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Artemether Bioavailability after Oral or Intramuscular Administration in Uncomplicated Falciparum Malaria

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The antimalarial activity of artemether following oral or intramuscular administration in the plasma of 15 adults with acute uncomplicated *Plasmodium falciparum* malaria was measured by bioassay. The peak concentrations in plasma following oral administration were higher in patients with acute illness (median, 1,905 mmol of dihydroartemisinin [DHA] equivalents per liter; range, 955 to 3,358 mmol of DHA equivalents per liter) than in patients in the convalescent phase (median, 955 mmol of DHA equivalents per liter; range, 576 to 1,363 mmol of DHA equivalents per liter), and clearance (CL/F) was lower in patients in the acute phase (1.11 liters/kg/h; range, 0.21 to 3.08 liters/kg/h) than in patients in the convalescent phase (median, 2.76 liters/kg/h; range, 1.56 to 5.74 liters/kg/h) ($P \leq 0.008$). Antimalarial activity in terms of the peak concentration in plasma (C_{max}) after oral administration was a median of 16 times higher than that after intramuscular administration. The ratio of the area under the plasma concentration-time curve during the first 24 h (AUC_{0-24}) after oral administration of artemether to the AUC_{0-24} after intramuscular administration was a median of 3.3 (range, 1 to 11) ($P = 0.0001$). In the acute phase, the time to C_{max} was significantly shorter after oral administration (median, 1 h; range, 0.5 to 3.0 h) than after intramuscular administration (median, 8 h; range, 4 to 24 h) ($P = 0.001$). Intramuscular artemether is absorbed very slowly in patients with acute malaria.

The artemisinin derivatives are a major advance in the treatment of malaria and are increasingly used in Southeast Asia for the treatment of multidrug-resistant *Plasmodium falciparum* malaria (19). Artemether, a lipid-soluble derivative of artemisinin, is relatively stable in biological fluids. It is variably hydrolyzed in vivo to the metabolite dihydroartemisinin (DHA), which is intrinsically more active as an antimalarial. Biotransformation is mediated mainly by hepatic and intestinal cytochrome P-450 3A4 (17). Artemether is used orally in combination with lumefantrine or mefloquine in the treatment of uncomplicated falciparum malaria or is given by intramuscular injection in severely ill patients. Intravenous or intramuscular artesunate, a water-soluble artemisinin derivative, and intramuscular artemether are increasingly used for the treatment of patients with malaria and vomiting or patients with severe malaria (2, 4, 5, 9, 11). Unlike artesunate, there is no intravenous preparation of artemether, as artemether is insoluble in water and must be dissolved in oils. Groundnut and sesame seed oils have been the most widely used. Intramuscular artemether is easy to administer and well tolerated and is an effective treatment for severe malaria in the rural tropics, where facilities for intravenous injection are not commonly available (2). It is particularly valuable in epidemics.

Chemical methods for the assay of artemisinin derivatives have limits of accurate quantitation of concentrations above those that provide a significant antimalarial effect. Bioassay gives an alternative and slightly more sensitive measure and provides the important clinical pharmacodynamic information, in that it describes the antimalarial activity in blood. However, bioassay does not distinguish between parent drugs and their active metabolites (15).

Despite considerable use in areas where malaria is endemic, there are relatively few data on the pharmacokinetics of artemether for the treatment of malaria (5–9, 14, 17, 18, 20). In healthy volunteers intramuscular artemether has a relatively low bioavailability relative to that of the oral preparation (15). We therefore conducted a randomized crossover assessment of the pharmacokinetic properties of artemether administered orally and intramuscularly in patients with uncomplicated falciparum malaria, with administration of a further oral dose during convalescence to assess the effects of malaria on drug absorption and disposition, using bioassay measurements of antimalarial activity.

