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Influence of Racial Factors and Weight on Pharmacokinetic Parameters of Chloroquine Following a Single Oral Dose

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Pharmacokinetic parameters following a single oral dose of chloroquine were determined in African and Asian subjects. The volume of distribution and half-life showed a direct relationship to weight. The time to maximum plasma concentration (t_{max}) showed a significant racial variation with Asians having an average of 0.9 hours and Africans 1.89 hours. This variation may have important implications in malaria chemotherapy and the handling of cases of chloroquine poisoning. The overall results of this study suggest that individualization of chloroquine dose regimen may be necessary.

Key words: Chloroquine, malaria, pharmacokinetics, choroquine poisoning, dose regimen

INTRODUCTION

The history of malaria dates as far back as 1550 BC where early measures to control the disease involved mainly vector control [1]. The use of chemotherapeutic agents against malaria was reported much later in the seventeenth century [2]. These early antimalarial agents were the alkaloids of cinchona bark. Chloroquine was introduced in 1934. This drug enjoyed the status of drug of choice for prophylaxis and treatment of acute attacks of malaria for a very long time until 1970s when cases of resistance to the drug started emerging [3,4]. Since then a number of alternative drugs and drug combinations have been tried [5].

The fact that malaria is widely spread throughout Tanzania necessitated decontrolling chloroquine availability so that the public could obtain it at short notice and without having to await the advice of scarce medical personnel. This brought with it two effects: improper dosing of chloroquine and misuse of the drug for suicide.

The questions of how many drugs and how often to administer it for a given therapeutic purpose are not easily answered. Basically two approaches have been used to answer these questions: empirical and kinetic [6,7,8].

The empirical approach is based on experience with a sufficient number of doses. The merit of the regimen is compared to no regimen at all. However, much information must be gathered and in the process some dosage regimens may have produced toxicity while others may have been ineffective.

The kinetic approach is based on the hypothesis that therapeutic and toxicity responses are related to the amount of drug in the body or to the plasma drug concentration. Given pharmacokinetic data following a single dose, the levels of drug in the body following multiple doses can be estimated. The appropriateness of a particular dosage regimen can then be evaluated in terms of the resultant time courses of drug levels, therapeutic response, and toxic effects.

Ultimately however, the value of a dosage regimen must be assessed by the therapeutic response produced. Pharmacokinetics simply facilitates the rapid achievement of an appropriate dose regimen and serves as a useful means of evaluating existing dosage regimens [9].

Whereas a number of authors have investigated the disposition of chloroquine following single oral and intravenous doses [10-13], racial and

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dietary factors have not been considered before. The aim of this study is therefore to investigate racial and dietary factors on the pharmacokinetic parameters of chloroquine following a single oral dose.

MATERIALS AND METHODS

Subjects

Six healthy adult male volunteers (3 Africans and 3 Asians) participated in the study. The mean age was 27 ± 5 years (range 22-32). Mean weight 69 ± 21 kg (range 48.3 - 89.9 kg). Ethical clearance for the study and informed consent were obtained from the subjects. The volunteers were instructed not to take any medication 3 weeks prior to the study and 4 weeks after chloroquine administration. All volunteers were non-smokers non-alcohol drinkers.

Drug Administration and Blood Sample Collection

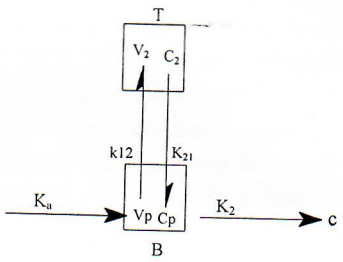
After an overnight fast, a single oral dose of 4 tablets of chloroquine phosphate (Keko Pharmaceutical Co.), equivalent to 600 mg chloroquine base was given to each volunteer and washed down with water. Blood samples were collected from the antecubital vein using a two way valve indwelling catheter. Blood sample were collected at 0, 0.5, 0.75, 1, 2, 3, and 4 hours after chloroquine administration. Further blood samples were taken weekly for 4 weeks.

The subjects were allowed to drink water and eat food 3 hours after chloroquine administration.

