Pharmacokinetic Profiles of Artesunate After Single Intravenous Doses at 0.5, 1, 2, 4, and 8 mg/kg in Healthy Volunteers: A Phase I Study

Qigui Li,* Louis R. Cantilena, Kevin J. Leary, George A. Saviolakis, R. Scott Miller, Victor Melendez, and Peter J. Weina
Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, Maryland; Division of Clinical Pharmacology and Medical Toxicology, Uniformed Services University of the Health Sciences, Bethesda, Maryland

Abstract. The pharmacokinetics of good manufacturing process injection of artesunate (AS) were evaluated after single doses at 0.5, 1, 2, 4, and 8 mg/kg with a 2-minute infusion in 40 healthy subjects. Drug concentrations were analyzed by validated liquid chromatography and mass spectrometry system (LC-MS/MS) procedures. The drug was immediately converted to dihydroartemisinin (DHA), with elimination half-lives ranging 0.12–0.24 and 1.15–2.37 hours for AS and DHA, respectively. Pharmacokinetic model-dependent analysis is suitable for AS, whereas DHA fits both model-dependent and -independent methods. Although DHA concentration was superior to that of AS with a 1.12–1.87 ratio of area under the curve (AUC) of DHA peak concentration of AS was much higher than that of DHA, with a 2.80- to 4.51-fold ratio of peak concentration (Cmax), Therefore, AS effectiveness has been attributed not only to its rapid hydrolysis to DHA, but also to itself high initial Cmax.

INTRODUCTION

Artemisinin class compounds act rapidly against drug-resistant Plasmodium falciparum strains and are widely used for the treatment of various malarias in humans. Dihydroartemisinin (DHA) is originally obtained by sodium borohydride reduction of artemisinin an endoperoxide containing sesquiterpene lactone, which was isolated by Chinese researchers and characterized as the antimalarial principle of the plant Artemisia annua. In vitro bioassay tests have shown DHA to be more potent than artemisinin. However, because of its poor solubility in water or oils, DHA has only been formulated as an oral preparation and has been used primarily as a semisynthetic compound for derivatization to the oil-soluble drugs, artemether and arteether, and the water-soluble drugs, artesunate (AS). DHA is similar to AS and is 3- to 5-fold more active and more toxic than other artemisinin derivatives. It can completely inhibit parasite growth within 2–4 hours and is the only artemisinin derivative with activity against all asexual blood-stage parasites. The effectiveness of AS has been mostly attributed to its rapid and extensive hydrolysis to DHA.

Artemisinins have been used in malaria treatments with monotherapy regimen since 1983. However, the monotherapy with the artemisinin derivatives was significantly discouraged after 2001 to prevent the emergence of resistance. For complicated and severe malaria, however, intravenous AS, as monotherapy initially, is still in first-line treatment of both adults and children in Asian countries and some areas in Africa. Severe malaria, which is much less common than uncomplicated disease, is difficult to define precisely, especially in regions where malaria is endemic, because other serious illnesses can coexist with malarial infection. Severe malaria is generally defined as acute malaria with major signs of organ dysfunction or high levels of parasitemia. In areas where malaria is endemic, young children are at high risk for severe malaria. Partial immunity develops in older children and adults after repeated infections, and they are thus at relatively low risk for severe disease. Pregnant women are also at increased risk for severe malaria.

Trying to replace quinine with a more effective, less expensive, and better tolerated drug to treat severe malaria, an initial trial using intramuscular arteether showed less toxicity but no clear mortality benefit over quinine. More recent trials have used intravenous AS with a more favorable pharmacokinetic profile. The SEAQUAMAT trial, a multicenter randomized trial conducted in Bangladesh, Thailand, Myanmar, Indonesia, India, and Vietnam, recently reported a 34.7% reduction in all-cause mortality associated with intravenous AS compared with intravenous quinine. This is the largest trial ever performed in severe malaria and the first to show conclusively a mortality benefit over standard quinine therapy. There is convincing evidence that for those who do develop severe malaria, intravenous AS will reduce the risk of death by one-third compared with quinine therapy.

After the SEAQUAMAT trials, intravenous AS was immediately recommended for patients with severe malaria by The European Network on Imported Infections Disease Surveillance (TropNetEurop). The most recent advance in antimalarial chemotherapy has been the use of artemisinin derivatives, especially intravenous AS, which may well revolutionize the management of complicated and severe malaria.

