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MAMA Decoction, Nigerian Herbal Antimalarial Preparation, Alters the Disposition of Amodiaquine in Healthy Humans

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: *MAMA Decoction* (MD) is prepared from the leaves of *Mangifera indica*, *Alstonia boonei*, *Morinda lucida* and *Azadirachta indica*. A co-administration of MD with amodiaquine led to synergism in the clearance of malaria parasites in a previous report. The pharmacokinetic basis for this observation was the subject of another study in mice which found significant MD-induced increase in the exposure and half-life of desethylamodiaquine, the major metabolite of amodiaquine.

Objective: This study aimed at evaluating previously identified murine herb-drug interactions in healthy human volunteers.

Materials and Methods: Single oral doses of amodiaquine (10 mg/kg) with/without MD (120 mg/kg) were co-administered to 16 healthy subjects in a three-period crossover design. Five millilitres of blood samples were collected employing sparse sampling from 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 h postdose, for each study period and analysed for amodiaquine and desethylamodiaquine contents. The effect of MD on amodiaquine disposition across study periods was investigated using a non-linear mixed-effect pharmacokinetic model which estimated population parameters with the stochastic approximation expectation maximization algorithm implemented in Monolix 2020R1.

Results: The disposition of amodiaquine and desethylamodiaquine was each described, adequately, by two- and one-compartment structural models respectively, and a first-order oral absorption rate. The co-administration of amodiaquine with MD resulted in about 41% decrease in the apparent volume of distribution of amodiaquine (V_{AQ}/F). Pre-administration of MD prior to amodiaquine led to a 22% decrease in V_{AQ}/F.

Conclusion: *MAMA* decoction appeared to decrease the tissue partitioning of amodiaquine in man. The consequence of this on effective parasite clearance in man is, not yet understood.

Keywords: Amodiaquine, Malaria, *MAMA Decoction*, Herb-drug interaction, Pharmacokinetics

INTRODUCTION

MAMA Decoction (MD), prepared from the leaves of *Morinda lucida, Azadirachta indica, Alstonia boonei* and *Mangifera indica* has been validated for chemosuppressive, prophylactic, and curative antimalarial activities in Nigeria (Adepiti *et al*., 2014; Odediran *et al*., 2014; Adepiti *et al*., 2020). Malaria, caused by *Plasmodium spp*., an endemic disease in Nigeria and most parts of the tropics is estimated to have affected about 247 million persons around the world in 2021 (WHO, 2022). Amodiaquine is a long-acting component of the World Health Organisation (WHO)-recommended artemisinin-based combination therapy (ACT) for malaria.

In a previous animal study, observed pharmacodynamic synergism between amodiaquine and MD presented a more effective parasite clearance of chloroquine-sensitive *Plasmodium* strain in infected mice resulting in increased survival of study animals was reported (Adepiti *et al.,* 2016). In an attempt to explaining these findings, Adepiti *et al* investigated the pharmacokinetic interaction between MD and amodiaquine in mice (Adepiti *et al.,* 2020b). This model assessed for changes in the pharmacokinetic profile of amodiaquine (and its major metabolite, desethylamodiaquine) after its concurrent administration with MD. Prolonged exposure to MD, prior to amodiaquine dosing, was also investigated in the same study. The pharmacokinetic interaction observed in the study suggested that MD altered the absorption/uptake processes and metabolism of amodiaquine (Adepiti *et al.,* 2020b).

This observation may be significant in view of the reported potential hepatotoxicity of amodiaquine (Larrey *et al.,* 1986; Taylor and White, 2004; German *et al*., 2007). Nevertheless, the observations in mice may not translate to similar findings in man due to species differences in xenobiotic handling, which are well documented (Lin, 1995; Martignoni *et al*, 2006; Toutain *et al*., 2010; Chu et al., 2013). Therefore, the present study provides the first of such insight into the nature of the possible pharmacokinetic interaction between MD and amodiaquine in healthy human subjects.

