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PHARMACOKINETICS AND DISPOSITION

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The effects of acute falciparum malaria on the disposition of caffeine and the comparison of saliva and plasma-derived pharmacokinetic parameters in adult Nigerians

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Abstract *Objectives*: The pharmacokinetics of caffeine and its dimethylxanthine metabolites were evaluated in Nigerians, for whom it is normal to consume caffeine-containing beverages during ill health and recuperation in the belief that caffeine aids early recovery from illness; however, there are no data defining the kinetics of caffeine in healthy and ill Nigerians.
Materials and methods: A single oral dose of 300 mg caffeine was given to ten healthy adult Nigerians and ten adults suffering from acute uncomplicated *Plasmodium falciparum* malaria infection. Caffeine and its dimethylxanthine metabolites were measured in plasma and saliva of healthy subjects and in plasma of patients suffering from malaria using high-performance liquid chromatography.
Results: The plasma pharmacokinetics of caffeine per se in both groups was similar ($P > 0.05$). The maximum plasma concentration (C_{max}) of paraxanthine was significantly lower ($P < 0.05$) in malaria (0.9 ± 0.4 μg/ml) than in healthy controls (1.4 ± 0.5 μg/m1), and the paraxanthine:caffeine area under the plasma concentration–time curve ratio, an index of cytochrome P_{450} (CYP)IA2 activity was significantly lower ($P < 0.05$) in malaria patients (0.5 ± 0.1) than in healthy controls (0.3 ± 0.2). The elimination half-life of theophylline was longer in malaria, while the area under the plasma concentration–time curve of theobromine was significantly higher ($P < 0.05$) in malaria (7.1 ± 3.4 μg ml^{-1} h) than in healthy adults (4.1 ± 2.2 μg ml^{-1} h). Excellent correlations were found between saliva and plasma concentrations of caffeine ($r^2 = 0.98$) with a mean saliva:plasma concentrations ratio of 0.7 ± 0.1. The plasma concentrations (C_{max} and AUC) were therefore higher than the corresponding salivary levels, so that the apparent oral clearance calculated for saliva exceeded the true oral clearance based on plasma data.
Conclusions: Acute *Plasmodium falciparum* malaria produced significant changes in the disposition of caffeine metabolites. Analysis of concentrations in saliva is a useful non-invasive method for monitoring the kinetics of caffeine and paraxanthine in Nigerians.

Key words Pharmacokinetics · Caffeine · Malaria

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Introduction

Caffeine, a trimethylxanthine, is widely consumed in Nigeria, with consumption mainly in the form of beverages and kola nuts. Consumption of caffeine-containing beverages is frequent in Nigeria during the course of acute illness and recovery because of the popular belief that caffeine improves appetite and promotes a state of general well being.

In Nigeria, one of the most common acute illnesses for which caffeine-containing beverages are usually consumed is *Plasmodium falciparum* malaria, a condition which accounts for 65% of notifiable diseases (Federal Ministry of Health Bulletin 1991) and a common cause of morbidity and mortality in the tropics. Malaria may alter the disposition of anti-malarial drugs including quinine (White et al. 1982, 1987, 1988; Sowunmi 1996) and halofantrine (Karbwang et al. 1991); however, Karbwang did not find altered disposition of mefloquine in uncomplicated malaria. The disposition of caffeine is significantly altered in adult Thai subjects suffering from malaria (Wilaitarana et al. 1994) and in

experimental rats infected with malaria (Kokwaro et al. 1993). However, there are no published data on the plasma pharmacokinetics of caffeine in either healthy Africans or Africans infected with malaria; Nigerians represent a racial group in which the morbidity and mortality from malaria is highest and consumption of caffeine-containing beverages is similarly high.

Caffeine is eliminated efficiently, principally by cytochrome P_{450}1A2 (CYPIA2), *N*-acetyltransferase (NAT2) and xanthine oxidase to dimethylxanthines, dimethyluric acids, monomethylxanthines and monomethyluric acid. In humans, the initial demethylations of caffeine, which account for 95% of metabolites, are catalysed by CYPIA2, with the 3N demethylation yielding paraxanthine being the principal pathway. Inter-ethnic, inter-individual and gender differences have been demonstrated in caffeine metabolism (Kalow 1986; Relling et al. 1992), with CYP1A2 and xanthine oxidase activities being lower in Black Americans than in Caucasian Americans (Relling et al. 1992). However, there is no documented study defining the pharmacokinetics of caffeine in Africans or in Africans suffering from malaria.

The main aims of this study were to evaluate the disposition of caffeine and its metabolites in healthy Africans and to investigate the influence of acute falciparum malaria on the disposition of caffeine.

