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Chloroquine excretion following malaria prophylaxis

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Urinary excretion of chloroquine and its desethyl-metabolite was monitored for up to 395 days after the last dose of oral chloroquine (300 mg base) taken once weekly for 10 weeks as malaria prophylaxis. Concentrations in plasma could be followed for up to 70 days after the last dose. A three exponential decay was applied to the urinary excretion data. The half-life of the terminal phase varied from 45 to 55 days for chloroquine and from 59 to 67 days for the metabolite. Mean residence time was approximately 20 days for the parent compound and 35 days for the metabolite, indicating that the terminal phases are of less importance for the effective half-lives.

Keywords chloroquine disposition

Introduction

Chloroquine is a drug with an unusual combination of pharmacokinetic properties such as an extremely large volume of distribution and a resulting very long half-life although total body clearance is not low. The drug has a high tissue affinity, especially to melanin (Lindqvist, 1973). Half-lives of 200–300 h have been calculated from plasma samples taken up to 30 days after a single dose by Gustafsson *et al.* (1983). These authors also estimated a plasma clearance of 0.4–0.9 l min^{-1}. Renal clearance accounted for 43–80% of total clearance.

Using spectrophotofluorometry Rubin *et al.* (1963) detected chloroquine in urine for 2 to 5 years after cessation of daily chloroquine intake of 150 to 450 mg of the base for years. We have now tried to characterize the terminal half-lives of chloroquine and its desethyl-metabolite using a specific h.p.l.c. assay (Alván *et al.*, 1982). Chloroquine in urine was monitored for more than a year after ending a few weeks prophylactic treatment.

Methods

Three healthy staff members aged 28 (KW), 36 (LG) and 38 (BL) years and weighing 54, 80 and 80 kg, respectively, were treated with 300 mg chloroquine base (chloroquine phosphate, Klorokin®, ACO Stockholm, Sweden) in a single dose given weekly for 10 weeks as malaria prophylaxis. One volunteer (KW) was female. After 9 weeks when an approximate steady-state was expected (considering a terminal half-life of about 300 h) 24 h urine collections were performed for 7 days. Thereafter the last chloroquine dose was given in the beginning of week 10. Urine collections for 24 h were performed daily for 7 days and this was repeated at 2, 3, 4 and 5 weeks after the last dose. For BL and LG 24 h collections were performed every second to sixth week for more than a year after the last dose.

Plasma samples were drawn into heparinized Venoject tubes before the last dose and then usually on day 7, 14, 21, 28 and 35. For BL and LG samples were then collected once weekly up to 10 weeks after the last dose. Sampling of

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blood was performed in different places and could not be strictly standardized. Thus, the centrifugation time varied between 5 to 15 min and the *g* force varied from 200 to 800 *g*. Aliquots of 10 ml from every 24 h urine collection and 4 ml of plasma were transferred into plastic tubes and stored at −20° C until anlaysis with h.p.l.c. in duplicate (Alván *et al.*, 1982). The method gives reproducible determination of chloroquine and desethylchloroquine down to 1 and 0.5 ng ml^{-1}, respectively.

Data analysis

Urinary excretion rate *vs* time data for the parent compound and the desethyl-metabolite were analysed by non-linear weighted least square regression analysis (Gomeni & Gomeni, 1979). The IGPHARM computer program was used. The time course of the urinary excretion rate was best described by a triexponential decline function:

$$C = A_1 \cdot e^{-\lambda_1 \cdot t} + A_2 \cdot e^{-\lambda_2 \cdot t} + A_3 \cdot e^{-\lambda_3 \cdot t}$$

where C = urinary excretion rate.

Statistical moment theory was applied to calculate mean residence time (MRT) for chloroquine and its metabolite utilizing urinary excretion data (Yamaoka *et al.*, 1978). MRT represents the time for 63.2% of the administered dose to be eliminated by all processes. In this pharmacokinetic analysis the contribution of the absorption phase has been disregarded as the absorption is rapid in relation to the slow elimination of drug from the body. The product of 0.693 and MRT_{iv} can be considered as an effective half-life for a drug requiring a multicompartment model (Gibaldi & Perrier, 1982).

Results

A total recovery of 39–67% of the administered dose was found after 10 weeks' of chloroquine intake. The desethyl-metabolite accounted for 10–16% of the total recovery. Both chloroquine and desethylchloroquine could be detected in urine for more than a year after cessation of malaria prophylaxis (Figure 1).

The predicted urinary excretion-rate curves for chloroquine are depicted in Figure 1 using the three compartment model. The concomitantly monitored plasma concentration for KW and BL showed some variability that was inconsistent with the decay in urine. MRT and the corresponding rate constants from the urinary excretion-rate data are shown in Table 1.