METHODOLOGY

Drugs and reagents

Amodiaquine dihydrochloride dihydrate, quinidine, HPLC-grade methanol, diethyl ether and acetonitrile were purchased from Sigma (St. Louis, Mo, USA). Triethylamine and ortho-phosphoric acid were from BDH Chemicals Ltd. (Dorset, Poole, UK), while desethylamodiaquine was supplied by TLC Pharmaceutical Standards (Ontario, Canada). Artesunate-amodiaquine tablets (ASAQ®) were purchased from Sanofi-Aventis (Maroc, Morocco).

Preparation of *MAMA Decoction*

The collection of the component plants and preparation of MD were carried out as previously described (Adepiti *et al.,* 2014). Briefly, the leaves of the plant components of MD were collected in March on the campus of Obafemi Awolowo University (OAU), Ile-Ife, Nigeria. They were identified and authenticated by Mr. A.T. Oladele, the Plant Curator of the Department of Pharmacognosy, OAU. Voucher specimens were deposited in the Herbarium of the Botany Department with numbers IFE 16534 (*Alstonia boonei* DeWild [Apocynaceae]), IFE 16536 (*Azadirachta indica* A. Juss [Meliaceae]), IFE 16537 (*Mangifera indica* L. [Anacardiaceae]) and IFE 16535 (*Morinda lucida* Benth [Rubiaceae]). The leaves were oven-dried at 40 °C and powdered separately. Fifty grams (50 g) of each of the four powdered plant materials were mixed and boiled in 2 L of distilled water for 1 h. The liquid extracts were filtered and concentrated in vacuo at 70 °C followed by freeze-drying.

Study design and sampling

Subject recruitment

The study recruited eighteen subjects whose demographics are presented in Table 1. All the volunteers were certified healthy by physicians before enrolment. Subjects who were on any medications, including caffeine-containing products, before enrolment, were excluded from the study. Pregnant and lactating women as well as smokers were also excluded.

Study Design

An open-label, three-period, non-randomized sequential study design was adopted.

In the first period, volunteers were administered a single oral dose of amodiaquine (10 mg/kg) after an overnight fast. Each volunteer provided a minimum of 5 blood samples that were drawn into heparinized tubes predose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24 and 48 h postdose. After a washout period of 7 days, the second study period, co-administration of amodiaquine with 0.25 L of MD (0.04% w/v gedunin content) was initiated and blood sampling as described

for the first period were collected. Another washout 7-day period was observed. In the third period, volunteers were initially administered 0.25 L of MD (0.04% gedunin content) for six days. On the seventh day, a similar dose of MD was co-administered with amodiaquine (10 mg/kg), and blood samples were drawn as previously described.

Sample analysis

The plasma concentrations of amodiaquine and desethylamodiaquine were determined as previously described (Adedeji *et al*., 2015) with a slight modification. In the present study, a mobile phase comprising triethylamine (2%) in distilled water and methanol (81:19) at a final pH of 2.2 was utilized for analysis. The assay was validated following standard protocols (Adepiti *et al*., 2020b). Drug and metabolite contents in plasma were determined from a calibration curve in the range of 2.5 µg/L to 300 µg/L. The intra and inter-assay precision were determined by analysis of four calibration concentrations in replicates of six samples on three different days of the assay. The intra- and inter-day assay precision is expressed as the coefficient of variation (% CV). The lower limit of detection (LLOD) and quantification (LLOQ) were determined and defined as the concentrations for which signal-to-noise ratios of 3 and of 10 were considered.

Pharmacokinetic data analysis

The concentration-*versus*-time data across periods of the study were analysed using a population approach. Pharmacokinetic parameters were estimated by a maximum likelihood estimation method using the stochastic approximation expectation maximisation (SAEM) algorithm implemented in Monolix 2020R1. A final structural model was identified from fitting study data to one-, two- and three-compartment structural models for both the drug, amodiaquine and its metabolite, desethylamodiaquine. The constant, proportional, and additive error models were assessed for the description of residual variability while assuming a log-normal distribution of pharmacokinetic parameters. Random effects were initially assumed to be independent with a diagonal variance-covariance matrix before further interrogations for correlations using a benchmark of ≥ 0.7. A suitable model was found using -2 x log-likelihood (Objective Function Variable, OFV) estimated by a linearization method, and the relative standard errors of parameter estimates.

