THE PHARMACOKINETICS OF ORAL DIHYDROARTEMISININ AND ARTESUNATE IN HEALTHY THAI VOLUNTEERS

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Abstract. The pharmacokinetics of oral dihydroartemisinin (DHA) following the dose of 2 and 4 mg/kg body weight dihydroartemisinin (Twisinin™, T-2 Program, Thailand) and 4 mg/kg body weight oral artesunate (AS; Guilin Pharmaceutical Works, Guangxi, China) were investigated in 20 healthy Thai volunteers (10 males, 10 females). All formulations were generally well tolerated. Oral DHA was rapidly absorbed from gastrointestinal tract with marked inter-individual variation. The pharmacokinetics of DHA following the two dose levels were similar and linearity in its kinetics was observed. Based on the model-independent pharmacokinetic analysis, median (95% CI) values for C_{max} of 181 (120-306) and 360 (181-658) ng/ml were achieved at 1.5 hours following 2 and 4 mg/kg body weight dose, respectively. The corresponding values for $AUC_{0-\infty}$, $t_{1/2z}$, CL/f and V_z/f were 377 (199-1,128) *vs* 907 (324-2,289) ng.h/ml, 0.96 (0.70-1.81) *vs* 1.2 (0.75-1.44) hours, 7.7 (4.3-12.3) *vs* 6.6 (3.1-10.1) l/kg, and 90.5 (28.6-178.2) *vs* 6.6 (3.1-10.1) ml/min/kg, respectively (2 *vs* 4 mg/kg dose). Oral AS was rapidly biotransformed to DHA, which was detectable in plasma as early as 15 minutes of AS dosing. Following 4 mg/kg dose, median (95% CI) value for C_{max} of 519 (236-284) ng/ml was achieved at 0.7 (0.25-1.5) hours. $AUC_{0-\infty}$, and $t_{1/2z}$ were 657 (362-2,079) ng.h/ml, 0.74 (0.34-1.42) hours, respectively. C_{max} of DHA following oral AS were significantly higher, but total systemic exposure was greater following oral DHA at the same dose level (4 mg/kg body weight). There was no significant sex difference in pharmacokinetics of DHA.

INTRODUCTION

Malaria is a leading cause of mortality and morbidity in developing areas of the world, and remains a major public health problem in endemic regions (Berman *et al*, 2001). Resistance to available drugs is increasing, and therefore creating a need for new drugs that are well tolerated and simple to use. In the face of this ominous situation, artemisinin and derivatives (artesunate, arteether, and dihydroartemisinin) have lately become a renewed hope for combating the emerging generations of resistant malaria (Hein and White, 1993; Harinasuta and Karbwang, 1994; McIntosh and Olliaro, 1998). These artemisinin drugs have different physicochemical properties and are available in a variety of formulations that influence their routes of administration and dosage regimens (de Vries and Dien, 1996; van Agtmael *et al*, 1999; Navaratnam *et al*, 2000).

Artesunate (AS) is a water-soluble hemisuccinate derivative of artemisinin that is widely used in the treatment of both uncomplicated (oral formulation) and severe falciparum malaria (intravenous or suppository formulation) (White, 1994; Barradell and Fitton, 1995; de Vries and Dien, 1996; Looareesuwan *et al*, 1996; Newton *et al*, 2003). Dihydroartemisinin (DHA), a reduced lactol derivative, is the main acting blood schizontocidal metabolite of the semisynthetic artemisinin derivatives, with activity 2-5 fold that of the parent drugs (Basco and Le Bras, 1993). DHA is the chemical intermediate in the production of AS and other semisynthetic artemisinin derivatives (Lin *et al*, 1987), as well as their principal active metabolite (Lee and Hufford, 1990). Although DHA is not sufficiently water-soluble

