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Short Communication

Evaluation of the effect of co-administered paracetamol on the gastro-intestinal absorption and disposition of chloroquine

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Introduction

The widespread occurrence of malaria in tropical Africa has led to the frequent use of chloroquine. In Nigeria, for instance, the diagnosis of malaria is synonymous with pyrexia of unknown origin since no routine blood films are examined to enable the physician to arrive at a correct and unambiguous diagnosis [1]. Chloroquine is often given by injection, especially to infants with fever.

There are numerous unpublished observations from various parts of Africa of sudden death soon after the intramuscular injection of a standard dose of chloroquine into children and adults with high fever due to malaria. Ayiteh-Smith *et al.* [2] associated increased chloroquine toxicity with hyperthermia. These authors attributed the toxicity of chloroquine to the deleterious effect of fever which enhances the rate of interaction of chloroquine with the biomembranes. It was concluded that the use of an analgesic to combat hyperthermia reduces the incidence of chloroquine toxicity.

Since chloroquine is often administered with an analgesic such as paracetamol in the treatment of malaria, there exists an immediate need to evaluate the effect of this analgesic on the absorption and disposition of chloroquine. This evaluation has been achieved through a controlled study involving two groups of subjects, the control group being given chloroquine alone and the test group being given chloroquine with paracetamol. Chloroquine levels in the plasma and urine have been determined using the combination of thin-layer chromatography and spectrophotometry devised by Essien [3]; this method is specific for chloroquine.

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Experimental

Subjects

Ten healthy volunteers (9 males, one female) between the ages of 21 and 32 years, and weighing 53–67 kg participated in this study. They were free from identifiable disease and had no previous history of any chronic disease state. Informed consent was obtained from each individual prior to the initiation of the study. Chloroquine-hypersensitive individuals were not selected. The subjects had not taken chloroquine for at least 1 year prior to the start of the study. For at least two weeks prior to and throughout the study period, they did not consume cimetidine, barbiturates or other drugs that may affect liver enzyme systems.

Study design

A controlled study with and without paracetamol was conducted. Subjects were randomly assigned to two groups (control and test) each of five subjects. The subjects abstained from alcohol for 48 h prior to and throughout the study period.

After an overnight fast, each subject drank 400 ml of water; then after 1 h, 5-ml blood (the blank) and urine samples were collected just before administration of either chloroquine (300 mg) or chloroquine (300 mg) with paracetamol (1000 mg). Each of the subjects in the control group took two tablets of chloroquine diphosphate (300 mg base) (Delagil®, Imarsel Chemical Co., Lagos, Nigeria); 200 ml of water was used by each subject to swallow the drugs. Three h after the start of the study, subjects were permitted food *ad libitum* subject to the restrictions previously mentioned.

Twelve 5 ml blood samples were collected from each subject for the determination of chloroquine concentration in the plasma, at the following times after oral administration of the drug: 1, 3, 6, 9, 12, 14, 24, 48, 72, 96, 120 and 144 h (sixth day). Venous blood samples were collected in heparinized tubes, and centrifuged at 1500 rpm to separate the plasma. The plasma was then collected and stored at −20°C until analysed for chloroquine content. Urine was collected for 0–1, 1–3, 3–6, 6–9, 9–12, 12–14, 14–24, 24–48, 48–72, 72–96, 96–120 and 120–144 h after administration of the dose. Aliquots of urine were stored at −20°C until completion of the analysis.

Drug analysis

Plasma and urine samples were analysed for chloroquine using the combination of thin-layer chromatography and spectrophotometry described by Essien [3]. The method, which is specific for chloroquine, enables the drug to be separated from its desethylated metabolites and other potentially interfering metabolites.

