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Pharmacokinetics of Amodiaquine after a Single Oral Dose in Ghanaian Children with Uncomplicated Malaria

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Abstract

Fifteen (15) Ghanaian children with uncomplicated malaria were administered oral amodiaquine (AQ) suspension (10 mg/kg body weight) in a single dose study. Urine samples were serially collected over a 30 h period and AQ in the unmetabolized form was determined by ultraviolet spectroscopy. The pharmacokinetic parameters investigated were the fraction of administered dose eliminated in the unmetabolized form in urine (fe), elimination rate constant (kel), elimination half-life ($t_{1/2}$), excretion rate constant (ke), metabolic rate constant (km), absorption rate constant (ka), and absorption half-life ($t_{1/2}a$). Extremely low fe values were obtained with a range of 0.0035 to 0.0083; mean, (0.0059 +/- 0.0011). The kel ranged from 0.1283 to 0.1823 h^{-1}; mean: 0.1553 +/- 0.0126 h^{-1}. The corresponding $t_{1/2}$ ranged from 4.0845 to 5.6647 h; mean: 4.8746 +/- 0.3691 h. The km ranged from 0.1280 to 0.1816 h^{-1}; mean: 0.1548 +/- 0.0125 h^{-1}, with a corresponding ke of between 0.0004 and 0.0012 h^{-1}; mean: 0.0008 +/- 0.0002 h^{-1}. Ka values of between 0.3586 and 0.5418 h^{-1}; mean: 0.4502 +/- 0.0428 h^{-1} were obtained. The corresponding $t_{1/2}a$ values estimated ranged from 1.4129 to 2.0271 h; mean: 1.7200 +/- 0.1435 h. The $t_{1/2}$ of AQ for Ghanaian males used was significantly higher ($p < 0.05$) than the females. Differences in pharmacokinetic parameters of AQ observed between Ghanaian children and those in the literature could be ascribed to factors such as variations in methodology of measurement, drug formulation, gender, state of health and ethnicity. The study confirmed the rapid absorption, extensive hepatic first-pass metabolism and low urinary excretion of unmetabolised AQ when administered orally.

Keywords: Amodiaquine, desethylamodiaquine, Urinary excretion, Elimination rate constant, Absorption rate constant, non-compartmental pharmacokinetics

INTRODUCTION

Malaria continues to be a major public health problem in the developing world especially in Sub-Saharan Africa, Latin America, and South East Asia. In areas of active malaria transmission the disease symptoms are more severe in infants, young people and pregnant women [1, 2]. In Sub-Saharan Africa, the burden of non-severe malaria fevers in 2000 was approximately 116 million clinical episodes in children under five years of age of which about 0.5 % progressed to severe hospitalized cases [3]. Despite the fact that malaria is endemic in most tropical regions, a total of 90 % of the disease-associated mortality occurs in Sub-Saharan Africa [2]. As a result of increased resistance to chloroquine and sulphadoxine-pyrimethamine observed in the 1990's leading to massive treatment failures, the WHO in 2001 recommended Artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria in endemic African countries. In Ghana artesunate-amodiaquine and artemether-lumefantrine are the first line ACTs for the treatment of uncomplicated malaria [4].

Amodiaquine (AQ) [4-(7-chloro-4-quinolylamino)-2-(diethylaminomethyl) phenol dihydrochloride] (Figure 1) is a 4-aminoquinolene antimalarial which act by inhibiting the degradation of haemoglobin in the food vacuole of plasmodium parasite [5]. After oral administration, AQ undergoes rapid and extensive metabolism in the hepatic system, to the active metabolite desethylamodiaquine (DEAQ) through a polymorphic CYP2C8 enzyme [6, 7]. The other minor metabolites are 2-hydroxy-desethylamodiaquine and N-bisdesethylamodiaquine (bis-DEAQ). Though both AQ and DEAQ have antimalarial activity *in vitro* [8, 9], DEAQ is assumed to be responsible for most of the antimalarial activity of the parent drug, AQ. In adults, the half-life of AQ is 4 h while that of DEAQ is between 3-18 days [10, 11].