Therefore, we still need AS monotherapy, if only for this single niche indication. Many other clinical trials for pharmacokinetic evaluation of AS have been conducted mostly in Asia and Africa. Peak concentration (Cmax) has been shown to be more important than plasma concentration (AUC) in producing the improved efficacy of antimalarial drugs as outlined in the above pharmacokinetics and pharmacodynamics (PK/PD) evaluation. Intravenous AS can provide sufficiently high peak concentrations in the patients and can provide the most rapid efficacy in parasite killing, showing that injectable AS is pharmacokinetic and pharmacodynamic superior compared with other artemisinins with various regimens, and the Cmax was shown to be from 605 to 18,909 ng/mL from AS plus DHA resulting from various dose regimens.

However, there is currently no commercially available product that is produced under good manufacturing process (GMP) conditions. The Walter Reed Army Institute of Research (WRAIR) has been developing a novel current GMP (cGMP) injection of AS since 2004, which is in the process of US FDA
and at 5, 20, and 40 minutes and 1, 2, 4, 6, and 8 hours after collection blood samples for the measurements of AS levels were permitted from 4 hours after dosing. Biological sample in bed). Normal activities, excluding strenuous exercise, light lunch was provided. Water, fruit juice, or decaffeinated remained in a fasting state until ~4 hours after dosing when a inspection of the injection site and subject’s response. Subjects nurse recorded the tolerance of the injection to include both start, and completion of injection. When completed, the study

Study design. This study was an open-label, ascending single dose, alternating group, safety, tolerance, and pharmacokinetic study. Injectable AS was administered intravenously to five groups of the subjects using escalating doses of 0.5, 1, 2, 4, and 8 mg in the fasting state (after a minimum 10-hour fast). All eight subjects in each dose group received the AS and placebo in a randomized sequence (1:1). The maximum concentration (C max ), and time to C max (T max ) was calculated by application

Non-compartmental analysis. The maximum concentration in plasma for each subject was read directly from the plasma concentration-time curves. For the determination of initial approach to PK parameters of AS in plasma after systemic application, a non-compartmental analysis (NCA) was performed using WinNonlin (version 5.2, Pharsight, Mountain View, CA). The area under the concentration-time curve (AUC) from the start of infusion at t₀ to the tₐ was calculated by application of the linear trapezoidal rule. The elimination half-life (t₁/2), maximum plasma concentration (C max ), and time to C max (T max ) of AS and its active metabolite, DHA, were also calculated. The log–linear trapezoidal rule was used to estimate the respective AUCₐ₀₉ₚ values, and the AUCₐ₀₉ₚ ratios of the metabolite to the parent compound AS were calculated to determine exposure to any metabolite compared with the parent drug.

Compartmental PK data analysis. To compare only the clinically relevant artemisinin concentrations (AS and DHA), the compartmental data analysis was based on a short-term intravenous infusion. Injectable AS and its active metabolite,
DHA, disposition was best described by a two-compartment model with a rapid initial distribution phase after intravenous administration. The input of the drug was assumed to follow zero-order kinetics, and elimination from the central compartment occurred with first-order kinetics. Compartmental analysis (CA) of concentration-time data for AS and DHA was also performed using the WinNonlin software with an intravenous infusion program. The first-order method with logarithmic transformation of all drug-concentration data was used throughout.

In addition to the evaluation of the weighted sum of squares, the evaluation of the goodness of fit and the estimated parameters was based on the Akaike information criterion, the variability (CV) of the parameter estimates, the random distribution of weighted residuals between measured and predicted concentrations with respect to time, and the absence of a significant correlation between independent model parameters (< 0.05). The drug plasma concentrations at the end of an intravenous infusion ($C_{\text{max}}$) was calculated from the corresponding model equations (intravenous infusion model, WinNonlin) at the respective time points. AUC$_{(0-t)}$ (where $t =$ the time point for the last sample on the pharmacokinetic profile in which quantifiable drug was detected) will be estimated using linear or linear/log trapezoidal calculation. If a model included more than one compartment with an elimination process, the single-clearance values were added to calculate the total clearance (CL). The ($V_s$) was obtained by adding the volumes of the different compartments (e.g., $V_s = V_1 + V_2$).