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to be formulated as an intravenous injection, it is cheaper to produce than other aremisinin derivatives. The production of this drug is simple with the high yield. Since AS is rapidly deesterified to DHA (Yang *et al*, 1985; Batty *et al*, 1998a; b; Zhao *et al*, 1988), it may be equally acceptable to administer DHA itself. DHA is currently in clinical use as formulated tablets/capsules or suppositories. Pharmacokinetic and bioavailability data for DHA, when given as an oral or suppository formulation, have been reported (Yang *et al*, 1985; Zhao *et al*, 1988; Na-Bangchang *et al*, 1997; 1998a, b; 1999; Batty *et al*, 1998a,b; Hung *et al*, 1999; Binh *et al*, 2001; Ilett *et al*, 2002). The objective of the present study was to describe the pharmacokinetics and tolerability of the two oral doses of a new oral formulation of DHA (Twisinin™, T-2 Program, Thailand) in healthy Thai volunteers. This was performed in comparison with oral formulation of AS (Guilin Pharmaceutical Works, Guangxi, China) which has been registered for clinical treatment of uncomplicated falciparum in Thailand.

MATERIALS AND METHODS

Subjects

Twenty healthy male and female Thai volunteers, aged between 20 and 35 years, weighing 46.7 to 59 kg, who were residents of the Bangkok area, participated in the study. Inclusion criteria included: non-lactating and non-pregnant (females), no significant abnormal findings on history or examination, particularly liver, kidney, cardiovascular diseases or peripheral neuropathy, no history of antimalarial drug ingestion in the preceding three months, and no other drugs or medications ingested in the preceding week. None was a smoker or alcohol drinker nor was on regular medication. Written informed consent for participation was obtained from all the volunteers before initiation of the study. The study was approved by the Ethics Committees of the Faculty of Tropical Medicine, Mahidol University and the Ministry of Public Health, Thailand.

At enrollment, a medical history was taken, including a full physical examination; each volunteer had a thorough physical examination, routine laboratory investigations, plain chest x-ray, urinalysis, and a 12-lead electrocardiogram (ECG).

Drug administration and study design

The trial design was a single randomized three-phases cross-over model. Study participants received, in random order, the following three study sessions: (i) a single oral dose of 2 mg/kg body weight DHA (Twisinin™: 50 or 100 mg per capsule, the T-2 Program, Thailand); (ii) a single oral dose of 4 mg/kg body weight DHA (Twisinin™: 50 or 100 mg per capsule; and (iii) a single oral dose of 4 mg/kg artesunate (AS: 50 mg per tablet; Guilin Pharmaceutical Works, Guangxi, China).

Compliance with all drug intake was under investigators' supervision. No food was allowed until 2 hours after drug intake. The washed-out period after each occasion was at least 2 days. Volunteers were hospitalized in the Bangkok Hospital for Tropical Diseases one day prior to, and on the day of pharmacokinetic study. No other concurrent drugs or alcohol were taken two weeks prior to, and during the study period.

Blood sample collection

Blood samples (5 ml each) were collected through an indwelling intravenous Teflon™ catheter, inserted into a forearm vein of the subject; the patency was maintained with sodium-heparinized saline. Samples for the assay of DHA, and/or AS were collected pre-dose, and at 15, 30, 45, 60, 90, and 120 minutes, and 3, 4, 6, and 8 hours after drug administration. Plasma samples were obtained through centrifugation within 10 minutes (1,500*g*, 15 minutes), and stored at -80ºC until analysis.

Adverse reaction monitoring

The volunteers were physically examined and adverse reactions during the study were recorded with the date and time at which they appeared and disappeared. Adverse effects were assessed on the basis of non-suggestive questioning by the study investigators. These included gastrointestinal, central nervous, cardiovascular, and dermatological effects, as well as other changes possibly attributable to the study drugs. Routine blood investigations (hematology and biochemistry), and urinalysis were performed prior to and at the end of (2 days after last drug administration) the study.

