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Research Article

EFFECTS OF FOOD ON THE PHARMACOKINETICS OF AMODIAQUINE IN HEALTHY VOLUNTEERS

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ABSTRACT

Amodiaquine (AQ) is a 4-aminoquinoline derivative which is intrinsically more active than the other 4-aminoquinoline, chloroquine, against *Plasmodium falciparum* parasites. The pharmacokinetic parameters of amodiaquine and its active metabolite following the administration of amodiaquine to healthy volunteers under fasted conditionS were compared with those when it was co-administered with food.

In an open, two-way crossover study, 16 healthy volunteers fasted overnight and were randomized to receive a single oral administration of 600 mg (3 tablets) of amodiaquine in the absence or presence of a standardized high-fat breakfast, administered 30 min before drug administration. Blood samples were collected up to 192 h and amodiaquine and desethyl amodiaquine were assayed by a validated HPLC method.

Relative to the fasting state, the administration of a single dose of amodiaquine after a high-fat breakfast resulted in delayed median Tmax values (20 min for amodiaquine and 3 h for desethylamodiaquine). The geometric mean ratios (GMR) of fed to fasting conditions indicated increased Cmax values for amodiaquine (GMR 1.40) (90% CI: 1.12-1.48) and desethylamodiaquine (GMR 1.48) (90% CI: 1.09-1.52) and increased AUC0-t values for amodiaquine (GMR 1.62) (90% CI: 1.42-1.86) and for desethylamodiaquine (GMR 1.26) (90% CI: 1.12-1.36).

Intake of AQ with a high fat meal resulted in a statistically significant increase in blood levels of amodiaquine and desethylamodiaquine which may affect its safety and tolerability. The findings of this study suggest that amodiaquine should not be administered with a high-fat meal.

Key words: Amodiaquine, Desethylamodiaquine, Food, Pharmacokinetics

INTRODUCTION

Food influences the rate and extent of drug absorption by a wide variety of mechanisms: for example delayed gastric emptying, increased peristalsis favouring dissolution of any drug, and alteration of transport mechanisms[1]. Food-drug interactions can be associated with alterations in the pharmacokinetic and pharmacodynamic profile of various drugs that may have clinical implications. The various phases in which food may interact with a co- administered drug are: (i) before and during gastrointestinal absorption; (ii) during distribution; (iii) during metabolism; and (iv) during elimination. A number of intrinsic and extrinsic factors influence the pharmacokinetics of a drug in both the fasted and the fed states. These include anatomical, pathological, and physiological factors as well as the physical and chemical properties of the drug, formulation, or excipients [1]. However, the influence of food is largely a matter of the design of the pharmaceutical formulation. In addition, the mechanism of 'food effect' may involve physiological and sensory responses to food, such as changes in gastrointestinal milieu and gastric emptying rate, reflex action, and may also involve the site and route (either portal or lymphatic) of drug absorption [1]. Although there is a vast amount of literature, there is still no rational scientific basis to predict the effect of food for a particular chemical entity or a chemical class of therapeutic agents. A mechanistic understanding of the effects of food may serve as a key to the pharmacokinetic optimization of patient therapy, both in outpatients and hospitalized patients of various age groups.

Amodiaquine is a 4-aminoquinoline derivative that has been widely used for treatment of malaria over the past 50 years [2]. It is intrinsically more active than the other 4-aminoquinoline, chloroquine, against *Plasmodium falciparum* parasites, which are moderately chloroquine resistant. The drug is therefore increasingly being considered as a replacement for chloroquine as a first line drug in Africa because of widespread chloroquine resistance [2].

The loss of chloroquine due to selection and spread of drug resistant *Plasmodium falciparum* parasites has greatly impacted malaria control, especially in highly endemic areas of Africa. Since chloroquine removal a decade ago, the guidelines to treat falciparum malaria suggest combination therapies, preferentially with an artemisinin derivative. One of the recommended partner drugs is amodiaquine, a pro-drug that relies on its active metabolite monodesethylamodiaquine, and is still effective in areas of Africa, but not in regions of South America [2].

Upon oral administration, amodiaquine is rapidly absorbed and extensively metabolized such that very little of the parent drug is detected in the plasma. The main metabolite of amodiaquine is *N*-desethylamodiaquine with other minor metabolites being 2-hydroxyl desethylamodiaquine and *N*-bis desethylamodiaquine [2].

Whereas the formation of desethylamodiaquine is rapid, its elimination is very slow with a terminal half-life of over 100 h. Amodiaquine and desethylamodiaquine both have antimalarial activity, but amodiaquine is 3 times more active (2). However, since amodiaquine is rapidly cleared and the formed desethylamodiaquine attains high plasma concentrations for a long time, amodiaquine is considered a prodrug, which is bioactivated to desethylamodiaquine.