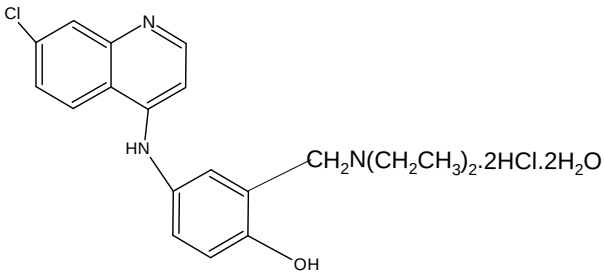

Fig. 1: Chemical structure of amodiaquine (AQ)

Recently, there have been reported cases of adverse effects associated with oral administration of AQ in Ghana, especially among children. These adverse effects are suspected to be caused by inappropriate dosing regimens of the drug. In spite of the extensive use of AQ, either in monotherapy or combination therapy in the treatment of uncomplicated malaria in Ghana and other developing countries for many years, the pharmacokinetic data of AQ in children is virtually non-existent in Sub-Saharan Africa and other

developing countries [12-16]. There is virtually no detailed pharmacokinetic study of AQ involving different subjects in terms of age, gender, race, and varying methods of drug analysis within the Sub-Saharan Africa region. In the West African sub-region for instance, pharmacokinetic investigations of the drug in only five Nigerian adults was found in the literature [17].

The practice of deducing paediatric doses by adjusting adult doses for body surface area or body weight is often inadequate particularly for the antimalarials. A better understanding of the pharmacokinetic profile of oral AQ in children would therefore facilitate its successful antimalarial therapy in Ghana and the West African sub-region. This study therefore seeks to investigate the pharmacokinetics of AQ, administered orally to Ghanaian children with uncomplicated malaria in South Suntreso Government Hospital, Kumasi, Ghana. The pharmacokinetics of AQ was based on urine data obtained after oral administration of AQ suspension to the children. The data obtained was compared to pertinent literature values.

MATERIALS AND METHODS

Amodiaquine powder (Purity: 99.5 % w/w; Manufacturing date: September 2005; Expiry date: September 2009) (Fisons Laboratories, UK), amodiaquine suspension (Manufacturing date: August 2006; Expiry date: August 2010) (Pfizer Ltd, UK), diethylamine and toluene (BDH Ltd. Poole, England) and isopropanol (Merck, Germany) were used.

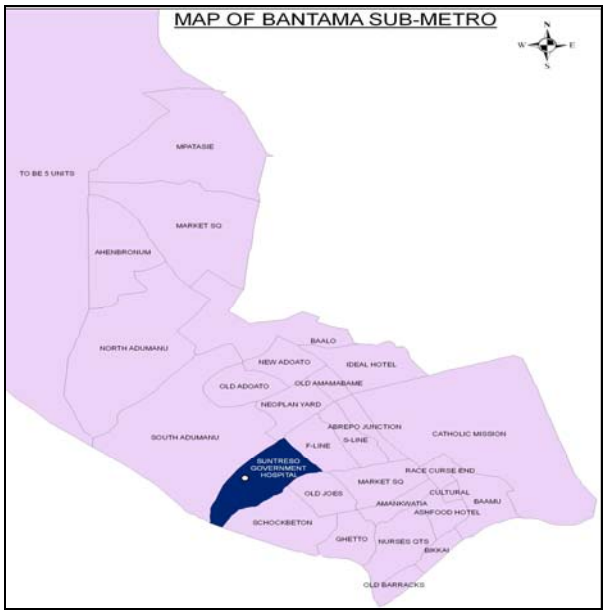

Fig. 2: Map of Bantama Sub-Metro in Kumasi, Ghana, showing Suntreso Government Hospital, the study site

Study site

The study was conducted at Suntreso Government Hospital, located in the Bantama Sub-Metropolitan area of Kumasi, the second largest city in Ghana (Figure 2). The study site selection was based on the high incidence of malaria in the Bantama Sub-Metropolitan area and the high enthusiasm and maximum co-operation shown by the medical staff of the hospital, especially the Medical Superintendent and the nurses at the children's ward.

