase and obtain accurate estimates of the areas under the concentration-time curves.

3 The mean (± s.d.) fraction of the oral dose absorbed, estimated from the blood and urine data, was 0.74 (±0.13). A wide range of estimates of the fraction of the oral dose absorbed was calculated from the plasma data (0.41 − 1.53), reflecting the difficulties of accurate measurement of hydroxychloroquine in plasma.

4 A period of 6 months is required to achieve 96% of steady-state levels of hydroxychloroquine with the usual once daily, oral dosage regimen. Pharmacokinetic factors may thus be partly responsible for the delayed action of the drug in rheumatic conditions.

5 Haemodialysis will not aid in the case of oral overdose with hydroxychloroquine. Although the proportionate increase in clearance may be large, the increase in the fraction of the dose excreted will be negligible. The extensive sequestration of the drug by tissues limits effectiveness of haemodialysis.

Keywords hydroxychloroquine bioavailability pharmacokinetics

Introduction

Hydroxychloroquine is a slow acting antirheumatic drug. The efficacy of hydroxychloroquine is similar to that reported for other disease modifying antirheumatic drugs, with 60–80% of adult rheumatoid arthritics improving with hydroxychloroquine therapy (Mainland & Sutcliffe, 1962; Hamilton & Scott, 1962; Kersley & Palin, 1959; Adams *et al.*, 1983; Dwosh *et al.*, 1977). However, the main reasons for discontinuing therapy differ between the slow acting antirheumatic drugs (Paulus, 1982). With gold and D-penicillamine it has been reported that toxicity is the main reason for discontinuation, but for the antimalarials, lack of clinical response is the principal reason for stopping therapy (Richter *et al.*, 1980; Husain & Runge, 1980). Low and/or variable bioavailability of the oral dosage form could be a reason for patients failing to attain or maintain adequate therapeutic concentrations. The bioavailability of the commercially available tablet of hydroxychloroquine, Plaquenil (Winthrop Laboratories), has not previously been reported in the literature.

In the bioavailability study described below five healthy volunteers received, in a random crossover design experiment, an oral dose of 155 mg hydroxychloroquine (one Plaquenil

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tablet containing 200 mg racemic hydroxychloroquine sulphate) and an intravenous infusion of 155 mg hydroxychloroquine (200 mg racemic hydroxychloroquine sulphate). Clinical implications of the results of this study for chronic therapy and for overdose situations are also considered in this paper.

Methods

Volunteers

Five healthy volunteers, three female and two male, were enrolled in the study. These volunteers have been described previously (Tett *et al.*, 1988). Informed consent was obtained from all volunteers, after full medical, haematological and biochemical tests were performed. Ophthalmological examination, including visual fields, was performed on each volunteer before and after receiving each dose. Haematological and biochemical examinations were also repeated after each dose. Standard audiological testing was performed at the beginning and at the end of each study for all the volunteers. The study received the approval of the Ethics and Research Committee of St Vincent's Hospital, Darlinghurst, NSW, Australia.

Assay

The samples were assayed for hydroxychloroquine and metabolites using the h.p.l.c. assay described previously (Tett *et al.*, 1985, 1986). The limit of sensitivity of the assay is 1 ng ml^{-1} for all compounds (relative standard deviation 10%). All glassware in contact with hydroxychloroquine was silanised with Aquasil siliconising liquid (Pearce Chemicals, Rockford, IL., USA).

Dose administration

The volunteers received, in a randomized crossover design, on separate occasions at least 5 months apart, a 155 mg infusion of hydroxychloroquine and a 155 mg hydroxychloroquine oral tablet. Volunteers 1, 4 and 5 were randomly allocated to receive the oral dose first. The volunteers fasted from 22.00 h on the evening prior to each dose, and received lunch 4 h after administration of the dose.

The preparation and administration of the infusion has been described previously (Tett *et al.*, 1988). Oral doses were administered as a single Plaquenil tablet (containing 200 mg hydroxychloroquine sulphate, equivalent to 155 mg racemic hydroxychloroquine base) with 200 ml of water. The volunteers were ambulatory.

