Published in final edited form as:

Ann Intern Med. 2015 October 6; 163(7): 498–506. doi:10.7326/M15-0910.

Intravenous Artesunate for the Treatment of Severe and Complicated Malaria in the United States: Clinical Use under an Investigational New Drug Protocol

Patrick S. Twomey, MD[1], **Bryan L. Smith, MD**[1], **Cathy McDermott, RN, MPH**[1], **Anne Marino, MD**[2], **William McCarthy, PhD**[1], **S. Patrick Kachur, MD**[3], **Janet Ransom, PhD**[2], and **Paul M. Arguin, MD**[3]

[1]United States Army Medical Materiel Development Activity (USAMMDA)

[2]FastTrack

[3]Centers for Disease Control and Prevention (CDC)

Abstract

Background—Quinidine gluconate, the only FDA-approved treatment for life-threatening malaria in the United States, has a problematic safety profile and is often unavailable in hospitals.

Objective—Assess the safety and clinical benefit of intravenous artesunate as a quinidine alternative

Design—Retrospective case series

Setting—United States hospitals

Patients—Patients with severe and complicated malaria received 4 doses of intravenous artesunate 2.4 mg/kg under a treatment protocol implemented by the Centers for Disease Control and Prevention (CDC). Protocol eligibility required the presence of microscopically confirmed malaria, the need for intravenous treatment, and an impediment to quinidine. From January 2007 through December 2010, 102 patients received artesunate. Age range was 1-72 years, with 90% adults and 61% males. At baseline, 35% had evidence of cerebral malaria and 17% had severe hepatic impairment.

Measurements—Clinical and laboratory data from each patient's hospital records were abstracted retrospectively, including information from baseline through a maximum 7-day follow-up. The abstracted data were presented before a physician committee for the evaluation of safety and clinical benefit outcomes.

Results—Seven deaths occurred (mortality 6.9%), with the most frequent adverse events being anemia (65% of patients) and elevated hepatic enzymes (49%). All deaths and most adverse events were attributed to the severity of malaria. Patients' symptoms generally improved or resolved within 3 days, and the median time to discharge from the Intensive Care Unit was 4 days, even for patients who had presented with severe liver disease or cerebral malaria. Over 100 concomitant medications were used, with no documented drug-drug interactions.

Limitations—Potential late-presenting safety issues might lie outside the 7-day follow-up period.

Conclusions—Artesunate was a safe and clinically beneficial alternative to quinidine.

Introduction

Approximately 1,500 cases of malaria are reported annually in the United States (US) (1). These cases are not endemic to the US, but occur in individuals with a history of recent travel or residence in malaria endemic areas. Roughly 10% of US malaria cases are considered severe by the World Health Organization (WHO) criteria (2, 3), with the vast majority of these being caused by *Plasmodium falciparum* (4-7). Patients with severe malaria are at risk for life-threatening complications including: renal failure, acute respiratory distress syndrome (ARDS), severe hemolytic anemia, and cerebral malaria. Among these, cerebral malaria is arguably the most dire, since it can present rapidly, often with minimal warning signs, and has a mortality rate of 15-30% with treatment and 100% when untreated (2, 4, 8-10). The only FDA-approved treatment for severe malaria in the United States is quinidine, a stereoisomer of quinine that once saw routine hospital use as a cardiac anti-arrhythmic medication (11, 12). With the development of newer and safer anti-arrhythmic agents many hospitals have dropped quinidine from their pharmacies (13, 14). Even when quinidine can be obtained, its intravenous regimen is complex, and its dosing fraught with safety concerns. In addition to having a substantial adverse event profile quinidine can react with many concomitant medications, requiring dosage adjustments and careful monitoring, typically in an Intensive Care Unit (ICU) setting (15-17).