Drug analysis

Concentrations of DHA and/or AS in the

plasma were determined by reductive mode high-performance liquid chromatography (HPLC-EC), according to the method of Na-Bangchang *et al* (1998b). The procedure involved the extraction of AS, DHA, and the internal standard - artemisinin (AN) with the mixture of dichloromethane and *tert*-methyl-butyl-ether (8:2, v/v). Chromatographic separation consisted of the mobile phase (acetonitrile: water containing 0.1 M acetic acid pH 4.8 = 45: 55%) running through the column (Nova-Pak™ C_{18}, 3.9 mm i.d. x 150 cm, 5 mm particle size). The average recoveries of AS, DHA-(α-anomer) 2 and 4 mg, and AN at the concentration range of 10-800 ng/ml were 81.9, 88.2, 101.1 and 84.3 %, respectively. The coefficients of variation (precision and repeatability) were below 10% for all three compounds at concentrations of 800, 400, 200, 500, and below 20% at concentration of 10 ng/ml. The limits of quantification for both AS and α-DHA in spiked plasma samples were 5 and 3 ng/ml, respectively.

Pharmacokinetic analysis

Pharmacokinetic parameters of DHA following the administration of a single oral dose of DHA or AS were calculated by model-independent (oral DHA, DHA as an active plasma metabolite of AS) and model-dependent (oral DHA) methods from plasma concentration-time data (Gibaldi, 1991).

Model-independent method. The time at which maximum plasma concentration occurred (t_{max}), and the maximum concentration (C_{max}) were obtained directly from concentration-time data. The area under the curve from zero time to the last observed time (AUC_{0-t}) was calculated by the linear trapezoidal rule for ascending data points and by the log-linear trapezoidal rule for descending data points. The area under the curve extrapolated from the last data point to infinity ($AUC_{t-\infty}$) was estimated by dividing the estimated concentration at the last data point with the elimination rate constant (λ_z). The total area under the curve ($AUC_{0-\infty}$) was calculated as $AUC_{0-t} + AUC_{t-\infty}$. The terminal elimination rate constant (λ_z) and half-life ($t_{1/2z}$) were estimated by log-linear regression of at least four last concentration-time data. The apparent total body clearance (CL/f) and apparent volume of distribution associated with terminal phase (V_z/f) were calculated as CL/f = dose/AUC and $V_z/f = (Cl/f)/\lambda_z$, respectively.

Model-dependent. To better characterize the absorption phase, a one-compartment open model with first order input and first-order elimination was fitted to the data by an iterative least squares curve fitting Program TopFit™. The observed concentrations were weighted as the reciprocal of the analytical variance. The adequacy of the pharmacokinetic models chosen was based on statistical methods to assess the validity of the models for describing the experimental data, *ie F*-ratio test, Akaike's information, Schwartz and Imbimbo criteria.

Statistical analysis

Statistical analysis of the data was performed with SPSS for Windows (SPSS Software, Gorichem, The Netherlands). The distribution of data was assessed for normality using the Schapiro-Wilks test. Data were expressed as medians with 95% CIs values.

The pharmacokinetics of DHA in healthy Thai volunteers following the administration of 2, 4 mg/kg body weight DHA, or 4 mg/kg body weight AS were compared using Kruskal Wallis test and Wilcoxon signed ranks test for non-normally distributed data. Comparison of pharmacokinetic parameters between sex (male, female) in each drug regimen was performed by Mann-Whitney *U*-test. Categorical data (adverse reactions) were analyzed by calculating chi-square with Yate's correction or by Fisher's exact test. Significance level for all tests was set at $\alpha < 0.05$.

RESULTS

Tolerability

All volunteers were healthy, verified by laboratory results, physical examination, and vital sign monitoring. Table 1 presents demographic and baseline laboratory (hematology/ biochemistry) data of the volunteers. Significant laboratory changes in some hematological or biochemical tests were noted at the end of the study (2 days after drug administration). Parameters which decreased at the end of the study included hemoglobin, hematocrit, total protein, albumin,

Table 1
Demographic and baseline laboratory data of 20 healthy Thai volunteers (10 males, 10 females); data are presented as median (95% CI) values.

