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Effects of antacids on the pharmacokinetics of lumefantrine in healthy volunteers: A pilot study.

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Abstract

Background: Artemether-lumefantrine (A-L), an artemisinin-based combination therapy (ACT), is a widely used antimalarial drug and it could be prescribed together with antacids since malaria may co-exist with peptic ulcer. This study aimed to determine possible interaction following concurrent administration of A-L and commonly used antacids, and to monitor possible corrected-QT (QTc) interval prolongation.

Methods: In a randomized crossover study, single oral dose of A-L (80/480 mg) tablet alone or in combination with antacid formulation (magnesium trisilicate, magnesium carbonate, sodium bicarbonate combination) were administered to 13 healthy volunteers after overnight fast. Blood samples were collected at predetermined time intervals and plasma samples for six volunteers were successfully assayed for lumefantrine using High performance Liquid Chromatography (HPLC). Electrocardiographic recording was carried out at predetermined times.

Results: The median lumefantrine $AUC_{0\text{-}96}$ of 173 µg.hr/ml (IQR: 72.11-688.51) and 221.96 µg.hr/ml (IQR: 64.21-465.47) were obtained when A-L was taken alone and in combination with antacid formulation respectively. The median lumefantrine C_{max} for A-L alone and for A-L plus antacid formulation were 5.92 µg/ml (IQR: 2.08-14.44) and 4.42 µg/ml (IQR: 3.84-14.30) respectively. The mean QTc intervals obtained at pre-dose, 6, 72 and 504 hours post-dose were 390.08±19.84, 406.23±19.04, 394.60±19.91 and 396.33±23.94 ms respectively. The lengthening of the QTc interval at 6 hr post-dose compared to zero (0) hr was statistically significant ($P<0.05$).

Conclusion: In this preliminary study, antacids did not appear to alter the reported erratic bioavailability of lumefantrine in human. Also, the limited increase in QTc interval caused by lumefantrine was not clinically significant.

Keywords: *Artemether-lumefantrine, QTc interval, antacids, antimalarial, drug interaction.*

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Résumé

Contexte: L'artéméther-luméfantrine (A-L), une association thérapeutique à base d'artémisinine (ACT), est un médicament antipaludique largement utilisé qui peut être prescrit avec des antiacides, car le paludisme peut coexister avec l'ulcère peptique. Cette étude visait à déterminer l'interaction possible après l'administration concomitante d'A-L et d'antiacides couramment utilisés, et à surveiller l'allongement possible de l'intervalle QT corrigé (QTc).

Méthodes : Dans une étude croisée randomisée, une dose orale unique de comprimé A-L (80/480 mg) seul ou en combinaison avec une formulation antiacide (trisilicate de magnésium, carbonate de magnésium, bicarbonate de sodium) a été administrée à 13 volontaires sains après une nuit de jeûne. Des échantillons de sang ont été recueillis à des intervalles de temps prédéterminés et des échantillons de plasma pour six volontaires ont été testés avec succès pour la luméfantrine en utilisant une Chromatographie liquide à haute performance (HPLC). L'enregistrement électrocardiographique a été effectué à des moments prédéterminés.

Résultats: La luméfantrine médiane $AUC_{0\text{-}96}$ de 173 µg.hr / ml (IQR: 72,11-688,51) et 221,96 µg.hr / ml (IQR: 64,21-465,47) ont été obtenues lorsque l'A-L était prise seule et en combinaison avec la formulation antiacide respectivement. La luméfantrine médiane Cmax pour A-L seul et pour A-L + formulation antiacide étaient 5,92 µg / ml (IQR: 2,08-14,44) et 4,42 µg / ml (IQR: 3,84-14,30) respectivement. Les intervalles QTc moyens obtenus avant administration de la dose, 6, 72 et 504 heures après administration étaient de 390,08 ± 19,84 ; 406,23±19,04 ; 394,60±19,91 et 396,33±23,94 ms respectivement. L'allongement de l'intervalle QTc à 6 heures post-dose par rapport à zéro (0) h était statistiquement significative (P0<05).