MATERIALS AND METHODS

Patients. Nonpregnant febrile, adults (age, >14 years) hospitalized at Paholpolpayuhasena Hospital, Kanchanaburi, western Thailand, in 1993 with uncomplicated acute *P. falciparum* malaria (defined as the presence of asexual stages of the *P. falciparum* parasite in peripheral blood and not fulfilling the World Health Organization [21] criteria for severe malaria) and vomiting were included in the study, provided that they gave fully informed consent and had not previously received significant antimalarial treatment. The patients were checked for pretreatment with quinine by a urine dipstick screening method (13). The study was approved by the Ethical and Scientific Review Subcommittee of the Royal Thai Government Ministry of Public Health.

Treatment and clinical procedures. Patients were randomized to receive initially either oral or intramuscular artemether at a dose of 2 mg/kg of body weight

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(equivalent to 6,702 nmol/kg; molecular weight of artemether, 298.4). Parenteral artemether was administered from ampoules of 80 mg of artemether/ml in groundnut oil (Kunming Pharmaceutical Factory, Kunming, People's Republic of China). Injections were given in the anterior thigh. Precise oral dosing was provided by taking the powder from 40-mg artemether capsules (Kunming Pharmaceutical Factory), weighing it, and replacing the weight-adjusted amount back in the capsule. Blood samples were taken through an indwelling forearm vein catheter at 0, 15, 30, 45, 60, 90, and 120 min and then 3, 4, 6, 8, 12, 18, and 24 h following drug administration. A second dose of artemether (2 mg/kg) was then given at 24 h by the alternative route. Blood samples were taken at the same time intervals at which they were taken on the first day. On day 3, mefloquine (15 mg/kg; Lariam; Roche) was given to complete the treatment. Hematocrit and parasitemia were measured every 6 h until parasite clearance (defined as the first negative thick film after 200 white blood cells were counted). The patients were asked to return for a convalescent-phase study, in which the hematocrit was checked and a blood film was checked for malaria parasites; and provided that the patient was fully recovered and blood smear negative for malaria, the same artemether oral dose (2 mg/kg) was readministered, followed by the same regimen of blood sampling described above. Samples were stored at −80°C until analysis 4 to 6 years later.

Drug assays. Antimalarial activity in plasma was measured by an in vitro *P. falciparum* bioassay (with chloroquine-resistant clone W2), in which antimalarial activity is expressed as DHA equivalents (14). The lower limit of quantitation of the bioassay was 8.9 nmol/liter, and mean interassay coefficients of variation were −3.05, −7.07, and −4.34% for DHA concentrations of 17.6, 44.0, and 175.8 nmol/liter, respectively. Dilutions were used for samples with concentrations >357 nmol/liter.

Pharmacokinetic and statistical analysis. The plasma antimalarial concentrations after intramuscular artemether fluctuated considerably, and modeling was not possible; the observed maximum plasma antimalarial concentration (C_{max}), the time to C_{max}, and the area under the plasma-concentration-time curve (AUC) were calculated. After oral administration, a one-compartment open model with first-order absorption and elimination gave the best fit (on the basis of the Akaike information criterion) to the plasma concentration-time data for all except two patients, whose data were processed by noncompartmental analysis. Standard pharmacokinetic parameters were derived (models 4 and 200; Pharsight, WinNonlin, version 3.1; SCI, Cary, N.C.) (1). The AUC from time zero to 24 h ($AUC_{0\text{-}24}$) was calculated by using the linear trapezoidal rule, and the AUC from time zero to infinity ($AUC_{0\text{–}\infty}$) was calculated by log-linear extrapolation. Apparent clearance (CL/*F*) was calculated as dose/$AUC_{0\text{–}\infty}$. Analyses were performed with SPSS software (version 8.0; SPSS Inc., Chicago, Ill.). Data were compared by the Wilcoxon and sign-rank tests.