**Data evaluation.** Statistical analysis was conducted with Microsoft Excel using a Student $t$ test for dependent samples to compare means of paired and unpaired samples between two groups.

**RESULTS**

**Safety and tolerability.** In this study, 30 healthy volunteers were treated with a single intravenous infusion over a total of five escalating doses of AS with PBS buffer, and 10 volunteers were administrated same volume of vehicle alone. For each subject, adverse events (AEs) were recorded throughout the post-dosing period. Single dose intravenous treatment with this formulation of AS was well tolerated in healthy volunteers at doses up to 8 mg/kg. No dose limiting toxicity was found for AS at those doses studied. There were no subject dropouts for AEs or other treatment-related issues. The safety and tolerability of intravenous AS are the subject of another manuscript in preparation.

**Table 1**

| Compartmental analyses of AS by intravenous infusion modeling after single intravenous administrations of 0.5, 1, 2, 4, and 8 mg/kg with a short-term infusion (2 minutes) in healthy volunteers* |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| PK parameters   | 0.5 mg/kg ($N=1$)† | 1 mg/kg ($N=5$) | 2 mg/kg ($N=6$) | 4 mg/kg ($N=6$) | 8 mg/kg ($N=6$) |
| $C_{\text{max}}$ (ng/mL) | 4,797 | 6,128 (48) | 19,420 (19) | 36,100 (24) | 83,340 (73) |
| $T_{\text{max}}$ (min) | 2 | 2 | 2 | 2 | 2 |
| AUC$_{(0-t)}$ (ng · h/mL) | 386 | 593 (37) | 1,595 (16) | 3,038 (25) | 6,994 (60) |
| $t_{1/2}$ distribution (h) | 0.04 | 0.05 (41) | 0.04 (24) | 0.04 (27) | 0.05 (38) |
| $t_{1/2}$ elimination (h) | 0.12 | 0.14 (22) | 0.24 (89) | 0.15 (7) | 0.21 (29) |
| CL (mL/min/kg) | 21.6 | 30.6 (38) | 21.4 (17) | 23.5 (31) | 26.2 (57) |
| $V_s$ (mL/kg) | 92 | 187 (46) | 106 (35) | 109 (26) | 165 (75) |
| MRT (h) | 0.07 | 0.10 (30) | 0.08 (21) | 0.08 (15) | 0.10 (36) |

*Data are presented as arithmetic mean (CV%).
†The all-parameter calculations were performed with WinNonlin 5.2 Version software with PK non-compartment model 202 (short-term infusion) and two-compartment model 10 (intravenous infusion).
‡One of six subjects was suitable for PK analysis because of detected limits in the other five cases.
NCA = non-compartmental analysis; CA = compartmental analysis; F = absolute bioavailability; MRT = mean residence time.

**CA of AS.** WinNonlin analysis resulted in two-compartment model of intravenous infusion with first-order elimination, which best fitted the set of observations of intravenous AS in these trials. The intravenous model with 2-minute infusion had a better and reasonable predictive performance than the intravenous bolus modeling, and the latter approach resulted in a 30% higher AUC value after calculation (Figure 1). Also, the non-compartment analysis (NCA) was considered inappropriate for our data set because the NCA with an inherent programming imperfection cannot count the $C_{\text{max}}$ on the end (2 minutes) of the infusion. Therefore, the final parameters estimates for the intravenous infusion in the two-compartment model are shown in Table 1 and the plasma concentration of AS after short-term infusion at doses of 0.5, 1, 2, 4, and 8 mg/kg are shown in Figure 2 (top). Five subjects were not able to be used for performing the PK modeling in the first cohort (0.5 mg/kg) because the drug concentration was well below the quantitative limit. After the short-term infusion (2 minutes), the plasma peak concentration ($C_{\text{max}}$) can be very high, from 4,797 ng/mL in the low-dose cohort of 0.5 mg/kg dose to as high as 83,340 ng/mL in the high dose cohort of 8 mg/kg. PK results indicated that the mean AUC$_{\text{inf}}$ in the subjects using CA modeling were ~30% higher compared with initial

**Figure 1.** Pharmacokinetic regression modeling comparison of intravenous bolus with non-compartmental analysis (dashed line), short-term intravenous infusion with non-compartmental analysis (dotted line), and short-term intravenous infusion with compartmental analysis (solid line) (raw data from volunteer ARTS-018 after single intravenous AS at 8 mg/kg).
parameters calculated by NCA (Figure 1). A comparison of the results indicated that the PK analysis of AS can be performed only with compartment modeling, and the data set is model dependent.