Conclusion: Dans cette étude préliminaire, les antiacides ne semblent pas modifier la biodisponibilité erratique de la luméfantrine chez les humains. De plus, l'augmentation limitée de l'intervalle QTc causée par la luméfantrine n'était pas cliniquement significative.

Mots - clés: *artéméther-luméfantrine, intervalle QTc, antiacides, antipaludéen, interaction médicamenteuse*

Introduction

Malaria disease burden continues to increase as the countries in which it is endemic face the risk of widespread resistance of the parasite to conventional anti-malarial drugs [1]. It is an important cause of death and illness in children and adults, especially in tropical countries. World Health Organization (WHO) recommended the use of artemisinin-based combinations (ACTs) in 2001 [2]. Artemether-lumefantrine (A-L) is the most widely used ACT today and is recommended as the first-line treatment in many tropical countries including Nigeria.

The combined effect of the drugs in the battle against malaria parasites is additional benefit of combination therapy. In the case of artemether-lumefantrine as stated by Lefevre *et al*, artemether has a short half-life (2-3 hrs in healthy individuals), and a fast onset of action, while lumefantrine with longer half-life has slow onset of action and hence clears residual parasite and prevents recrudescence [3]. A-L has a wide therapeutic index with high variability in lumefantrine plasma levels, mostly influenced by food intake. Lumefantrine plasma level has also shown to be influenced by other drugs such as mefloquine when the two drugs are co-administered [3].

This suggests the possibility of drug-drug interaction between A-L and other drugs. Although, A-L has a wide therapeutic window and is very effective against multi-drug resistant *Plasmodium falciparum* malaria, significant interaction may alter plasma concentration to such a degree that the clinical efficacy of the drug may be affected. *In-vitro* study showed that antacids *markedly* adsorbed lumefantrine [4], suggesting that antacids may decrease the bioavailability of lumefantrine and diminish its anti-malarial activity. Peptic ulcer may co-exist with malaria, hence such ulcer patients may be taking A-L with antacids.

Generally, drug-drug interaction is a common phenomenon in polypharmacy. It is therefore essential to investigate and confirm this *in vitro* result with *in-vivo* studies to predict the clinical implications. In addition, an antimalarial drug, halofantrine (an aryl amino alcohol), an antimalarial with similar structure to lumefantrine has been reported to have significant pharmacokinetic interaction with antacid in Nigerians [5].

Hence, it is important to also investigate *in-vivo* for possible interaction between lumefantrine and antacids, as information on this is lacking. Also, cardiotoxic potential of aryl amino class of antimalarial agents including halofantrine [6-8] and quinidine [9] has been reported. Although the reports so far indicated that lumefantrine has no potential cardiotoxic effect [10-12], QTc interval was monitored in this study to evaluate the effect of concomitant administration of antacids with lumefantrine on the QTc interval of lumefantrine. This study therefore evaluated the effects of antacids on the bioavailability of lumefantrine, it also monitored the QTc interval changes in healthy subjects.

Methods

Subjects

Thirteen (13) healthy subjects (10 males and 3 females) aged between 19 and 39 years and weighing between 51 and 88.5 Kg participated in the study. However, complete data for pharmacokinetic determination were obtained for six subjects (4 males and 2 females) aged between 19 and 35 years and weighing 19 to 70 Kg. Their vital signs (blood pressure, temperature) were checked by a physician prior to commencement of the study to ensure subject's eligibility to participate in the study. Subjects that are pregnant were excluded from the study. This study was approved by the joint University of Ibadan/University College Hospital (UI/UCH) Ethical Review Committee, University of Ibadan, Nigeria. The subjects were recruited after giving their informed consent.