Blood sampling

Blood samples (20 ml) were collected into siliconised Vacutubes (Johns Mallinckrodt, Australia), containing 125 iu heparin, at the following times (via an indwelling cannula over the first day and thereafter by venepuncture):

Following the infusion dose in all volunteers and the oral dose in volunteer 1: 0(blank), 0.25, 0.5 (end of infusion), 0.75, 1, 1.25, 1.5, 2, 2.5, 3.5, 4.5, 6.5, 8.5, 13, 24, 32, 48, 72, 96, 120, 168 h, then once a week until the limit of sensitivity of the assay was reached.

The supposition that absorption of the oral dose was rapid proved to be incorrect and the greatest frequency of blood sampling following oral administration of hydroxychloroquine to volunteer 1 occurred too early, when hydroxychloroquine concentrations were very low. Therefore, sampling times following the oral dose in volunteers 2–5 were: 0(blank), 0.75, 1.5, 2, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, 13, 24, 32, 48, 72, 96, 120, 168 h, then once a week until the limit of sensitivity of the assay (1 ng ml^{-1}) was reached.

To obtain the plasma samples, 10 ml of the collected blood was centrifuged at 1200 *g* for 20 min within 30 min of collection, as recommended for chloroquine samples by Bergquist & Domeij-Nyberg (1983), and the plasma aspirated into a 10 ml Plain Tube (Disposable Products). All samples were stored frozen at −22° C until analysis.

Urine sampling

An aliquot of urine was collected from each void for 72 h following the dose, then once weekly for a period of 24 h, commencing 12 h before each blood sampling time. The date, time and total volume were recorded, and a 10 ml sample was stored at −22° C in a Plain Tube (Disposable Products) for analysis.

Data treatment

As described previously (Tett *et al.*, 1988), the equation

$$C = \sum_{i=1}^{3} C_i e^{-\lambda i t}$$

was fitted to the concentration-time data (blood and plasma) following the infusion. C is the

concentration predicted if the infusion dose had been administered as a bolus dose at time (t) zero.

The equation

$$C = \sum_{i=1}^{3} C_i e^{-\lambda i t} - C_4 e^{-\lambda_4 t}$$

was fitted to the oral concentration-time data (plasma and blood), using the nonlinear regression program Funfit. The weight assigned to each observation was the reciprocal of the concentration squared.

Area under the concentration-time curve (AUC) was calculated by integration of the fitted equation and also using the trapezoidal rule with an extrapolation correction (Gibaldi & Perrier 1982). Terminal elimination half-lives ($t_{½}$) were calculated from $t_{½} = \ln 2/\lambda_3$. The fraction of the oral dose absorbed, F, was estimated from blood and plasma data using dose-normalised AUC ratios.

The absorption rate of hydroxychloroquine from the oral tablet was estimated using a least squares method of deconvolution with first order absorption (Cutler, 1978). The fraction of the oral dose absorbed was fixed, using the area under the blood concentration-time curve ratio, and k_a, the absorption rate constant, was calculated by nonlinear regression (NAG library routine). The absorption half-life was calculated as $\ln 2/k_a$.

The total amount of hydroxychloroquine excreted unchanged in the urine was estimated by adding the amounts excreted in the urine collection intervals; for times greater than 72 h, linear interpolation was used to estimate the amounts excreted between the collection intervals.

The extent of absorption, F, was also obtained from the urine data using the equation

$$F = \frac{D_{iv} \cdot A_{e(\infty),oral}}{D_{oral} \cdot A_{e(\infty),iv}}$$

where $A_{e(\infty),oral}$ or $_{iv}$ is the amount excreted unchanged in the urine after the oral or the iv dose respectively. F was also estimated using the equation of Øie & Jung (1979), which does not assume constant renal clearance:

$$F = \frac{1}{D_{oral}}\left[(D_{iv} - A_{e(\infty),iv})\frac{AUC_{oral}}{AUC_{iv}} + A_{e(\infty),oral}\right]$$

The average steady-state concentrations (C_{av}), following multiple dosing, were predicted from the single dose studies using the equation

$$C_{av} = AUC/\tau$$

where τ is the dosing interval and AUC is the area under the blood-concentration time curve in the single oral dose study.