Artemisinin derivatives have been studied for their antimalarial properties since the early 1970's (18), with a mechanism of action hypothesized to involve the production of oxygen radicals that interfere with parasite function (19). Among the artemisinins, artesunate is the most widely used because it can be delivered intravenously with a reliable pharmacokinetic profile (20, 21). Artesunate is a lifesaving drug that kills the majority of malaria parasites very rapidly, with any residual parasites being eliminated by post-artesunate treatment with a follow-on oral antimalarial drug (22). Artesunate has been proven superior to quinine against malaria in two large studies in endemic regions (9, 10), and the drug is currently recommended as the first-line treatment for severe malaria by the World Health Organization (WHO) (22). In the developing world, artesunate is now being employed in the initial treatment of severe and complicated malaria caused by *P falciparum* (23). The product in use, however, is not manufactured according to current good manufacturing practice (cGMP) guidelines and is not FDA-approved for use in the US (23).

Since 2004, the Walter Reed Army Institute of Research (WRAIR) has been developing a novel cGMP formulation of IV artesunate that has pharmacokinetics comparable to non-cGMP preparations (21, 24). This drug has been successfully tested in Phase 1 (21, 25) and Phase 2 (24) trials. In 2007, domestically manufactured cGMP artesunate from WRAIR was first made available to treating physicians and hospitals in the US through the Centers for Disease Control and Prevention (CDC) in Atlanta for compassionate use under an Investigational New Drug (IND) protocol (26). To assess the safety, tolerability, and clinical benefit of intravenous artesunate among US patients with severe and complicated malaria, medical records for patients enrolled in this treatment IND protocol were evaluated from the period of January 1, 2007 to December 31, 2010.

Methods

Design and Conduct of the Evaluation

This was a retrospective analysis of clinical data from patients with severe or complicated malaria who received intravenous artesunate in the United States according to the CDC treatment IND #76,725 protocol, designated protocol CDC-060, which was approved by the Institutional Review Board (IRB) of the CDC, Atlanta, GA, USA. All patients or their legal representatives provided written informed consent prior to treatment. The protocol for the retrospective abstraction of data collected during CDC-060 was sponsored by the Office of the Surgeon General, Department of the Army, also in accordance with the CDC-060, IRB approved protocol. Copies of all medical records for patients enrolled in the CDC-060 protocol (period January 1, 2007 to December 31, 2010) were sent from the treating hospitals to the CDC for the data abstraction process. Using these medicals records, trained clinical professionals from the US Army and the CDC abstracted specific demographic and clinical information for the period beginning 24 hours prior to the patient's first dose of artesunate through the time of ICU discharge or a maximum of 7 days. These data were de-identified and recorded onto data abstraction templates (DATs). Data in the DATs were quality assured by two separate medical professionals not involved in the initial abstraction, and then finally presented before a Clinical Benefits Endpoint Committee (CBEC) consisting of at least 5 health care providers. All decisions regarding clinical benefit and safety outcomes for each patient were made by a majority vote of the CBEC. Results of the CBEC meetings were recorded in the DATs, and then entered into the database for analysis according to a predetermined statistical analysis plan (SAP).

Treatments

The US Army WRAIR supplied artesunate to the CDC as a sterile, dry-filled powder, pre-packaged with a phosphate buffer diluent for reconstitution. When a treating physician contacted the CDC malaria hotline [Tel: 770-488-7788 or 770-488-7100 after hours], artesunate was released if all protocol CDC-060 enrollment criteria were met. Artesunate was shipped to the treating hospital rapidly from one of 9 CDC Quarantine Stations located across the US. Upon receipt at the treating hospital, artesunate to be reconstituted and administered in 4 weight-based doses (2.4 mg/kg), with the first dose infused immediately, and the remaining 3 doses given at 12, 24, and 48 hours after the first. After their last artesunate dose, patients commenced follow-on oral antimalarial therapy (not supplied by the CDC) after a minimum 4-hour waiting period. Choice of follow-on antimalarial lay with the treating physician. Patients were to be treated in a hospital ICU, where they received appropriate concomitant medications and supportive treatments. However, other antimalarials were to be stopped during the period of artesunate administration.