Three continuous covariates (age, height, and body weight) and a categorical covariate (sex) were tested. The study periods were also encoded as categorical covariates. The inclusion of a covariate in the model was based on a forward selection method that retained a covariate that led to a decrease in the OFV. The covariate model was finalised by a backward approach where added covariates were removed one at a time. In addition, covariate relevance in the model was assessed by a combination of the likelihood ratio test and the Wald test, setting the value of *P* denoting a significant change at < 0.05.

The final model was evaluated using the goodness-of-fit plots, individual weighted residuals the normalized prediction distribution errors, and the visual predictive check. Further, 2500-bootstrap estimates and 95% confidence intervals were generated for each of the secondary estimates comprising T_{max}, $C_{max,}$ and AUC_{0-48h}.

RESULTS AND DISCUSSION

The lower limits of quantification (LLOQ) were 4.54 µg/L and 3.14 µg/L for amodiaquine and desethylamodiaquine, respectively, while corresponding LLOD for amodiaquine and desethylamodiaquine were 1.50 µg/L and 1.03 µg/L; respectively. Intra-assay and inter-assay imprecisions were less than ± 9% for amodiaquine, and desethylamodiaquine.

In the present study, sixteen of eighteen volunteers completed the 3-period study with a total of 206 and 220 plasma concentration points acquired for amodiaquine and desethylamodiaquine, respectively. Two volunteers were withdrawn before the completion of the study. Plasma concentration values that were lower than the LLOQ (especially for amodiaquine) were censored for fitting (M3 method) during analysis as previously described (Beal, 2001). A first-order process described the oral absorption of amodiaquine. While a two-compartment structural model fitted the disposition data of amodiaquine, a one-compartment structural model was found adequate for its major metabolite, desethylamodiaquine (Figure 1).

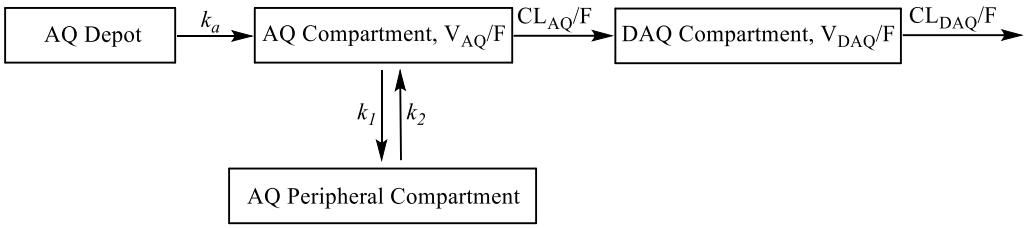

Figure 1. A structural compartment model describing the pharmacokinetics of amodiaquine and desethylamodiaquine in healthy Nigerian subjects.

Key: k_a: Oral absorption rate constant; AQ: Amodiaquine, DAQ: Desethylamodiaquine, CL_{AQ}/F: Apparent clearance of amodiaquine; V_{AQ}/F: Apparent volume of distribution of amodiaquine; CL_{DAQ}/F: Apparent clearance of desethylamodiaquine; V_{DAQ}/F: Apparent volume of distribution of desethylamodiaquine; k_1 and k_2: Inter-compartment transfer rate constants

Random effects were described by a diagonal variance-covariance matrix and estimated for the apparent volume of distribution of amodiaquine (V_{AQ}/F), apparent clearance of amodiaquine (CL_{AQ}/F), apparent volume of distribution of desethylamodiaquine (V_{DAQ}/F) and inter-compartment rate constant (k_2). Proportional error models effectively accounted for residual variability in parameter estimates of amodiaquine and desethylamodiaquine.

