KINETICS OF THE UPTAKE AND ELIMINATION OF CHLOROQUINE IN CHILDREN WITH MALARIA

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- 1 Ten children with *Plasmodium falciparum* malaria were treated with 25 mg/kg chloroquine over 3 days and observed for 7 days.
- 2 Chloroquine was determined in the red blood cells and plasma, and the red blood cell/plasma chloroquine concentration ratio was correlated with the disappearance of the parasites from the blood. It was found that this ratio decreased with the disappearance of the parasites and remained almost steady after the parasites had disappeared completely from the blood.
- 3 The half-life ($t_{1/2}$) and the elimination rate constant of the 'terminal' elimination slope ($\lambda\beta$) of the plasma log concentration-time curve were estimated to be 135.9 ± 9.92 h and 0.005 ± 0.001 h⁻¹ (s.d.) respectively.
- 4 The $t_{1/2}$ and $\lambda\beta$ calculated from the red blood cell log concentration-time curve were not significantly different from the corresponding values calculated from the plasma log concentration-time curve.

Introduction

Although chloroquine has been the drug of choice in the treatment of malaria for over 30 years and although its pharmacokinetics have been extensively studied in healthy volunteers (McChesney *et al.*, 1962, 1967) there is very little information on the kinetics of absorption and elimination of the drug when actually used in the treatment of malaria. Aderounmu *et al.* (1980) measured the plasma chloroquine concentration at varying intervals in the course of treating malarial children with chloroquine and concluded that therapeutic plasma levels were still present 5 days after the last dose of the drug. The plasma concentrations were not determined during the first 24 h after starting treatment hence no information on the absorption characteristics were provided by their study. The number of samples obtained by them over the 7-day study period (4 in all) was too small to permit a proper definition of the elimination phase of the concentration-time curve.

Plasmodium species, the causative organism of malaria, is an intraerythrocytic parasite (at least during the acute infection) and so the erythrocyte concentration of chloroquine during malaria infection should also be of interest. The present study aims at filling these gaps in our knowledge of the pharmacokinetics of chloroquine by investigating the plasma and erythrocyte uptake and elimination of chloroquine in children with acute malaria infection.

Methods

The study was carried out on ten children (six males and four females) aged between 6 months and 6 years. They all had acute *P. falciparum* malaria which was diagnosed by finding the early trophozoites of the parasite in the peripheral blood film. They were admitted to the children's ward of the University College Hospital, Ibadan, Nigeria, for the duration of the study. The protocol of the study was carefully explained to the parents of the children and they all gave their consent voluntarily. Children with any other diseases in association with malaria were excluded. Also excluded were children with moderate to high pyrexia (temperature over 39°C) and anaemia (packed cell volume less than 35%), and those who could not tolerate oral drug because of vomiting or any other reason. As a rule patients who were considered too ill to participate in a pharmacokinetic study were excluded.

Each child received a total of 25 mg/kg chloroquine base over 3 days according to the following schedule—10 mg/kg on the first and second days and 5 mg/kg on the third day. Chloroquine was given orally as Nivaquine syrup (May and Baker). Venous blood was taken before the first dose of chloroquine and at 0.5, 1, 2, 4, 8, 12 and 24 h after the dose. Subsequently blood was taken at 24 h intervals for a total of 7 days. Approximately 3 ml blood was withdrawn on each occasion into a lithium heparin bottle

and immediately centrifuged to separate the plasma from the red blood cells. The samples were then put in screw-capped glass bottles and stored frozen until analysed.

Plasma and erythrocyte (RBC) chloroquine was determined by a fluorimetric method as previously described by us (Adelusi & Salako, 1980). The lower limit of sensitivity of this method was 5 ng/ml and the percentage recovery was over 95%.

Duplicate thick and thin blood films were prepared for each blood sample and examined for malaria parasites by light microscopy.

Elimination half-lives were estimated from the linear portions of the appropriate slopes of the log concentration-time curves, and the elimination rate constants were calculated from the formula,

$$\lambda = 0.693/t_{1/2}$$

Half-life of absorption into the plasma was determined by the method of residuals (Rowland & Tozer, 1980) using the formula,

$$\bar{C} - C_t = \frac{Qa - ka}{V(ka - \lambda\alpha)} \cdot e^{-ka \cdot t}$$

where: $\bar{C}$ is the concentration when the log linear part of the initial decline phase is extrapolated to zero time,

C_t is the observed plasma concentration at time t ,

Qa is the amount absorbed,

V is the apparent volume of distribution,

ka is the absorption rate constant, and

$\lambda\alpha$ is the elimination rate constant of the initial decline phase.