Study design

Fifteen (15) Ghanaian children (7 males and 8 females) of ages between 8 and 12 years (mean: 10.10 +/- 0.7 years), confirmed clinically by a medical practitioner to have febrile illness and *Plasmodium* parasitaemia, were recruited into the study. The selected patients were all inpatients at the hospital and were capable of taking drugs orally. Exclusion criteria used were failure by parent/guardian to provide informed consent, history of liver or kidney diseases, severe malnutrition and severe or complicated malaria. Prior to AQ administration to the patients, blank urine samples were collected overnight. AQ suspension was administered orally to the patients (10 mg/kg body weight, single dose) after which urine samples were serially collected over a period of 30 h. Both the blank and test urine samples were frozen immediately after collection and kept at approximately 4^{o} C in a refrigerator until analysis [18]. The study was approved by the Ethics Committee of Suntreso Government Hospital, Kumasi, Ghana.

Determination of amodiaquine in urine samples

The liquid-liquid extraction technique with minor modifications was employed in the extraction of AQ from the urine samples [18]. Ten (10) ml of the urine samples (both control and test) was pipetted and transferred into a 125 ml separating funnel. A solvent system made up of diethylamine-toluene-isopropyl alcohol (1:4:5 v/v/v), was used to extract AQ from the urine samples [18]. The extraction of AQ in the urine samples was achieved using two successive 5 ml portions of the solvent system into a 10 ml volumetric flask. The absorbance of the combined extract was determined with an ultraviolet spectrophotometer (Cecil CE 8020, Cecil Instruments, UK) at a wavelength of 340 nm. The amount of AQ in test urine samples was determined using regression data obtained from calibration plots of AQ (1 – 5 µg/ml) in blank urine. The concentration values obtained were used to complete urinary excretion-time plots for the patients.

Pharmacokinetic analysis

The study employed only urine data analysis. A non-compartmental model concept of method of residuals was applied to the excretion rate – time curve to investigate the absorption kinetics of the drug [19]. Pharmacokinetic parameters estimated from this analysis include the absorption rate constant (ka), and absorption half-life ($t_{1/2}a$), elimination rate constant (kel) and elimination half-life ($t_{1/2}$). A fit of one-compartmental with a first order elimination or monoexponential decay to the amount of drug remaining to be excreted (A.R.E.) data led to the estimation of other pharmacokinetic parameters, namely: the fraction of administered dose eliminated in the unmetabolized form in urine (fe), excretion rate constant (ke) and the metabolic rate constant (km). The pharmacokinetic parameters of AQ obtained in the current study were compared to that of literature values [10, 17] using the Student's t-test. P-values < 0.05 were considered to be significant.

RESULTS AND DISCUSSION

Table 1 and Figure 3 show the AQ urinary excretion data and urinary excretion – time curves for patient 001. Similar results were obtained for the other patients used in the study. Analysis of the urinary excretion – time curves resulted in the estimation of the absorption rate constant ka, and its corresponding absorption half-life ($t_{1/2}a$). Table 2 shows the pharmacokinetic data of AQ determined for the 15 Ghanaian children used in the study. Generally, high absorption rate constant (ka) values of orally administered AQ were observed in all the patients thereby indicating faster rate of absorption. Accordingly, the corresponding absorption half life ($t_{1/2}a$) values were generally low. The high ka values observed confirmed AQs rapid absorption following its oral administration [20].

