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The Effect of Co-administered Drugs and Food on the Absorption of Artemether–Lumefantrine Tablet

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Authors' contributions

The work was done by both authors. Author SOA did the literature search and gathered the materials for the review. Author AOO supervised, scrutinized and edited the review. Both authors approved the final manuscript.

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ABSTRACT

The physicochemical properties of drugs, their dosage forms and routes of administration affect the rate and extent of drug absorption. Oral administration of drugs presents with variable absorption profiles due to multifarious factors. The first fixed-dose artemisinin-based combination therapy (ACT), artemether-lumefantrine widely employed for the treatment of uncomplicated *Plasmodium falciparum* malaria is being threatened by the report of rapidly developing drug resistance in some part of the world. Success from this therapy has been linked to the synergistic effect of the component drugs which is anchored on the artemether and more importantly, lumefantrine exposure. The drug and food effect on the pharmacokinetic profiles of artemether and lumefantrine antimalarial agents are reviewed.

Keywords: Food; drugs; artemether-lumefantrine; absorption; bioavailability; malaria.

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1. INTRODUCTION

The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) for the treatment of uncomplicated *Plasmodium falciparum* malaria [1]. Nigeria among many other African countries has selected artemether-lumefantrine (AL) as a first-line treatment for uncomplicated falciparum malaria [1-3]. AL is the only fixed-dose ACT that is deployed on a large scale. Clinical trials have demonstrated high efficacy with the current applied standard therapeutic AL dosage regimen but the real-life situations surrounding the use of the drug may present a different efficacy profile [4].

The real-life situations involve the physiological conditions of malaria patient, co-morbidities frequently experienced and other socio-cultural practices in that circumstance [5]. Patients with malaria are often averse to food such that food intake may be low during malaria episodes. The anorexia in malaria patients makes dietary advice difficult [5,6]. The concomitant administration of food has been reported to affect AL absorption [1,4,5]. Food intake significantly enhances the bioavailability of both artemether and lumefantrine and this being more apparent for the highly lipophilic lumefantrine component [1-6]. A meal with only a small amount of fat of about 1.6 g was considered sufficient to achieve adequate exposure to lumefantrine [6]. Lumefantrine has been reported to be absorbed and cleared more slowly (terminal elimination of 3 – 4 days in malaria patients) and accumulates with successive dose [7]. Variation in fat content of meals therefore may contribute to the erratic nature of lumefantrine pharmacokinetic profile thereby affecting treatment outcomes [8].

Studies on AL in healthy volunteers have not identified any clinically significant drug-drug interaction. Extensive studies on perceived co-administered drugs based on chronic ailments upon which malaria may suffice, such as hypertension, diabetes, arthritis among others, will be necessary in order to point out possible drug - drug interaction with malaria [9,10].

The structural conformation of lumefantrine to the aryl aminoalcohol group of antimalarials i.e. quinine, mefloquine and halofantrine, gives a pointer to describing the possible physicochemical behaviour of lumefantrine [11]. Halofantrine absorption is enhanced by co-administration with fatty meal just as lumefantrine is, in the event that the absorption of lumefantrine is enhanced beyond a safe level in the body, the dreaded side effect of QT prolongation for which halofantrine was withdrawn may be obvious. van Vugt and other researchers have reported that there was no toxicity with high systemic exposure of lumefantrine [11-13].

The nature and composition of food can vary considerably especially in African setting and more so considering the socio-cultural beliefs surrounding meal intake in malaria circumstances [5].

2. ARTEMETHER–LUMEFANTRINE PHARMACOKINETIC PROFILE

Artemether and lumefantrine exhibit complementary pharmacokinetic profiles. The peak concentrations of artemether and its main active metabolite dihydroartemisinin (DHA) occur at approximately 2 hours post-dose. The absorption of lumefantrine however starts after a lag-time of over 2 hours with peak plasma concentration at about 6 – 8 hours after administration [14,15]. The bioavailabilities of artemether and lumefantrine have been reported to have an increase of 2-fold and 16-fold, respectively following a high fat meal in healthy volunteers [16,17]. Food has also been reported to increase the bioavailability of lumefantrine by approximately 2-fold in malaria patients. This is probably due to the low volume of food ingested by acutely ill patients [4,18]. Artemether and lumefantrine are both highly bound to serum proteins to a high extent (95.4% and 99.7%, respectively). The active metabolite of artemether is however bound to serum protein to a lower extent (47- 70%), therefore more available [19].