	Male	Female
Age (y)	21 (20, 33)	23 (21, 35)
Body weight (kg)	53.7 (47.8, 59)	49.3 (46.7, 51.6)
Hematology		
Hemoglobin (mg/dl)	13.85 (11.8, 15.1)	12.7 (11.4, 13.8)
Hematocrit (%)	43 (36, 46)	39.5 (36, 42)
Red cells (x 10^{12} /l)	1.44 (4.57, 6.78)	4.67 (4.01, 6.41)
Platelets (x 10^{9} /l)	233 (203, 310)	309 (192, 328)
White cells (x 10^{9} /l)	7.7 (5.1, 9.8)	7.4 (4.5, 9.3)
PMN (%)	49 (37, 61)	49.5 (42, 62)
Lymphocyte (%)	36 (26, 55)	41 (27, 49)
Monocyte (%)	6 (0, 11)	6 (2, 7)
Eosinophil (%)	5 (2, 12)	3 (1, 13)
Biochemistry		
Direct bilirubin (mg/dl)	0.15 (0.1, 0.6)	0.165 (0.006, 0.25)
Total bilirubin (mg/dl)	0.685 (0.36, 2.4)	0.595 (0.32, 1.3)
Alkaline phosphatase (U/l)	64.5 (44, 112)	67.5 (44, 79)
SGOT (U/l)	22 (15, 50)	18 (16, 24)
SGPT (U/l)	20 (12, 98)	11 (7, 19)
Total protein (g/dl)	7.35 (6.3,7.9)	7.65 (7.2,8.2)
Albumin (g/dl)	4.75 (4.3, 4.9)	4.5 (4.2, 4.6)
Globulin (g/dl)	2.6 (2, 3.1)	3.0 (2.6, 3.4)
Creatinine (mg/dl)	0.9 (0.78, 1.2)	0.75 (0.65, 0.9)
BUN (mg/dl)	11.5 (8.3, 17.7)	9.95 (7, 13.8)
Glucose (mg/dl)	93 (80, 113)	86 (81, 115)
Sodium (mmol/l)	141.5 (139, 145)	142 (139, 144)
Potassium (mmol/l)	3.8 (3.6, 4.8)	4.15 (3.7, 4.6)
Chloride (mmol/l)	106 (104, 108)	106.5 (105, 108)
Bicarbonate (mmol/l)	24.5 (24, 26)	24.5 (24, 26)

globumin, while parameter which increased at the end of the study was platelet count. However, these values returned to normal within 2 weeks after the termination of the drugs. None of the volunteers complained of adverse reaction or drug-related effect during the study.

Pharmacokinetics

Median plots of plasma concentration-time profiles of DHA and/or AS following the administration of a single oral dose of 2 or 4 mg/kg body weight DHA, or 4 mg/kg body weight AS in 20 healthy Thai volunteers are shown in Figs 1a and 1b. Oral DHA was rapidly absorbed from gastrointestinal tract with marked inter-individual variation. In most cases, the drug was detectable in plasma within 15 minutes of dosing; it disappeared thereafter from systemic circulation within 3-8 hours. Oral AS was rapidly biotransformed to DHA, which was detectable in plasma as early as 15 minutes of AS dosing. Considerable inter-individual variation in plasma DHA concentrations following both oral formulations of DHA and AS was observed. Systemic exposure of AS itself was seen only during 15 minutes to 1 hour but with markedly low concentrations.

The pharmacokinetics of DHA (median and 95% CI) following a single oral dose administration of 2 or 4 mg/kg body weight DHA, or 4 mg/kg body weight AS in 20 healthy Thai volunteers, calculated based on model-independent and

Table 2
Pharmacokinetics of DHA (model-independent) following a single oral dose of 2 or 4 mg/kg body weight DHA (Twisinin™), or 4 mg/kg body weight AS (Guilin Pharmaceutical Works) in healthy Thai males (n=10) and females (n=10) data are presented as median (95% CI) values.

