The pharmacokinetic properties of intramuscular artesunate and rectal dihydroartemisinin in uncomplicated falciparum malaria

Kenneth F. Ilett,^{1,2} Kevin T. Batty,^{1,3,4} Shane M. Powell,^{1,3} Tran Quang Binh,⁵ Le Thi Anh Thu,⁵ Hoang Lan Phuong,⁵ Nguyen Canh Hung⁶ & Timothy M. E. Davis³

¹Department of Pharmacology, University of Western Australia, Nedlands, ²Clinical Pharmacology and Toxicology Laboratory, Western Australian Centre for Pathology and Medical Research, Nedlands, ³Department of Medicine, University of Western Australia, Fremantle Hospital, Fremantle, ⁴School of Pharmacy, Curtin University of Technology, Bentley, Australia, ⁵Tropical Diseases Research Center, Cho Ray Hospital, Ho Chi Minh City and ⁶Bao Loc Hospital, Lam Dong Province, Vietnam

Aims To obtain pharmacokinetic data for artesunate (ARTS) and its active metabolite dihydroartemisinin (DHA) following i.m. ARTS and rectal DHA administration.

Methods Twelve Vietnamese patients with uncomplicated falciparum malaria were randomized to receive either i.v. or i.m. ARTS (120 mg), with the alternative preparation given 8 h later in an open crossover design. A further 12 patients were given i.v. ARTS (120 mg) at 0 h and rectal DHA (160 mg) 8 h later.

Results Following i.v. bolus, ARTS had a peak concentration of $42 \mu\text{M}$ (16 mg l^{-1}), elimination $t_{1/2}=3.2 \text{ min}$, $\text{CL}=2.8 \text{ l h}^{-1} \text{ kg}^{-1}$ and $V=0.22 \text{ l kg}^{-1}$. The C_{max} for DHA was $9.7 \mu\text{M}$ (2.7 mg l^{-1}), $t_{1/2}=59 \text{ min}$, $\text{CL}=0.64 \text{ l h}^{-1} \text{ kg}^{-1}$ and $V=0.8 \text{ l kg}^{-1}$. Following i.m. ARTS, C_{max} was $2.3 \mu\text{M}$ (3.7 mg l^{-1}), the apparent $t_{1/2}=41 \text{ min}$, $\text{CL}=2.9 \text{ l h}^{-1} \text{ kg}^{-1}$ and $V=2.6 \text{ l kg}^{-1}$. The relative bioavailability of DHA was 88%, C_{max} was $4.1 \mu\text{M}$ (1.16 mg l^{-1}) and $t_{1/2}=64 \text{ min}$. In the rectal DHA study, relative bioavailability of DHA was 16%.

Conclusions For patients with uncomplicated falciparum malaria i.m. ARTS is a suitable alternative to i.v. ARTS, at equal doses. To achieve plasma DHA concentrations equivalent to parenteral administration of ARTS, rectal DHA should be given at approximately four-fold higher milligram doses. Further studies are needed to determine whether these recommendations can be applied to patients with severe malaria.

Keywords: artesunate, dihydroartemisinin, falciparum malaria, intramuscular injection, pharmacokinetics, rectal administration

Introduction

Artemisinin and derivatives such as artesunate and artemether have become an integral component of malaria treatment protocols in many tropical countries, especially where multidrug resistant *Plasmodium falciparum* has emerged. These artemisinin drugs have different physico-chemical and pharmacokinetic properties and are available in a variety of formulations that influence their routes of administration and dosage regimens [1–3]. Artesunate

(ARTS), the only water-soluble derivative in clinical use, has been administered by the intravenous (i.v.), intramuscular (i.m.), oral and rectal routes at doses ranging from 2 mg kg^{-1} to more than 6 mg kg^{-1} [2–9]. Whilst i.v. administration of ARTS is indicated for patients who have severe falciparum malaria, particularly those in coma, venous access may not be possible where only basic health care facilities exist. In addition, even when drugs can be given intravenously, patient discomfort and inconvenience, staff time, and risks such as overhydration and thrombophlebitis may make i.v. less attractive than i.m. or rectal administration.