Patients

To be eligible for artesunate treatment under the CDC-060 protocol, a patient must have met at least one criterion in each of 3 groups of enrollment criteria, designated A, B and C. Group A Criteria required microscopic confirmation of malaria or a strong clinical suspicion of severe malaria when microscopic diagnosis was unavailable. Group B Criteria confirmed the patient's need for IV treatment due to one or more of the following: inability to tolerate

oral medications; high density parasitemia (≥5%); or evidence of severe malaria [impaired consciousness; seizures; circulatory collapse/shock; pulmonary edema or ARDS; acidosis; acute renal failure; abnormal bleeding or disseminated intravascular coagulation (DIC); jaundice; or severe anemia with hemoglobin < 7 g/dL)]. Group C Criteria verified the patient's need for artesunate due to at least one of the following factors: problems with quinidine availability; failure (parasitemia >10% of baseline value at 48 hours after starting IV quinidine); intolerance; or contraindications. Patients were excluded if they had a known allergy to artesunate.

Endpoints

Although efficacy was not formally assessed, changes in specific clinical benefit parameters were treated as secondary outcomes. Clinical benefit endpoints included the following: time to negative parasitemia, time to follow-on oral therapy, time to discharge from the ICU, and change in enrollment B Criteria vs. baseline. For each enrollment B Criterion present at baseline, day-by-day determinations were made as to whether the criterion had resolved, improved, deteriorated, or was unchanged.

Safety was assessed from data obtained from clinical assessments, laboratory measurements, adverse events (AEs), and deaths. Physical exam findings and adverse events were coded according to Medical Dictionary for Regulatory Affairs (MedDRA) version 14.0, and adverse event severity was graded based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3. An adverse event's relationship to artesunate was determined by a majority consensus of the CBEC.

Statistical Analysis

Frequency tables were used to summarize categorical data, while continuous variables were summarized using descriptive statistics. Confidence intervals (CI) (95%) for outcomes and AE rates were reported. Changes in enrollment B Criteria were presented as the frequency and percentages of patients that had changes since baseline. Subgroup analyses of the data were performed by segregating patients according to the following parameters: baseline level of hepatic impairment [as measured by the Model for End-Stage Liver Disease (MELD) formula] (27); baseline level of renal impairment [as determined by the estimated glomerular filtration rate (eGFR)] (28); and baseline presence of markers for cerebral malaria (i.e., seizures, impaired consciousness, or need for ventilator support). Additional subgroup analyses were performed for patients with concurrent antimalarial use during artesunate administration and for patients with quinidine exposure at any time prior to or during artesunate administration. Results of the subgroup analyses were displayed using Kaplan-Meier survival curves and were compared using the Log-Rank test, Wilcoxon rank sum test, and Tarone-Ware test for statistical significance. All calculations were performed using SAS version 9.2.

Role of the Funding Source

Funding was provided by Office of the Surgeon General, Department of the Army, USA.

Results

Patients

A total of 128 patients (the Enrolled Population) from hospitals across the US were enrolled during the time period studied. Among these, 102 consented to artesunate treatment and received at least one dose of the drug, comprising the Safety Population. The Safety Population included: 62 (61%) males, 40 (39%) females, 64 (63%) Black/African Americans, 26 (25%) Caucasians, 9 (9%) Asians, and 3 (3%) undisclosed race. The mean age was 38.1 years (range, 1-72 years), with 92 adults (age ≥15) and 10 children.

Malaria was confirmed by microscopy in 96% of the Safety Population, and mean baseline parasitemia was 13.8%. The most frequent reason for requiring parenteral treatment was parasitemia ≥5% (present in 66% of patients), followed by jaundice in 47%, and inability to take oral medications in 35%. The main reason for patients being given artesunate was that artesunate was available more quickly than quinidine (61% of cases). Consistent with protocol enrollment Criteria C, prior exposure to quinidine occurred in 46 patients, with the majority of these having received quinidine for 1 day before beginning artesunate.

Regarding baseline clinical status, 14% patients presented with severe or life-threatening renal impairment, 17% had severe or life-threatening liver impairment, and 35% had baseline markers for cerebral malaria. There were 3 pregnant patients, all presenting in their third trimester. Numbers of patients with other concurrent medical conditions were as follows: diabetes (11), asthma (5), asplenia (2); human immunodeficiency virus (HIV) infection (2); hepatitis A (1); hepatitis B (1); and glucose-6-phosphate dehydrogenase (G6PD) deficiency (1).