Pharmacokinetic Parameters	2 mg/kg DHA	4 mg/kg DHA	4 mg/kg AS
C_{max} (ng/ml)[a]	181 (120-306)	360 (181-658)	519 (236-284)
$AUC_{0-\infty}$ (ng.h/ml)[b]	377 (199-1,128)	907 (324-2,289)	657 (362-2,079)
t_{max} (h)[c]	1.5 (0.75-2.0)	1.5 (0.75-3.0)	0.7 (0.25-1.5)
λ_z (/h)[d]	1.009 (0.532-1.375)	0.802 (0.668-1.284)	1.301 (0.678-2.832)
$t_{1/2z}$ (h)[e]	0.96 (0.70-1.81)	1.2 (0.75-1.44)	0.74 (0.34-1.42)
V_z/f (l/kg)	7.7 (4.33-12.3)	6.6 (3.1-10.1)	-
CL/f (ml/min/kg)	90.5 (28.6-178.2)	72.2 (31.9-113.6)	-

[a]Significant difference between 2 and 4 mg/kg body weight DHA with p = 0.0001 (95% CI = 151-246); and between 2 mg/kg body weight DHA and 4 mg/kg body weight AS with p = 0.006 (95% CI = 202-430); and between 4 mg/kg body weight DHA and AS with p = 0.02 (95% CI = 9-235).
[b]Significant difference between 2 and 4 mg/kg body weight DHA with p = 0.00001 (95% CI = 425-689); and between 2 mg/kg body weight DHA and 4 mg/kg body weight AS with p = 0.0005 (95% CI = 98-420); and between 4 mg/kg body weight DHA and AS with p = 0.02 (95% CI = -481to -48).
[c]Significant difference between 2 mg/kg body weight DHA and 4 mg/kg body weight AS with p = 0.0002 (95% CI = -1 to -0.5); and between 4 mg/kg body weight DHA and AS with p = 0.00005 (95% CI = -14 to -0.5).
[d]No statistical test was performed.
[e]Significant difference between 2 mg/kg body weight DHA and 4 mg/kg body weight AS with p = 0.0097 (95% CI = -0.044 to -0.0009); and between 4 mg/kg body weight DHA and AS with p = 0.0005 (95% CI = -0.56 to -0.21).

Table 3
Pharmacokinetics of DHA (model-dependent) following a single oral dose of 2 or 4 mg/kg body weight DHA (Twisinin™) in healthy Thai males (n=10) and females (n=10); data are presented as median (95% CI) values.

Pharmacokinetic parameters	2 mg/kg DHA	4 mg/kg DHA
C_{max} (ng/ml)	144 (91-260)	283 (105-632)
$AUC_{0-\infty}$ (ng.h/ml)	415 (211-1,280)	919 (408-2,480)
t_{max} (h)	1.45 (0.81-2.2)	1.46 (0.81-2.2)
t_{lag} (h)	0.25 (0.11-0.25)	0.24 (0.19-0.25)
k_a (/h)	0.83 (0.51-2.59)	0.83 (0.42-3.84)
$t_{1/2a}$ (h)	0.83 (0.27-1.35)	0.84 (0.18-1.65)
k_e (/h)	0.82 (0.51-1.24)	0.81 (0.41-1.21)
$t_{1/2}$ (h)	0.83 (0.2-1.35)	0.86 (0.39-10.1)
V_c/f (l/kg)	4.8 (2.5-10.6)	5.2 (2.2-7.6)
CL/f (ml/min/kg)	82.4 (25.3-171.9)	68.6 (24.5-103.6)

[a]Significant difference between 2 and 4 mg/kg body weight DHA with p = 0.00001 (95% CI = 107 to 208).
[b]Significant difference between 2 and 4 mg/kg body weight DHA with p = 0.00001 (95% CI = 411 to 749).

model-dependent methods, are summarized in Tables 2 and 3, respectively. The fitting of the concentration-time curves of DHA either when given as oral DHA to a one-compartment model with first-order input and output yielded satisfactory results in all volunteers. Pharmacokinetics of DHA calculated using both methods were generally in good agreement. No significant absorption lag-time was observed from the time of drug administration until it was first detectable in the plasma. Large inter-individual variation among the pharmacokinetic parameters was noted, particularly with $AUC_{0-\infty}$ and CL/f as reflected by the values of coefficients of variation for both parameters (40-45%).