A summary of model estimates for both drug and metabolite is presented in Table 2, and relevant plots indicative of the appropriateness of the final model are provided in Figures 2 and 3. While the covariate model showed no influence of sex, body weight, or height on pharmacokinetic parameters, the intake of MD significantly altered the apparent volume of distribution of amodiaquine (V_{AQ}/F) as described by Equation 2.

$$V_{AQ_i} = V_{AQ_{pop}} \, x \, e^{\beta_{V_{AQ}} \cdot Intervention=G_1} \, x \, e^{\beta_{V_{AQ}} \cdot Intervention=G_2} \, x \, e^{\eta_{V_{AQ},i}} \qquad \text{Equation 2}$$

For period 2 when amodiaquine was co-administered with MD, $G_1 = 1$ and $G_2 = 0$; and for period 3 when subjects were pre-treated with MD before a co-administration of *MD* with amodiaquine, $G_1 = 0$ and $G_2 = 1$ (where G is a categorical covariate 'intervention').

The final model described a 40.96% reduction in the population estimate of V_{AQ}/F when *MD* was co-administered with amodiaquine. A similar pattern of decrease (↓ 21.81%) in V_{AQ}/F was also noted when subjects were pre-administered MD for a few days before a co-administration with amodiaquine. Other parameters derived directly from the structural model were, however, unaffected distinctly as seen in Figure 4, where a 25% boundary of variation, across study periods, is presented for key estimates. Additional pharmacokinetic parameters comprising time to reach maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}) and area under the time-concentration curve ($AUC_{0\text{-}48h}$) are presented in Table 3.

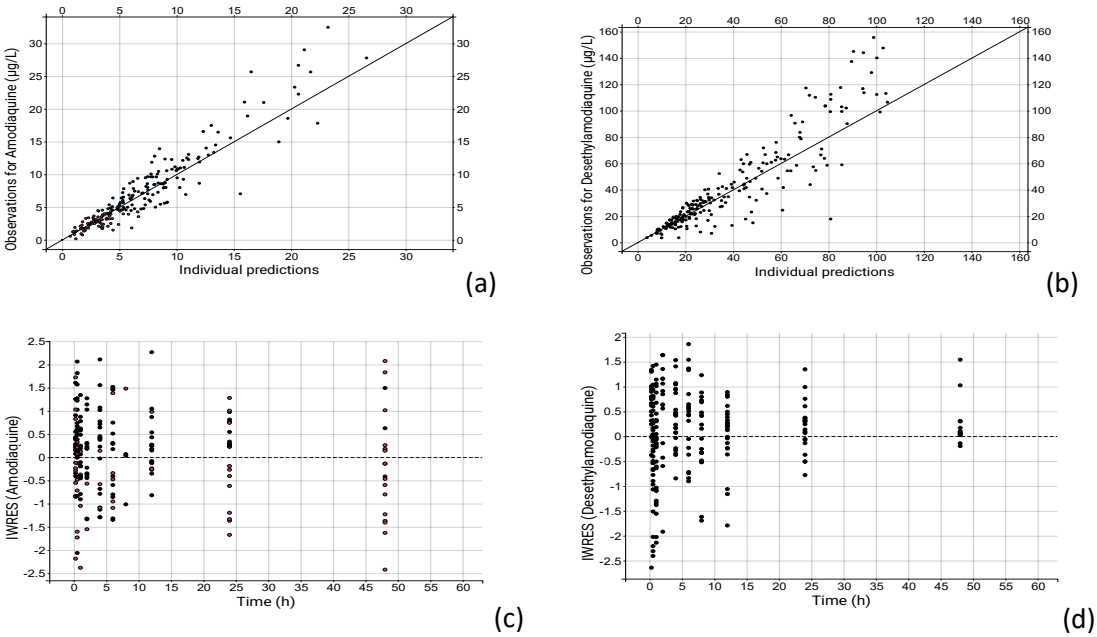

Figure 2. Goodness-of-fit plots of final pharmacokinetic model describing the disposition of amodiaquine and desethylamodiaquine in healthy subjects

Key: Observations versus prediction plots for amodiaquine and desethylamodiaquine are presented in plots (a) and (b). Plots of individual-weighted residuals (IWRES) is shown in (c), and a corresponding plot for desethylamodiaquine is shown in (d).