Treatment Compliance

In the Safety Population, 93 (91%) of 102 patients completed artesunate treatment. Of the 9 (9%) who did not, 5 had evidence of cerebral malaria at baseline and expired before all 4 doses of artesunate could be administered. Contrary to the CDC-060 protocol, 1 patient received concomitant quinidine during artesunate dosing, while an additional 45 patients were administered concomitant antimalarial medications other than quinidine while receiving artesunate. The most commonly used concomitant antimalarial was doxycycline (35 patients).

As oral follow-on treatment, 41 (40.0%) patients received atovaquone-proguanil, 19 (18.6%) doxycycline, 5 (4.9%) clindamycin, 3 (2.9%) primaquine, and 2 (2.0%) mefloquine. The remaining 32 patients could not yet tolerate oral medications at Day 7 follow-up.

Clinical Benefit

Among 87 patients defined as “evaluable” (patients who met enrollment criteria, received artesunate, and had microscopic confirmation of *P falciparum*), the median time to negative parasitology was 42.7 hours. No differences in time to negative parasitology were observed in the subgroup analyses (i.e., baseline level of renal or hepatic impairment or baseline markers for cerebral malaria). Patients who received concurrent antimalarials (n=38

evaluable) during artesunate administration did not show a statistically significant difference in time to negative parasitology (Figure 1) compared with the remaining 49 evaluable patients who did not receive concurrent antimalarials (43 hours vs. 51 hours, respectively; p=0.942). Patients who were exposed to quinidine (n=43 evaluable) did not show a statistically significant difference in time to negative parasitology (Figure 2) compared with the 44 evaluable patients who had no quinidine exposure (41 hours vs. 50 hours, respectively; p=0.608).

In the Safety Population, 73 (72%) of 102 patients were discharged from the ICU within 7 days after beginning artesunate, with a median time to discharge of 4 days. Patients with severe liver disease or markers of cerebral malaria at baseline likewise left the ICU within 4 days. Among the 87 evaluable patients (defined above), a statistically significant difference (p=0.004) in time to discharge from the ICU was observed for patients with quinidine exposure (median 6 days) compared with those who were not exposed to quinidine (4 days). A similar finding, although not statistically significant, was observed for patients who had received concurrent antimalarials during artesunate administration (discharge in 5 days) compared with patients who had not received concurrent antimalarials (discharge in 4 days; p=0.256). In addition, patients who had presented with renal failure (eGFR severe or life-threatening) at baseline, tended to remain in the ICU longer (median 7 days) compared with patients without this level of renal impairment (median of 4 days, p=0.018).

Evaluation of time to follow-on antimalarial therapy was confounded by the large number of patients who required exclusion from the analysis because their physicians had co-administered other antimalarial medications in conjunction with artesunate. In the 49 patients who could be evaluated for this endpoint, 39 (80%) successfully transitioned to oral antimalarial treatment in a mean of 3.8 days. No differences in time to start of oral therapy were observed in any of the subgroup analyses performed.

Analyses of changes in enrollment B Criteria (**Table 1**) indicated that the clinical signs and symptoms of severe malaria improved or resolved in a majority of patients by Day 3 of artesunate treatment. Exceptions were subjects with ARDS, acute renal failure, or abnormal bleeding.

Safety

Seven patients expired, with all deaths attributed to the severity of malaria rather than to artesunate. All of the deceased patients (**Table 2**) had presented with evidence of cerebral malaria and moderate-severe hepatic injury at baseline, and most (5 of 7) expired before their artesunate regimen could be completed. Five had baseline hyperparasitemia ranging from 12% to 90%, 2 were elderly (age > 70 years); 2 were diabetic, and 1 had concurrent HIV infection.

A total of 278 AEs were reported (**Table 3**), with 92.2% of patients experiencing at least 1 AE. The most commonly reported AE was anemia (65% of patients), followed by increased hepatic transaminases (49%), thrombocytopenia (18%), hyperbilirubinemia (14%), acute renal failure (10%) and ARDS (8%). The majority of AEs (55%) were assessed as Grade 1-mild or Grade 2-moderate in severity, 25% were Grade 3-severe, and 20% were Grade 4-

life-threatening. Thirty percent (31/102) of patients experienced a Grade 4 AE, with the most frequently reported being anemia (13 reports), followed by respiratory failure/collapse/ARDS (9 reports). No Grade 4 AE was considered "definitely" related to artesunate by the CBEC.