RESULTS

Clinical responses. Sixteen adult Thai and Karen patients (three females) hospitalized with uncomplicated falciparum malaria were enrolled in the study. The patients presented after having been ill with fever, headache, anorexia, nausea, and vomiting for 3.1 ± 0.6 days (mean ± standard deviation [SD]). The median age was 30 years (range, 14 to 51 years), and the mean ± SD body weight was 52.1 ± 5.3 kg (range, 42 to 65 kg). The geometric mean level of parasitemia on admission was 45,415/μl (95% confidence interval [CI], 13,909 to 148,286/μl), and the mean ± SD hematocrit was 40.8% ± 4.2%. All patients made rapid and uncomplicated recoveries. The mean ± SD parasite clearance time was 36.1 ± 14.4 h.

There were no significant differences in clinical or laboratory features between patients who received oral or intramuscular artemether first ($P > 0.05$). Nine patients returned for the convalescent-phase oral dose study a median of 12 days (range, 4 to 27 days) after initial admission. No patient had malaria parasites on thick films at follow-up. The characteristics of the 9 patients who returned for follow-up did not differ from those of the 15 patients studied during the acute phase of illness ($P > 0.05$). No adverse effects from the study drug, apart from severe pain at the injection site in one patient, were noted.

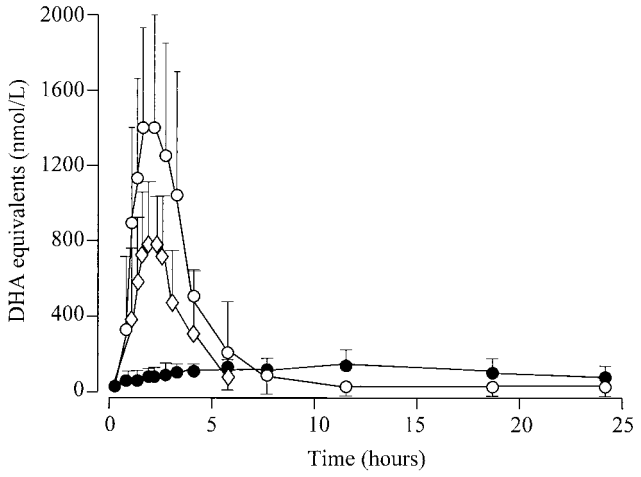

FIG. 1. Mean ± SD antimalarial bioactivity in plasma in DHA equivalents following intramuscular artemether administration in the acute phase (●), oral administration in the acute phase (○), and oral administration in the convalescent phase (◇) in patients with falciparum malaria.

Drug measurements. Quinine was detected in the admission urine samples of three patients. The bioassay method adjusted for this potential confounder by calibrating the value for the baseline plasma sample as zero DHA equivalents and assuming that the much lower antimalarial activity contributed by the slowly eliminated quinine (half-life, 16 to 18 h [19]) did not change during the sampling period. The same approach accommodates the antimalarial action of mefloquine (half-life, 2 to 3 weeks [19]) in the convalescent-phase study samples. The only other drugs taken by the patients immediately before or during the study were acetaminophen ($n = 10$), metoclopramide ($n = 4$), aluminum hydroxide ($n = 1$), cimetidine ($n = 1$) ampicillin ($n = 1$), kaolin-pectin (Kaopectal; $n = 1$), and diazepam ($n = 1$). None of these drugs are known to interact with artemether.