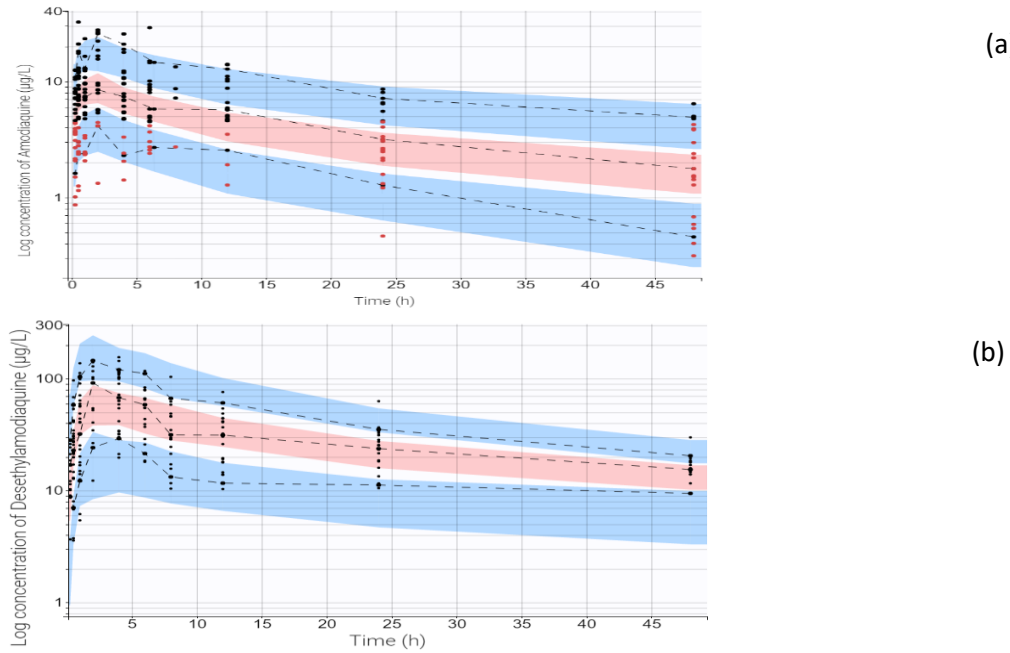

Figure 3. Visual predictive checks (corrected) of the final pharmacokinetic model for amodiaquine (a) and desethylamodiaquine (b)

Key: Observed concentrations are represented by 'scattered dots' while the solid lines represent the 10th, 50th and 90th percentiles of observations. Colour dots in (a) corresponds to values simulated in place of BLQ values. The shaded portions are the 90% prediction intervals of the corresponding percentiles.