The fraction of steady state concentration (f_{ss}) reached in the Nth dosing interval was calculated using the equation of Perrier & Gibaldi (1982).

$$f_{ss} = \frac{AUC - \sum_{i=1}^{n} (C_i.e^{-N\lambda_i\tau})/\lambda_i}{AUC}$$

where n is the number of exponential terms in the fitted equation.

The amount of drug eliminated between time zero and time t was calculated using the equation

$$\text{amount eliminated} = CL.\int_0^t C.dt$$

Statistical analysis

Unless otherwise indicated parameters are expressed as mean ± s.d. Analysis of variance and Student's t-test were performed using the Epistat microcomputer statistical package. Probability values for a difference between tested means, reported as ($P = \ldots$), were considered statistically significant if $P < 0.05$.

Results

Pharmacokinetic analysis

The mean parameters of the fitted equations following the oral dose are shown for blood and plasma data in Table 1. Equation parameters following the infusion dose have been reported previously (Tett *et al.*, 1988). Figure 1 shows hydroxychloroquine blood concentration-time plots for one volunteer following the intravenous and oral doses. Blood concentrations were, on average, seven times plasma concentrations.

The lag-time before absorption commenced following the oral dose, calculated from the time intercept at zero concentration, ranged from 0 to 0.85 h (mean 0.43 h). Peak concentrations were observed 2 to 4.5 h after the oral dose was administered (mean 3.2 h). Maximum plasma drug concentrations following the oral doses ranged from 34–79 ng ml^{-1} (mean 46 ng ml^{-1}). Peak blood drug concentrations following the oral doses ranged from 188–427 ng ml^{-1} (mean 244 ng ml^{-1}). The absorption rate constant

Table 1 Mean (± s.d.) parameter estimates of the exponential equations fitted to the concentration-time data following the oral dose

Blood							
C_1	λ_1	C_2	λ_2	C_3	λ_3	C_4	λ_4
257	0.084	29	0.0031	6.8	0.00058	424	0.94
±149	±0.015	±13	±0.0006	±2.8	±0.00019	±269	±0.57
Plasma							
C_1	λ_1	C_2	λ_2	C_3	λ_3	C_4	λ_4
132	0.217	5.26	0.0172	2.59	0.00089	142	0.68
±145	±0.080	±1.41	±0.0132	±1.02	±0.00025	±147	±0.76

units of C ng ml^{-1}; λ h^{-1}

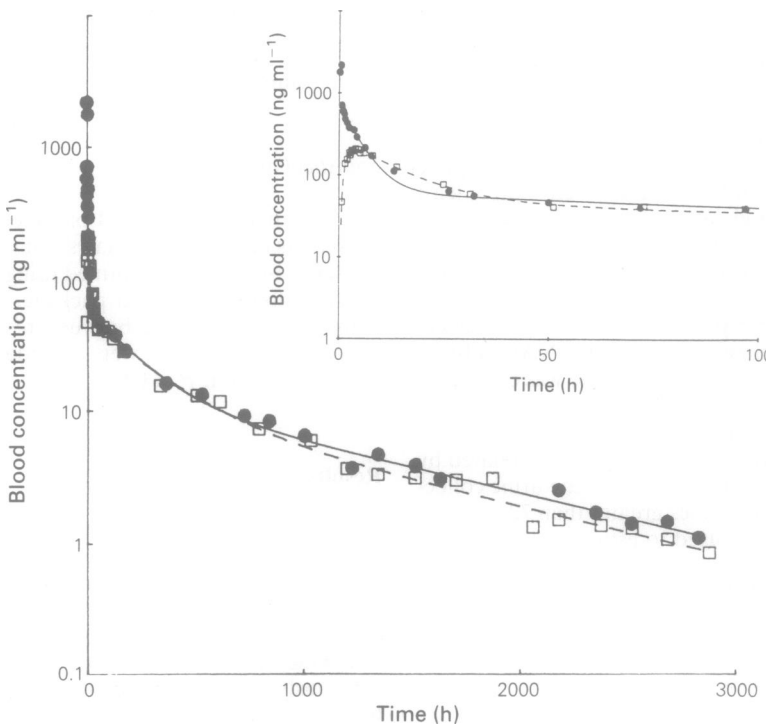

Figure 1 Log blood concentration-time plots for volunteer four following the 155 mg infusion (●) and the 155 mg oral tablet (□) of hydroxychloroquine. The solid (infusion) and the broken (oral) lines indicate the nonlinear least squares regression fitted curves. The inset shows an expanded time scale.

of hydroxychloroquine from the oral tablet ranged between 0.069 h^{-1} and 0.362 h^{-1} (mean 0.194 h^{-1}) (Table 2).