Of the 3 pregnant women enrolled, 1 delivered her child before her artesunate treatment began. The remaining 2 were dosed while still pregnant, had no Grade 4 AEs, and delivered healthy infants vaginally within 1 month after recovering from malaria.

One of the 2 enrolled patients with concurrent HIV expired, as did 2 of the 11 diabetic patients treated with artesunate. There were no deaths among patients with concurrent Hepatitis A or B infection, asthma, G6PD deficiency, or asplenia.

Because the protocol permitted the use of concomitant medications (other than antimalarials) to treat the clinical manifestations of severe malaria, substantial polypharmacy was observed. Over 100 different concomitant medications were administered (**Table 4**), including: acetaminophen (91 patients) or nonsteroidal anti-inflammatory drugs (53 patients) for fever and pain; cephalosporins (56 patients), vancomycin (34 patients), or penicillins (26 patients) for concurrent bacterial infections; ondansetron for nausea and vomiting (51 patients); and anticoagulants for thrombosis prophylaxis (31 patients). No drug-drug interactions were reported.

Discussion

Overall, European surveillance networks (TropNetEurop and SIMPID data) have reported a case-fatality rate of about 15% for severe "imported" malaria (29). Although artesunate has not yet been studied widely against severe malaria in Europe (30), quinine treatment there has produced fatality rates of 8%-11% in studies in France (31, 32) and the United Kingdom (33). In comparison, mortality was only 6.9% (7 of 102) using artesunate in the current CDC-060 protocol, with all deaths being related to the consequences of severe malaria. In addition, advanced age (34, 35) or concurrent HIV infection (36) likely contributed to the fatal outcomes of 3 patients.

In general, AEs were consistent with symptoms expected in patients with severe malaria (37). Anemia and hepatopathology, the most frequently reported AEs overall, are common findings in individuals with severe malaria and may be attributed to the disease process alone (32, 38-40). Other Grade 4 AEs (e.g., thrombocytopenia, ARDS, acute renal failure, and cerebral edema) are also well-documented complications of severe malaria (32, 37-40).

The data captured in the shift tables indicated that the clinical signs and symptoms of severe malaria improved or resolved in a majority of subjects by Day 3. Exceptions were patients with ARDS, acute renal failure, or abnormal bleeding, all of which are malaria complications that carry an extraordinary risk for poor outcomes (41, 42). Given that fact, these patients would not be expected to recover quickly.

Overall, based on the evaluation of multiple parameters, artesunate was of clinical benefit to subjects with severe and complicated malaria. Artesunate produced rapid and effective

parasite clearance, with a median time to negative parasitology of 42.7 hours. However, it is important to keep in mind that these reported parasitemia estimations were made at the clinical sites and were not verified for accuracy. It is possible that parasite clearance times may have been shorter if labs were including gametocytes in their parasitemia estimations (43).

No differences in time to negative parasitology were observed in any of the subgroup analyses performed, including patients with prior exposure to quinidine or patients given concomitant antimalarials. Median time to starting a follow-on oral therapy was 4 days, independent of baseline renal, hepatic, or neurological status. Median time to discharge from the ICU was also 4 days, even for patients who had severe liver disease or cerebral malaria at baseline. This finding, in particular, highlights the clinical benefit of artesunate among patients with dire clinical presentations.

In CDC-060, artesunate was administered in a treatment context of intense polypharmacy. There were more than 100 different concomitant medications employed. Furthermore, there were additional pharmacologic risks inherent to the ICU environment, including high and prolonged dosing regimens, adjuvant toxicity, and the impact of end-organ dysfunction (44). In spite of these challenges, artesunate was used safely in a clinical context that presented a high risk for drug-drug interactions.

One potential limitation of this evaluation was the relatively brief 7-day follow-up, which did not permit the tracking of any potential late-presenting safety issues. In light of recent reports of delayed hemolysis having occurred in some patients who received artesunate for severe malaria, longer term follow-up of hematologic parameters has now been recommended (45).