Study design

The study was a randomized two-way, open label, crossover design in which subjects were randomized into two groups (Group 1 and Group 2). On the first day (first arm) of the study, after an overnight fast, 80/480mg Coartem® tablet was administered to the subjects under group 1 while subjects in group 2 were given 30ml of antacid (Moko® Mist.Mag Trisilicate) formulation commercially available, followed by 80/480mg Coartem® 10mins later. The subjects remained in a fasted state for up to 3 hrs post dose.

The antacid formulation used contains magnesium trisilicate, light magnesium carbonate and sodium bicarbonate. The formulation containing mixture of antacids was used in this study since in ideal clinical situation, antacids are usually prescribed as formulation of different antacids. After a washout period of three weeks, the drugs were interchanged between the two groups (Group 2 now took only 80/480mg Coartem® while group 1 took 80/480mg Coartem® and 30ml antacid). Drug administration was carried out by a Pharmacist. The subjects remained in the study site for 12 hours during each treatment period. Only twelve subjects returned for the second arm of the study. One subject

did not report. The same type of foods were given to the subjects during the study periods (During the first 12 hours of the two study arms) and none of the subjects took any other antimalarial drug for at least two weeks before commencement of the study. This study was carried out in the Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Ibadan. No other drug, alcohol or caffeine-containing beverage was allowed during the study periods. Participants were interviewed from time to time for possible adverse drug reaction.

Electrocardiographic evaluation

Electrocardiographic screening was performed on volunteers recruited for the study prior to drug intake (0), at 6, 72 and 504 hours post dose. This was performed by a consultant cardiologist at cardiology unit of the University College Hospital (UCH), Ibadan. The computer ECG readings were confirmed manually by the cardiologist. The mean QTc interval at 0 hour was compared with the mean QTc interval at 6, 72, and 504 hours post dose.

Sample collection

Venous blood (4ml each) was collected at pre-dose (0) and at, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours post dose from each volunteer in the first arm of the study, while in the second arm, venous blood (4ml each) were collected at pre-dose (0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 144, 192 and 240 hours post dose from each volunteer. The blood samples were collected by venipuncture by Phlebotomists and transferred into lithium heparin tubes. The samples were centrifuged immediately at 4000 rpm for 5 minutes and the plasma was transferred into cryo vials and stored at -20°C until analyzed.

Lumefantrine analysis

The plasma samples were analyzed for lumefantrine using High Performance Liquid Chromatography (HPLC) method.

Chemicals and reagents

Lumefantrine reference standard was obtained from United State Pharmacopoeia (USP), USA through the Centre for Drug Discovery, Development and Production (CDDDP), University of Ibadan. All chemicals and solvents used in this study were of analytical grade. HPLC grade acetonitrile and methanol were purchased from suppliers. The brands used were; Sigma Aldrich (Germany) for acetonitrile and methanol, and ortho-phosporic acid; JT Baker (USA). Tetrahydrofuran (THF) obtained was also Sigma Aldrich (Germany) and potassium dihydrogen phosphate was SCP (England).

Chromatographic condition

Chromatography was performed with a HPLC system (Agilent Technologies 1200 series) consisting of a quaternary pump, a syringe loading sample injector with a 20 µl sample loop coupled to a variable wavelength detector (VWD) which was operated at 265nm. Chromatographic separations were performed on a C_8 reversed phase Zorbax Eclipse XDB 150 x 4.6mm, 5 µm particle size at ambient temperature. The mobile phase consisted of acetonitrile: 25 mM KH_2PO_4 buffer (70:30 v/v) adjusted to pH of 4.0 with orthophosphoric acid and pumped at a flow rate of 1ml/min. Halofantrine was used as an internal standard.

Extraction procedure

For plasma drug extraction, 12 µl of 500 µg/ml halofantrine internal standard was added to 0.4 ml of plasma in a 5ml extraction tube. An amount (0.788 ml) of chilled acetonitrile was added (for protein precipitation) to the measured plasma containing the internal standard to obtain a final volume of 1.2 ml. Thereafter, it was vortex mixed for 1 minute and centrifuged at 4000 rpm for 5 minutes. The supernatant was injected into the HPLC. The concentration of halofantrine in the final solution was 5µg/ml.