No significant difference was found in any of DHA pharmacokinetic parameters between male and female volunteers following the administration of either dose of DHA (2 or 4 mg/kg body weight), or as a single oral dose of 4 mg/kg body weight AS.

Model-independent analysis. Marked differ-

ences in the pharmacokinetic parameters of DHA were observed following the oral dose regimens of DHA and AS. Oral DHA at the dose level of 2 mg/kg body weight resulted in a significantly lower C_{max} and $AUC_{0-\infty}$ of DHA compared with 4 mg/kg body weight dose of DHA or AS. With respect to DHA, C_{max} increased proportionally with the dose with a median ratio of 2.3. C_{max} of DHA following the same dose of AS (4 mg/kg body weight) was significantly higher than that following DHA, but greater $AUC_{0-\infty}$ was achieved following DHA. In addition, t_{max} of DHA following AS was found to be significantly shorter than that following DHA at either dose level.

Model-dependent analysis. Pharmacokinetics of DHA following the two dose levels of DHA (2 and 4 mg/kg body weight) were generally comparable and consistent with the values calculated using model-independent method. Only two significant differences in dose-dependent pharmacokinetic parameters were noted; C_{max} and $AUC_{0-\infty}$ following the higher dose level were approximately double that seen in the model-independent analysis.

DISCUSSION

The pharmacokinetics of AS and DHA have been addressed in a few studies, with varying routes of administration, ethnicity of the subjects and disease states (Yang *et al*, 1985; Zhao *et al*, 1988; Na-Bangchang *et al*, 1997; 1998a; 1999; Batty *et al*, 1998a,b; Hung *et al*, 1999; Binh *et al*, 2001; Ilett *et al*, 2002). The concentration-time profiles of DHA following the administration of the oral doses of both DHA and AS observed in the present study were generally in accord with those previously reported. No marked sex diffrences in DHA pharmacokinetics was observed following either oral DHA or AS, which supports a previous report in healthy Vietnamese volunteers (Hung *et al*, 1999). The current formulation of oral DHA (Twisinin™) was rapidly absorbed from the gastrointestinal tract; C_{max} was attained at approximately 1-2 hours of dosing. The pharmacokinetic profile was generally well described by a one-compartment open model with first- order input and output, characterising the rapid absorption, distribution and elimination phase. Elimination half-life was estimated to be in the range of 0.8-1.5 hours. Little is known about the ultimate phase of dihydroartemisinin in human body. The *in vitro* studies using rat isolated perfused liver (IPRL) and microsomes have identified glucuronide conjugate as a sole and principal metablite of DHA (Maggs *et al*,1997). The extent of the hepatic extraction of oral DHA is unknown. Oral AS (Guilin Pharmaceutical Works, China) was almost immediately biotransformed to the active metabolite, DHA. Systemic exposure to AS itself was very low (C_{max} of less than 200 ng/ml in most cases) and was observed only during a short period, the first hour, after drug intake. In contrast, its plasma metabolite, DHA, attained a relatively high C_{max} within 0.25-1.5 hours of AS dosing. Distribution/elimination of this metabolite was also rapid. The apparent elimination half-life was estimated to be in the range of 0.4-1.4 hours.