The mean terminal elimination half-life calculated from the blood data was 50 ± 16 days following the oral dose which is not statistically different from 44 ± 12 days calculated following the intravenous dose (P = 0.47). Using plasma data, the mean terminal elimination half-life calculated was 32 ± 9 days following the oral dose, again not statistically different from 26 ± 10 days calculated following the intravenous dose (P = 0.15). Analysis of variance indicates that the shorter half-lives calculated from the plasma data are statistically different from those calculated from the blood data (P = 0.03).

Table 2 shows the fraction of the oral dose of hydroxychloroquine absorbed by each volunteer, calculated using AUC ratios for the blood data (determined by integration of the fitted

Table 2 Estimates of the fraction of the oral dose absorbed using a) areas under the blood concentration-time curves ratios corrected for dose, b) amount excreted unchanged in the urine ratios corrected for dose and c) the method of Øie & Jung (1979)

Subject	*Fraction absorbed*			$t_{1/2}(h)$ *absorption*
	a) AUC ratios	*b) Urine excretion*	*c) Øie & Jung's method*	
1	0.84	0.66	0.81	10.0*
2	0.76	0.95	0.80	2.9
3	0.88	0.57	0.79	4.1
4	0.89	0.59	0.79	5.5
5	0.59	0.69	0.62	1.9
Mean	0.79	0.69	0.76	3.6
±s.d.	±0.12	±0.15	±0.08	±2.1

* Not included in calculating mean and s.d.

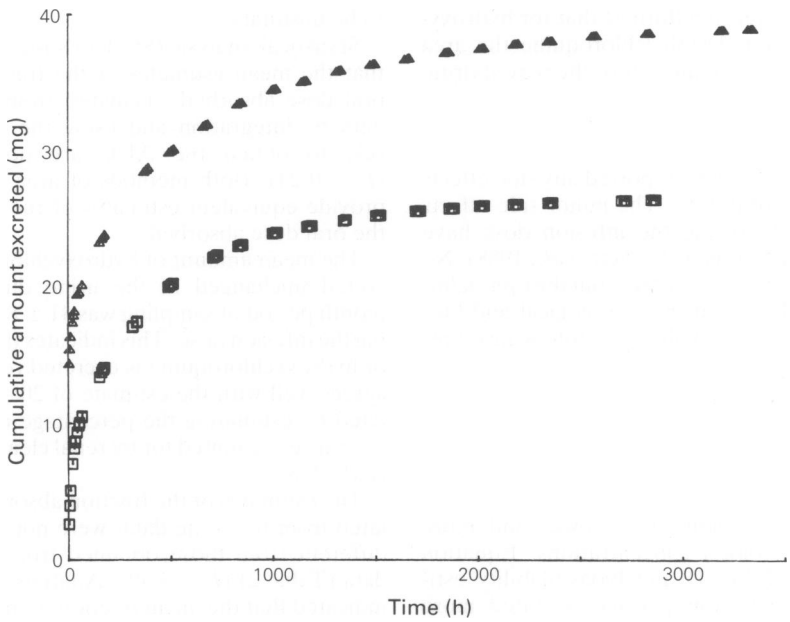

Figure 2 Cumulative urinary excretion of unchanged hydroxychloroquine *vs* time for volunteer five following the 155 mg infusion (▲) and the 155 mg oral tablet (□) of hydroxychloroquine.

equations), using the amounts excreted unchanged in the urine and using the method of Øie & Jung (1979). The results are not statistically different ($P = 0.69$). The calculated fraction of hydroxychloroquine absorbed from the oral tablet using the AUCs calculated from the plasma data varied widely (0.41 to 1.53).