Data analysis

Pharmacokinetic analysis was performed using both multi-compartmental and non-compartmental approaches. Five model-independent pharmacokinetic variables were determined from each set of plasma chloroquine concentration–time data: (1) the observed peak concentration (C_{max}); (2) the corresponding observed peak time (T_{max}); (3) the area under the plasma drug concentration–time curve (AUC) from the time of drug administration to the end of the sample collection period ($AUC_{0-6\ days}$) and adjusted to infinity ($AUC_{0-\infty}$) (calculated using the linear trapezoidal rule for the absorption phase and the log trapezoidal rule for the disposition phase); (4) the plasma clearance rate (Cl/F) (Cl = clearance, F = fraction of drug absorbed), calculated using

the dose-area relationship; and (5) the apparent volume of distribution (V/F) (V = apparent volume of distribution), calculated from the relationship:

$$V/F = \frac{D}{AUC_{0-\infty}\,\beta},$$

where β is the elimination rate constant and D is the administered dose of chloroquine.

The average renal clearance rate (Cl_R/F) of chloroquine was determined from the relationship:

$$Cl_R/F = \frac{Ae^{6\,\text{days}}}{AUC_{0-6\ \text{days}}},$$

where Cl_R is the renal clearance, and $Ae^{6\,\text{days}}$ is the total amount of unchanged chloroquine excreted in the 6-day period following drug administration. F was used in the calculation of the apparent plasma clearance rate (Cl/F), the apparent volume of distribution (V/F), and the average renal clearance rate (Cl_R/F) because there was no intravenous drug administration to determine the absolute bioavailability of chloroquine [5].

In addition, a semilogarithmic plot of plasma concentration as a function of time was constructed, and a two-compartment open model [4] was used to calculate the absorption, fast disposition and slow disposition rate constants. The intestinal absorption of chloroquine from the tablets was assumed to be first-order. The first-order rate constant of absorption (Ka) was determined for each subject using the method of residuals [5]. This method is valid when both Ka and the fast disposition, first-order rate constant (α) are larger than the slow disposition, first-order rate constant (β) and Ka is greater than α [5] (Table 1).

Statistical analysis

Student's t-test for unpaired data at the 0.05 level of significance was used to evaluate the effects of paracetamol on chloroquine absorption and disposition.

Results

The mean ($\pm$s.d.) plasma chloroquine concentration–time data obtained following oral administration of chloroquine given alone and with paracetamol are shown in Fig. 1.

The mean values with respective relative standard deviations of C_{max}, T_{max}, $AUC_{0-6\ \text{days}}$, $Ae^{6\,\text{days}}$ and Ka for each group are shown in Table 1. Analysis of these absorption variables revealed no significant differences ($P > 0.05$) between the groups.

Furthermore, no significant differences ($P > 0.05$) were observed in the values of α, β, V/F, Cl/F and Cl_R/F between the groups.

Discussion

The elimination of chloroquine in man is by hepatic metabolism and renal excretion; while renal excretion accounts for over 50% of chloroquine clearance, hepatic elimination accounts for over 40%. On the other hand, paracetamol is largely cleared

Table 1
Chloroquine absorption and disposition constants obtained from the control group (chloroquine alone) and the test group (chloroquine with paracetamol) subjects

Variable	Control group		Test group	
	Mean	RSD (%)	Mean	RSD (%)
Absorption constants				
C_{max} (μg ml^{-1})	7.20	13.10	8.50	14.12
T_{max} (h)	9.00	24.00	9.00	24.00
K_a (h^{-1})	0.39	25.60	0.38	3
$AUC_{0-6\ days}$ (μg day ml^{-1})	10.40	10.48	12.61	9.60
$Ae^{6\ days}$ (μg)	118.70	7.37	124.85	8.13
$AUC_{0-\infty}$ (μg day ml^{-1})	13.86	8.66	16.85	9.67
Disposition constants				
α (h^{-1})	0.06	33.33	0.07	14.28
β (day^{-1})	0.23	17.39	0.20	25.00
$t_{1/2}$β (day)	3.00	11.66	3.50	4.29
Cl/F (1 day^{-1} kg^{-1})	0.33	27.27	0.30	16.66
V/F (l kg^{-1})	1.43	10.49	1.52	7.24
Cl_R/F (1 day^{-1} kg^{-1})	0.17	17.64	0.17	47.06
Fe†	0.53	5.66	0.55	27.30

* RSD = Relative standard deviation.
† *Fe* = Fraction of the dose excreted unchanged for the first 6 days.