The development of i.m. and rectal ARTS regimens is dependent on valid pharmacokinetic data and clinical evidence that use of these routes results in comparable

Correspondence: Dr Kevin Batty, Lecturer, School of Pharmacy, Curtin University of Technology, GPO Box U1987, Perth 6845, Western Australia. Tel.: [618] 9266 3941; Fax: [618] 9266 2769; E-mail: Kevin.Batty@curtin.edu.au

Received 22 March 2001, accepted 15 August 2001.

efficacy to i.v. administration. As a first step in this process, we have conducted a pharmacokinetic evaluation of alternative routes of administration of ARTS and its active metabolite dihydroartemisinin (DHA) in patients with uncomplicated falciparum malaria. Pharmacokinetic data for ARTS and DHA, following i.v., oral and rectal administration of ARTS have been published [5, 10–14], but there has been no comprehensive pharmacokinetic study of i.m. ARTS. Hence, our first objective was to determine the pharmacokinetic properties of ARTS and DHA following i.m. ARTS administration to patients with uncomplicated falciparum malaria. Our second objective was an investigation of the pharmacokinetic properties of DHA suppositories. DHA is the chemical intermediate in the production of ARTS and other semisynthetic artemisinin derivatives [15] and their principal active metabolite [16]. Although DHA is not sufficiently water-soluble to be formulated as an i.v. injection, it is cheaper to produce than the artemisinin derivatives and is now available as oral tablets and rectal suppositories. We have shown that DHA has a high oral bioavailability in healthy volunteers and comparable bioavailability to oral ARTS in patients with falciparum malaria [17]. The present study provides the first report of the pharmacokinetic properties of DHA when administered rectally to adult patients with uncomplicated falciparum malaria.

Methods

Patients

Twenty-four patients with uncomplicated falciparum malaria were recruited from the Bao Loc region of Lam Dong Province in Vietnam. All patients gave written, informed consent in Vietnamese. The diagnosis was confirmed by microscopic examination of thick and thin blood films, and a complete clinical assessment including drug history was completed. Patients were excluded if they had impaired consciousness, jaundice (serum bilirubin $>50 \mu\text{mol l}^{-1}$), renal impairment (serum creatinine $>250 \mu\text{mol l}^{-1}$ after rehydration), anaemia (venous haematocrit $<20\%$), hyperparasitaemia ($>150\,000$ asexual forms per μl whole blood from thick film analysis) or if informed consent could not be obtained. Patients were not recruited if they had been treated with ARTS or DHA in the previous 8 h, artemisinin in the previous 12 h, or artemether in the previous 24 h. These criteria ensured that patients were excluded for a period at least five times the elimination half-life of the drug (approximately 40 min for DHA, 2 h for artemisinin and 4 h for artemether [2, 3]). The study was approved by the Ministry of Health, Vietnam, and the University of Western Australia Human Rights Committee.

Study design and procedures

In the intramuscular (i.m.) study, 12 patients were randomized by a predetermined, computer-generated schedule to receive either i.v. ARTS (120 mg dissolved in 1 ml of 5% w/v sodium bicarbonate injection and diluted to 10 ml with 5% w/v dextrose for administration as a bolus over 2 min) or i.m. ARTS (120 mg dissolved in 1 ml 5% w/v sodium bicarbonate injection and given as a bolus into the gluteal muscle), with the alternative preparation given 8 h later in an open crossover design. ARTS was obtained from the Guilin No. 2 Pharmaceutical Factory, Guangxi, China. A single dose of mefloquine (750 mg) was administered 24 h after admission to the study. Venous blood samples (15 ml immediately prior to dosing and 3 ml thereafter) were obtained from the arm opposite to that used for drug administration. In the case of i.v. ARTS, sampling times were at 0, 5, 7, 9, 12, 15, 20, 30, 45, 60, 75, 90 min and 2, 2.5, 3 and 4 h after dosing. For i.m. ARTS, sampling was at 0, 10, 15, 20, 30, 45, 60, 75, 90 min and 2, 2.5, 3, 4 and 5 h. Blood was collected into fluoride-oxalate tubes and chilled immediately to prevent ARTS degradation by plasma esterases. Samples were centrifuged within 30 min to minimize haemolysis and the separated plasma was stored below -20°C until analysed. Thick and thin blood films were prepared from the hourly samples, and 4 hourly thereafter, until parasite clearance. Vital signs including oral temperature and urine output were monitored every 4 h. Patients were discharged when afebrile and aparasitaemic.

In the suppository study, 12 patients were given i.v. ARTS (120 mg) initially and rectal DHA (160 mg, comprising 2×80 mg suppositories; Guilin No. 2 Pharmaceutical Factory) 8 h later, and a single dose of mefloquine (750 mg) was administered 24 h after admission to the study. To ensure that patients received prompt, efficacious treatment on admission to hospital, and because the pharmacokinetic properties of DHA suppositories in falciparum malaria were unknown, the order of administration was not randomized for this study. Previous studies have shown no order effect on the pharmacokinetic parameters of a dose that is given 8 h after i.v. ARTS administration [10, 14]. Following i.v. ARTS administration, venous blood samples were obtained as described above. For rectal DHA, sampling was at 0, 15, 30, 45, 60, 75, 90, 105 min and 2, 2.5, 3, 3.5, 4, 6 and 8 h. Blood collection, sample processing and patient monitoring were as described above.