Artemether is extensively and rapidly metabolised by the liver and it undergoes substantial first-pass metabolism. The liver microsomes CYP3A4/5 metabolize artemether to the biologically active DHA via demethylation [19,20].

A study conducted to compare the pharmacokinetics of artemether on administration of AL alone versus AL with mefloquine revealed a significant decrease in plasma concentration of artemether without a significant increase in DHA plasma concentration [17]. This is indicative of drug induced enzyme induction in the metabolism of artemether.

Similarly, lumefantrine is N-debutylated by CYP3A4 in human liver microsomes. N-desbutyl lumefantrine has been reported to have an in vitro antiparasitic effect 5 – 8 fold higher than the parent molecule [19-21]. The plasma concentration of N-desbutyl lumefantrine represents 1% of the parent exposure, in terms of the area under the curve (AUC) [21]. Artemether and DHA are rapidly cleared from plasma with an elimination half life of about 2 hours while lumefantrine is eliminated slowly with a terminal half life of 2 – 3 days in healthy volunteers and 4 – 6 days in patients with *P. falciparum* malaria [19,22].

Demographic characteristics such as gender and body weight have been reported to have no statistically significant effects on the pharmacokinetics of artemether and lumefantrine [21,23]. No urinary excretion data are available for the drugs in humans and no specific pharmacokinetics studies have been carried out in patients with renal or hepatic insufficiency, or in the geriatrics [19,24]. Studies conducted in infants and children with malaria in Africa, after a single dose of crushed tablet of AL, revealed that the artemether and DHA plasma concentrations were not significantly different from the data observed in adult malaria patients in Thailand [24,25].

3. ARTEMETHER/ LUMEFANTRINE INTERACTIONS WITH CO-ADMINISTERED DRUGS

Some specific pharmacokinetic and pharmacodynamic drug-drug interactions involving AL administration have been documented in a study with ketoconazole. The study evaluates the drug – drug interaction between ketoconazole a potent CYP3A4 inhibitor, in a randomized, open-label crossover trial performed in 16 healthy volunteers taking a single dose AL with a single dose or with multiple doses of ketoconazole [9]. There was a 2.4 fold increase in artemether, DHA and lumefantrine exposure without increased side effect or changes in electrocardiographic parameter. In another study involving co-administration with mefloquine and quinine, the sequential oral administration of mefloquine taken as 500 mg, 250 mg and 250 mg prior to 6 doses of 4 x (20/120 mg) tablets revealed no significant effect on the plasma concentrations of artemether or the artemether/DHA ratio. However, a 32% reduction in plasma exposure (Cmax and AUC) of lumefantrine was noted. Mefloquine - induced decrease in bile production has been recorded which may have a role to play in lumefantrine absorption. In clinical settings, the concurrent use or follow - up use of AL with mefloquine is not anticipated [17].

The potential pharmacokinetic interaction on concurrent administration of AL with quinine has been investigated. A randomized study of healthy volunteers given a 2-hour intravenous infusion of quinine at the time of the last dose of AL in a six-dose regimen revealed that there was no significant alteration in the pharmacokinetic profiles of either drug caused by the presence of the other. The plasma concentration of artemether and its active metabolite DHA was however reduced following the administration of quinine. Limited data exist with respect to co-administration of AL and anti-retroviral drugs in healthy or HIV - infected patients. A study conducted on the co-administration of lapinavir / ritonavir (400/100 mg twice daily) concurrently with AL resulted in 2.4 fold increase in lumefantrine exposure, a significant decrease in DHA exposure and a non significant decrease in artemether exposure. No change in DHA/artemether ratio and no alterations in the pharmacokinetics of lapinavir or ritonavir. Ritonavir like ketoconazole is a potent inhibitor of CYP3A4 hence the observed increase in lumefantrine exposure [9,26].