Materials, methods and subjects

The study was undertaken at the Clinical Pharmacology Unit of the University College Hospital, Ibadan, Nigeria, and was part of a wider study of the pharmacokinetics of caffeine in healthy subjects and other disease conditions. Ethical permission for the study was given by the Joint University of Ibadan/University College Hospital, Ibadan, Nigeria, Ethical Committee. Written informed consent was obtained from each volunteer. Subjects with a history of renal or hepatic diseases were excluded.

Control group

Ten healthy adults, with a mean age of 32.1 ± 7.6 years (age range 18–40 years) and weighing 59.8 ± 12.3 kg (range 38–82 kg) (Table 1) participated in the study. The subjects were all non-smokers, were not receiving any medication and all abstained from alcohol and kola nuts in the preceding 2 weeks and throughout the study.

Patient group

Ten patients aged 15.7 ± 2.5 years (range 12–20 years) and weighing 45.3 ± 14.9 kg (range 25–58 kg) were enrolled into the study (Table 1). Patients were enrolled if the following criteria were met: fever in the preceding 24–48 h or pyrexia at presentation, pure *Plasmodium falciparum* parasitaemia with a peripheral parasite density of more than 5000 asexual forms per microlitre in blood, no history of anti-malarial drug administration in the 2 weeks preceding presentation, negative urine test for 4-aminoquinoline (Dill-Glazko) and sulphonamides (Lignin) and/or absence of other concomitant illness. The mean oral temperature at enrolment into study was 38.1 °C ± 0.9 (range 36.6–39.1 °C), while the mean parasitaemia at similar time was 202,601 ± 417,465 parasites per microlitre of blood (range 8817–1,382,660 parasites per microlitre of blood). The patients were treated with i.m. artemether at a dose of 3.2 mg/kg body weight at presentation and 1.6 mg/kg body weight daily for the next 4 days. The i.m. route was chosen for two reasons: (1) patients showed relatively high parasitaemia and (2) oral anti-malarial therapy may introduce other confounding variables such as the possibility of drug interaction with caffeine within the gastrointestinal tract.

Conduct of study

All patients and volunteers fasted overnight and, at 0800 hours, were given orally 300 mg caffeine dissolved in 150 ml water; food intake was allowed 3 h after administration of caffeine. An indwelling cannula was inserted into the antecubital vein and kept patent with heparinised saline. Venous blood (5 ml) was drawn into heparinised tubes before and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24 and 36 h after caffeine administration. All subjects rinsed their mouths after caffeine was administered and prior to saliva collection. Unstimulated saliva was collected into clean tubes at the same times as venous blood sampling.

Chemicals

Caffeine (137X), paraxanthine (17X), theobromine (37X) and theophylline (13X) were all obtained form Sigma Chemical Company (Poole, United Kingdom). 4-Nitrophenol and high-performance liquid chromatography (HPLC)-grade chloroform were supplied by BDH (United Kingdom) and HPLC-grade methanol by Fisons Scientific Equipment (United Kingdom).

Preparation of samples

Extractions and analysis of samples was based on the modified method of Dobrocky et al. (1994). After centrifugation at 2000g rpm for 10 min, 500 µl plasma or saliva was pipetted into a clean tube, and 100 µl of 60% perchloric acid was added. The mixture was vortexed for 30 s and 200 µl 1 M NaOH was added. After standing for 10 min, the alkalinised mixture was acidified with 1 M HCl, and 4-nitrophenol (5 µg in 50 µl methanol) was added as internal standard and vortexed for another 30 s.

The mixture was then extracted by shaking with 6 ml chloroform:isopropanol (85:15 v/v) and subsequently centrifuged at 2000g rpm for 10 min. The organic phase was removed and evaporated to dryness at 40 °C under a stream of oxygen-free nitrogen. The residue was reconstituted in 200 µl of a mixture of buffer (0.02 M sodium acetate and 0.013 M ammonium acetate) and methanol (90:10 v/v). A 100-µl aliquot of the residue was injected onto the HPLC column (15 cm × 4 mm i.d. Lichrosorb RP18 column) which was maintained at 44 °C. The mobile phase of aqueous buffer (0.02 M sodium acetate plus 0.013 M ammonium acetate) and methanol (90:10 v/v) was pumped at 1.5 ml/min. The eluate peaks were detected at 285 nm using a Waters Lambda-Max 486 detector with integration using a Waters 745 data module.