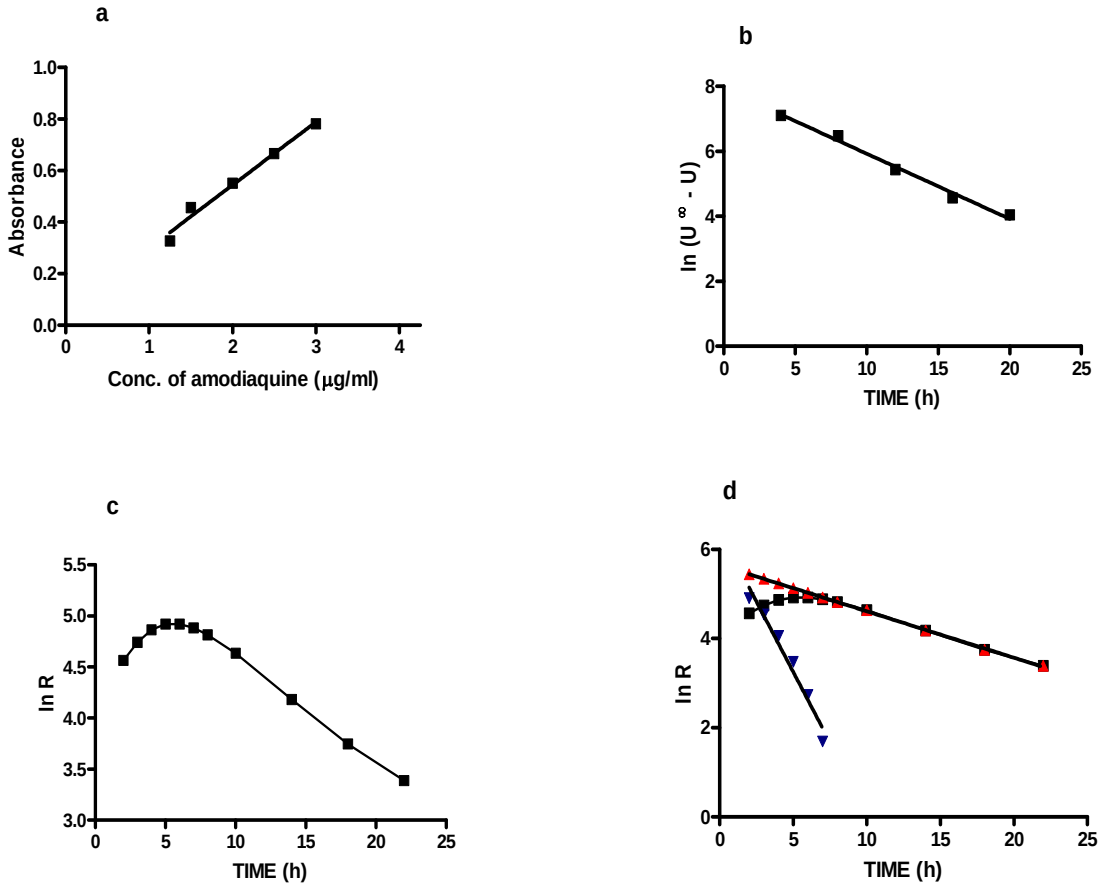

Fig. 3: Urinary excretion-time plots for Patient 001. a) Calibration curve, b) A.R.E plot, c) Excretion rate plot, d) Residual plot (U = cumulative amount of unmetabolised AQ in urine; U^{∞} = cumulative amount of AQ excreted unchanged at time infinity; R = rate of excretion; A.R.E = amount of AQ remaining to be excreted)

Table 1: Urinary excretion data for patient 001

Test samples	*Time interval dt. (h)*	*Urine vol. (ml)*	*Urine conc. (μg/ml)*	*Amt. excreted du. (μg)*	*Cum. Amt. excreted U. (μg)*	*Midpt. time t. (h)*	*Rate of excretion du/dt (μg/ml)*	*A.R.E U^{∞}-U. (μg)*
T1	0 – 4	50	8.0785	405.0	405.0			1585.8
	4.00					2	101.25	
T2	4 – 8	48	11.7186	561.6	966.6			1024.2
	4.00					6	140.40	
T3	8 – 12	74	5.7022	421.8	1388.4			602.4
	4.00					10	105.45	
T4	12 – 16	500	0.2667	350.0	1738.4			252.4
	4.00					14	87.50	
T5	16 – 20	261	0.1481	104.4	1842.8			148.0
	4.00					18	26.10	
T6	20 – 24	148	0.3853	148.0	1990.8			0.0
	4.00					22	37.00	