It has been demonstrated that food intake simultaneous with or just before drug administration can affect drug pharmacokinetics. Amodiaquine is likely to be taken with food, and modification of the dosing regimen may be required in the event of any subsequent significant change in the pharmacokinetics. Therefore, we examined the effect of food on the pharmacokinetics of amodiaquine by administering it after fasting and high-fat meals.

MATERIALS AND METHOD

Chemicals and reagents:

Amodiaquine dihydrochloride and desethylamodiaquine dihydrochloride were obtained from Parke-Davis, U.S.A. and quinidine from BDH Laboratory Supplies, Poole, England. Amodiaquine dihydrochloride tablets (Parke-Davis, U.S.A.) were purchased from a retail pharmacy in Nigeria. HPLC grade acetonitrile and methanol, and analytical grade diethylether, perchloric acid, sodium hydroxide and hydrochloric acid were purchased from Sigma (Sigma-Aldrich chemical company, Germany).

Instruments and Chromatographic conditions:

A Mersham Pharmacia Biotech IP-900 liquid chromatography. (U.S.A) (AKTA) fitted with a variable UV detector (model P-900) was used for the analysis. The stationary phase was a reversed-phase C18 column {Eclipse-XDB-C18-3.5 µm (200 x 4.6 mm I.D.)}. The solvent system for HPLC consisted of acetonitrile: 0.02 M potassium dihydrogen phosphate (10:90). The pH of the mobile phase was adjusted to 4.0 with orthophosphoric acid. The mobile phase was pumped through the column at a flow rate of 1.0 ml/min. The experiments were performed at ambient temperature. The method was a slight modification of Gitau et al. (2004) [3].

Whirl mixer (Fissions), precisions pipettes (MLA), table centrifuge (Gallenkamp) and digital sonicator (Gallenkamp) were used for the extraction procedure.

Analytical Procedure

To 1 mL of plasma placed in a 15-ml screw capped extraction tube were added 20 µL of 500 µg/mL quinidine solution (internal standard) and 2 ml of acetonitrile before mixing for about 15 seconds, followed by mechanical tumbling for 15 min. After centrifuging for 10 min at 3000 g, the liquid phase was transferred to a clean tube, to which was added 2 ml of ammonia. The mixture was then extracted by mechanical tumbling for 15 min, with 2 x 5 ml of diethyl ether. After centrifugation and separation, the combined organic phases were evaporated to dryness and the residue was reconstituted in 100 µL of methanol while a 50 µL aliquot was injected onto the HPLC column.

Calibration curve based on peak area ratio was prepared by spiking drug-free plasma with standard solutions of amodiaquine and monodesethylamodiaquine to give concentration ranges of 2 – 30 ng/mL and 20 – 300 ng/ mL respectively. The samples were taken through the extraction procedure described above.

Subjects

Twelve males and four females adult Nigerians aged between 30 and 38 years and weighing between 64 and 75 kg took part in the study. They were all judged healthy by a physician on the basis of medical history, clinical examination, biochemical, and hematological screening prior to entry into the study. Subjects were excluded from participating if they met one of the following criteria: pregnancy, breast feeding, and history of hypersensitivity reactions to amodiaquine or similar agents (Chloroquine, Quinidine, Quinolones), use of any medications that could potentially interact with the study drug, any liver function test more than three times the upper limit of normal, or evidence by history or physical examination of gastrointestinal, psychiatric, cardiovascular or neurological disorders. All participants gave written informed consent, and approval was obtained from the Research Ethics Board and safety Committee of the Federal Medical Centre, Abeokuta, Ogun state.

Study design, Drug administration and Sample collection

The study was an open-label, crossover pharmacokinetic study. A single oral dose of 600 mg amodiaquine dihydrochloride tablets was given to each of the sixteen volunteers with and without food in a crossover design after an overnight fast. The caloric contents of the high-fat meal were 900 kcal, according to the recommendations of US Food and Drug Administration guidance [4]. The food consisted of a standard breakfast of rice with some vegetables, egg, meat and 300 ml of whole milk. Eight subjects received amodiaquine without food, and the other Eight received same with food. They were later reversed after a washout period of two weeks. Blood samples (5 ml) were withdrawn by venipuncture from the forearm of each subject prior to and at 0.08, 0.25, 0.5, 1.5, 3, 5, 24, 48 and 192 hours after drug administration into heparinised tubes. They were immediately centrifuged (3000 g at 20° C for 10 min) to separate plasma. The plasma aliquots were stored at -20 °C until analyzed.