Preparation of lumefantrine and halofantrine stock solutions

Stock solutions containing 1 mg/ml lumefantrine was prepared by first dissolving lumefantrine in THF and making up to the required volume with 50% tetrahydrofuran in acetonitrile. Series of standard solutions were made from the stock solution using the same solvent. Stock solution containing 1 mg/ml halofantrine was also prepared in methanol and 500 µg/ml halofantrine was made from the stock. The standard solutions of lumefantrine and halofantrine prepared were used to spike the drug free plasma to make a calibration curve. The percent coefficient of variation (% CV) for intra day precision was lower than 4% with a range of 1.31-3.96%, while % CV for the interday ranged from 4.0-19.34% with 19.34 % obtained for the lowest concentration. The percentage deviation of the mean value for the three concentrations determined from the true value (a measure of the accuracy) ranged from 0.7-4.2%

Pharmacokinetics and statistical analysis

Pharmacokinetic parameters were determined using WinNonlin version 5.3. The Mann-Whitney U test

was used to compare pairs of data between treatments for Area Under the Curves (AUCs) and peak plasma concentration (Cmax). The student t-test was used to compare difference in the mean QTc intervals at 0 hour compared to 6, 72 and 504 hours. A *P*-value of 0.05 was considered significant.

Results

Pharmacokinetic parameters of lumefantrine

No adverse reaction was reported by any of the volunteers hence artemeter-lumefantrine was well tolerated. Lumefantrine was also well resolved from halofantrine (internal standard) with retention times of 2.9 and 4.1 minutes for halofantrine and lumefantrine respectively.

The median lumefantrine $AUC_{0\text{-}96}$ when the drug was taken alone and in combination with antacids were 173 (IQR: 72.11- 688.51) and 221.96 µg.hr/ml (IQR: 64.21- 465.47) respectively, while the median peak plasma concentrations of lumefantrine were 5.92 µg/ml (2.08- 14.44) and 4.42 µg/ml (3.84- 14.30) following administration of the drug alone and after co-administration with antacids respectively. Table 1 shows the result of the Mann-Whitney U test for the comparison of pairs of data for AUC and C_{max} while Table 2 shows other pharmacokinetic paramaters obtained for lumefantrine from each of the six volunteers after administration of 80/480 mg artemether-lumefantrine (coartem®) and when coartem® was co-administered with 30 mls of antacid formulation.

Table 1: Comparison of AUC and C_{max} between treatments

Outcome	Drug Lumenfantrine *Median (IQR)*	Lumenfantrine + Antacid *Median (IQR)*	U test	P
$AUC_{0\text{-}96}$ (µg.hr/ml)	173 (72.11, 688.51)	221.96 (64.21, 465.47)	17.00	0.94
C_{max} (µg/ml)	5.92 (2.08, 14.44)	4.42 (3.84, 14.30)	14.00	0.59

IQR- Interquartile range

Electrocardiographic evaluation

Of the thirteen volunteers with electrocardiograms recorded, 76.9% were males and 23.1 % were females. Table 3 compares mean QTc interval values at pre-dose with mean QTc interval at 6, 72 and 504 hours post- dose for the thirteen volunteers evaluated. However, only ten and twelve volunteers were evaluated at 72 and 504 hours respectively. The other subjects did not report at that time. For the group that took A-L with antacid (with lower mean AUC), there was 2.95% lengthening of the mean QTc interval from zero (0) to 6 hours, while for the group that took A-L alone, there was about 5.5% lengthening of the mean QTc interval from 0 to 6 hours.

Table 3: Comparison of mean QTc interval at 0 hr for the thirteen volunteers with mean QTc intervals at 6, 72 and 504 hr.