Clear resolution of peaks was obtained after extraction of plasma or saliva, with retention times for theobromine, paraxanthine, theophylline and caffeine at 5.8, 7.8, 8.12 and 13.1 min, respectively. Calibration curves were made with known amounts of caffeine and dimethylxanthines in blank plasma or saliva within the concentration range 0–10 µg/ml for caffeine and 0–5 µg/ml for the dimethylxanthines. The limits of measurements/quantification were approximately 0.01 µg/ml for caffeine and 0.02–0.06 µg/ml for the plasma/saliva metabolites (these values varied slightly depending on the chromatographic conditions). The inter-assay coefficients of variation measured at 2.5 µg/ml for theophylline, paraxanthine and theobromine were 1.7%, 2.3% and 3.3%, respectively, while the inter-assay coefficient of variation of 2.2% was measured at concentrations of 5 µg/ml for the caffeine.

Data analysis

Batches of samples were analysed in duplicate sets, each with a series of standards. The concentrations of caffeine and metabolites

Table 1 Mean (±SD) demographic and plasma caffeine kinetic characteristics of healthy adults and subjects with malaria. Subjects 1C–10C were healthy controls. Subjects 1M–10M were patients suffering from malaria. Temperature and parasite counts were taken on admission into study

Subjects	Age (years)/ gender	Weight (kg)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg ml^{-1} h)	Ratio 17X/137X	Clearance (ml/min/kg)	Temperature °C	Parasite counts (×1000)
1C	40/Male	60	5.7	47.8	0.60	1.74	–	–
2C	28/Male	38	7.0	76.2	0.54	1.29	–	–
3C	39/Male	68	8.5	69.1	0.25	1.06	–	–
4C	42/Male	82	4.1	19.5	0.53	3.12	–	–
5C	37/Female	56	14.8	96.3	0.30	0.95	–	–
6C	23/Male	52	10.0	86.7	0.33	1.11	–	–
7C	33/Male	54	7.4	28.2	0.43	3.27	–	–
8C	18/Male	56	4.2	47.3	0.63	1.89	–	–
9C	29/Male	58	6.6	43.2	0.62	2.00	–	–
10C	32/Male	74	4.0	42.0	0.53	2.05	–	–
Mean ± SD	32.1 ± 7.6	59.8 ± 3.8	7.2 ± 3.0	55.6 ± 24.0	0.48 ± 0.13	1.85 ± 0.77	–	–
1M	15/Male	58	7.1	51.6	0.42	1.67	37.6	8.8
2M	16/Male	44	6.0	66.4	0.41	1.71	39.1	109.1
3M	17Female	75	24.4	150.6	0.13	0.44	39.7	65.6
4M	18/Male	46	7.3	45.7	0.52	2.38	37.2	29.3
5M	12/Female	25	8.5	25.1	0.18	7.97	38.5	180.0
6M	18/Male	58	5.5	25.8	0.35	3.34	36.6	1382.7
7M	15/Female	35	8.2	64.9	0.55	2.20	38.4	95.6
8M	20/Female	45	8.0	88.4	0.49	1.26	37.8	33.4
9M	15/Female	35	9.7	102.1	0.10	1.40	38.4	65.1
10M	12/Male	32	10.2	126.3	0.22	1.24	38	56.5
Mean ± SD	15.7 ± 2.5**	45.3 ± 14.9*	9.5 ± 5.2	74.7 ± 39.7	0.34 ± 0.16	2.36 ± 2.01	38.13 ± 0.90	202.6 ± 396.1

*$P < 0.05$; **$P < 0.01$ compared with controls using student's t-test

were calculated from peak height ratios of compounds of interest compared with 4-nitrophenol using linear regression analysis of the standards analysed with that set of samples.

The maximum concentrations in plasma or saliva (C_{max}) and time of C_{max} (t_{max}) are the observed values. The terminal half-lives ($t_{1/2}$) of caffeine and metabolites were calculated using least-squares regression analysis applied to the post-peak, log–linear part of the plasma/saliva concentration–time curves by visual inspection. The areas under the plasma/saliva concentration–time curves (AUC) of caffeine and metabolites were calculated using the trapezoidal rule and extrapolated to infinity by dividing the last measurable plasma concentration by the terminal slope. The ratio of AUC of paraxanthine and caffeine extrapolated to infinity served as an index of CYP1A2. The oral clearance of caffeine in plasma was calculated assuming an oral bioavailability of 1 using the equation:

$$\text{Oral clearance} = \text{dose}/(\text{AUC} \times \text{body weight in kg})$$

The data generated were analysed using the student's t-test, Mann-Whitney U rank sum test and regression analysis. Values of $P < 0.05$ were taken as significant.