Figure 2 shows a representative plot of the cumulative amount of hydroxychloroquine excreted unchanged in the urine vs time for one volunteer. The amount of hydroxychloroquine excreted unchanged in the urine following the infusion was 34.7 mg, 33.1 mg, 48.0 mg, 51.0 mg and 39.4 mg for volunteers 1 to 5 and following the oral dose was 24.9 mg, 30.6 mg, 27.0 mg, 30.2 mg and 27.7 mg for volunteers 1 to 5.

Peak blood concentrations of desethylhydroxychloroquine following the oral doses and infusions ranged from 6.9 ng ml^{-1} to 17.0 ng ml^{-1} (mean 11.7 ng ml^{-1}) and from 16.2 ng ml^{-1} to 48.2 ng ml^{-1} (mean 32.5 ng ml^{-1}) respectively. Desethylchloroquine maximum blood

concentrations following oral administration of 155 mg of hydroxychloroquine ranged from 2.9 ng ml^{-1} to 18.2 ng ml^{-1} (mean 11.7 ng ml^{-1}) and following intravenous administration ranged from 4.8 ng ml^{-1} to 28.2 ng ml^{-1} (mean 17.5 ng ml^{-1}). Peak blood concentrations of both metabolites were observed at approximately the same time as peak blood hydroxychloroquine levels, at means of 4.7 h and 5.2 h after the oral dose for desethylhydroxychloroquine and desethylchloroquine respectively. The metabolite half-lives calculated following the oral dose are longer than the half-life of the parent drug and are similar to those reported previously following intravenous administration of hydroxychloroquine (Tett *et al.*, 1988). The error in the areas under the metabolite blood concentration-time curves was very large because of the very slow elimination rates and the low blood concentrations of the metabolites. The area for desethylhydroxychloroquine was roughly a quarter to a third of that for hydroxychloroquine; for desethylchloroquine the area was one sixth to one quarter of the parent drug.

Side effects

None of the volunteers reported any side effects following the oral dose. The minor side effects experienced following the infusion dose have been described previously (Tett *et al.*, 1988). No abnormalities were reported from the ophthalmological, audiological, haematological and biochemical tests on the volunteers following either dose.

Discussion

Plasma concentrations were lower and more variable than blood concentrations. Equation parameters (Table 1) and bioavailability estimates obtained from plasma exhibited more variability than those from blood data, probably as a result of the difficulty of achieving complete separation of plasma from cells (Tett *et al.*, 1988) and the shorter period over which hydroxychloroquine could be quantified owing to the much lower plasma concentrations. Half-lives were shorter ($P = 0.03$) when calculated from plasma data compared with those calculated from blood data. This is probably an artefact attributable to the shorter sampling period possible from plasma (Tett & Cutler, 1987; Tett *et al.*, 1988). From the results of this study it is recommended that blood data, not plasma, be used in future studies of hydroxychloroquine. The same recommendation was made by Miller *et al.* (1987).

The blood hydroxychloroquine concentration-time data following the infusion were best fitted by triexponential equations as judged by Akaike's Information Criterion (Yamaoka *et al.*,1978). After oral administration, equations with four exponential terms were required; three as for the intravenous fits and one extra to account for the absorption process (Akaike's Information Criterion and inspection of the residuals).

The absorption half-life of the oral tablet, calculated using least squares deconvolution analysis with a first order absorption rate, ranged from 1.9 to 10 h (mean 3.6 ± 2.1 h). The long absorption half-life of 10 h calculated for volunteer one, the first subject to receive an oral dose, is considered to be the least reliable as this blood sampling schedule was the same as that used following the infusion dose, which proved to be unsuitable.

Statistical analysis (Student's *t*-test) indicates that the mean estimates of the fraction of the oral dose absorbed calculated from the blood data by integration and using the trapezoidal rule to obtain the AUC are not different ($P = 0.24$). Both methods of area assessment provide equivalent estimates of the fraction of the oral dose absorbed.

The mean amount of hydroxychloroquine excreted unchanged in the urine during the 5 month period of sampling was 41 ± 8 mg following the infusion dose. This indicates that 23–25% of hydroxychloroquine is excreted renally. This agrees well with the estimate of 20–30% calculated by estimating the percentage of the total clearance accounted for by renal clearance (Tett *et al.*, 1988).