In addition, the mean $C_{\text{max}}$ and $AUC_{\text{inf}}$ for AS in the subjects with the higher dose were roughly double that with the lower dose level and increased in proportion with high correlations ($r^2 = 0.9924–0.9971$) to the dose in all five dose groups (Figure 3A, B, top).

**NCA of DHA.** The plasma concentrations of DHA, an active metabolite of AS, after short-term infusion at doses of 0.5, 1, 2, 4, and 8 mg/kg, are shown in Figure 2 (bottom). Table 2 shows the mean parameters (CV%) in a first approach for the NCA. The mean $C_{\text{max}}$ and $AUC_{\text{inf}}$ for DHA were increased in a dose-dependent manner in all five dose cohorts. Mean $T_{\text{max}}$ was shown in a range of 0.12–0.40 hours, and the elimination $t_{1/2}$ was in a range of 0.96–2.14 hours. The mean body clearance over bioavailability ($CL/F_{\text{obs}}$) and volume of distribution at steady state over bioavailability ($V_{ss}/F_{\text{obs}}$) ranged 13.6–26.5 mL/min/kg and 1,701–2,403 mL/kg, respectively, in the subjects with five dose groups.

**CA of DHA.** Plasma concentrations versus time curves of DHA, an active metabolite of AS, for 30 volunteers are shown in Figure 2 (bottom). A two-compartment model was used to best fit the kinetics of DHA given at AS doses of 0.5, 1, 2, 4, and 8 mg/kg in the Phase 1 trial. With the CA, all parameters were very similar to the NCA. The comparison of CA and NCA pharmacokinetic parameters for all the five cohort of volunteers is given in Table 2. Mean peak concentration was in a range of 453–5,584 ng/mL with the CA method and 428–4,744 ng/mL with the NCA analysis within a 0.84–0.95 ratio of $C_{\text{max}}$/NCA/CA. Mean $AUC_{\text{inf}}$ value ranged 384–10,309 ng · h/mL with the CA calculation and 385–10,410 ng · h/mL with the NCA estimation within an $AUC_{\text{inf}}$/NCA/CA ratio of 1.00–1.02. Similarly, the elimination half-life of DHA with CA and NCA analyses ranged 1.15–2.37 and 0.96–2.14 hours, respectively (Table 2). Also, mean clearance over bioavailability (CL/F) of DHA was in the range of 13.7–22.2 mL/min/kg with the CA method and 13.6–26.5 mL/min/kg with the NCA assay, within
independent PK modeling. AS, can be performed either with model-dependent or model-suggested that the PK analysis of DHA, as a metabolite of ratio of C max AS/DHA . DHA also showed a longer half-life of was much higher than that of DHA with a range of 2.80–4.51 ratio of AUC DHA/AS , but the peak concentration (C max ) of AS 0.98–1.00 ratio of the CL/F NCA/CA . The comparison results indicating that AS is a superior antimalarial agent in terms of combination in healthy volunteers*.

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>0.5 mg/kg (N = 6)**</th>
<th>1 mg/kg (N = 6)</th>
<th>2 mg/kg (N = 6)</th>
<th>4 mg/kg (N = 6)</th>
<th>8 mg/kg (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C max (ng/mL)</td>
<td>428 (15)</td>
<td>802 (22)</td>
<td>1,286 (20)</td>
<td>3,148 (30)</td>
<td>4,744 (36)</td>
</tr>
<tr>
<td>T max (min)</td>
<td>0.16 (66)</td>
<td>0.25 (56)</td>
<td>0.16 (63)</td>
<td>0.12 (0)</td>
<td>0.40 (65)</td>
</tr>
<tr>
<td>AUC inf (ng · h/mL)</td>
<td>379 (19)</td>
<td>1,008 (29)</td>
<td>1,801 (17)</td>
<td>4,645 (24)</td>
<td>10,057 (28)</td>
</tr>
<tr>
<td>AUC 0-6h/CL/F</td>
<td>385 (18)</td>
<td>1,082 (26)</td>
<td>1,850 (17)</td>
<td>4,886 (24)</td>
<td>10,410 (26)</td>
</tr>
<tr>
<td>t 1/2 absorption (h)</td>
<td>0.96 (26)</td>
<td>1.54 (41)</td>
<td>1.15 (23)</td>
<td>1.37 (9)</td>
<td>2.14 (38)</td>
</tr>
<tr>
<td>CL/F obs (mL/min/kg)</td>
<td>22.2 (17)</td>
<td>16.4 (26)</td>
<td>18.5 (19)</td>
<td>13.6 (28)</td>
<td>14.4 (27)</td>
</tr>
<tr>
<td>V/F obs (mL/Kg)</td>
<td>1734 (25)</td>
<td>2201 (49)</td>
<td>1860 (37)</td>
<td>1701 (27)</td>
<td>2403 (34)</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.10 (19)</td>
<td>1.83 (26)</td>
<td>1.53 (15)</td>
<td>1.79 (10)</td>
<td>2.36 (22)</td>
</tr>
</tbody>
</table>