Pharmacokinetic, pharmacodynamic and statistical analysis

Plasma samples were assayed by a previously validated h.p.l.c. assay with limits of quantification for ARTS and

DHA of approximately 80 nM and 70 nM, respectively [18]. The between-run coefficients of variation for ARTS at 900 nM and 4970 nM were 5% and 6%, respectively. For DHA at 1070 nM and 4730 nM the between-run coefficients of variation were 11% and 9%, respectively. Stability of ARTS (780 and 4560 nM) and DHA (1060 and 6160 nM) in plasma has been assessed for up to 12 months at -25°C and found to be within $\pm 7.6\%$ of replicate samples stored at -80°C (Batty KT, PhD Thesis, University of WA, 1999).

Pharmacokinetic parameters (area under the plasma concentration-time curve from zero to infinity, $\text{AUC}(0,\infty)$, for i.v. and i.m. administration, or zero to 8 h, $\text{AUC}(0,8\text{ h})$, for rectal administration; elimination half-life, $t_{1/2}$; elimination rate constant, k ; mean residence time, MRT; clearance, CL; volume of distribution, V ; maximum concentration in plasma, C_{max} ; time of maximum plasma concentration, t_{max}) were determined from the plasma concentration-time data using noncompartmental analysis [19]. Bioavailability of DHA following i.m. ARTS was calculated as $F = (\text{AUC}_{\text{i.m. (DHA)}} / \text{AUC}_{\text{i.v. (DHA)}})$. Bioavailability of DHA following rectal DHA was calculated as $F = (\text{AUC}_{\text{rectal DHA}} / \text{AUC}_{\text{i.v. (DHA)}}) \times (\text{Dose}_{\text{i.v.}} / \text{Dose}_{\text{rectal}})$. Pharmacokinetic parameters derived for DHA assume complete bioconversion from ARTS [16].

Blood films were stained (Giemsa) within 12 h of preparation and examined by a single microscopist. Thick films were used to determine parasite density in all patients. The time to reach 50% of the original parasite count (PCT_{50}) was determined by simple linear interpolation of the parasite count – time data. Fever clearance time (FCT) was taken to be the first oral temperature $< 37.5^{\circ}\text{C}$.

The study was designed to detect a 30% difference (80% power at $P < 0.05$) in the principal parameters of interest, AUC and CL. Data are expressed as mean $\pm$ s.d. or median (interquartile range) as appropriate. Statistical analyses were performed using SigmaStat[®] Version 2.0 (SPSS Inc., Chicago, USA; 1997).

Results

Clinical course

Demographic and biochemical data from the patients are given in Table 1. Sampling from one patient in the i.m. study was incomplete and the results for this patient were therefore excluded from the analysis. The demographic characteristics were consistent with previous studies of patients with uncomplicated falciparum malaria from the same region [10, 14].

Table 1 Demographic data. Group 1 patients received i.v. or i.m. artesunate at 0 h, with the alternative route of administration used at 8 h. Group 2 patients received i.v. artesunate at 0 h and rectal dihydroartemisinin at 8 h. Data are presented as mean $\pm$ s.d. unless otherwise indicated.

	Group 1 (ARTS i.v./i.m.)	Group 2 (ARTS i.v./ DHA rectal)
Sex (M/F)	11/0	8/4
Age (years)	30 ± 7	27 ± 7
Weight (kg)	55 ± 8	53 ± 5
Body Mass Index (kg m^{-2})	20.0 ± 2.0	20.2 ± 1.6
Temperature ($^{\circ}\text{C}$)	39.0 ± 0.8	39.2 ± 0.8
Haematocrit (%)	38 ± 4	38 ± 3
Parasitaemia (μl^{-1}) ^a	3491 (1051, 11 587) ^a	2259 (693, 7362) ^a
Glucose (mmol l^{-1})	6.7 ± 2.0	6.7 ± 1.3
Creatinine ($\mu\text{mol l}^{-1}$)	125 ± 35	97 ± 17
Bilirubin ($\mu\text{mol l}^{-1}$)	9 ± 9	13 ± 12
ALT (units l^{-1})	35 ± 17	33 ± 18
PCT_{50} (h)	7.4 ± 6.2	4.2 ± 3.2
FCT (h) ^b	$36 (30\text{--}47)^b$	$24 (20\text{--}42)^b$

^aGeometric mean and 95% confidence interval; ^bMedian and interquartile range.