The pharmacokinetics of DHA following a single oral dose of 2 or 4 mg/kg body weight DHA were generally similar. This was indicated by the comparable values of dose-independent pharmacokinetic parameters. Linearity of DHA kinetics was seen at these two dose levels, which was ascribed by the proportional increase in $AUC_{0-\infty}$ with the dose (mean $AUC_{0-\infty}$ ratio of 2.4). It appears that the bioavailability of the current formulation of oral DHA (Twisinin™) is markedly low (approximately 50%) when compared with the formulation produced by Guilin Pharmaceticals, China (Cotexin™: tablet) or Arenco nv, Belgium (Dihydroartemisinin™: capsule) (Na-Bangchang *et al*, 1997; Hung *et al*, 1999). In a previous study in healthy Thai volunteers following 300 mg of Dihydroartemisinin™ (Arenco-nv, Belgium), median (range) $AUC_{0-\infty}$ and C_{max} of 2,010 (636-4,079) ng.h/ml and 679 (307-1,000) ng/ml were achieved, respectively (Na-Bangchang *et al*, 1997). Furthermore, in a study in healthy Vietnamese volunteers following 240 mg of Cotexin™, median (range) $AUC_{0-\infty}$ and C_{max} of 1,867 (420-3,535) ng.h/ml and 466 (128-787) ng/ml were attained, respectively (Hung *et al*, 1999).

It was noted that the pharmacokinetics of DHA following oral DHA and AS doses showed noticeable differences in pharmacokinetic. The

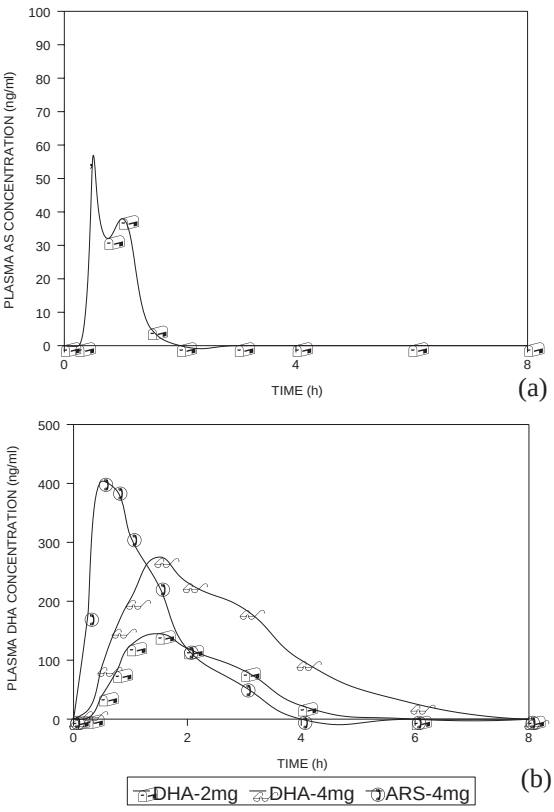

Fig 1–Median plasma concentration-time profiles of (a) artesunate (AS) following the dose of oral 4 mg/kg body weight oral AS, and (b) dihydroartemisin (DHA) following the doses of oral 2 and 4 mg/kg body weight oral DHA.

Disposition of DHA, when the drug was given as oral AS, was greatly influenced by the kinetics of the parent compound itself, *ie*, formation of DHA was rate-limited by kinetics (absorption, distribution, and metabolism) of AS. Higher C_{max} of DHA was attained at faster time following the oral AS, but total systemic exposure was higher following oral DHA given at the same dose level (4 mg/kg body weight). This may suggest that absorption of DHA from oral formulation may be more erratic but relatively complete compared with oral AS. DHA is poor water solubility, which means that it can only be administered orally or rectally. Previous data, however, showed that the bioavailability of orally administered DHA was only 45% relative to the DHA from intravenous AS (Binh *et al*, 2001).

In conclusion, the oral formulation of both AS and DHA were well tolerated. No clinically adverse reaction or drug-related effect was observed during the study. Nevertheless, adequate therapeutic plasma concentrations following the administration of the current formulation of oral DHA (Twisinin™) may not be guaranteed. This is of concern, especially in patients with malaria, whose absorption of the drug by the oral route may be erratic and incomplete.

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