Each blood sample was centrifuged and the plasma separated. The chloroquine was extracted from the plasma by modifying the procedure described by Essien and Ifudu [8] and analysed at 343 nm using a PYE Unicam SP 8-100 UV/visible spectrometer. Second and third doses were simulated using a pharmacokinetic programme. The batch of chloroquine used was assayed before the study to determine content.

Pharmacokinetic Calculations

The plasma chloroquine concentration-time profiles were fitted by a linear computer programme. The data was treated according to a two compartment open model with elimination from the central compartment according to the scheme below.



All rate processes in this model were assumed to be first order where:

V_p = Volume of the central compartment (B)
V_2 = Volume of the tissue compartment (T)
C_2 = Tissue concentration
D = The administered dose
C_p = Plasma concentration
$K_{12}+K_{21}$ = Distribution rate constants
K_a = The absorption rate constant

The amount absorbed, A, was expressed in terms of the plasma volume V_p according to the equation:

$$A/V_p = C_p + K_e \int_0^n C_p.dt + T_{tn}$$

Where:

t_n = Time at t =n
K_e = The elimination rate constant
C_p = Concentration of drug in plasma
T = Concentration of drug in the tissues

Tissue concentrations were calculated by the Loo-Riegelman and Wagner Nelson equation as follows:

$$T_{tn}=T_{tn-1}e^{-K21\Delta t}+\frac{(K_{12})}{(K_{21})}CP_{tn-1}[1-e^{-K21\Delta t}]+\frac{K_{12}\Delta Cp.\Delta t}{2}$$

A plot of the percentage unabsorbed against time was used to calculate the value of absorption rate constant. The volume of distribution was calculated using the area method such that:

$$V_d = \frac{D_o}{\beta\,[AUC]}$$

Where:

D_o = Dose administered at time 0
β = The overall elimination rate constant
[AUC] = Total area under the curve obtained by the trapezoidal rule.

The time to maximum plasma concentration, t_{max} was calculated from the equation:

$$t_{max} = \frac{1}{K_a - K_e} \ln \frac{K_a}{K_e}$$

It should be noted that this time depends on the values of K_a and K_e, and is independent of the size of the dose.

Total clearance values were obtained from the relationship:

$$C_{TB} = \frac{D_o}{[AUC]}$$

Where C_{TB} = Total body clearance.

RESULTS

Table 1: Content and Pharmacokinetic profile of Chloroquine in tablets, Keko Brand batch No 922203

TEST	MEASURED VALUE	B.P. SPECIFICATION	REMARKS
Average Tablet weight (mg)	247.3	250 ± 10	Pass
Chloroquine content (%)	101.2	100 ± 7.5	Pass
Disintegration time (min)	8.8	< 30 min	Pass
Dissolution time (min)	12.0	< 15 min	Pass

Table 2: Pharmacokinetic parameters of chloroquine in healthy human volunteers

Volunteer No	1	2	3	4	5	6
Race	Asian	Asian	Asian	African	African	African
Weight (kg)	48.3	89.2	89.9	50.6	60.5	70.1
V_p (L)	3092	2917	3238	2514	3033	2726
V_d (L)	6664	25244	28205	8198	8292	13686
C_{TB} (Lhr)	27	26	26	22	178	16.4
K_a (hr^{-1})	1.54	1.38	1.53	0.73	0.79	0.67
[AUV] ($\mu gL^{-1}hr^{-1}$)	22084	22927	20012	17052	33695	36531
$\beta(hr^{-1}) \times 10^{-3}$	4.1	1.04	1.07	2.73	2.15	1.25
T½	168.9	669.9	648.5	253.7	322.0	573.7
Cp_{max} (μgL^{-1})	150.7	78.4	72.1	124.6	106.5	90.0

t_{max} average for Asians	0.91 hr	SD ± 0.038
t_{max} average for Africans	0.89 hr	SD ± 0.088
k_a average for Asians	1.519 hr^{-1}	SD ± 0.120
k_a average for Africans	0.727 hr^{-1}	SD ± 0.066