The estimates of the fraction absorbed, calculated from the urine data, were not statistically different from those obtained from the blood data (Table 2) ($P = 0.49$). Analysis of variance indicated that the mean fraction of the oral dose absorbed estimated from plasma data was also not demonstrably different from the blood and urine means ($P = 0.21$). However, considering the problems with the collection of the plasma data and the large variability of the estimates calculated from the plasma data, the blood and urine data are considered to give more reliable estimates of the fraction of the oral dose absorbed. The mean fraction of the hydroxychloroquine oral dose absorbed is therefore 0.74 (±0.13), using the combined results from blood and urine.

The estimate of the fraction of the oral dose absorbed, calculated from urine data, is poten-

tially sensitive to variability in renal clearance. The estimates from the areas under the blood concentration-time curves are not as sensitive since renal clearance at 20% of total clearance is not a substantial fraction of the total clearance. The fractions of the oral dose absorbed, calculated using the method of Øie & Jung (1979), which does not require the assumption of constant renal clearance, were not statistically different from those obtained using the conventional blood AUC ratios (oral to iv) corrected for dose or from those obtained using the urine data (Table 2) ($P = 0.69$).

Possible cause of incomplete absorption

The absorption half-lives determined in this study were comparable with small intestinal transit times, suggesting that the residence time in the small intestine could be an important determinant of the extent of absorption. An alternative explanation of the incomplete absorption of hydroxychloroquine is the operation of a significant first-pass effect. A hepatic extraction ratio (non-renal blood clearance/hepatic blood flow rate) of 0.06 is obtained from the data of Tett *et al.* (1988). On the basis of this value it would be concluded that first-pass hepatic extraction is a minor factor, accounting for only 6% of the dose. This is the appropriate value if distribution within blood is rapid. On the other hand, if distribution of the drug between plasma and cells is slow, the extraction ratio based on blood data would underestimate the extent of first pass extraction. For in that case, the extraction ratio calculated from whole blood data would owe its small value to the fact that drug contained within blood cells (about 90%) would not be available for elimination. But immediately following absorption, if cell uptake is slow, drug would remain in plasma and be more available for extraction. On this interpretation the mean hepatic clearance for hydroxychloroquine from plasma of 622 ml min^{-1} corresponds to an extraction ratio from plasma of about 1. The observed bioavailability could then be taken to indicate that following absorption about 20–30% of hydroxychloroquine remains in plasma by the time the drug enters the liver (the rest having entered the cells), and that the drug remaining in the plasma when it enters the liver is completely extracted. The kinetics of blood cell uptake are broadly consistent with this possible mechanism. Uptake into red blood cells is very rapid (half-times are in the order of seconds, *in vitro*; Ferrari & Cutler, unpublished observations) while French *et al.* (1987) and Raghoebar *et al.* (1986) report equilibration times in *in vitro* studies of about 1 h for uptake into white cells.

However, the pattern of metabolite formation after oral and iv dosing, observed in the present study, does not support a significant hepatic first-pass effect. In this study metabolites were found in blood and plasma at lower concentrations following the oral dose than following the infusion, whereas elevated metabolite concentrations following the oral dose are expected if a significant first-pass effect operated.

Therapeutic implications of the oral hydroxychloroquine data

Chronic dosing When hydroxychloroquine is administered for rheumatic diseases the dose, either 155 mg or 310 mg, is generally given orally once daily. Response often takes up to 4 to 6 months to become apparent. It remains to be established whether pharmacokinetic or pharmacodynamic factors are responsible for this delay in action.

Using the mean values of the parameters of the equation relating blood concentration to time following the single oral 155 mg dose in this study (Table 1), it is possible to calculate the expected average steady-state concentration of hydroxychloroquine and the concentrations achieved at any time during the approach to steady-state (Table 3). The average steady-state blood concentrations after dosing of 155 mg or 310 mg every 24 h were predicted to be 987 ng ml^{-1} and 1974 ng ml^{-1} respectively. Blood from one patient who had received 155 mg of hydroxychloroquine daily for 6 months was shown to contain a drug concentration of 704 ng ml^{-1} (Tett *et al.*, 1985).