Pharmacokinetics. The mean intramuscular artemether dose was 6,730 nmol/kg of body weight (95% CI, 6,574 to 6,885 nmol/kg). Intramuscular artemether was absorbed erratically and very slowly, yielding peak antimalarial concentrations in a median of 8 h (range, 4 to 24 h), whereas the oral doses in the acute and convalescent phases yielded peak antimalarial concentrations in median times of 1.0 h (range, 0.5 to 3.0 h) and 1.5 h (range, 0.5 to 4.0 h), respectively ($P = 0.001$ and 0.012, respectively) (Fig. 1). No antimalarial activity was detected after intramuscular administration to one patient. No significant differences in pharmacokinetic parameters were found if artemether was given intramuscularly first or second (i.e., after or before the oral dose) ($P > 0.02$). The median C_{max} of the antimalarial after oral administration in the acute phase was 1,905 DHA equivalents nmol/liter (range, 955 to 3,358 DHA equivalents nmol/liter), whereas it was 955 DHA equivalents nmol/liter (range, 576 to 1,363 DHA equivalents nmol/liter) in the convalescent phase; but it was only 121 DHA equivalents nmol/liter (range, 20 to 370 DHA equivalents nmol/liter) after intramuscular administration ($P = 0.012$ and 0.001, respectively) (Fig. 1; Table 1). The median $AUC_{0\text{–}\infty}$ after intramuscular administration was 2,718 nmol · h/liter (range, 557 to

16,034 nmol · h/liter), whereas it was 6,045 nmol · h/liter (range 2,172 to 32,286 nmol · h/liter) after oral administration in the acute phase ($P = 0.17$). The median AUC_{0-24} after intramuscular administration was 1,775 nmol · h/liter (range, 382 to 7,057 nmol · h/liter), whereas it was 5,250 nmol · h/liter (range, 2,172 to 9,221 nmol · h/liter) after oral dosing in the acute phase ($P = 0.001$). C_{max} and $AUC_{0-\infty}$ were significantly lower after oral administration in the convalescent phase than after oral administration in the acute phase ($P = 0.008$ and 0.008, respectively) (Table 1).

The mean ± SD elimination half-life of antimalarial activity did not differ significantly after oral administration in the acute or convalescent phase, but CL/*F* was significantly higher during the convalescent phase than during the acute phase of illness ($P = 0.008$). The median CL/*F* was 2.46 liters/kg/h (range, 0.48 to 12.03 liters/kg/h) after intramuscular administration and did not significantly differ from that after oral administration in the acute or convalescent phase ($P > 0.1$). Relative to intramuscular administration, the median relative bioavailability (*F*) of oral artemether in patients with acute malaria was 2.0 (range, 0.7 to 17.4). This ratio does not differ significantly from 1 ($P = 0.6$). However, absorption was delayed considerably, such that, comparing the AUC in the first 24 h (AUC_{0-24}), the median *F* was 3.3 (range, 1.0 to 11.1), which is significantly different from 1 ($P = 0.0001$). The antimalarial activity profiles for the three patients who had taken some quinine before the study were not different from those for the remaining patients.

DISCUSSION

Oral artemether is absorbed rapidly and reliably. The antimalarial activity-time profile after oral administration of artemether was similar to that described previously, as determined by the same bioassay technique (14). Maximum antimalarial concentrations occurred within 3 h of administration. During convalescence the significantly lower $AUC_{0-\infty}$ of oral artemether and DHA combined probably resulted from expansion of the apparent volume of distribution and improved systemic clearance on recovery with increased presystemic (first-pass) intestinal and hepatic metabolism (12). This study cannot distinguish confidently between the pharmacokinetic effects of disease-reducing clearance in the acute phase or autoinduction-increasing clearance in the convalescent phase, although only three doses were given over >7 days, so the latter explanation seems less likely (16).

Oral administration during the acute phase gave peak antimalarial activities which were approximately 16 times higher than those after intramuscular administration. Intramuscular artemether dosing was also associated with a considerable delay to the C_{max}. The relative bioavailability of antimalarial activity during the first 24 h, the period that is likely to be the most important clinically, of oral artemether given during the acute phase was over three times that of intramuscular artemether. The one patient with no detectable antimalarial activity after the administration of intramuscular artemether may have been a nonabsorber (9), although an error in drug administration cannot be entirely excluded. The reduced antimalarial activity after intramuscular administration reflects slow absorption from the oil depot at the injection site. The approximately threefold reduction in the AUC following intramuscu-