Results

The plasma concentration–time curves for caffeine and paraxanthine in normal subjects and malaria are shown in Figs. 1 and 2. The subjects and patients' characteristics and the kinetic parameters of caffeine are described in Table 1. The maximum observed plasma concentrations of paraxanthine (C_{max}) were significantly lower ($P < 0.05$) in patients with malaria (0.90 ± 0.36 μg/ml) than in healthy subjects (1.35 ± 0.52 μg/ml), but the C_{max} values of caffeine, theophylline and theobromine were similar ($P > 0.05$) in both groups (Table 2). The times of C_{max} (t_{max}) in the two groups were similar ($P > 0.05$) (Table 2).

The $AUC_{0-\infty}$, of caffeine, paraxanthine and theophylline in both healthy controls and in malaria patients (Table 1 and Table 2) were similar ($P > 0.05$); because of significant differences in body weights, the $AUC_{0-\infty}$ values were adjusted to 70 kg, but this did not result in significant differences in the AUC of caffeine, paraxanthine and theophylline (Table 2).

There was wide inter-individual variability in $t_{1/2}$ and oral clearance of caffeine in the healthy subjects (Table 1) as has been reported in previous studies in other populations; similar variability was found in patients suffering from malaria (Table 1). There were no significant differences in caffeine oral clearance or $t_{1/2}$ between the two groups.

The mean paraxanthine:caffeine ratio, an index of CYPIA2 activity was slightly but significantly lower in the malaria group (Table 1), primarily because of the higher AUC of caffeine, with the mean values in subjects suffering from malaria representing 70% of the value in healthy controls ($P = 0.03$) (Table 1).

No significant correlation was found between plasma oral clearance and parasite density at commencement of study (0 h) ($r^2 = 0.06$; $P > 0.05$), 8 h ($r^2 = 0.08$; $P > 0.05$) and 12 h ($r^2 = 0.07$; $P > 0.05$), although a weak correlation not corrected for log or comparisons was found at 4 h post-caffeine administration and plasma oral clearance ($r^2 = 0.29$; $P < 0.05$). Similarly, body temperature at the same time points was not significantly correlated with the plasma oral clearance of caffeine.

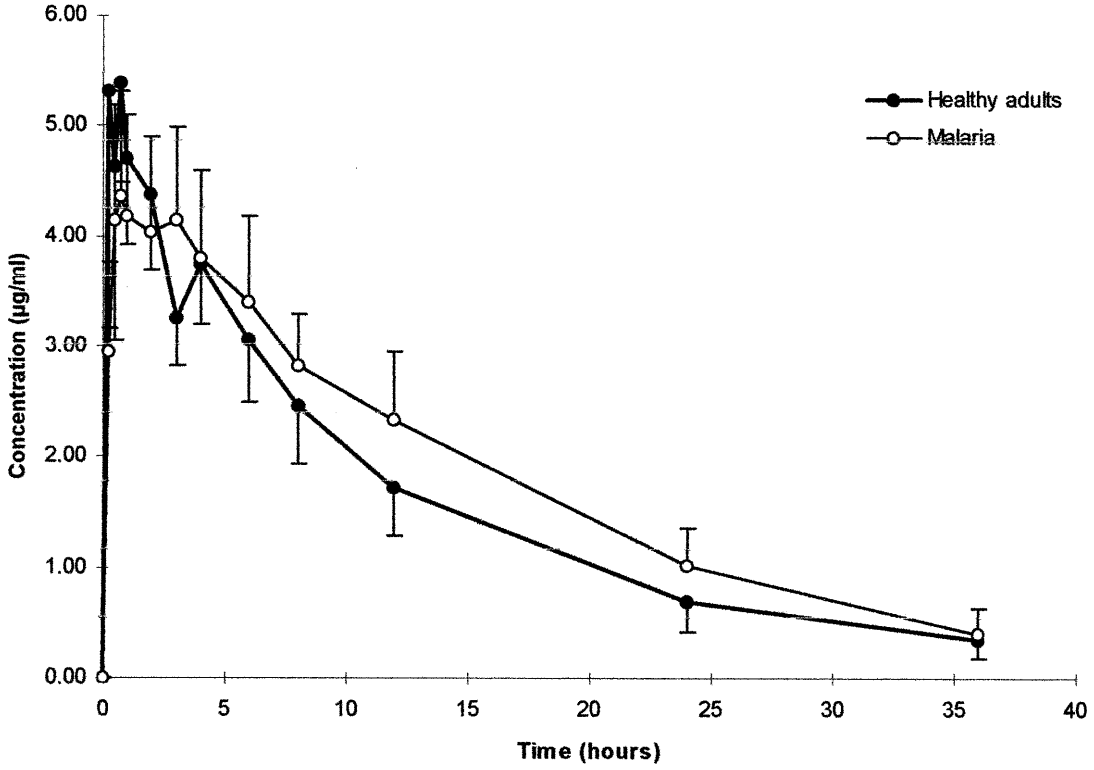

Fig. 1 Plasma caffeine concentration–time curve in healthy adults ($n = 10$) and those with malaria ($n = 10$) (mean ± SD)