Pharmacokinetic analysis

Pharmacokinetic data from the i.m. study are summarized in Table 2 and presented in Figure 1. In the patients who received i.m. ARTS first, the mean ($\pm$ s.d.) clearance of DHA following i.m. ARTS ($0.60 \pm 0.13\text{ l h}^{-1}\text{ kg}^{-1}$) was lower than the clearance of DHA in patients who received i.m. ARTS second ($0.84 \pm 0.20\text{ l h}^{-1}\text{ kg}^{-1}$; $P = 0.04$, $\alpha = 0.05$, power = 48%, 95% CI for difference of means = $-0.48, -0.012$). In the patients who received i.v. ARTS first, mean clearance of DHA following i.v. ARTS ($0.76 \pm 0.22\text{ l h}^{-1}\text{ kg}^{-1}$) was greater than the clearance of DHA in patients who received i.v. ARTS second ($0.51 \pm 0.13\text{ l h}^{-1}\text{ kg}^{-1}$), although this was not statistically significant ($P = 0.06$, $\alpha = 0.05$, power = 40%, 95% CI for difference of means = $-0.50, 0.01$). As the statistical power was below the desired 80% in both cases, and we cannot exclude a Type I error, all pharmacokinetic data have been pooled in Table 2.

Following i.v. administration, ARTS had a mean extrapolated peak concentration of $42\text{ }\mu\text{M}$ (16 mg l^{-1}) and a mean $t_{1/2}$ of 3.2 min. Following i.m. therapy, C_{max} for ARTS was $2.3\text{ }\mu\text{M}$ (3.7 mg l^{-1}) and the apparent $t_{1/2}$ was 41 min. The mean absorption time of ARTS ($\text{MAT} = \text{MRT}_{\text{i.m.}} - \text{MRT}_{\text{i.v.}}$) was $55 \pm 29\text{ min}$ and, assuming first order kinetics, the absorption rate constant ($k_a = 1/\text{MAT}$) was 1.1 h^{-1} . Pharmacokinetic data for DHA following i.v. and i.m. ARTS administration

Table 2 Pharmacokinetic parameters for ARTS and DHA following i.v. and i.m. ARTS (120 mg (312.5 µmol); Group 1 and i.v. ARTS (120 mg (312.5 µmol) followed by rectal DHA (563 µmol (160 mg); Group 2. Data are given as mean ± s.d. unless otherwise indicated.

Group 1	Intravenous ARTS (n = 11)		Intramuscular ARTS (n = 11)	
	ARTS	DHA	ARTS	DHA
Dose (µmol kg ⁻¹)	5.7 ± 0.8	—	5.7 ± 0.8	—
t _{1/2} (min)	3.2 ± 2.1	59 ± 23	41 ± 18	64 ± 21
MRT (min)	4.1 ± 1.2	83 ± 28	59 ± 29	114 ± 22
CL (l h ⁻¹ kg ⁻¹)	2.8 ± 1.5	0.64 ± 0.22	2.9 ± 1.2 ^c	0.73 ± 0.21 ^c
V (l kg ⁻¹)	0.22 ± 0.16	0.8 ± 0.2	2.6 ± 1.2 ^c	1.1 ± 0.4 ^c
AUC (µmol l ⁻¹ h)	2.7 ± 1.4	10.1 ± 4.0	2.6 ± 1.9	8.7 ± 3.4
C _{max} (µM)	42 ± 24 ^a	9.7 (7.7–12.0) ^b	2.3 (2.0–4.8) ^b	4.1 (3.2–4.6) ^b
t _{max} (min)	—	7.0 (5.5–11.2) ^b	12 (10–15) ^b	45 (34–60) ^b
Bioavailability	—	—	—	0.88 ± 0.19

Group 2	Intravenous ARTS (n = 12)		Rectal DHA (n = 11 ^d)
	ARTS	DHA	DHA
Dose (µmol kg ⁻¹)	5.9 ± 0.5	—	10.7 ± 1.0
t _{1/2} (min)	4.4 ± 0.8	50 ± 12	—
CL (l h ⁻¹ kg ⁻¹)	2.1 ± 0.8	0.48 ± 0.14	—
V (l kg ⁻¹)	0.22 ± 0.12	0.55 ± 0.12	—
AUC (µmol l ⁻¹ h)	3.2 ± 1.1	11.6 ± 4.1	3.4 ± 1.3 ^c
C _{max} (µM)	43 ± 16 ^a	9.6 (8.8–14.0) ^b	0.75 (0.55–1.11) ^b
t _{max} (min)	—	9 (8–13.5) ^b	240 (158–360) ^b
Bioavailability (%)	—	—	16 (13–25) ^b