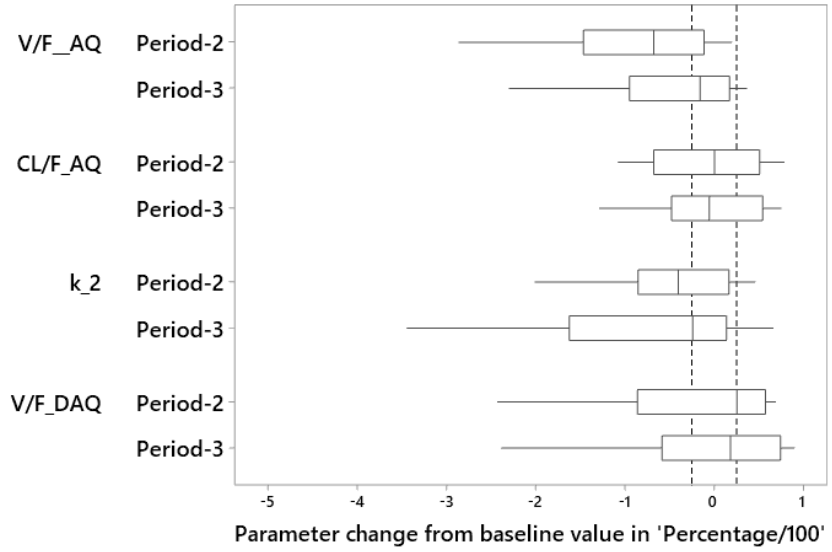

Figure 4. A box plot of mean parameter estimates and their derived interquartile ranges
Boxes show the effect of the co-administration of *MD* (period 2) and the pre-administration of *MD* (Period 3) on pharmacokinetic parameter estimates of amodiaquine in healthy subjects. The broken lines delineate the ±0.25 boundaries which are representative of 25% variations from baseline values of parameters; CL/F_AQ: oral clearance of amodiaquine; V/F_AQ: volume of distribution of amodiaquine in the central compartment; V/F_DAQ: volume of distribution of desethylamodiaquine in the central compartment; k_2: inter-compartment rate constant for amodiaquine

While the present model and its limited number of covariates provided a reasonably good fit of the empirical data on amodiaquine (Figures 2a, 2c, and 3a), the dispersions in desethylamodiaquine observations were largely unexplained by available covariates (Figures. 2b, 2d and 3b). Nonetheless, the limited mechanistic insight into the interaction between MD and amodiaquine provided by the present model pointed to a significant MD-induced alteration of the apparent volume of distribution of amodiaquine in man (Fig. 4). This structural model assumed that the conversion of amodiaquine to desethylamodiaquine accounted for its systemic clearance. Moreover, no model improvement was derived from estimating the fraction of the parent drug that converted to metabolites. The addition of body weight and height as allometric function did not improve model fit.

This study presents an identifiable structural model, comparable and consistent with previous compartmental models describing the disposition of amodiaquine in man (Tarning *et al*., 2012; Ali *et al*., 2018), which was developed.

Therefore, the authors hypothesized that the diuretic phytochemical constituents of MD components (Shah et al., 2010) actively increased the renal clearance of amodiaquine; especially in urine (Winstanley *et al*., 1987). This might have been accompanied by a re-distribution of amodiaquine from peripheral tissues into the blood thus cancelling out likely detectable changes in amodiaquine exposure.

In the absence of other competing physiological factors, the observed reduction in the volume of distribution of amodiaquine in the presence of MD suggested a decrease in the distribution of amodiaquine into peripheral tissues. This is further buttressed by an insignificant difference in the plasma clearance and maximum plasma concentrations (Tables 2-3) of amodiaquine across all periods of the study.

This study demonstrated that the pharmacokinetics of AQ was altered by the administration of MD. In an earlier study, the pharmacokinetic basis for the synergism observed in the co-administration of MD with AQ, in the clearance of malaria parasites, was evaluated in mice using a non-compartmental approach (Adepiti *et al.*, 2016; 2020b). Since both agents are antimalarials, a synergistic admixture would be considered a promising therapeutic option, consistent with the currently recommended combination therapy approach to the effective treatment of malaria (Beal, 2001). Although MD precipitated increased C_{max}, exposure, and half-life of amodiaquine and desethylamodiaquine in mice, the non-compartmental approach utilised in the previous study afforded a limited understanding of the associated

Table 1. Demographics of the study population

Population (*n = 16*)	
Age in *years* (mean, interquartile range)	21.4, 20.0 – 23.0
Height in *metres* (mean, interquartile range)	1.70, 1.6 – 1.7
Body weight in *kg* (mean, interquartile range)	63.5, 56.0 – 63.5
Gender	
Male	13
Female	3