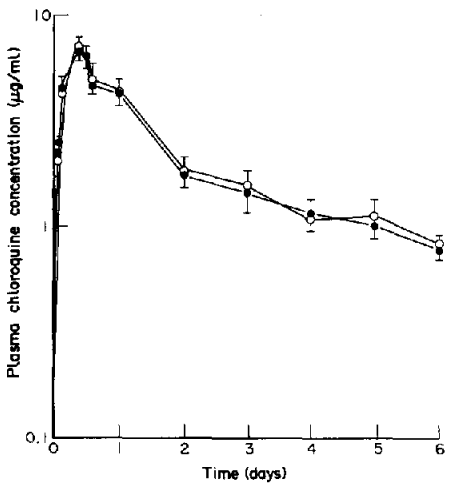

Figure 1
A semi-log plot mean (±s.d.) plasma chloroquine concentration versus time in the control group (closed circles) and the test group (open circles) subjects. Subjects in the control group took chloroquine alone while subjects in the test group took chloroquine with paracetamol.

from the blood through biotransformation by hepatic microsomal enzymes [6]. Thus, the clearance of the two drugs by biotransformation may suggest a possible interaction when the two drugs are taken together.

In the present study, the rate of absorption of chloroquine was not affected by the co-administration of paracetamol (Table 1). Both drugs are known to be rapidly and completely absorbed. The absorption rate constant (0.39 h^{-1}) obtained with the control group in this study is not markedly different from the value of 0.5 h^{-1} previously reported by Tulpule and Krishnaswamy [7]. Although the extent of chloroquine absorption appeared to be slightly elevated (by 21%) in the test group, this was not statistically significant ($P > 0.05$). The slight increase in the extent of chloroquine bioavailability could be attributed to the competition between the two drugs for clearance by cytochrome P-450 mixed function oxidases of the liver. Whereas this is a minor route for paracetamol metabolism [8], C-oxidation (Cyt. P-450) and N-oxidation constitute the major routes for chloroquine metabolism [3].

The plasma clearance rate (Cl/F), apparent volume of distribution (V/F), and average renal clearance rate (Cl_R/F) of chloroquine were estimated since an intravenous dose of the drug was not used to determine the absolute bioavailability (F) of chloroquine in these subjects [5]. The plasma clearance rate of chloroquine in the test group was *ca* 0.30 l kg^{-1} day^{-1}, and this is not significantly different ($P > 0.05$) from the plasma clearance rate of 0.33 l kg^{-1} day^{-1} obtained for the control group. This slight difference could be attributed to the reduced intrinsic hepatic clearance (hepatic elimination) of chloroquine in the presence of paracetamol which probably competed with chloroquine for binding sites on the cytochrome P-450 mixed function oxidases. For drugs such as chloroquine [4], which exhibit two-compartment kinetics, the total clearance rate gives a direct measure of hepatic elimination [9]. The slight increase (6%) in the apparent volume of distribution in the test group, although not statistically significant, is probably a clearance effect.

There was no significant difference ($P > 0.05$) in the values of the plasma half-life of chloroquine obtained in the control and test groups (control group, 3.00 ± 0.35 days; test group, 3.50 ± 0.15 days). The half-life observed for chloroquine is similar to that previously reported in healthy volunteers and malaria patients [10, 11].

By 6 days, the renal excretion of chloroquine was *ca* 53 and 55% of the plasma clearance rate in the control and test groups, respectively. These values are similar to a previous report of 57% in healthy volunteers [4]. These percentages of plasma clearance rates observed in this study are associated with average renal clearance rates of 0.11 and 0.17 l kg^{-1} day^{-1} for the control and test groups, respectively.

It is reasonable therefore to infer that there is no significant alteration of the pharmacokinetics of chloroquine due to co-administered paracetamol. The toxicity of chloroquine in hyperthermia may be related to the increase in the rate of biochemical reactions with elevated temperature. Thus, the use of paracetamol in combination with chloroquine in malaria therapy is justified on the basis that paracetamol (an analgesic and antipyretic agent) relieves the febrile and painful muscle conditions manifested in malaria.

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