^aValue extrapolated to the end of the 2 min i.v. ARTS injection.^bMedian (interquartile range).^cApparent clearance (CL/F) and apparent volume of distribution (V/F).^dInadequate data obtained from one patient.^eAUC(0,8 h).

were similar, except for C_{max} and t_{max} ($P < 0.001$; Mann–Whitney Rank Sum Test).

Data from the rectal study also are summarized in Table 2 and are presented in Figure 2. Pharmacokinetic parameters following i.v. ARTS administration were similar to those from previous studies in demographically comparable subject groups [10, 14]. Valid pharmacokinetic data following rectal DHA were obtained from 11 of the 12 patients and based on these results, the median relative bioavailability of rectal DHA was 16% (range 9% to 59%). Eight patients had a relative bioavailability in the range of 9–19% whilst the other three patients had values of 26%, 29% and 59%.

Discussion

The present study was designed to provide pharmacokinetic information relating to the intramuscular and rectal administration of artemisinin drugs in the treatment of falciparum malaria. The principal advantage of i.m. ARTS over i.v. injection is the feasibility of administration by health workers with limited training, especially if given

into the anterior thigh. In addition, problems associated with venous access, such as line sepsis and inadvertent overhydration, may be greater in a peripheral health care facility in the rural tropics than in a large, well-equipped central hospital. In the case of rectal DHA, suppositories can be inserted by untrained personnel. Although nonoral routes of administration have clear advantages in severely ill patients, either i.m. or rectal therapy would be preferable to oral dosing in a patient with uncomplicated malaria who is nauseated or vomiting, or when observation and monitoring of such a patient is difficult, such as during transfer to a more central health care facility.

Clinical studies have shown that i.m. ARTS has similar efficacy to i.v. ARTS [8, 20] but a lack of comprehensive pharmacokinetic data has precluded the determination of equivalent doses for the i.v. and i.m. routes. Benakis *et al.* [21] provided very limited data in a conference communication in 1993, suggesting that ARTS and DHA had elimination half-lives of 29 and 95 min, respectively. There has been no subsequent report of pharmacokinetic data for ARTS following i.m. administration. Indeed, the results of Benakis *et al.* [21] are at variance with several

Figure 1 Plasma concentration-time profile for artesunate ($\blacktriangle$) and dihydroartemisinin ($\bullet$) following 312.5 μ mol (120 mg) i.v. ARTS, and for artesunate ($\triangle$) and dihydroartemisinin ($\circ$) following 312.5 μ mol i.m. ARTS, administered to 11 Vietnamese patients with uncomplicated falciparum malaria. Data are shown as mean + s.d..

recent pharmacokinetic studies which have shown that the elimination $t_{1/2}$ of ARTS is less than 5 min and the $t_{1/2}$ of DHA is in the order of 40–60 min [10–14,17, 22]. The discrepancy may have been due to a lack of recognition by Benakis *et al.* [21] that the pharmacokinetic properties of drugs administered by the i.m. route are absorption rate dependent [23]. Therefore, we considered it appropriate to conduct this clinical pharmacokinetic study of i.m. ARTS in falciparum malaria, selecting uncomplicated cases to ensure that our initial pharmacokinetic data were obtained in a stable clinical setting.

In the present study, the AUC for ARTS was similar following i.v. and i.m. administration (Table 2), indicating that ARTS is well absorbed from the intramuscular site and subsequently converted to DHA. Compared with i.v. administration, the $C_{\max}$ for ARTS was 20-fold lower following i.m. administration and the apparent $t_{1/2}$ 10-fold longer, while the $t_{1/2}$ for DHA was not significantly different between the two routes of administration. These data suggest that elimination of ARTS is absorption rate dependent, as would be expected following i.m. administration of a drug with rapid clearance [23]. An important comparison between this study and a previous report of oral ARTS administration [14] shows that the $t_{\max}$ for DHA following i.m. ARTS occurred 45 min earlier and the $C_{\max}$ was approximately 60% higher (4.1 μ M compared with 2.6 μ M). Therefore, the i.m. route can

Figure 2 Plasma concentration-time profile for artesunate ($\blacktriangle$) and dihydroartemisinin ($\bullet$) following 312.5 μ mol (120 mg) i.v. ARTS ($n=12$), and for dihydroartemisinin ($\circ$) following 563 μ mol (160 mg) rectal DHA ($n=11$), administered to Vietnamese patients with uncomplicated falciparum malaria. Data are shown as mean + s.d. Inset shows individual concentration-time profile for each patient (grey lines) and mean data (black line $\pm$ s.d.).

be considered superior to oral administration of ARTS, with respect to the pharmacokinetic profile.