	No of volunteers (N)	Mean QTc ± SD (ms)	p-value
QTc 0 hr and QTc 6 hr	13	390.08 ± 19.84 406.23 ± 19.04	0.01[a]
QTc 0 hr and QTc 72 hr	10[b]	389.40 ± 16.66 394.60 ± 19.91	0.30
QTc 0 hr and QTc 504 hr	12[c]	390.08 ± 19.20.73 396.33 ± 23.94	0.13

a Statistically significant
b 10 volunteers reported at 72 hr, their mean QTc value at 72 hr was compared to the mean QTc value for onl the 10 volunteers at 0 hr.
c 12 volunteers reported at 504 hr

Discussion

A-L is the most widely used ACT today and is recommended as the first-line treatment in many tropical countries. It is essential that the safety and pharmacokinetics of this treatment be well characterized when A-L is co-administered with antacids since patients can have medical conditions warranting that. Based on the evidence that antacid affected the pharmacokinetics of halofantrine and on the fact that no information exists on the *in-vivo*interaction between antacids and lumefantrine, we hypothesized that antacids may affect the plasma levels of lumefantrine. To test this hypothesis, we carried out an *in-vivo* study in humans and plasma samples were analysed for lumefantrine.

Table 2: Pharmacokinetic parameters of lumefantrine (LF) obtained following single oral dose of 80/480 artemether-lumefantrine alone and when co-administered with antacids to six volunteers.

Sub.	Weight (kg)[a]	C_{max} (μg/ml)[b]		t_{max} (hr)[a]		AUC_{0-96} (μg.hr/ml)[b]		$t_{1/2}$ (hr)[a]		Cl/f (L/hr/kg)[a]		Vd/f (L/kg)[a]		
		A-L	A-L+	A-L	A-L+	A-L	A-L+	A-L	A-L+	A-L	A-L+	A-L	A-L+	Alone
Ant.	Alone	Ant.	Alone	Ant.	alone	Ant.	alone	Ant.	alone	Ant.				
002	54	8.60	4.74	4	12	197.056	227.39	66.22 (2.75 days)	46.0 (1.92 day)	0.03	0.03	2.78	2.12	
005	58	2.39	3.47	4	3	73.42	60.24	14.79	57.59 (2.4 days)	0.11	0.08	2.30	6.66	
006	59.5	1.16	4.09	96	1	68.19	65.53	-	59.74 (2.49 days)	-	0.08	-	6.93	
014	70	3.24	20.91	96	10	149.56	395.18	130 (5.42 days)	44.32 (1.85 days)	0.02	0.01	2.91	0.80	
015	61.5	11.99	12.10	72	48	603.38	676.33	268.38 (11.18 days)	53.35 (2.22 days)	0.008	0.007	0.70	0.51	
016	51	21.77	3.96	48	72	943.88	216.52	92.04 (3.84 days)	-	0.009	-	1.21	-	
=	=	5.92 = 14.44)	8.21 (72.11-7.01	53.33 (64.21-42.16	24.3 = 28.95	173 = 688.51)	221.96 = 465.47)	114.29 = 95.78	52.2 = 6.85	0.035 = 0.043	0.041 = 0.036	1.98 = 0.98	3.40 = 3.16	(2.08-

a = mean ± SD, b = median (IQR), Sub. = subjects, A-L = artemether-lumefantrine (Coartem®), Ant. = Antacid