The plasma samples were analyzed for amodiaquine and monodesethylamodiaquine to obtain their baseline pharmacokinetics and then to evaluate the effect of food on the pharmacokinetics of amodiaquine.

Pharmacokinetic Evaluation

The pharmacokinetic (PK) parameters for amodiaquine and monodesethylamodiaquine were calculated with the computer program WinNonLin (version 1.5). The data were analyzed using noncompartmental analysis. The parameters that could be established were as follows: time point of maximum observed concentration in plasma (Tmax); concentration in plasma corresponding to Tmax

(Cmax); terminal half-life (T1/2); area under the plasma concentration *versus* time (C-t) curve (AUC_T). The terminal half-life was calculated from the terminal elimination rate constant: k. This rate constant was calculated by means of linear regression of the final part of the ln C-t curve. The final half-life could be calculated by T1/2 = ln (2)/k = 0.693/k. For the calculation of the elimination rate constant, we used the three final concentrations of the C-t curve (24, 48, and 192 h). The AUC_T was calculated by the logarithmic trapezoidal rule. The volume of distribution (Vd) was not included because the actual Vd cannot be calculated correctly because the bioavailability is not known.

Statistical evaluation was performed with the statistical program SPSS 7.0. Direct comparisons of the raw data were performed using the two-tailed paired *t* test. To evaluate a food effect, the data were log transformed and evaluated using the Wilcoxon test.

RESULTS

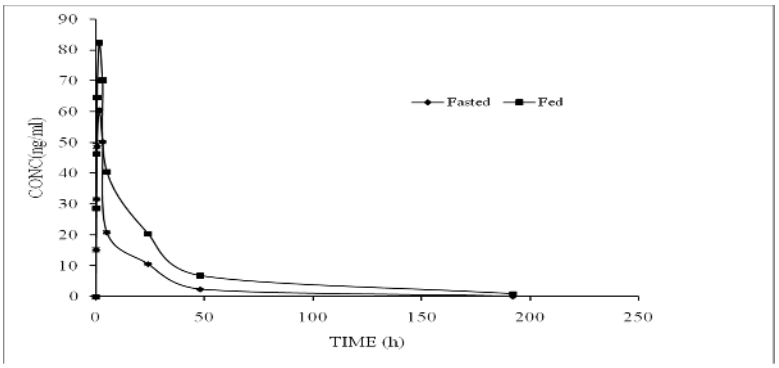
All subjects could tolerate the dose of 600 mg amodiaquine. The most frequently reported adverse event was mild nausea (twelve subjects). Mild abdominal pain occurred in a further three subjects. There were no serious adverse events during the study and no withdrawal due to adverse events or for any other reason.The result as shown in Table 1 shows that relative to the fasting state, the administration of amodiaquine after a high-fat breakfast resulted in a delayed median Tmax values for amodiaquine (20 min) and for desethylamodiaquine (3 h). The geometric mean ratios (GMR) of fed to fasting conditions indicated increased Cmax values for amodiaquine (GMR 1.40) (90% CI: 1.12-1.48) and desethylamodiaquine (GMR 1.48) (90% CI: 1.09-1.52) and increased AUC_T values for amodiaquine (GMR 1.62) (90% CI: 1.42-1.86) and for desethylamodiaquine (GMR 1.26) (90% CI: 1.12-1.36). The mean Cmax of amodiaquine was significantly higher in the fed regimen than in the fasted one (38%, $P < 0.05$), with a corresponding increase in the Cmax of desethylamodiaquine (44%, $P < 0.05$). There was also a significant increase in the AUC_T of amodiaquine and desethylamodiaquine in the fed regimen (36%, $P < 0.05$ and 32%, $P < 0.05$), respectively. The mean plasma concentration–time profiles of amodiaquine after oral administration of amodiaquine 600 mg to 16 healthy volunteers under fasting, and high-fat meal conditions, respectively, and that for desethylamodiaquine are shown in Figure 1.

There were no significant differences between the treatment groups regarding adverse events, vital signs, and laboratory tests, (data not shown).

Table 1: Effect of food on the pharmacokinetic parameters of amodiaquine and desethylamodiaquine

Parameters	Fasting	High-fat meal	Significance
Amodiaquine			
Cmax (ng/ml)	50.0 ± 1.2	68.2 ± 5.6	$P < 0.05$
Tmax (h)	0.8 ± 0.08	1.08 ± 0.06	$P < 0.05$
AUC	160.80 ± 15.22	254.68 ± 22.14	$P < 0.05$
T1/2	6.21 ± 0.82	5.92 ± 0.74	$P > 0.05$
Desethylamadiaquine			
Cmax (ng/ml)	192 ± 17.24	226 ± 24.28	$P < 0.05$
Tmax (h)	4.20 ± 0.82	5.53± 0.96	$P < 0.05$
AUC	2054 ± 86.21	2671± 84.34	$P < 0.05$

A.