The pharmacokinetic properties of rectal DHA have been investigated in healthy volunteers previously [24]. However, due to its relatively low mean $C_{\max}$ (390 nm) and delayed $t_{\max}$ (4.7 h) in this context [24], we sought to obtain more detailed pharmacokinetic data from patients with uncomplicated malaria before considering its assessment in patients with moderate-severe malaria. In addition, we chose to give i.v. ARTS prior to the rectal DHA to ensure that conventional therapy was administered promptly in all cases. This strategy was supported by the fact that previous randomised, cross-over studies of i.v. and oral ARTS had shown no order effect on the pharmacokinetic properties of ARTS or DHA [10].

Rectal administration of DHA in our patients resulted in a low, prolonged plasma concentration-time profile (Figure 2). The median bioavailability of rectal DHA in the present study (16%) was under-estimated by approximately 3% (corrected $F \approx 0.19$) because we used AUC(0,8 h) following the rectal dose and related this to

AUC(0,∞) from the corresponding i.v. dose (Table 2). Previous reports of the pharmacokinetics of DHA following rectal DHA [24] or ARTS [25] administration in healthy volunteers, and ARTS suppositories to children with uncomplicated falciparum malaria [5, 9], have shown the apparent $t_{1/2}$ of DHA following rectal DHA to be approximately 5-fold longer than that following rectal ARTS (5 h *vs* approximately 40–60 min). These observations suggest that DHA absorption from the colon may be rate-limiting.

Although the data from the present study do not allow a comprehensive pharmacokinetic characterization (Table 2), the $C_{\max}$ for DHA in our patients (0.75 μM for a 10.7 $\mu\text{mol kg}^{-1}$ dose) was approximately 5-fold higher than that in a study of DHA suppositories in healthy volunteers (0.4 μM for a 28 $\mu\text{mol kg}^{-1}$ dose [24]) but comparable with the $C_{\max}$ for DHA following administration of ARTS suppositories to healthy volunteers (0.6 μM for a 6.8 $\mu\text{mol kg}^{-1}$ dose [25]). Thus, the bioavailability of rectal DHA may be higher in patients with malaria than in healthy volunteers.

Several issues regarding the use of rectal DHA and ARTS remain unresolved. Different commercially available suppository formulations have been used at the manufacturer's recommended dose in the present study and in recent investigations in children [5, 6], but there are no comparative biopharmaceutical data for these products. As all available pharmacokinetic data have been obtained from volunteers and patients with mild to moderate malaria, it may be invalid to assume that severely ill patients have similar DHA plasma concentration profiles and can be given similar doses. Nevertheless, rectal ARTS has been used successfully to treat patients with severe malaria [26] and we have found that the pharmacokinetic properties of ARTS and DHA in severe falciparum [13], uncomplicated falciparum [14] and vivax malaria [10] are similar. Furthermore, studies with oral and rectal artemisinin, including a comparative clinical pharmacokinetic study [27], have shown that equivalent doses have similar efficacy regardless of the route of administration. Considering the *in vitro* IC_{50} values for DHA among standard isolates of *P. falciparum* (range 0.8–3 nM [28]) and the IC_{50} values for ARTS in 256 clinical isolates of *P. falciparum* (range 0.5–27 nM [29]), the available evidence suggests that therapeutic plasma concentrations of DHA can be achieved by administration of DHA suppositories.

Based on the high bioavailability of i.m. ARTS and previous reports of its clinical efficacy, it is apparent that in patients with uncomplicated falciparum malaria, i.m. ARTS is a suitable alternative to i.v. ARTS, at equivalent doses. By contrast, preliminary pharmacokinetic data and the limited evidence of clinical efficacy for rectal DHA indicate that further studies are required. Results of the present study suggest that, compared with standard

parenteral ARTS doses, 4–5-fold higher molar DHA doses (3–4-fold higher milligram doses) may be required. In addition, blood sampling for at least 12–16 h would be necessary to obtain more robust pharmacokinetic data.