PK comparison of AS and DHA parameters. The conversion data of AS to DHA is presented in Table 2. In all five dose cohorts, the plasma concentration (AUC) of DHA was significantly more than that of AS with a range of 1.12–1.87 ratio of AUC DHA/AS , but the peak concentration (C max ) of AS was much higher than that of DHA with a range of 2.80–4.51 ratio of C max AS/DHA . DHA also showed a longer half-life of 1.15–2.37 hours compared with AS (whose half-life of 0.12–0.24 hours) which is 7.12- to 12.68-fold longer. If we count a 0.98–1.00 ratio of the CL/F NCA/CA . The comparison results suggested that the PK analysis of DHA, as a metabolite of AS, can be performed either with model-dependent or model-independent PK modeling.

A dose-dependent increase of C max and AUC_{inf} for DHA in the subjects were shown in a high correlation (r^2 = 0.9692–0.9963) to the dose in all five dose cohorts (Figure 3C, D, bottom).

**DISCUSSION**

In this study, high peak concentrations of AS and DHA with dose-dependent kinetics were shown. Previous PK/PD evaluations showed that the rapid efficacy of the artemisinins is principally caused by the peak drug concentration (Table 3). Intravenous AS is the fastest killer of parasites in the treatment of human malaria out of the five artemisinin derivatives, indicating that AS is a superior antimalarial agent in terms of performance of PK/PD. In Table 3, intravenous AS provides the highest peak concentration (C max ) with the shortest time of lag phase in parasite exclusion (1.92 hours) and the lowest area under the inhibitory curve (AUIC, 397.3% · h/μg). In vitro bioassay tests have shown DHA to be more potent than artemisinin and similar in potency to AS. Although the plasma concentration of DHA in humans may result in an even faster effect and increase the survival of severe patients because of the safer and dose-dependent increase of C max of AS and DHA shown in this study.

Similar to prior literature, the results show that AS is rapidly converted to DHA. The active metabolite was detected in all volunteer plasma until 6 hours, whereas the parent drug was undetectable at time points as early as 1–2 hours after the single short-term infusion. In vitro bioassay tests have shown DHA to be more potent than artemisinin and similar in potency to AS. Although the plasma concentration of DHA in humans may result in an even faster effect and increase the survival of severe patients because of the safer and dose-dependent increase of C max of AS and DHA shown in this study.

The resulting C max shown in this study compares very well to other publications, where the C max has been shown to be from 605 to 18,909 ng/mL for AS plus DHA, all resulting from doses of AS either as 120 mg/person or 2.4 mg/kg in various malaria trials. Although these dose regimens are still not enough to cure severe and complicated malaria in 100% of patients, there is now convincing evidence that, for those who do develop severe malaria, intravenous AS will reduce the risk of death by approximately one third. The data are also encouraging that an increase in dose of intravenous AS in humans may result in an even faster effect and increase the survival of severe patients because of the safer and dose-dependent increase of C max of AS and DHA shown in this study.