B.

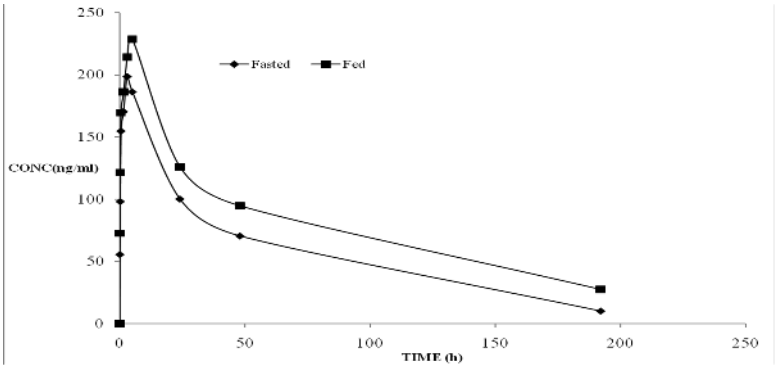


Figure 1: Plasma concentration – time profile of (A) Amodiaquine and (B) Desethylamodiaquine following administration of 600 mg amodiaquine to 16 healthy volunteers with or without food.

DISCUSSION AND CONCLUSION:

This study was performed to examine the effect of food on the pharmacokinetics of amodiaquine, a 4-aminoquinolone antimalarial drug. As a high-fat diet frequently affects drug absorption, this study attempted to determine the maximum effect of food on the pharmacokinetics of amodiaquine by drug administration after a high-fat meal. The differences in pharmacokinetics between fed conditions and the fasting condition were assessed by *T*max, *C*max and AUC_T.

Pharmacokinetic interactions of orally administered drugs and food components have been extensively reviewed [5,6]. Food can affect bioavailability of drugs by altering the physiology of the gastrointestinal tract and by direct influence on the formulation and/or drug itself. Direct effects of food on the formulation can result from changes in solubility of the active drug ingredient through physicochemical interactions. Physiologic changes that can influence bioavailability include change in the rate of gastric emptying, changes in gastric secretions, and effects on active transport of drugs. Dietary constituents also can affect the biotransformation of a drug in the gastro-intestinal lumen, gastrointestinal wall, and liver. Drug bioavailability can be increased, decreased, delayed, or unchanged by the presence of food. Critical factors that determine the outcome of such interactions include the nature of the drug and food as well as the timing of food consumption. Different food components can have different effects, and food may interact in opposite ways even with drugs that are chemically related[6] .

The co-administration of a high-fat meal with 600 mg amodiaquine induced a marked increase in *T*max and *C*max for amodiaquine. There was also, on average, an increase in the AUC_T in the 'fed' relative to the 'fasted' state.

In the study, the absorption rate was found higher after a high-fat meal. This might have resulted from the lipophilicity of amodiaquine. In general, drugs with a high lipophilicity exhibit increased absorption when they are administered with a high-fat diet [5], which increases pancreatic and biliary secretion, resulting in an increased dissolution rate. Amodiaquine is lipophilic, displaying a 0.80–1.85 octanol/water partition coefficient (Log P) in approximately pH 1 to pH 7 [7]. Thus, it can be inferred that the increased solubility by the high-fat meal was responsible for the higher absorption rate of amodiaquine compared with the fasting state.

Previous reports have shown that amodiaquine is well absorbed from the gastrointestinal tract [8]. Its elimination half-life is approximately 3–4 h and amodiaquine is rapidly cleared by extensive metabolism followed by excretion of metabolites in the urine. The delayed *T* max and increase *C* max observed in the 'fed' session of the present study are probably due to a faster gastric emptying time after food intake. The increase in AUC_T in the 'fed' condition, however, suggests that, when amodiaquine is co-administered with food, its bioavailability is increased. Despite our small sample size, we detected the well-known amodiaquine-related adverse drug reactions. Clinically important adverse events were reported by a quarter of these volunteers, even though all were healthy and only two doses were administered two weeks apart (rather than the daily administration for 3 days recommended for malaria treatment).

Intake of amodiaquine with a high fat meal resulted in a statistically significant increase in blood levels of amodiaquine and desethylamodiaquine which may affect the safety and tolerability of the study drug.

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