The aim of the CDC-060 treatment IND protocol was to make cGMP artesunate available to US patients with severe and complicated malaria for whom standard of care quinidine was problematic or unavailable. Data abstracted from CDC-060, as presented here, indicate that artesunate was safe and clinically beneficial in the vast majority of US patients who were treated with the drug during the targeted period, thus supporting the use of artesunate as a quinidine alternative.

Acknowledgments

Aarti Agarwal, Veronica Baechler, Melissa Briggs, John T. Brooks, Cristina Cardemil, Kevin R. Clarke, Gregory Deye, Tarayn A. Fairlie, Susan Fracisco, Julie Gutman, Asim Jani, Keren Z. Landman, Sheryl Lyss, Monica E. Parise, Philip Peters, Alexander Rowe, Isaac See, Laurence Slutsker, Katherine Tan, and Andrew Terranella.

References

1. Centers for Disease Control and Prevention (CDC). Malaria Facts. Updated: March 26, 2014. Available at : http://www.cdc.gov/malaria/about/facts.html. Accessed: October 14, 2014
2. World Health Organization (WHO). Guidelines for the Treatment of Malaria. 2nd. World Health Organization; Geneva: 2010. p. 35-37.
3. WHO. Severe Falciparum malaria. Transactions of the Royal Society of Tropical Medicinne and Hygiene. 2000; 94(Suppl 1):1–90.

4. Lon C, Timmermans A, Buathong N, et al. Severe Malaria in Battambang Referral Hospital, an area of Multidrug Resistance in Western Cambodia: A Retrospective Analysis of Cases from 2006-2009. Malaria Journal. 2013; 12:217. [PubMed: 23802651]
5. Abdallah TM, Abdeen MT, Ahmed IS, et al. Severe Plasmodium falciparum and Plasmodium vivax Malaria among Adults at Kassala Hospital, Eastern Sudan. Malaria Journal. 2013; 12:148. [PubMed: 23634728]
6. Bartoloni A, Zammarchi L. Clinical Aspects of Uncomplicated and Severe Malaria. Mediterr J Hematol Infect Dis. 2012; 4(1)
7. Nadjm B, Behrens R. Malaria: An Update for Physicians. Infect Dis Clin N Am. 2012; 26:243–259.
8. Higgins SJ, Kain KC, Liles WC. Immunopathogenesis of Falciparum Malaria: Implications for Adjunctive Therapy in the Management of Severe and Cerebral Malaria. Expert Rev Anti Infect Ther. 2011; 9(9):803–19. [PubMed: 21905788]
9. Dondorp A, Nosten F, Stepaniewska K, et al. for the Southeast Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) Group. Artesunate versus Quinine for the Treatment of Severe Falciparum Malaria: A Randomised Trial. Lancet. 2005; 366:717–25. [PubMed: 16125588]
10. Dondorp AM, Fanello CI, Hendriksen ICE, et al. for the African Quinine Artesunate Malaria Trial (AQUAMAT) Group. Artesunate versus Quinine for the Treatment of Severe Falciparum Malaria in African Children (AQUAMAT): An Open-Label, Randomised Trial. Lancet. 2010; 376:1647–57. [PubMed: 21062666]
11. CDC. Diagnosis and Treatment of Malaria in the United States. Updated: July 1, 2013. Available at: http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf. Accessed: January 8, 2014
12. CDC. Treatment Guidelines: Treatment of Malaria (Guidelines for Clinicians). Updated: 2013. Available at: http://www.cdc.gov/malaria/resources/pdf/clinicalguidance.pdf. Accessed: January 8, 2014
13. Viskin S, Wilde AA, Krahn AD, Zipes DP. Inaccessibility to quinidine therapy is about to get worse. J Am Coll Cardiol. Jul 23.2013 62(4):355. [PubMed: 23624205]
14. Viskin S, Wilde AA, Guevara-Valdivia ME, Daoulah A, Krahn AD, Zipes DP, Halkin A. Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries. J Am Coll Cardiol. Jun 11; 2013 61(23):2383–7. [PubMed: 23583244]
15. White NJ. The treatment of malaria. N Engl J Med. Sep 12; 1996 335(11):800–6. [PubMed: 8703186]
16. Wroblewski HA, Kovacs RJ, Kingery JR, et al. High risk of QT interval prolongation and torsades de pointes associated with intravenous quinidine used for treatment of resistant malaria or babesiosis. Antimicrob Agents Chemother. Aug; 2012 56(8):4495–99. [PubMed: 22615288]
17. Phillips RE, Looareesuwan S, White NJ, et al. Hypoglycaemia and antimalarial drugs: Quinidine and the release of insulin. Br Med J (Clin Res Ed). May 17; 1986 292(6531):1319–1321.
18. White NJ. Qinghaosu (Artemisinin): The Price of Success. Science. 2008; 320:330–4. [PubMed: 18420924]
19. Meshnick SR. The Mode of Action of Antimalarial Endoperoxidases. Trans R Soc Trop Med Hyg. 1994; 88(Suppl 1):S31–32. [PubMed: 8053021]
20. Ilett KF, Batty KT, et al. The Pharmacokinetic Properties of Intramuscular Artesunate and Rectal Dihydroartemisinin in Uncomplicated Falciparum Malaria. Br J of Clin Pharmacol. 2002; 53(1): 23–30. [PubMed: 11849191]
21. Li Q, Cantilena LR, Leary KJ, et al. Pharmacokinetic Profiles of Artesunate after Single Intravenous Doses of 0.5, 1, 2, 4, and 8 mg/kg in Healthy Volunteers: A Phase I Study. Am J Trop Med Hyg. 2009; 81(4):615–21. [PubMed: 19815876]
22. World Health Organization. Guidelines for the Treatment of Malaria. 2nd. WHO; Geneva: 2010. available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf?ua=1. Accessed: 07 July 2014
23. CDC. Published reports of delayed hemolytic anemia after treatment with artesunate for severe malaria--worldwide, 2010-2012. MMWR Morb Mortal Wkly Rep. Jan 11; 2013 62(1):5–8. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6201a2.htm. Accessed: January 8, 2014. [PubMed: 23302816]