A dose-dependent increase of C max and AUC_{inf} for DHA in the subjects were shown in a high correlation (r^2 = 0.9692–0.9963) to the dose in all five dose cohorts (Figure 3C, D, bottom).
that of DHA with 2.80–4.51 ratio of \( C_{\text{max}} \) AS/DHA. It is known that DHA has a longer half-life of 1.15–2.37 hours, which is 7.12- to 12.68-fold longer than AS, which has a short half-life of 0.12–0.24 hours. Therefore, the effectiveness of AS has been attributed to its rapid and extensive hydrolysis to DHA, which gives a 30% higher AUC value than the intravenous infusion. Compared with NCA and intravenous bolus modeling, the two-compartment intravenous infusion model best described the disposition PK data of intravenous AS, which should be a model-dependent fitting, in this study.

In conclusion, the study presented here underlines the need for appropriate PK analysis with AS and its metabolite, DHA. Because this is in reality a short-term intravenous infusion, results from PK analysis of the data set of intravenous AS is more suitably a model-dependent rather than model-independent fitting. Considering that most intravenous AS is given through a short-term infusion in clinical use, CA may be necessary for PK evaluation of intravenous AS.

Received March 19, 2009. Accepted for publication June 29, 2009.

Financial support: This study was supported by the US Army Research and Material Command.

Disclaimer: The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting true views of the Department of the Army or the Department of Defense.

### Table 3

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>AS</th>
<th>AS</th>
<th>DHA</th>
<th>QHS</th>
<th>AM</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>First loading dose</td>
<td>120 mg</td>
<td>100 mg</td>
<td>120 mg</td>
<td>500 mg</td>
<td>3.2 mg/kg</td>
<td>4.8 mg/kg</td>
</tr>
<tr>
<td>Maintaining dose</td>
<td>Oral 100 mg at 8 hours</td>
<td>Oral 100 mg</td>
<td>Oral 200 mg</td>
<td>Oral 600 mg</td>
<td>1.6 mg/kg ( \times 4 )</td>
<td>1.6 mg/kg ( \times 5 )</td>
</tr>
<tr>
<td>Total dose</td>
<td>220 mg and mefloquine†</td>
<td>50 mg twice a day ( \times 4 )</td>
<td>100 mg ( \times 4 )</td>
<td>250 ( \times 2 ) + 5</td>
<td>3,000 mg</td>
<td>9.6 mg/kg</td>
</tr>
</tbody>
</table>

PK parameters (Day 1)*

- **C_{\text{max}}** (ng/mL): 2646 (DHA); 11343 (AS); 1052 (DHA); 198 (AS); 437.5; 588.0; 74.9; 110.1
- **T_{\text{max}}** (h): 0.13; 0.75; 1.4; 2.4; 6.0; 8.2
- **T_{\text{lag}}** (h): 0.2; 0.45
- **AUC_{0-24h}** (ng \( \cdot \) h/mL): 2378 (DHA); 1146 (AS); 1334 (DHA); 210 (AS); 1.329; 2.601; 1.230; 4.702
- **t_{1/2}** (absorption, h): 0.67 (DHA); 0.05 (AS)
- **t_{1/2}** (elimination, h): 0.70 (DHA); 0.85 (DHA); 2.3; 7.83; 22.7
- **MRT (h):** 1.95 (DHA); 2.71; 7.41; 13.94; 42.9

PD parameters (Day 1)*

- **Time of lag phase (h):** 1.92; 2.81; 4.03; 5.76; 7.26; 8.89
- **AUC (%) or MPC:** 397.3; 921.2; 1,167.9; 1,464.4; 1,613.4; 2,463.5
- **PC_{50}** (h): 3.18; 8.48; 10.05; 13.95; 15.63; 19.68
- **E_{\text{max}} (%) or MPC:** 0.0011; 0.0016; 0.2132; 0.0100; 0.0030; 0.5504
- **Cut rate (%)**

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Intravenous</th>
<th>Oral</th>
<th>Oral</th>
<th>Oral</th>
<th>Intramuscular</th>
<th>Intramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS AS DHA QHS AM AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*These data were fitted with WinNonlin (V5.0) by the authors.
†Oral 750 mg mefloquine at 24 hours after intravenous injection.

PK = pharmacokinetics; PD = pharmacodynamics; MRT = mean residence time; PC_{50} = mean time for parasitemia to fall by half; AUIC = area under inhibitory curve; QHS = artemisinin; DHA = dihydroartemisinin; AM = artether; AE = artether; AS = artemisinic acid; MPC = minimum parasiticidal concentration; IM = intramuscular.
REFERENCES