Only eight healthy volunteers had complete paired saliva and plasma samples (two sets of saliva samples were discarded because of incomplete data). The saliva-derived pharmacokinetic parameters for caffeine and paraxanthine (Table 3) and the relationship between saliva and plasma parameters are shown in Table 3 and Fig. 3. There was an excellent correlation between the plasma and saliva caffeine concentrations (0.74 ± 0.10; $r^2 = 0.98$) (Fig. 3) and a similar value for paraxanthine (0.79 ± 0.10; $r^2 = 0.88$) (Fig. 4). Except for the expected difference for oral clearance of caffeine calculated using saliva, all pharmacokinetic parameters were similar in both body fluids.

Fig. 2 Plasma paraxanthine concentration–time curve for healthy adults and those with malaria (mean ± SD)

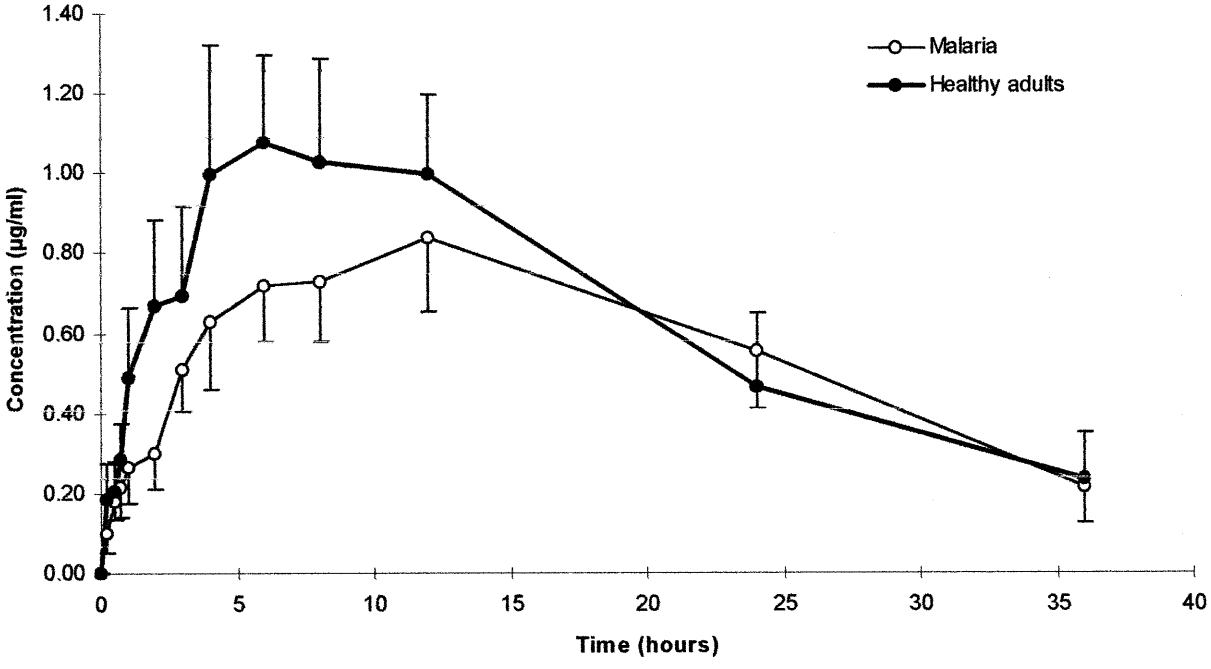

Table 2 Mean ± SD pharmacokinetic profile in plasma of caffeine and its metabolites in healthy adults and subjects with malaria. *AUC* area under the concentration–time curve; C_{max} peak concentration; t_{max} time to reach C_{max}; $t_{1/2}$ elimination half-life