By plotting the residuals ($\bar{C} - C_t$) against time on a semilogarithmic graph paper, a straight line was obtained, the slope of which is $-ka/2.3$. The absorption half-life representing the time taken for the residual values ($\bar{C} - C_t$) to diminish by one half was also determined.

Results are given in the text and Table 1 as means $\pm$ s.d. Comparisons between different means are made using Student's t -test and P values less than 0.05 are regarded as significant.

Results

Figure 1 shows the mean plasma and red blood cell log concentration-time curves for all the ten patients during the initial 24 h after the first dose of chloroquine. Each curve shows an absorption phase followed by a decay phase. Mean maximum concentration was 0.25 $\mu\text{g/ml}$ in plasma and 4.61 $\mu\text{g/ml}$ in red blood cells and this was achieved in both plasma and erythrocytes 2 h after administering the drug. The half-life of absorption into the plasma was $0.56 \pm$

Figure 1 Mean red blood cell ($\blacktriangle$) and plasma ($\bullet$) log concentration-time curves in ten children during the initial 24 h after the first dose of 10 mg/kg chloroquine given orally.

0.14 h and this corresponded to an absorption rate constant of $1.31 \pm 0.30 \text{ h}^{-1}$.

The half-life estimated from the linear portion of this initial log concentration-time curve was $8.1 \pm 1.17 \text{ h}$ for plasma and $7.8 \pm 1.12 \text{ h}$ for red blood cells. The difference was not significant. The values for the corresponding elimination rate constants were $0.088 \pm 0.014 \text{ h}^{-1}$ for plasma and $0.091 \pm 0.014 \text{ h}^{-1}$ for red blood cells. The difference between the two was also not significant (Table 1).

Figure 2 shows the mean plasma and red blood cell log concentration-time curves for the entire 7-day period of study. The part of the curve in broken lines between the 24 and 72 h experimental points has been inserted to correspond to the peaks and troughs which must have occurred following the repeat administration of the drug at 24 and 48 h. After the last dose of chloroquine the curves showed a slow decline, the time course for the plasma being approximately parallel to that for the red blood cells. The half-life of the terminal slope was $135.9 \pm 9.92 \text{ h}$ for plasma and $131.5 \pm 8.98 \text{ h}$ for red blood cells. The difference between the two values was not significant. The elimination rate constant for the terminal slope was $0.0051 \pm 0.0010 \text{ h}^{-1}$ for plasma and $0.0053 \pm 0.0012 \text{ h}^{-1}$ for red blood cells. The difference between

Table 1 Pharmacokinetic parameters for chloroquine obtained from the red cell (RBC) and plasma log concentration-time curves in children given 25 mg/kg chloroquine in multiple oral dosage.

Each value is the mean $\pm$ s.d. for ten children.

	RBC	Plasma
$t_{1/2}(\alpha)$ (h)	7.78 ± 1.12	8.06 ± 1.17
$\lambda\alpha$ (h^{-1})	0.091 ± 0.014	0.088 ± 0.014
$t_{1/2}(\beta)$ (h)	131.5 ± 6.98	135.9 ± 7.92
$\lambda\beta$ (h^{-1})	0.0053 ± 0.0012	0.0051 ± 0.0010
$C_{\max}$ ($\mu\text{g/ml}$)	4.61 ± 0.45	0.25 ± 0.03
$t_{\max}$ (h)	1.75 ± 0.25	2.01 ± 0.31

$t_{1/2}(\alpha)$ is the half-life for the initial 24 h after the first dose.

$\lambda\alpha$ is the elimination rate constant for the initial 24 h after the first dose.

$t_{1/2}(\beta)$ is the half-life of the terminal phase.

$\lambda\beta$ is the elimination rate constant for the terminal phase.

$C_{\max}$ is the maximum concentration reached at time $t_{\max}$.

the two values was similarly not significant (Table 1). It can however be seen from Table 1 that the values of these pharmacokinetic parameters obtained from the terminal slope of the log concentration-time curves were significantly different from the values obtained in the first 24 h.