All subjects were Nigerians, and healthy, non-smokers

Table 2. Estimates of the basic and final pharmacokinetic model describing the disposition of amodiaquine in healthy subjects administered *MAMA* decoction

	Basic Model		Final Model	
Fixed effect	Estimate	RSE (%)	Estimate	RSE (%)
Amodiaquine				
*ka*_pop (h^{-1})	0.348	16.5	0.349	21.9
V_{AQ}/F_pop (L)	8,430	18.3	6,840	28.9
$\beta_{Intervention\ (Period\ 2)}$_$V_{AQ}$/F			0.533	34.7
$\beta_{Intervention\ (Period\ 3)}$_$V_{AQ}$/F			0.257	63.7
CL_{AQ}/F_pop (L/h)	1,730	12.3	1,780	12.2
k_1_pop (h^{-1})	1.54	5.7	1.45	17.1
k_2_pop (h^{-1})	0.147	19.4	0.147	21.0
Desethylamodiaquine				
V_{DAQ}/F_pop (L)	91.4	18.5	87.4	19.6
CL_{DAQ}/F_pop (L/h)	215	7.44	218	7.31
Random effect				
ω_V_{AQ}/F	0.616	10.1	0.579	10.3
ω_CL_{AQ}/F	0.666	13.8	0.657	13.7
ω_k_2	0.577	15.9	0.560	14.8
ω_V_{DAQ}/F	0.905	16.4	0.938	16.1
Residual error (µg/L)				
b_{AQ}	0.361	17.0	0.352	18.5
c_{AQ}	0.861	10.9	0.883	11.3
b_{DAQ}	0.283	26.3	0.244	36.5
c_{DAQ}	1.05	9.68	1.1	9.35
-2 × log likelihood	2554.62		2550.10	-

AQ: Amodiaquine, DAQ: Desethylamodiaquine, *ka*: oral absorption rate, V/F: volume of distribution in the central compartment, CL/F: oral clearance of amodiaquine, *k*: inter-compartment rate constant

Table 3. Secondary estimates of the final model describing the disposition of amodiaquine in healthy subjects administered concomitant doses of *MAMA* Decoction and amodiaquine

	Mean	**95% CI**	**RSE (%)**
Baseline (Period 1: amodiaquine only)			
Amodiaquine			
ka (h^{-1})	0.49[a]	-	-
β_{AQ} (h^{-1})	0.026	0.024 – 0.028	4.85
T_{max}_AQ (h)	2.34	1.38 – 3.80	27.78
C_{max}_AQ (µg/L)	18.62	11.99 – 26.77	20.78
$AUC_{0\text{-}48h}$_AQ (h × µg/L)	184.39	118.32 – 260.58	19.77
Desethylamodiaquine			
β_{DAQ} (h^{-1})	0.0080	0.0069 – 0.0089	6.31
T_{max}_DAQ (h)	3.30	2.25 – 4.75	19.39
C_{max}_DAQ (µg/L)	155.93	110.47 – 211.22	16.43
$AUC_{0\text{-}48h}$_DAQ (h × µg/L)	1,709.76	1,390.63 – 2,053.22	9.90
Period 2 (Co-administration of amodiaquine with *MD*)			
Amodiaquine			
ka (h^{-1})	0.31[a]		
β_{AQ} (h^{-1})	0.030	0.026 – 0.034	7.29
T_{max}_AQ (h)	1.95	1.56 – 2.41	11.28
C_{max}_AQ (µg/L)	10.72	7.67 – 14.33	22.3
$AUC_{0\text{-}48h}$_AQ (h × µg/L)	65.32	50.02 – 82.19	12.58
Desethylamodiaquine			
β_{DAQ} (h^{-1})	0.0083	0.0073 – 0.0090	5.19
T_{max}_DAQ (h)	3.50	2.50 – 4.88	17.14
C_{max}_DAQ (µg/L)	109.04	82.99 – 138.49	13.03
$AUC_{0\text{-}48h}$_DAQ (h × µg/L)	789.81	615.06 – 975.64	11.61
Period 3 (Pre-treatment with *MD* before a co-administration of amodiaquine with *MD*)			
Amodiaquine			
ka (h^{-1})	0.29 [a]		
β_{AQ} (h^{-1})	0.026	0.021 – 0.030	8.92
T_{max}_AQ (h)	2.77	1.88 – 3.84	18.41
C_{max}_AQ (µg/L)	20.58	13.56 – 28.98	18.89
$AUC_{0\text{-}48h}$_AQ (h × µg/L)	147.96	85.79 – 218.92	23.14
Desethylamodiaquine			
β_{DAQ} (h^{-1})	0.0089	0.0085 – 0.0091	1.86
T_{max}_DAQ (h)	4.16	2.88 – 5.63	17.31
C_{max}_DAQ (µg/L)	115.81	76.77 – 158.48	17.61
$AUC_{0\text{-}48h}$_DAQ (h × µg/L)	807.83	639.94 – 987.94	10.95