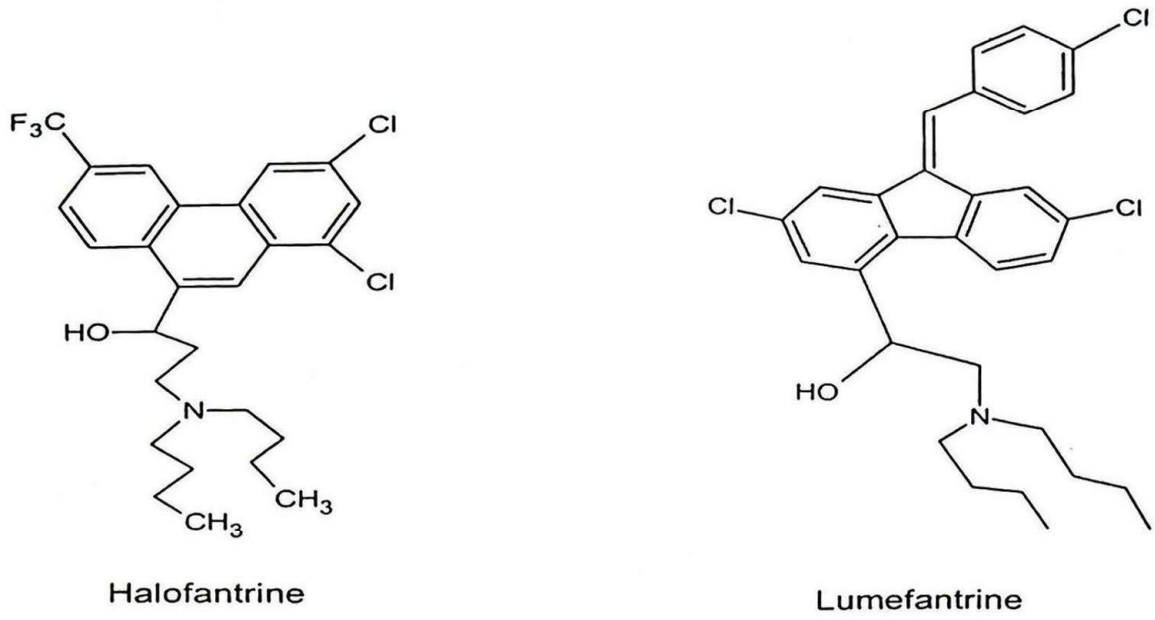

Fig 1: Structures of halofantrine and lumefantrtine

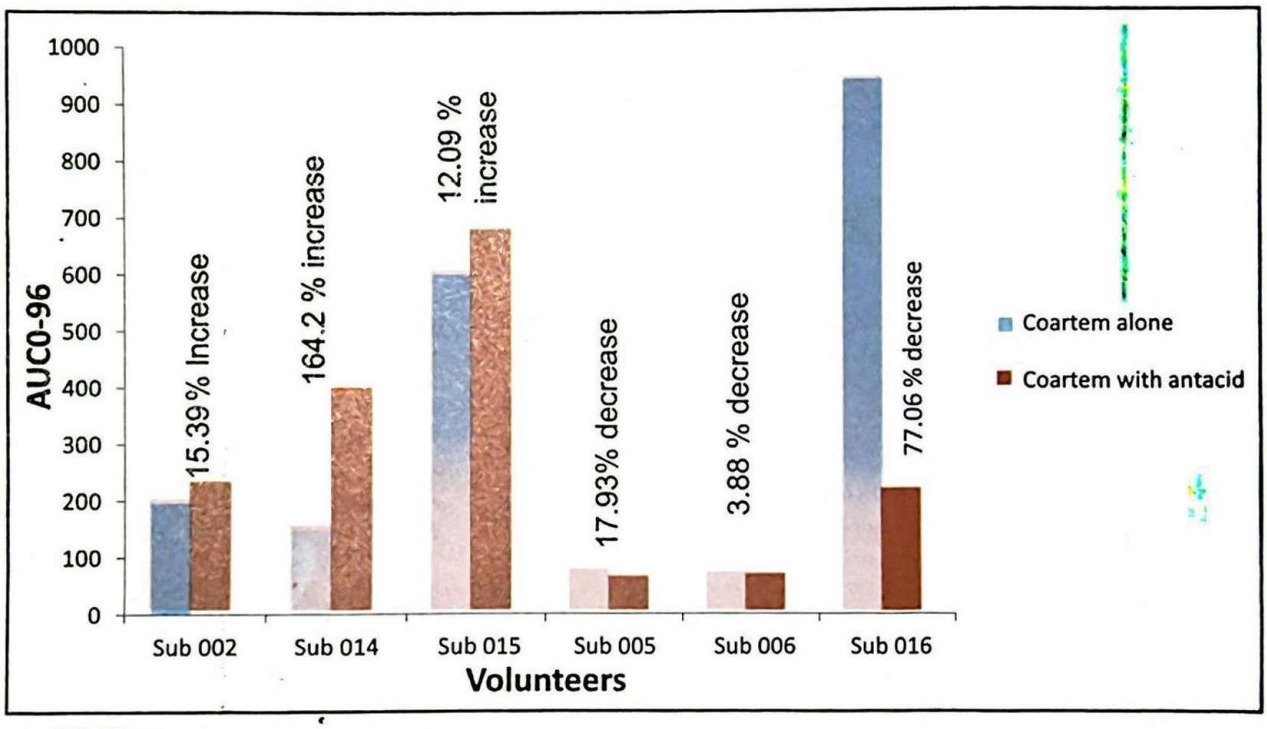

Fig 2: Comparison of AUC_{0-96} of lumefantrine when artemether-lumefantrine was taken alone and when taken with antacids.

A wide variability in AUC existed within and between subjects. This is comparable to the reports that lumefantrine has a low and variable bioavailability, with very erratic absorption. The absorption of lumefantrine is dependent on food especially fatty foods hence, a 16-fold increase in bioavailability of lumefantrine when taken with fatty food has been reported [13, 14]. Levefre *et al.* reported mean AUC_{0-264} value of 195± 119 μg.hr/ml for lumefantrine [15]. In another study, they reported mean AUC_{0-816} value of 2290±1450 μg.hr/ml and a median time of peak plasma concentration (t_{max}) of 64 hour (54-70) for lumfantrine [3], in healthy Caucasian subjects. This result is comparable to the large variations in AUCs observed in the present study. However, there was no significant difference between the median AUCs obtained in this study for both treatments ($P > 0.05$).

The volunteers were in a fasted state during drug administration and for up to 3 hours post dose. The fasting state may contribute to the low and variable AUCs observed. In addition, lumefantrine is a substrate of permeability glycoprotein (p-gp) [16] and active efflux by P-gp across the intestine could partly contribute to the low/variable bioavailability of lumefantrine. Also, p-gp is polymorphic [17] and