We recommend that i.m. ARTS be considered in situations where access to trained health care personnel or hospital facilities is limited. Rectal DHA offers an alternative to the oral route for ARTS or DHA, particularly when the patient is vomiting or unable to co-operate with oral administration. However, with rectal DHA there was a 3-fold range in bioavailability (9%–29%) for 10 of the 11 patients in this study. Whilst we are cognizant of the limitations of the rectal plasma concentration–time data from the present study, a simulation of plasma concentration–time profiles for combinations of i.v./oral ARTS and i.m. ARTS plus rectal DHA is shown in Figure 3. This simulation indicates that concurrent administration of 120 mg i.m. ARTS and 320 mg rectal DHA (the DHA dose being twice that used in the present study) could provide an adequate plasma concentration of DHA for at least 8 h, thus allowing a patient to be transferred to hospital from remote locations. Both efficacy and supporting pharmacokinetic studies would be required to confirm this proposal.

In the past 5 years, a substantial body of valid pharmacokinetic data for ARTS and DHA has been

Figure 3 Simulated plasma concentration–time profile for dihydroartemisinin after simultaneous administration of 120 mg i.m. ARTS and 320 mg rectal DHA (—; AUC(0,8 h) = 15.7 $\mu\text{mol l}^{-1}$ h), simultaneous administration of 120 mg i.v. ARTS and 100 mg oral ARTS (····; AUC(0,8 h) = 14.2 $\mu\text{mol l}^{-1}$ h) and administration of 120 mg i.v. ARTS followed by 100 mg oral ARTS 4 h later (– –; AUC(0,8 h) = 13.5 $\mu\text{mol l}^{-1}$ h). Simulations are based on data from present study and Batty *et al.* [14].

reported for dosage forms including i.v. and i.m. injections, oral tablets and rectal suppositories. As demonstrated by our simulation (Figure 3), we believe that the next stage of investigation should include development of rational dosage regimens for clinical states ranging from uncomplicated to severe malaria, in settings from remote primary care facilities to tertiary care hospitals.

This work was supported by a Project Grant from the National Health and Medical Research Council of Australia (TMED and KFI). KTB was a recipient of an NHMRC Dora Lush (Biomedical) Scholarship. We acknowledge the support and assistance of Professor Trinh Kim Anh, Professor Nguyen Van Kim, Dr Truong Xuan Mai, Dr Vu Duong Bich Phuong, Mr Nguyen Phuc Tien and Mr Vuong Van Chon, Cho Ray Hospital, and Dr Vo Thanh Chien, Dr Huynh Van Thien, Dr Vu Nam Bien, Mrs Dang Thi Vinh Thuan and staff of the Malaria and Biochemistry & Haematology Departments, Bao Loc Hospital.