ka: Absorption rate, k_e: Elimination rate from central compartment, β: Hybrid elimination rate constant of the two-compartment model, T_{max}: Time to reach maximum plasma concentration, C_{max}: Maximum plasma concentration, AUC: Area under the time vs concentration curve, CI: Confidence interval. [a]: Values are estimates of the final model incorporating the effect of MD intervention across study periods. Mean values and corresponding 95% CI were generated from 2500 bootstraps, RSE: Relative Standard Error

mechanistic description of the observed interaction. Moreover, the likelihood of species differences in the handling and metabolism of AQ and plant components of MD limits a full extrapolation of such animal data to man.

Previous data from a similarly designed study in mice had suggested that components of MD inhibited the metabolism of amodiaquine and desethylamodiaquine (Adepiti *et al*., 2020b), however, the present study in man observed no such influence. Such observation was reported in an herb-drug interaction study involving the co-administration of *Hibiscus sabdariffa* (hibiscus flower) with simvastatin. In mice, the aqueous extract of *H. sabdariffa* potentiated the antihyperlipidaemic activity of simvastatin in low doses. However, in humans, the extract resulted in a reduction in exposure to simvastatin (Showande *et al*., 2017)

Herb-drug interaction is an emerging discipline. This interaction may lead to both pharmacokinetic and pharmacodynamic outcomes. Some interactions may be negligible clinically, while some may have significant public-health importance (Surana *et al*., 2021; Radeva-Llieva *et al*., 2022). Therefore, there is the need for sustained research into the co-administration of herbal and orthodox medicines.

CONCLUSION

The study established that MD altered the pharmacokinetics of amodiaquine in man by perturbing its distribution. This contrasted a previous report in mice where inhibitions of the metabolism of amodiaquine and that of its major metabolite, desethylamodiaquine, were observed. The synergism between MD and amodiaquine may yet be unaffected by the pharmacokinetic interaction in man. Thus, future studies designed to capture full pharmacokinetic and pharmacodynamic data in man would be desirable for the optimum deployment of MD-amodiaquine admixture in malaria.

Ethical considerations

Approval for the study was obtained from the Health Research Ethics Committee of the Institute of Public Health, Obafemi Awolowo University, Ile-Ife, Nigeria (IPHOAU/12/585). All the subjects provided written informed consent, and the study was conducted following the Declaration of Helsinki and the National Policy on Good Clinical Practice.

List of abbreviations

MD-*MAMA Decoction*; T_{max} maximum plasma concentration, C_{max} -maximum plasma concentration; $AUC_{0\text{-}48h}$ - area under the time-concentration curve; V_{AQ}/F- apparent volume of distribution of amodiaquine; CL_{AQ}/F- apparent clearance of amodiaquine; V_{DAQ}/F- apparent volume of distribution of desethylamodiaquine; k_2 and inter-compartment rate constant; LLOQ- Lower limit of quantification; SAEM-Stochastic approximation expectation maximization

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