U = cumulative amount of unmetabolised AQ in urine; U^{∞} = cumulative amount of AQ excreted unchanged at time infinity; A.R.E = amount of AQ remaining to be excreted

The data from the study showed extremely low fe (fraction of administered dose eliminated in the unmetabolized form in urine) values of oral AQ in the patients. This is an indication of the drug's extensive first-pass metabolism by the hepatic system. This effect involves the biotransformation of AQ to various metabolites which includes the major metabolite DESQ. This principal metabolite, DESQ, has been established to be more active, *in vivo,* than the parent drug, AQ [21]. The absolute value of fe may serve as an indication of the bioavailability (F) of the drug under investigation. A high fe value is generally, an indication of high bioavailability and hence high levels of plasma concentrations of the drug under investigation. However, in the case of AQ, the biotransformed compound DESQ is the more active compound. Hence a low fe value of AQ would have no overall negative effect on the bioavailability of the parent compound.

The km (metabolic rate constant of the fraction of administered dose eliminated in the metabolized form in urine) values at 95 % CI observed ranged from 0.1280 to 0.1816 h^{-1}, mean: 0.1548 +/- 0.012 h^{-1}. Ironically, the estimated mean km value was almost identical to the estimated mean of the overall elimination rate constant kel value of 0.1553 +/- 0.0126 h^{-1}. This is a further reflection of AQ's extensive metabolic clearance. The secondary pharmacokinetic parameter ke (elimination rate constant of the fraction of the administered dose eliminated in the unmetabolized form in urine) estimated at 95 % CI limits ranged between 0.0004 and 0.0012 h^{-1}, mean: 0.0008 +/- 0.0002 h^{-1}. Generally, low ke values were observed in all the patients compared with the corresponding km values. These observations, once again indicate that AQ undergoes extensive metabolic clearance and that its renal clearance is relatively low [22].

Other pharmacokinetic parameters of oral AQ of valuable clinical importance estimated were the elimination rate constant (kel) and its corresponding elimination half life ($t_{1/2}$). The urinary excretion rate - time data obtained was subjected to non-compartmental model analysis from which kel of AQ was calculated. From Table 2, kel at 95 % CI ranged between 0.1283 and 0.1823 h^{-1}, mean: 0.1553 +/- 0.0126 h^{-1} while $t_{1/2}$ at 95 % CI ranged from 4.0845 to 5.6645 h, mean: 4.8746 +/- 0.3691 h. Statistical analyses carried out on the pharmacokinetics data, with respect to gender, indicated significant differences between the male and the female patients used in the study (Table 3). Kel values were statistically higher in the females (0.19 h^{-1}) than in the males (0.11 h^{-1}). Subsequently, the corresponding elimination half-life ($t_{1/2}$) values in female (3.71 h) patients were statistically lower than those in the males (6.28 h). Gender-related differences in pharmacokinetics may principally be due to molecular and physiological factors. Molecular factors involves differences in drug transporters and drug metabolising enzymes between males and females, while physiological factors include lower body weight and size, higher percentage body fat, lower glomerular filtration rate and variation in gastric motility in females compared to males [23].