4. FOOD EFFECT ON CONCURRENT ADMINISTRATION WITH ARTEMETHER- LUMEFANTRINE

Food (especially dietary fat) has been reported to enhance the bioavailability of artemether and lumefantrine. A study using healthy volunteers ingesting AL tablets with a high fat meal and in a fasted condition leaves the clinical conditions of a malaria patient in between the two models. An acutely ill malaria patient may not comply with the dietary advice of ingesting the first dose with a fatty meal because of the nauseating and anorexic condition. The nature and quantity of food with the corresponding quantity of fat present may vary considerably among individuals and geographical settings. Various reports have been documented on the type of food and the estimated content of fat contributory to enhancement of lumefantrine absorption [5,6]. Table 1 expresses the different type of diet / drink co-administered that can enhance lumefantrine absorption [27]. The ingestion of

milk adds to the cost and complexity of malaria treatment especially in tropical countries where milk is not a common feature in diets and occurrence of high prevalence of lactose intolerance. The dose-response relationship with respect to varying geographical diets may give a proper clinical picture in those areas. The key or pivotal issue is adequate lumefantrine absorption/exposure. Fatty meals have been reported to increase lumefantrine exposure, the effect of other types of food on lumefantrine exposure have not been evaluated. The absorption of lumefantrine has been assessed in children with *P. falciparum* malaria in five African countries. The relative lumefantrine exposure in 315 children receiving AL within a randomized trial were analyzed according to concomitant consumption of different food stuffs or no food at all [28]. The relative increase in mean lumefantrine absorption was 1.57 in patients drinking milk and 2.74 in those eating pancakes compared with those who ate nothing [5,28].

The nature and composition of common meals in different geographical location vary. Table 1 shows the Food and Drug Administration (FDA) standard breakfast and the experimental breakfast in Uganda and Thailand [29]. Premji et al. [6] concluded in their work that African diet contained enough fat to give sufficient lumefantrine absorption. It will make more meaning to find out how much of fat that can give too low or high lumefantrine exposure as some African foods seldom contain essentially very high fat or devoid of it.

5. NIGERIAN DIET IN ACUTE MALARIAL CONDITIONS

Efficacy studies are undertaken under controlled conditions in which administered drugs are of assured quality and total adherence is guaranteed. Effectiveness trials are aimed at measuring how a drug would perform under real-life situations (i.e., how a drug performs when taken unsupervised). It will be needful to assess drug exposure from a typical diet in acute malaria in Nigeria. Nigeria has a population of over 140 million who are at risk of malaria and an established socio-cultural diversity with respect to meals taken at different seasons or time of the year. In malaria cases, meals are also defined and this seems to be related to the belief in some parts of the country. In Eastern Nigeria, it is believed that eating too much oil causes malaria. It is also believed that too much oil in meals can induce and aggravate the vomiting that accompanies acute malaria [30]. Some special diets in different parts of Nigeria given in acute malaria cases are detailed in Table 2.

Table 1. Food and Drug Administration Standard Breakfast and Experimental Breakfast in Uganda and Thailand [29]

Description	Content of breakfast
Food and Drug Administration	Two eggs; 2 strip bacon, 1 slice of toast with butter, 2 hash potatoes + 240 mL full fat milk.
Uganda	10 g fat from (300ml milk + 13 g peanuts.
Thailand	6.4 g fat content from (200 mL carton chocolate milk
	6.4 g fat from 250 mL chocolate milk
Sub Saharan Africa (Children)	15 – 30 g/day breast feeding
	10 g/day post weaning phase
	30 – 60 g/day normal diet.

Table 2. Commonly administered meals in acute malaria cases in different parts of Nigeria

Parts of Nigeria	Diets in malaria
Western region	Corn pap, Bean Cake
Northern region	Millet pap, fruits (Carrot etc.)
Eastern region	Corn pap, Cassava starch pepper soup, fruits

According to the report by Premji et al. [6] African diets consisted essentially of cereals (maize, millet, sorghum and rice) and the starchy roots (potatoes, sweet yam, yam and cassava). In Nigeria, as in other parts of Africa, the same types of food are embraced with minor difference with respect to the processing [5,30-33].