References

- van Agtmael MA, Eggelte TA, van Boxtel CJ. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. *Trends Pharmacol Sci* 1999; **20**: 199–205.
- Navaratnam V, Mansor SM, Sit N, Grace JM, Li Q, Olliaro P. Pharmacokinetics of artemisinin-type compounds. *Clin Pharmacokinet* 2000; **39**: 255–270.
- de Vries PJ, Dien TK. Clinical pharmacology and therapeutic potential of artemisinin and its derivatives in the treatment of malaria. *Drugs* 1996; **52**: 818–836.
- Barradell LB, Fitton A. Artesunate. A review of its pharmacology and therapeutic efficacy in the treatment of malaria. *Drugs* 1995; **50**: 714–741.
- Krishna S, Planche T, Agbenyega T, *et al.* Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria. *Antimicrob Agents Chemother* 2001; **45**: 509–516.
- Halpaap B, Ndjave M, Paris M, Benakis A, Kremsner PG. Plasma levels of artesunate and dihydroartemisinin in children with *Plasmodium falciparum* malaria in Gabon after administration of 50 milligram artesunate suppositories. *Am J Trop Med Hyg* 1998; **58**: 365–368.
- Cao XT, Bethell DB, Pham TP, *et al.* Comparison of artemisinin suppositories, intramuscular artesunate and intravenous quinine for the treatment of severe childhood malaria. *Trans R Soc Trop Med Hyg* 1997; **91**: 335–342.
- Hien TT, Phu NH, Mai NT, *et al.* An open randomized comparison of intravenous and intramuscular artesunate in severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1992; **86**: 584–585.
- Sabchareon A, Attanath P, Chanthavanich P, *et al.* Comparative clinical trial of artesunate suppositories and oral artesunate in combination with mefloquine in the treatment of children with acute falciparum malaria. *Am J Trop Med Hyg* 1998; **58**: 11–16.
- Batty KT, Le AT, Ilett KF, *et al.* A pharmacokinetic and pharmacodynamic study of artesunate for vivax malaria. *Am J Trop Med Hyg* 1998; **59**: 823–827.
- Navaratnam V, Mansor SM, Mordi MN, Akbar A, Abdullah MN. Comparative pharmacokinetic study of oral and rectal formulations of artesunic acid in healthy volunteers. *Eur J Clin Pharmacol* 1998; **54**: 411–414.
- Benakis A, Paris M, Loutan L, Plessas CT, Plessas ST. Pharmacokinetics of artemisinin and artesunate after oral administration in healthy volunteers. *Am J Trop Med Hyg* 1997; **56**: 17–23.
- Davis TM, Phuong HL, Ilett KF, *et al.* Pharmacokinetics and pharmacodynamics of intravenous artesunate in severe falciparum malaria. *Antimicrob Agents Chemother* 2001; **45**: 181–186.
- Batty KT, Thu LT, Davis TM, *et al.* A pharmacokinetic and pharmacodynamic study of intravenous *vs* oral artesunate in uncomplicated falciparum malaria. *Br J Clin Pharmacol* 1998; **45**: 123–129.
- Lin AJ, Klayman DL, Milhous WK. Antimalarial activity of new water-soluble dihydroartemisinin derivatives. *J Med Chem* 1987; **30**: 2147–2150.
- Lee IS, Hufford CD. Metabolism of antimalarial sesquiterpene lactones. *Pharmacol Ther* 1990; **48**: 345–355.
- Binh TQ, Ilett KF, Batty KT, *et al.* Oral bioavailability of dihydroartemisinin in Vietnamese volunteers and in patients with falciparum malaria. *Br J Clin Pharmacol* 2001; **51**: 541–546.
- Batty KT, Davis TM, Thu LT, Binh TQ, Anh TK, Ilett KF. Selective high-performance liquid chromatographic determination of artesunate and alpha- and beta-dihydroartemisinin in patients with falciparum malaria. *J Chromatogr B* 1996; **677**: 345–350.
- Heinzel G, Woloszczak R, Thomann P. *Topfit*, Version 2.0.; *Pharmacokinetic and Pharmacodynamic Data Analysis System for the PC*. Stuttgart: Gustav Fischer, 1993.
- Ha V, Nguyen NH, Tran TB, *et al.* Severe and complicated malaria treated with artemisinin, artesunate or artemether in Viet Nam. *Trans R Soc Trop Med Hyg* 1997; **91**: 465–467.
- Benakis A, Paris M, Plessas CT, Hien TT, Waller D, White NJ. Pharmacokinetics of sodium artesunate after im and iv administration. *Am J Trop Med Hyg* 1993; **49**(Suppl): 293.
- Newton P, Suputtamongkol Y, Teja-Isavadharm P, *et al.* Antimalarial bioavailability and disposition of artesunate in acute falciparum malaria. *Antimicrob Agents Chemother* 2000; **44**: 972–977.
- Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*, 4th Edition. Philadelphia. Lea & Febiger., 1991.
- Zhao KC, Song ZY. Pharmacokinetics of dihydroqinghaosu in human volunteers and comparison with qinghaosu. *Acta Pharm Sin* 1993; **28**: 342–346.
- Benakis A, Paris M, Loutan L, Plessas CT, Plessas ST. Pharmacokinetic study of a new pharmaceutical form of artesunate (Plasmotrim-200 Rectocaps) administered in healthy volunteers by rectal route. *Jap J Trop Med Hyg* 1996; **24**(Suppl 1): 39–45.
- Looareesuwan S, Wilairatana P, Molunto W, Chalermrut K, Olliaro P, Andrial M. A comparative clinical trial of sequential treatments of severe malaria with artesunate suppository followed by mefloquine in Thailand. *Am J Trop Med Hyg* 1997; **57**: 348–353.
- Ashton M, Nguyen DS, Nguyen VH, *et al.* Artemisinin kinetics and dynamics during oral and rectal treatment of uncomplicated malaria. *Clin Pharmacol Ther* 1998; **63**: 482–493.

- 28 Skinner TS, Manning LS, Johnston WA, Davis TM. In vitro stage-specific sensitivity of *Plasmodium falciparum* to quinine and artemisinin drugs. *Int J Parasitol* 1996; **26**: 519–525.
- 29 Price RN, Cassar C, Brockman A, *et al.* The *pfmdr1* gene is associated with a multidrug-resistant phenotype in *Plasmodium falciparum* from the western border of Thailand. *Antimicrob Agents Chemother* 1999; **43**: 2943–2949.