Table 3: Maximum concentrations of chloroquine following the first dose and simulated second and third doses of chloroquine 600mg and 300 mg respectively

Volunteer No.	1	2	3	4	5	6
Weight (kg)	48.3	50.6	89.2	70.1	60.5	89.9
Cp_{max} after 1st dose (600mg) μgL^{-1}	150.7	124.6	78.4	90.0	106.5	72.1
Cp_{max} after 2nd dose (600mg) μgL^{-1}	232.1	193.1	101.4	132.5	174.9	92.8
Cp_{max} after 3rd dose (600mg) μgL^{-1}	230.1	194.8	84.5	128.9	187.2	77.1

Table 4: Chloroquine Concentration profiles of volunteer 1 and 3 in the plasma and tissue

Time (hrs)	Volunteer 1		Volunteer 3	
	Plasma-free drug (mcg/L)	Tissue-bound drug (mcg/L)	Plasma-free drug (mcg/L)	Tissue-bound drug (mcg/L)
0	0	0	0	0
0.5	105	25	18	8
0.75	140	35	60	38
1	150.7	44	78.4	44
2	144	70	23	80
3	120	90	11	100
4	115	100	10	105
12	101	107	9	104
24	100	106	8.5	103

Figure 1 shows the concentration-time profile of chloroquine in plasma and tissue against time for volunteer 1 (weight 48.3 kg). The minimum effective concentration of chloroquine for treatment of chloroquine-sensitive malaria is 95.85 µg/L. As can be seen, this subject surpasses this level and yet remains below the concentration level at which side-effects start to manifest (191.7µg/L).

The plasma and tissue profile for chloroquine in subject 3 is shown in Figure 2. For this subject the chloroquine concentration does not even touch the minimum cidal concentration of 95.58 µg/L (0.3 µmol/L). In such a case a positive blood slide for malaria parasite would definitely be expected and the parasites regarded as resistant to chloroquine despite the patient taking the recommended dose.

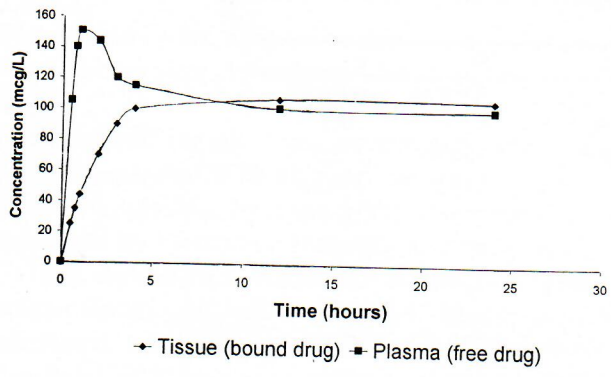


Figure 1: Concentration of chloroquine in plasma and tissues as a function of time

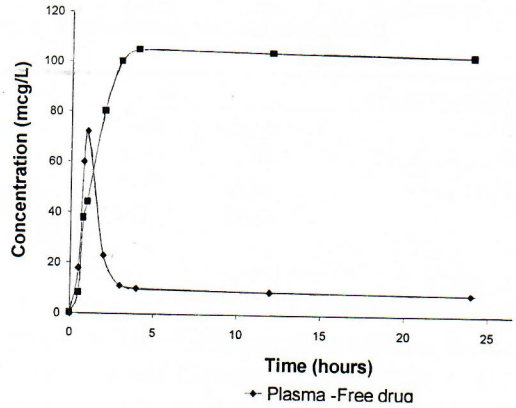


Figure 2: Concentration of chloroquine in plasma and tissue as a function of time

For patient no. 5 (60.5kg), the plasma concentrations which correspond to the first second and third doses are 106.5, 174.9 and 187.2μg/L (Table 3). respectively. They all fall above the minimum and below the maximum limits. This is just what is required.

DISCUSSION

Chloroquine was found to have an extraordinarily large apparent volume of distribution an indication of extensive tissue binding (Table 2) with volumes being largest in heavier volunteers (80-90kg) compared to the lighter ones.