therefore may be expressed differently in different individuals thereby leading to variation in lumefantrine AUC in volunteers. Furthermore, lumefantrine is predominantly metabolized by CYP3A4 [18] and this enzyme was shown to be polymorphic [19].

In the presence of polymorphism, high C_{max} and AUC may be observed due to poor metabolism of the drug. The AUCs reported from previous studies [3, 15] were in healthy Caucasian volunteers, this study is unique in that it was conducted on Africans. The difference in values obtained compared to the reported AUCs in Caucasians may be as a result of genetic polymorphism of CYP3A4. It has also been reported that lumefantrine concentration and AUC values measured in two Malaysian volunteers were much higher than the values obtained with Chinese volunteers [20].

The median C_{max} obtained after administration of A-L alone was higher than the value obtained when the A-L was given in combination with antacids. However, the difference in the median C_{max} was not statistically significant ($P > 0.05$). This is in contrast with significant reduction in C_{max} and AUC reported when halofantrine, a similar drug, was co-administered with magnesium carbonate [5]. Figure. 2 which compares the AUCs obtained when A-L was taken alone and when combined with antacids, revealed that 50% of the volunteers had their AUCs increased when A-L was co-administered with antacids. Weakly acidic or weakly basic drugs are normally absorbed in their unionized form and lumefantrine is a weakly basic drug with pKa of 9 [21].