Discussion

After 9 to 10 weeks of chloroquine-therapy we were able to recover 39–67% of the given dose

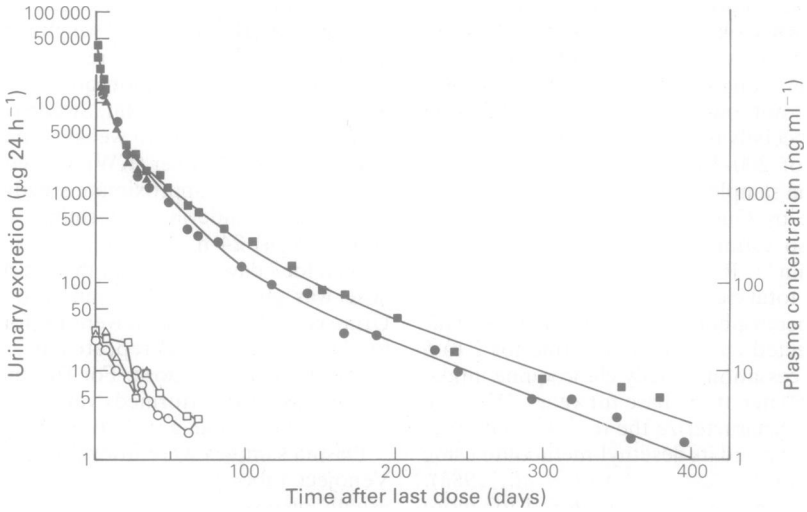

Figure 1 Urinary excretion-rate (top) of chloroquine (μg 24 h^{-1}) 1–395 days after the last weekly dose of 300 mg chloroquine base. Initially approximate steady state. (LG = ●, BL = ■, KW = ▲). The predicted elimination curves using a three-compartment model are depicted in two subjects (LG and BL). Plasma concentrations (ng ml^{-1}, right *y*-axis) were monitored on day 1 to day 70 (LG = ○, BL = □) or on day 1 to day 35 (KW △) after the last dose (bottom).

Table 1 Kinetic data derived from a three-compartment model of urinary excretion-rate data for chloroquine and desethylchloroquine: elimination from approximate steady-state

	Chloroquine					*Desethylchloroquine*				
Subject	$t_{1/2}\lambda_1$ *(days)*	$t_{1/2}\lambda_2$ *(days)*	$t_{1/2}\lambda_3$ *(days)*	*MRT (days)*	r^2	$t_{1/2}\lambda_1$ *(days)*	$t_{1/2}\lambda_2$ *(days)*	$t_{1/2}\lambda_3$ *(days)*	*MRT (days)*	r^2
LG	2.5	13.9	47.8	18.6	0.985	1.5	17.0	62.0	34.1	0.997
BL	2.8	20.0	55.0	21.7	0.997	1.4	12.0	59.1	42.8	0.997
KW	2.1	12.7	45.1	21.6	0.988	1.7	21.9	66.8	—*	0.976

*Not calculated due to lack of accuracy.

when collecting urine during one dosing interval. This is in the same range as the recovery of 38–74% of a single dose of 300 mg chloroquine base given orally or intravenously (Gustafsson *et al.*, 1983).

The urinary excretion of both chloroquine and its desethyl-metabolite can be interpreted according to a tri-exponential model. The half-life of the terminal phase considerably exceeds that of 6–14 days reported earlier and based on plasma samples collected up to 53 days after a single dose of chloroquine (Gustafsson *et al.*, 1983). The estimate of the terminal half-life will depend on the length of the sampling period if there is a number of small but deep compartments present late in the decay curve.

Since calculated MRT for chloroquine was around 20 days which is close to the half-life of the λ_2-phase, the λ_3-phase is of minor quantitative importance for the overall disposition of chloroquine. MRT for desethylchloroquine varied from 34 to 43 days and was more close to the estimated half-life during the λ_3-phase indicating that the terminal phase is of some quantitative importance for the elimination. It should be noticed that our estimates of the compounded rate constants λ_1 and λ_2 are to some extent influenced by the fact that the subjects were in an approximate steady state when the decay was followed. The terminal log linear phase will by definition not be influenced.

The fluctuations in the elimination curves of chloroquine in plasma shown in Figure 1 are probably due to varying *g*-force when handling the samples and this underlines the necessity of proper handling of plasma to get reproducible results (Bergqvist & Domeij-Nyberg, 1983; Rombo *et al.*, 1985).

In conclusion, chloroquine and its desethyl-metabolite are eliminated extremely slowly with terminal half-lives of some 50 and 60 days, respectively. The functionally important or 'effective' half-lives as calculated by using MRT are shorter, some 20 and 40 days, respectively.

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