Parameters	Healthy adults	Malaria subjects
Numbers studied	10	10
Caffeine		
C_{max} (μg/ml)	5.9 ± 2.8	4.9 ± 1.8
t_{max} (h)	1.1 ± 1.0	1.3 ± 1.2
$AUC_{0-\infty}$ (μg ml^{-1} h)	55.6 ± 24.0	74.7 ± 39.7
Normalised $AUC_{0-\infty}$ (μg ml^{-1} h per 70 g)	45.4 ± 17.6	50.4 ± 39.8
$t_{1/2}$ (h)	7.2 ± 3.0	9.5 ± 5.2
Clearance (ml/min/kg)	1.9 ± 0.8	2.4 ± 2.0
Paraxanthine		
C_{max} (μg/ml)	1.4 ± 0.5	0.9 ± 0.4*
t_{max} (h)	7.9 ± 3.7	11.4 ± 7.1
$AUC_{0-\infty}$ (μg ml^{-1}h)	24.7 ± 9.0	23.8 ± 11.4
$t_{1/2}$ (h)	9.1 ± 9.0	11.6 ± 5.3
Theophylline		
C_{max} (μg/ml)	0.21 ± 0.10	0.14 ± 0.09
t_{max} (h)	10.3 ± 7.6	13.8 ± 7.3
$AUC_{0-\infty}$ (μg ml^{-1}h)	7.2 ± 5.6	6.1 ± 4.1
$t_{1/2}$ (h)	14.4 ± 7.4	17.7 ± 4.8*
Theobromine		
C_{max} (μg/ml)	0.20 ± 0.04	0.24 ± 0.09
t_{max} (h)	10.2 ± 6.0	12.4 ± 6.9
$AUC_{0-\infty}$ (μg ml^{-1}h)	4.1 ± 2.2	7.1 ± 3.4*
$t_{1/2}$(h)	14.5 ± 8.4	17.4 ± 11.6

*$P < 0.05$ compared with healthy subjects using student's *t*-test

Table 3 Mean ± SD comparative pharmacokinetics of caffeine and paraxanthine in plasma and saliva of eight healthy adults. *AUC* area under the concentration–time curve; C_{max} peak concentration; t_{max} time to reach C_{max}; $t_{1/2}$ elimination half-life

Parameter	Plasma	Saliva
Caffeine		
C_{max} (μg/ml)	5.8 ± 3.2	4.8 ± 8.0
t_{max} (h)	1.5 ± 1.8	1.3 ± 1.0
$AUC_{(0-\infty)}$ (μg ml^{-1}h)	51.9 ± 26.9	35.5 ± 18.9
Corrected $AUC_{(0-\infty)}$ (μg ml^{-1} h per 70 kg)	42.6 ± 20.8	29.9 ± 16.7
$t_{1/2}$(h)	6.0 ± 1.7	7.1 ± 3.8
Oral clearance (ml/min/kg)	1.8 ± 0.7	2.8 ± 1.2*
Paraxanthine		
C_{max} (μg/ml)	1.5 ± 0.6	1.0 ± 0.4
t_{max} (h)	7.0 ± 3.4	8.0 ± 2.8
$AUC_{0-\infty}$ (μg ml^{-1}h)	29.1 ± 9.4	16.8 ± 9.9
$t_{1/2}$ (h)	10.5 ± 4.4	6.9 ± 8.7

*$P < 0.05$ compared with healthy subjects using student's *t*-test for paired data

The paraxanthine:caffeine ratios increased with time in both saliva ($r^2 = 0.94$) and plasma ($r^2 = 0.98$), and a significant correlation ($r^2 = 0.88$) was demonstrated between saliva and plasma paraxanthine:caffeine ratios calculated from the AUC data (Fig. 5). Correlation of the saliva paraxanthine:caffeine ratio with systemic oral clearance in different subjects (Table 1) was best at 4 h post-caffeine administration ($r^2 = 0.74$) and the correlation was lower ($r^2 = 0.33$) at 8 h.

Discussion

Significant inter-individual variability in caffeine metabolism has been documented (Kalow 1986; Relling et al. 1992) and this was demonstrated in this study as a 3.7-fold and 4.4-fold variability, respectively, in the $t_{1/2}$ values in healthy adults and patients with malaria. The wide variability is comparable with the reports in healthy Caucasians (Campbell et al. 1987; Scott et al. 1988) and Asians suffering from malaria (Wilaitarana et al. 1994).