6. GASTRIC MOTILITY AND GASTRIC EMPTYING TIME

Disease state affects gastrointestinal (GI) motility and gastric emptying. Inter-subject variations in bioavailability of some drugs due to physiological factors have a complex interplay with the nature of food. The different types of food may alter gastric emptying time to varying extent and possibly the rate and extent of drug absorption. In a study on paracetamol, a commonly co-administered drug with AL involving 14 patients,

the maximum plasma concentration ranged from 7.4 – 37.0 mg/mL and the time to reach the maximum concentration ranged from 30 – 180 minutes. These parameters of bioavailability were related to the gastric emptying half-life found in these patients. The gastric emptying is principally affected by the patient's emotional state, certain drugs, types of food ingested and even the patient's posture after eating [34]. The effect of food and other physiological factors that may possibly affect gastric emptying in the presence of AL have not been evaluated.

Gastric emptying strongly affects the rate and extent of intestinal drug absorption and metabolism. Many disease conditions, drugs used to treat ailments or food intake affect stomach emptying and/or transit. A delay in stomach emptying may reduce the rate of drug absorption since the rate of drug delivery to the site of absorption is prolonged [35]. Table 3 gives an overview of the factors that affect gastric emptying and thereby the absorption of drugs.

Table 3. Factors affecting gastric emptying [34]

Factors	Influence on GE
Emotional state	
Stress	Increase or decrease
Depression	Decrease
Anxiety	Increase
Type of meal	
Fatty acids/fat	Decrease
Carbohydrates	Decrease
Amino – acids	Decrease
pH of stomach content	
Decrease	
Increase	
Disease state	Decrease
Gastric ulcers	Decrease
Hyperthyroidism	Decrease
Hyperthyroidism	
Drugs	
Amytryptyline	Decrease
Metoclopramide	Increase

Socio-culturally, drugs are believed to go with food and patients often use mealtimes to remind them to take their medications. The influence of food on drug absorption has long been recognized and several reports have been published on the influence of food on drug bioavailability. Food may influence drug absorption indirectly through physiological changes in the GI tract. The changes may be caused by the food and/or directly through physical or chemical interactions between the molecule of the drug and food components [29]. When food is ingested, stomach emptying is delayed, gastric secretions are increased stomach pH is altered and splanchnic blood flow may increase. Food may also interact directly with drugs either chemically (e.g., chelation or physically by absorbing the drug, thereby acting as a barrier to absorption). In general, gastro intestinal absorption of drug is favoured by an empty stomach as the nature of food-drug interaction is complex and unpredictable [29,35]. Ingestion of AL on empty stomach in acutely ill malaria patients has been welcomed with vomiting in most cases due to the disease state and odour of the drug.

7. DRUG PHYSICOCHEMICAL PROPERTIES AND ABSORPTION

The drug whether a weak base or a weak acid and its pKa determine the extent of ionization according to the pH partition hypothesis at various pH values (pH 1.3 for stomach and 6.0 for intestine). The concept of absorption potential was also used to describe absorbability based on the partition coefficient, the solubility, dose and fraction unionized. Lipophilicity is a major determinant for predicting the extent of membrane permeation and is often correlated with the partition coefficient [36,37]. For such drugs absorption is the rate limiting step while the converse is true for hydrophilic or polar agents [36]. In hydrophilic or polar drugs, the membrane resistance is higher than the aqueous layer resistance. However, when drugs possess both hydrophilic and lipophilic qualities, they permeate the membrane well so that blood perfusion rate becomes the overall rate-limiting step for absorption [38-40].

8. APPLICATION OF PHYSIOLOGICAL MODELS TO PREDICT FOOD EFFECT ON DRUGS

Most drugs are administered orally and the mechanism by which food changes the drug absorption is well understood. Increased systemic exposure of drugs with food is often seen for lipophilic drugs and is attributable to improved solubilization due to higher bile salt and lipid concentration. Negative food effects are seen for hydrophilic drugs where food impedes permeation. Qualitative prediction of food effect is often possible based solely on the Biopharmaceutical Classification System (BCS)

of the drug [35]. Many drugs have been categorized based on this scheme. Gu and co workers were able to categorize 80% of a set of 92 drugs as having negative, positive or no food effect based on their dose, solubility and permeability [34].