It cannot be predicted from the present data when therapeutic concentrations of hydroxychloroquine are likely to be reached as a therapeutic concentration range has not yet been established for hydroxychloroquine. However, the predictions of Table 3 do indicate that blood concentrations which are estimated to be achieved after 4 months of daily dosing with

Table 3 Approach to steady state with hydroxychloroquine oral dosing once daily

Time	*Fraction of steady state*	*Average blood concentration 155 mg daily*	*310 mg daily*
14 days	0.45	444 ng ml^{-1}	888 ng ml^{-1}
30 days	0.63	622 ng ml^{-1}	1244 ng ml^{-1}
60 days	0.78	770 ng ml^{-1}	1540 ng ml^{-1}
120 days	0.91	898 ng ml^{-1}	1796 ng ml^{-1}
180 days	0.96	948 ng ml^{-1}	1895 ng ml^{-1}

155 mg of hydroxychloroquine are achievable with only 2 weeks of daily dosing with 310 mg of hydroxychloroquine. It appears from this preliminary evidence that a higher dosing rate, say for the first 2 weeks, would be beneficial to more quickly attain steady-state blood concentrations. Based on calculations from this single dose study of hydroxychloroquine, 6 months is required to achieve 96% of steady-state concentrations (Table 3). Pharmacokinetic factors appear to be partly responsible for the delayed action of the drug.

The metabolites, desethylhydroxychloroquine and desethylchloroquine, might be expected to accumulate with chronic dosing because of their extremely long half-lives. Average steady-state concentrations for the metabolites cannot be calculated reliably from the present data owing to error in areas under the concentration-time curves as discussed previously. However, preliminary estimates indicate that the metabolites will not reach higher blood concentrations than the parent drug. Based on the areas reported above, desethylhydroxychloroquine should have a steady-state concentration roughly a quarter to a third that of hydroxychloroquine while desethylchloroquine should have a steady-state concentration approximately one sixth to one quarter that of the parent drug. These estimates are in reasonable agreement with observations on blood from one patient who had received 155 mg of hydroxychloroquine daily for 6 months; the sample contained 219 ng ml^{-1} of desethylhydroxychloroquine, about one third the concentration of hydroxychloroquine, and 77 ng ml^{-1} of desethylchloroquine, about one tenth the concentration of the parent drug (Tett *et al.*, 1985).

Overdose

The oral pharmacokinetic data for hydroxychloroquine provides a basis for considering a proposed therapy for treating overdose patients. Haemodialysis blood clearance of chloroquine was recently reported to be around 60 ml min^{-1} (Akintonwa *et al.*, 1986), an increase of approximately 50% over normal total blood clearance for chloroquine. Haemodialysis may thus be considered a desirable treatment to enhance the elimination of the drug in overdose cases. Chloroquine overdose victims have been reported to die, usually, within the first 3 h after oral self administration (Cann & Verhulst 1961; DiMaio & Henry 1974). No literature reports of overdoses with hydroxychloroquine have been found.

The amount of hydroxychloroquine eliminated from the body at any time can be calculated using the mean parameter values for the equation relating blood concentration and time following the oral dose (Table 1), and the mean clearance calculated by Tett *et al.* (1988) of 92 ml min^{-1} (from blood). Thus, after an oral dose only about 1.3% of the dose is eliminated by all routes in the first 3 h.

Assuming that hydroxychloroquine haemodialysis clearance is similar to that calculated by Akintonwa *et al.* (1986) for chloroquine, haemodialysis treatment for the first 3 h after an oral overdose increases the total amount of drug eliminated by all routes only to about 2.1% of the dose. Even this is an overestimate of the extra amount excreted. The equation parameters were not adjusted to account for changes in their values during haemodialysis as a result of the more rapid decline in blood concentrations with increased clearance. Therefore following an oral overdose, treatment by haemodialysis for 3 h would increase the amount eliminated by less than 1% of the dose.

Thus despite the fact that the clearance may be increased by a large percentage by haemodialysis, the net increase in elimination is insignificant. This is due to the extensive sequestration of the drug by tissues, which is a major factor in determining the disposition characteristics of hydroxychloroquine. Therefore it appears to be more important to try to prevent or reduce absorption of hydroxychloroquine in a case of overdose rather than attempt haemodialysis.

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