Table 2: Pharmacokinetic parameters of amodiaquine (AQ) after a single oral dose (10mg/Kg body weight) in fifteen (15) Ghanaian children with uncomplicated malaria

Patient Code	*Fe*	*Kel* (h^{-1})	$t_{½}$ (h)	*Ke* (h^{-1})	*Km* (h^{-1})	*Ka* (h^{-1})	$t_{1/2a}$ (h)
001	0.0066	0.1041	6.6571	0.0007	0.1081	0.6312	1.0979
002	0.0024	0.1247	5.5573	0.0003	0.1244	0.5411	1.2807
003	0.0044	0.1411	4.9114	0.0006	0.1405	0.4111	1.6857
004	0.0136	0.1080	6.4167	0.0015	0.1065	0.2600	2.6654
005	0.0019	0.1884	3.6784	0.0004	0.1880	0.3923	1.7665
006	0.0084	0.1062	6.5254	0.0009	0.1053	0.4917	1.4094
007	0.0014	0.2224	3.1160	0.0003	0.2221	0.4471	1.5500
008	0.0033	0.1528	4.5353	0.0005	0.1523	0.4200	1.6500
009	0.0018	0.2212	3.1329	0.0004	0.2208	0.8898	0.7788
010	0.0012	0.2273	3.0488	0.0003	0.2270	0.4118	1.6829
012	0.0125	0.1119	6.1930	0.0014	0.1105	0.2580	2.6860
013	0.0134	0.2168	3.1965	0.0029	0.2139	0.5893	1.1759
014	0.0033	0.1096	6.3230	0.0004	0.1092	0.2651	2.6141
015	0.0069	0.1794	3.8629	0.0012	0.1782	0.4059	1.7073
MEAN	0.0059	0.1553	4.8746	0.0008	0.1548	0.4502	1.7200
STDEV	0.0044	0.0488	1.4297	0.0006	0.0485	0.1657	0.5557
SEM	0.0011	0.0126	0.3691	0.0002	0.0125	0.0428	0.1435
95% CI	0.0035 – 0.0083	0.1283 – 0.1823	4.0845 – 5.6647	0.0004 – 0.0012	0.1280 – 0.1816	0.3586 – 0.5418	1.4129 – 2.0271

STDEV = standard deviation of the mean; SEM = standard error of the mean;
95% CI = 95% confidence interval levels or limits

Table 3: Student's t-test of mean half lives between males and females in current study (Ghanaian children with uncomplicated malaria)

	Males	**Females**
Mean +/- SEM	6.28 +/- 0.11	3.71 +/- 0.27
N	7	8
SEM=STDEV/ sqrt (n)	0.11	0.27
$SEM^2 = \sigma^2/n$	0.01	0.07
$\sigma d^2 = \sigma_1^2/n_1 + \sigma_2^2/n_2$	0.01 + 0.07 = 0.08	
σd = sqrt (σd^2)	=sqrt (0.08) = 0.28	
$t = (x_1 - x_2) / \sigma d$	= (6.28 – 3.71) / 0.28 = 9.18	

x_1 = mean half-life of the male Ghanaian children, x_2 = mean half-life of the female Ghanaian children, SEM = standard error of the mean, N = sample size in each sample, σ^2 = estimate of variance; σd^2 = variance of the difference between the two means, df = $(n_1 + n_2 – 2)$ = number of degrees of freedom

The pharmacokinetic parameters kel and $t_{1/2}$ obtained in the current study involving Ghanaian children with malaria were compared, in separate analysis, with those published in the literature on healthy Caucasian male adults [10] and Zambian adults with uncomplicated malaria [17]. There was no significant difference between the current study involving Ghanaian children and healthy Caucasian adult's data ($p > 0.05$) in the disposition of AQ in the two sub populations (Table 4). The observations imply that age factor probably have little or no influence on the disposition of orally administered AQ. The occasionally observed adverse reactions or effects of orally administered AQ in Ghana are usually experienced throughout the entire population and not limited to children.

Table 4: The student's t – test of mean $t_{1/2}$ between Ghanaian children and Caucasian adult's [10].