Table 4. Physicochemical properties of drugs and effect on absorption [39,40]

Drug class	Rate of absorption	Extent of absorption
Acid labile drugs	Reduced	Reduced
Insoluble drugs	Reduced	Increased
Drugs with good water and lipid solubility	Reduced	Unaffected

The use of physiological based absorption models incorporating biorelevant drug solubility measurements can give quite accurate quantitative prediction of food effect. Data relating to the physicochemical and *in vitro* drug properties, biorelevant solubility and dissolution, and *in vivo* pre-clinical and clinical pharmacokinetics are useful input for prediction of drug absorption (Table 4).

9. PHYSIOLOGICAL BASED PHARMA-COKINETIC MODELING APPLIED TO FOOD EFFECT

It is important to have a physiological based pharmacokinetic model applied to food effect on drugs. The model should account for impact of food on the GI tract physiology, drug dissolution and permeation. Lipophilic drugs such as lumefantrine are associated with increased systemic exposure which is attributable to improved solubilization facilitated by the intestinal fluid (containing high bile salt and lipid concentrations). Negative effects are seen with hydrophilic drugs where the drug permeation is impeded. This means that accurate qualitative prediction is based on the Biopharmaceutical Classification System (BCS) of the drug [37]. A physiological based absorption model can therefore be advanced and developed for food effect prediction by integrating various predictive data such as physicochemical drug properties, in vitro data, biorelevant dissolution data and an in vivo study results. Yu and Amidon reported on compartmental absorption and transit model (CAT). GastroPlus™, is the first physiological based absorption model to be produced as commercial software and based on CAT model. The CAT model has been developed further with the addition of features like pH - dependent solubility and permeability to produce the advanced CAT (ACAT) [36-38]. The ACAT model represents the GI tract and comprises of nine compartments corresponding to the stomach, duodenum, jejuneum (two compartments), ileum (three compartments), caecum and the ascending colon. The model highlights the pH, volume and permeability characteristics of the corresponding GI regions. The transit of drugs along the GI for each of the compartments is modeled as a first order process and the transit time is based on the physiological value for the corresponding region [37]. When a drug is considered, drug – specific input data for solubility, permeability, Log P, pKa, particle size, and dose are fed into the models of dissolution and absorption. For dissolution, a model based on the Nernst-Brunner modification of Noyes-Whitney equation is used [38,39].

10. PREDICTIONS OF SOLUBILITY, PRECIPITATION, DISSOLUTION RATE AND PERMEABILITY

The regional solubility of a drug based on the fraction ionized at each compartmental pH according to Henderson - Hasselbalch equation was described by Hendriksen. He showed that simulating the absorption for weak bases will require at least two measured values of solubility to characterize the solubility versus pH curves [39,40]. This determination involves the use of aqueous buffers in the models to give the desired pH. The estimation of *in vivo* solubility involves the presence of bile salts and lipids in the intestinal fluids. This has made the introduction of biorelevant media estimating biorelevant solubility expedient. Several studies have demonstrated the importance of biorelevant solubility measurements in media such as fasted state simulated intestinal fluid (FaSSIF). The use of FaSSIF is required for accurate simulation of absorption of very lipophilic drugs. In drugs where biorelevant solubility differs significantly from aqueous solubility such as lumefantrine, it is appropriate to consider the bile salt concentrations in the different parts of the intestine [38,39-44]. The factors that enhance bile secretion will help describe the pattern of absorption of drugs taken at that instance. About 95% of the released bile salts undergo entero-hepatic circulation with re-absorption occurring at the ileum.

11. FINAL REMARKS

The knowledge of the mechanism underlying the effect of food or drugs on the absorption of drugs can be applied to AL for reliable quantitative predictions to optimize the usefulness of the antimalarial drug. Furthermore, the application of models that can evaluate the effect of the different components of the diverse meal types in Africa will go a long way in predicting the levels of exposure of the drugs.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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