In the intestine (where most drug absorption occur) with pH of about 6.8, lumefantrine exists more in ionized compared to unionized form. Antacids increase the pH of a medium and consequently, can cause rise in gastric pH [22]. Hence, taking antacid formulation with A-L, may raise the pH of the gastrointestinal tract thereby causing more of the lumefantrine to be in unionized absorbable form. The rise in pH could increase the percentage of the drug absorbed, hence increase in the AUCs observed in some subjects. On the other hand, the other half of the volunteers had their AUCs decreased when A-L was given together with antacids. This decrease is similar to the *in-vitro* result where antacids were found to directly adsorb lumefantrine significantly [4]. The observed decrease in AUCs in some subjects could be as a result of adsorption of the drug by the antacids which in turn, reduced the percentage of the drug absorbed. The reason why one half of the participants showed decrease and the other half increase in AUC is unclear.

These differences in C_{max} and AUC confirmed the erratic nature of lumefantrine bioavailability between individuals and races. Genetic polymorphism in CYP3A4 may be a contributing factor to these variations. However, conclusion can only be made if genotype studies are carried out in different races and individuals to determine the expression of CYP3A4 and the effect of the genotypes on lumefantrine concentration. The small sample size in our study is a limitation and may have biased the results obtained. Another limitation of this study was the 17 months delay in analysis of plasma samples after sample collection, also the stability of lumefantrine was not determined.

However, the samples were constantly monitored to ensure they remained in frozen states during storage. Again, blood sample collection was truncated at 96 hour in the first arm which did not allow for evaluation of the terminal phase of lumefantrine pharmacokinetic parameters because of its long half-life. Nevertheless, the sampling time was extended to 240 hour to allow evaluation of the terminal phase pharmacokinetic parameters in the second arm but the effect of antacids on the C_{max} and AUC was evaluated from zero time to 96 hours.

Furthermore, abnormal QTc prolongation on the electrocardiogram is an independent risk factor for sudden cardiac death [23]. From the results of electrocardiographic recording carried out in this study as shown in Table 3, it could be seen that at 6 hour, which was about the t_{max} for some volunteers, there was significant ($P < 0.05$) prolongation of QTc interval. Again at 72 and 504 hour, the mean QTc interval became lower than what was obtained at 6 hour. This is an indication that, QTc interval prolongation depended on the plasma concentration of lumefantrine. Similar report was given for halofantrine (a similar drug); the QT interval lengthening of halofantrine was dependent on the dose [6]. In addition, the 2.95% lengthening (from zero to 6 hours post dose) of the mean QTc interval for the group that took A-L with antacid (with lower median C_{max}) compared to 5.5% lengthening for the group that took A-L alone, may not be significant, however, lower percentage lengthening of the QTc interval observed for the group that took A-L with

antacids (with lower median C_{max}) further suggests the dependence of QTc interval prolongation on the plasma concentration of lumefantrine.

Although, there was statistically significant prolongation of mean QTc interval at 6 hours post dose (406.23±19.04 ms) when compared to the mean value at zero hour (390.08±19.84 ms), the prolongation was still within normal limits and hence may not lead to cardiotoxicity since abnormally prolonged QTc interval in men should be >450 and >470 ms in women [23]. This result showed that lumefantrine is well tolerated which is in agreement with previous reports which suggested that lumefantrine has no cardiotoxic potential [10-12, 24, 25].

In conclusion, this preliminary study showed that antacids did not significantly influence the bioavailability of lumefantrine in human. Lumefantrine's erratic bioavailability was also observed in co-administration of antacid with lumefantrine. Also the significant prolongation of the QTc interval by lumefantrine at 6 hours post-dose showed no evidence of potential cardiotoxic effect. Hence the treatment was well tolerated. However, further studies with larger sample size as well as in fed state is recommended. This may be necessary to confirm this finding and the clinical implications since QTc interval prolongation seem to be dependent on lumefantrine concentration and food is also known to cause significant increase in the lumefantrine area under the curve (AUC).

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