The half-life ($t_{½}$) was extremely long (7-28 days). Chloroquine elimination is complex and there are reports of a triphasic elimination phase. Heavier individuals again showed longer half-lives as they have comparably more tissue available for the drug to bind. Care should therefore be exercised when giving multiple doses of this drug to avoid accumulation. Stereoselectivity in chloroquine body disposition could also be responsible for the discrepancy in half-lives. Chloroquine binding to plasma proteins is stereoselective, favouring S (+) - chloroquine (67% vs 35% for R - enantiomer [7].

The total body clearance (C_{TB}) and the elimination rate constant (β) did not differ significantly with the race or weight, but was essentially the same in all volunteers. In contrast to many metabolic pathways, it seems that renal handling of chloroquine is not under genetic control or influenced by weight.

The time to maximum plasma concentration (t_{max}) did not vary with weight but showed a significant racial variation with Asians t_{max} average = 0.9 hr, and Africans t_{max} average = 1.89hr. Asians therefore absorb chloroquine faster than their African counterparts. This could have been attributed to dietary factors. These two observations namely t_{max} and k_a can have a significant contribution to saving lives in chloroquine poisoning. Chloroquine carries the highest mortality of all antimalaria drug overdoses and the fact that this information is apparently available, encourages the use of chloroquine in suicide attempts (6). It follows therefore that it would be easier to treat an African 1 to 1 ½ hours after a suicide attempt with chloroquine than an Asian, for the reason that the Asian will have absorbed most of it.

The high values of the volume of distribution and the long half life exhibited by chloroquine shows that distribution rather than elimination determines the plasma concentrations of this drug. Plasma concentrations are a function of tissue saturation. This is also shown by the values of Cp_{max} obtained (Table 2) with lighter volunteers showing higher plasma concentrations compared to heavy ones.

Figure 1 represents plots of the amount of chloroquine in the plasma and tissues against time for volunteer 1 (48.3kg). Concentrations of chloroquine for treatment of chloroquine sensitive malaria is 95.85 μg/L. Side effects are seen above 191.7 μg/L [5]. The pharmacokinetics following this study show that if volunteer 1 is given a second dose of 600mg 24 hours following the first dose and a third dose of 300 mg 24 hours following the second dose, expected plasma concentrations will be 231.1 and 230.1 μg/L respectively. This will have exceeded the maximum permissible plasma chloroquine concentrations of 191.7 μg/L. This volunteer will not comply with the regimen. It should be born in mind that in curative doses, chloroquine can prolong the electrographic QTC interval. In overdose, the principal effects of chloroquine are on the cardiovascular system with major cardiac conduction disturbances and shock. Chloroquine prolongs the QRS and QTC intervals, increases V wave height and depresses the ST segment. Large fluctuations in potassium concentration can also occur.

Volunteer 3 (89.9kg) figure 2, shows an unnecessarily high amount of chloroquine in the tissues compared to what is required in the plasma. Since plasma levels of this drug are important, most of the drug bound in the tissue is not available for treatment. If a second dose of 600mg is given 24 hours after the first dose and a third dose of 300mg given 24 hours after the second dose, expected plasma concentrations will be 92.8 and 77.1 μg/L respectively. These

concentrations are well below the cidal chloroquine concentrations required for treatment. Parasitaemia will not be cleared and therapy will be deemed to have failed due to resistance, while the actual reason is the sub-optimal concentration of chloroquine in blood. There is therefore a need to individualize dosage regimens based on pharmacokinetic parameters of chloroquine.

Assessment of the relative importance of variables like disease, nutrition and ethnic origin is a difficult task. Genetic and environmental factors are often indistinguishable as diseases have geographical dependent incidence, diets and beverages [7].

Although the emergence of chloroquine resistant *Plasmodium falciparum* is a serious problem, any documentation of resistance in previously sensitive strains requires the careful exclusion of confounding factors, such as noncompliance, inadequate drug administration and dosage, and more importantly, the influence of drug-drug or drug-disease interactions. Hence, the development of sensitive and specific analytical methods and careful planning of pharmacokinetic studies are key to the adequate recognition of these important factors, and to the safe and effective use of existing antimalarial agents [7].

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