The present study demonstrated that paraxanthine is the principal metabolite of caffeine metabolism in Nigerians, as has been reported previously in healthy Caucasians (Tang et al. 1983; Zylber-Katz et al. 1984) and Asians (Kalow 1986). There are few studies of caffeine metabolism in malaria but, Kokwaro et al. (1993) demonstrated that paraxanthine is the principal metabolite of caffeine metabolism in infected experimental rats. The metabolism of caffeine to paraxanthine is principally mediated by hepatic CYP1A2, which may be evaluated by the ratio of paraxanthine:caffeine concentrations in biological samples (Fuhr and Rost 1994). The CYP1A2 activity measured by plasma paraxanthine:caffeine concentrations in this study was reduced by approximately 31% compared with healthy Nigerian controls. Elimination of caffeine is dependent on hepatic microsomal activity as caffeine is a capacity-limited or low-clearance drug (Anastacio et al. 1982), and this study confirmed that hepatic CYP1A2 activity was lower by 31% in malaria.

The lower CYPIA2 activity may be mediated by tumour necrosis factor (TNF) and/or interleukin-6 (IL-6), which are released in response to malaria and/or fever, and these factors have been shown to cause up to 50% reduction in hepatic CYP activity in infected rats with heavy parasitaemia (Kokwaro et al. 1993). It is well established that drug elimination may be influenced by several factors, such as concomitant medication, smoking habit and age, that influence microsomal oxidative metabolism (Powell and Cate 1986); the presence of coexisting diseases may exert additional effects on drug disposition (Wynne et al. 1990). The only confounding factors in our volunteers included malaria, artemether and fever; however, there was no significant correlation demonstrated at 4 h post-dosage between caffeine oral clearance and fever, though moderate correlation was demonstrated between parasite density and plasma oral clearance.

There have been no reports of the influence of artemether on oxidative metabolism of drugs. It is therefore possible that the slightly reduced paraxanthine:caffeine ratios indicative of CYPIA2 activity demonstrated in this study may be related to malaria parasitaemia. A more pronounced effect of malaria infection has been found in children, since the $t_{1/2}$ was almost threefold higher in children with malaria than in healthy controls (Akinyinka et al. this issue). The parasitaemia counts of over one million parasites per micro-

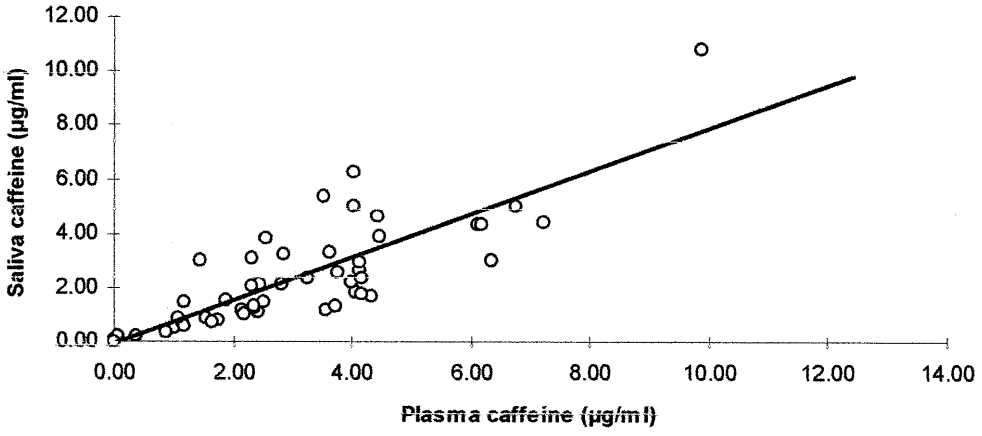

Fig. 3 Correlation between caffeine concentrations in plasma and saliva in healthy adults ($n = 8$)

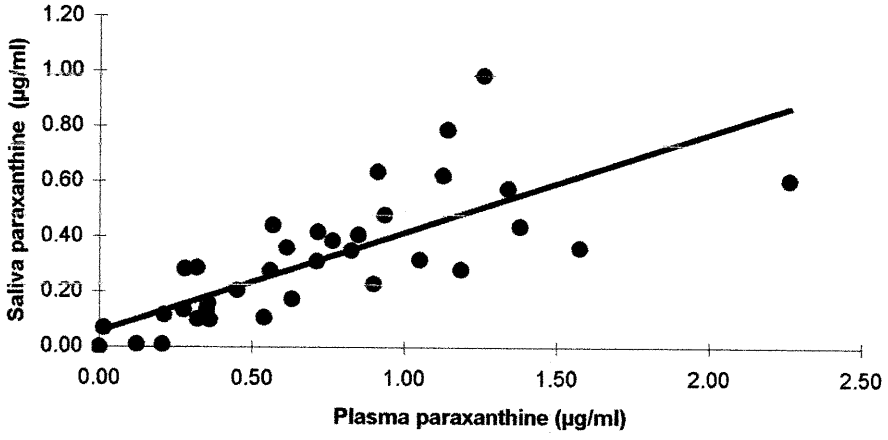

Fig. 4 Correlations between paraxanthine concentrations in plasma and saliva of healthy adults ($n = 8$)