The red blood cell chloroquine concentration was higher than the plasma concentration throughout the sample period. In Figure 3, the RBC/plasma chloroquine concentration ratio was plotted against time. This showed a progressive fall from a peak value of 21 at the beginning of treatment to a value of about 5.3, 72 h after starting chloroquine. Subsequently, the RBC/plasma chloroquine concentration ratio remained steady at approximately this level until the last sampling time. Figure 3 also shows the rate of disappearance of parasitaemia with time. Maximum parasitaemia was present at the beginning of treatment and had completely disappeared at 72 h. The fall in RBC/plasma chloroquine concentration ratio thus appeared to correspond to the disappearance of parasitaemia.

Discussion

The results of this study show a rapid absorption of chloroquine in children with malaria such that within 0.5 h of administering the drug, concentrations many times higher than the minimum therapeutic level of $0.01 \mu\text{g/ml}$ (Goodman & Gilman, 1975) have been reached in both plasma and red blood cells. The results indicate that provided there is no clinical contraindication to the oral administration of chloroquine, the drug is absorbed sufficiently rapidly and in

Figure 2 Mean red blood cell ($\blacktriangle$) and plasma ($\bullet$) log concentration-time curves in ten children. Chloroquine was given orally at arrows 0 and 1 (10 mg/kg) and arrow 2 (5 mg/kg).

Figure 3 RBC/plasma chloroquine concentration ratio (Δ) and percentage parasitaemia ($\circ$) plotted against time. Percentage parasitaemia is relative to pre-treatment parasite count taken as 100%. Each point represents the mean for ten children.

sufficient amounts to make parenteral administration unnecessary. This is very important in view of the well-known danger of sudden collapse and death in some children given parenteral chloroquine for malaria (Tuboku-Metzger, 1964; Olatunde, 1970).

The plasma half-life of 8.1 h obtained from the decline phase of the log concentration-time curves following the first dose of chloroquine was much less than the half-life of 135.9 h obtained from the terminal slope after the last dose. This finding is consistent with the polyexponential nature of the decline of chloroquine blood levels (Frisk-Holmberg *et al.*, 1979) since a drug whose log concentration-time curve can be described by a polyexponential curve would be expected to have a rate of decline in the first 24 h different from the rate after 5 or more days. This is further borne out by the finding in this study of an elimination rate constant in the initial decline phase which was 15 times higher than the rate constant of the terminal slope.

The long half-life obtained from the terminal slope of the chloroquine log concentration-time curve in this study agrees with earlier findings in healthy adult volunteers (McChesney *et al.*, 1962; McChesney *et al.*, 1967). Our results thus show that age and malaria infection do not substantially affect the rate of disappearance of chloroquine from the plasma. The observation that peak concentrations occurred in the plasma and erythrocyte at the same time and that the concentrations declined in the two blood fractions at approximately the same rate suggests that equi-

librium is reached rapidly between plasma and red blood cells and that the two behave pharmacokinetically as a single compartment with respect to chloroquine except for the complication of intraerythrocytic parasitaemia.

Although chloroquine appears from this study to be rapidly absorbed, the extent of its absorption cannot be determined from this study since the drug was not given intravenously as well. There is evidence from animal studies (Salako & Adelusi, 1982) that absorption though high may not be 100%. It would therefore not be helpful to calculate from our data such pharmacokinetic characteristics as total clearance, volume of distribution and bioavailability.

One striking finding in this investigation is the relatively high RBC/plasma chloroquine concentration ratio during the height of the parasitaemia with progressive fall as the parasitaemia declined. A similar phenomenon has been observed in experimental infection of mice with *Plasmodium berghei* by Macomber *et al.* (1966). They found an erythrocyte/plasma chloroquine concentration ratio of approximately 100 in mice infected with *P. berghei* and an RBC/plasma chloroquine concentration ratio of only 10 in uninfected mice. The higher concentration of chloroquine in erythrocytes compared to plasma is itself not surprising since chloroquine is well known to be concentrated in most tissues of the body. However, the increased concentration in the presence of malaria and the apparent dependence of the concentration on the degree of parasitaemia is of interest.

The increased concentration of chloroquine in erythrocytes during malaria infection may result from a combination of factors the most important of which is uptake of chloroquine by malaria parasites (Macomber *et al.*, 1967; Warhurst & Hockley, 1967).

This is the first time that the kinetics of uptake and elimination of chloroquine will be studied in children with malaria. Although the results obtained in this study do not show major differences from those

already known from studies in healthy adults, the data presented here should provide a more convincing basis for the rational use of chloroquine in children with acute malaria.

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