	STUDY DATA $t_{1/2}$	**CAUCASIANS DATA $t_{1/2}$**
Mean +/- SEM	4.8746 +/- 0.3691 h	5.200 +/- 1.7000 h
N	15	7
$SEM^2 = \sigma^2/n$	0.1362	2.8900
$\sigma d^2 = \sigma_1^2/n_1 + \sigma_2^2/n_2$	=0.1362 + 2.8900 = 3.0262	
σd = SQRT (σd^2)	= SQRT (3.0262) = 1.7396	
$t = (\bar{x}_1 – \bar{x}_2)/ \sigma d$	= (5.2 - 4.8746) / 1.7396 = 0.1871	

x_1 = mean half-life of Ghanaian children, x_2 = mean half-life of healthy Caucasian adults, SEM = standard error of the mean, N = sample size in each sample, σ^2 = estimate of variance; σd^2 = variance of the difference between the two means, df = $(n_1 + n_2 – 2)$ = number of degrees of freedom

However, in contrast to the above observations, statistical comparison of the present study data with that of Zambian adult's with uncomplicated malaria revealed significant differences ($p < 0.05$) in the pharmacokinetics of orally administered AQ between the two sub-populations (Table 5).

Table 5: Student's t-test analysis between study group and Zambian adult's data [17].

	STUDY DATA $t_{1/2}$	**ZAMBIANS DATA $t_{1/2}$**
Mean +/- SEM.	4.9 +/- 0.37	3.7 +/- 0.35
N	15	14
$SEM^2 = \sigma^2/n$	0.1369	0.1225
$\sigma d^2 = \sigma_1^2/n_1 + \sigma_2^2/n_2$	= 0.1369 + 0.1225 = 0.2594	
σd = SQRT (σd^2)	= SQRT(0.2594) = 0.5093	
$t = (x_1 - x_2) / \sigma d$	= (4.9 – 3.7) / 0.5093 = 2.35	

x_1 = mean half-life of Ghanaian children, x_2 = mean half-life of Zambia adults, SEM = standard error of the mean, N = sample size in each sample, σ^2 = estimate of variance; σd^2 = variance of the difference between the two means, df = $(n_1 + n_2 - 2)$ = number of degrees of freedom

Winstanley *et al.* [17], reported that the half life ($t_{1/2}$) of oral AQ in fourteen (14) Zambian adults was, mean: 3.7 h, range: (2.9 – 4.5) h at 95% CI limits. The corresponding elimination rate constant (kel) at 95% CI was mean: 0.19 h^{-1}, range: (0.15 – 0.24) h^{-1}. In this current study of Ghanaian children, the half life ($t_{1/2}$) was mean: 4.9 h, range (4.0 – 5.8) h; and the corresponding elimination rate constant (kel) values were, mean 0.15 h^{-1}, range: (0.12 – 0.17) h^{-1} estimated at 95 % CI limits. Essentially, the estimated mean elimination rate constant (kel) value of 0.15 h^{-1} obtained in the current study was significantly lower ($p < 0.05$) than that of 0.19 h^{-1} obtained in Zambian adults with uncomplicated malaria. The estimated mean elimination half-life ($t_{1/2}$) of oral AQ in Ghanaian children of 4.9 h was significantly higher ($p < 0.05$) than that obtained in the Zambian adults (3.7 h). This implies that the possibility of a manifestation of the drug's potential adverse effects or reactions within the study population of Ghanaian children would be relatively higher than that in the Zambian sub-population. The study lends credence to the fact that pharmacokinetics in children are different, to a greater or lesser extent, than those of adults. In general, important pharmacokinetic parameters such as absorption, plasma protein binding, metabolism and excretion levels in children are reduced while that of the volume of distribution is increased [24]. These observations are suspected to be caused by genetic or hereditary differences between the two groups. Other possible factors may include drug formulation, dietary, environmental, geographical, demographical and study methodology differences. Thus, various factors must be taken into consideration in the determination of appropriate doses of AQ and other drugs for children.

CONCLUSIONS

The study has confirmed the rapid absorption and hepatic clearance of orally administered amodiaquine in Ghanaian children. Significant differences were observed in the half life of amodiaquine between the male and female children used in the study indicating the possible effect of gender on amodiaqine disposition. There were significant differences in the half life of amodiaquine in Ghanaian children observed in the current study and that of Zambian adults while no significant difference was observed between the current study and that reported for Caucasians in the literature.

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