TABLE 1. Values of pharmacokinetic parameters after oral administration to patients in the acute or convalescent phase of falciparum malaria[a]

Phase (no. of patients)	Dose (nmol/kg)[b]	AIC[b]	T_{max} (h)	C_{max} (nmol/liter)	T_{lag} (h)	K_{01} (h^{-1})	$t_{1/2}$ (h)	*V*/*F* (liters/kg)	CL/*F* (liters/kg/h)	AUC_{0-24} (nmol · h/liter)	$AUC_{0-\infty}$ (nmol · h/liter)
Acute (16)	6,747 (6,600–6,896)	170 (158–183)	1.0 (0.5–3.0)	1,905 (955–3,358)	0.18 (0–0.71)	3.13 (0.60–6.68)	1.34 (0.62–10.73)	2.83 (1.06–16.75)	1.11 (0.21–3.08)	5,250 (2,172–9,221)	6,045 (2,172–32,286)
Convalescent (9)	6,725 (6,624–6,825)	115 (104–127)	1.5 (0.5–4.0)	955 (576–1,363)	0.31 (0.21–0.45)	2.66 (0.51–8.58)	1.47 (0.57–3.23)	4.62 (3.93–10.77)	2.76 (1.56–5.74)	2,430 (1,168–4,291)	2,430 (1,168–4,291)
P value[c]	0.9	0.018	0.2	0.008	0.6	0.9	0.9	0.1	0.008	0.008	0.008

[a] Unless indicated otherwise, values are medians (ranges). Bioassay values are in DHA equivalents. To convert DHA equivalents from nanomoles per liter to nanograms per milliliter, divide by 3.517. Abbreviations: AIC, Akaike information criterion; T_{max}, observed time to C_{max}; T_{lag}, absorption lag time; K_{01}, absorption rate constant; $t_{1/2}$, elimination half-life; *V*/*F*, total apparent volume of distribution per kilogram of body weight; *F*, fraction of the oral drug that is absorbed. The other abbreviations are defined in the text.

[b] Values are means (95% CIs).

[c] *P* values by the paired test for nine subjects studied in the acute and convalescent phases.

lar administration is explained by the lower level of biotransformation of artemether to the metabolite DHA, which is approximately three times more potent than the parent drug as an antimalarial in vitro (3). As intramuscular artemether is absorbed so slowly, the 24-h sampling time may be insufficient to characterize the profile of the concentrations in plasma and therefore may underestimate absorption and, thus, total AUC. However, from a therapeutic standpoint it is the antimalarial activity in blood in the hours following the first administration of a parenteral drug that is critical, particularly in patients with severe malaria.

Comparisons of the pharmacokinetics of artesunate, artemether, and DHA have suggested that either oral DHA or artesunate provides greater antimalarial activity than similar doses of oral artemether in the combination treatment of uncomplicated falciparum malaria (10, 14). This study suggests that intramuscular artemether has unfavorable pharmacokinetic characteristics in patients with uncomplicated malaria. Yet, this route of administration is used mainly in patients with severe malaria, in which muscle perfusion may be impaired and absorption may be further compromised. Studies with severely ill African children have also shown slow and erratic absorption (9). However, in comparison to intramuscular quinine, intramuscular artemether has been shown to be an effective treatment for severe malaria in large randomized studies (2). It is possible that the intrinsic superiority of artemether over quinine is offset by its pharmacokinetic disadvantages. The rate of absorption of the injected drug from the oil depot may be influenced by the oil itself. Recent studies comparing artemether and arteether absorption indicated even slower absorption of arteether injected in sesame seed oil (8). Use of alternative oils to dissolve these lipophilic drugs may accelerate absorption. On clinical and pharmacokinetic grounds, it is likely that the more potent intramuscular or intravenous artesunate would be superior to intramuscular artemether for the parenteral treatment of falciparum malaria (5, 11).

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