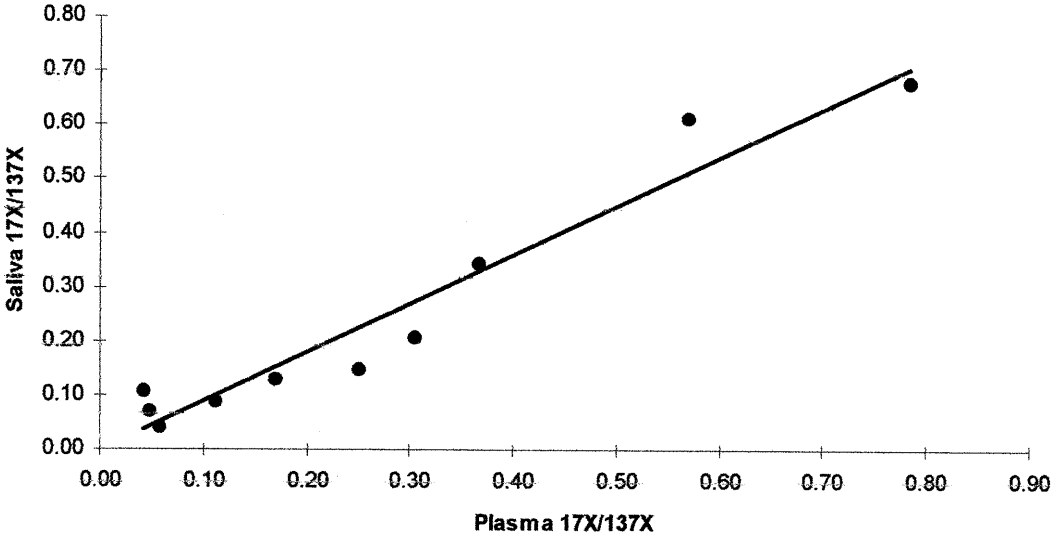

Fig. 5 Correlation between plasma paraxanthine:caffeine ratio in plasma and saliva in healthy adults

litre of blood demonstrated in this study are not uncommonly found in endemic areas (Sowunmi et al. 1996a, b; Sowunmi and Oduola 1997) and are not infrequently associated with normal liver and renal functions, which was the picture in this study group. Therefore, the impaired disposition of caffeine and its metabolites demonstrated in this study was not related to impaired metabolism of caffeine because of the severity of parasitaemia.

Several studies have demonstrated that saliva-derived pharmacokinetic parameters showed good to excellent correlation with the same parameters obtained from plasma (Newton et al. 1981). In the current study, the concentrations of caffeine in saliva exhibited a constant

relationship with plasma concentrations, with a mean ratio of 0.74 ± 0.10, which was similar to previously reported values of the 0.74 (Newton et al. 1981) and 0.79 (Zylber-Katz et al. 1984) in healthy adults. The saliva: plasma ratios were higher in the absorption phase than in the elimination phase which suggested rapid diffusion of caffeine into saliva or inefficient cleansing of mouth after caffeine administration (Newton et al. 1981); however, efforts were made to ensure good cleansing of mouth following the administration of caffeine in these volunteers.

The elimination $t_{1/2}$ and AUC values of both caffeine and paraxanthine, and the CYP1A2 activity defined from both body fluids were similar, with good correlation between saliva and plasma, therefore confirming the utility of saliva as a convenient body fluid to define the pharmacokinetics of caffeine. The present study in healthy Nigerians confirms previous reports of a significantly larger apparent "oral clearance" of caffeine calculated from saliva rather than plasma data (Newton et al. 1981; Zylber-Katz et al. 1984).

Conclusions

This study confirmed that paraxanthine is the principal metabolite of caffeine metabolism in healthy Nigerians and those suffering from malaria, and also demonstrated that the paraxanthine:caffeine ratio as a measure of CYP1A2 activity was significantly lowered in malaria. The observed difference in the CYP1A2 activity may have implications for drug metabolism in malaria. This study confirms the clinical usefulness of saliva for monitoring caffeine kinetics. The simplicity and pain-free collection of saliva and the excellent correlation between plasma and saliva concentrations ensure that plasma-derived kinetic indices of caffeine and paraxanthine, such as the $t_{1/2}$ value, could be predicted from saliva as well as determining the CYP1A2 activity level based on the paraxanthine:caffeine ratio.

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