24. Kremsner PG, Taylor T, Issifou S, Kombila M, Chimalizeni Y, Kawaza K, Bouyou Akotet MK, et al. A simplified intravenous artesunate regimen for severe malaria. J Infect Dis. 2012; 15:312–9. [PubMed: 22180622]
25. Miller RS, Li Q, Cantilena LR, Leary KJ, Saviolakis GA, Melendez V, Smith B, Weina PJ. Pharmacokinetic profiles of artesunate following multiple intravenous doses of 2, 4, and 8 mg/kg in healthy volunteers: Phase 1b study. Malar J. 2012; 11:255. doi: 10.1186/1475-2875-11-255. [PubMed: 22853818]
26. CDC. Artesunate is available to treat severe malaria in the United States. 2012. Last Reviewed: November 9, 2012. Available at: http://www.cdc.gov/malaria/diagnosis_treatment/artesunate.html. Accessed: 28 January 2014
27. Kamath PS, Kim WR. The Model for End-Stage Liver Disease (MELD). Hepatology. 2007; 45:797–805. [PubMed: 17326206]
28. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). National Institutes of Health. Estimating GFR: MDRD Study Equation. Last Updated: February 6, 2013. Available at: http://nkdep.nih.gov/lab-evaluation/gfr/estimating.shtml. Accessed: January 14, 2014
29. Mühlberger N, Jelinek T, Behrens RH, et al. Age as a risk factor for severe manifestations and fatal outcome of falciparum malaria in European patients: Observations from TropNetEurop and SIMPID surveillance data. Clin Infect Dis. 2003; 36:990–995. [PubMed: 12684911]
30. Kreeftmeijer-Vegter AR, van Genderen PJ, Visser LG, Bierman WF, Clerinx J, van Veldhuizen CK, de Vries PJ. Treatment outcome of intravenous artesunate in patients with severe malaria in the Netherlands and Belgium. Malar J. 2012; 11:102. [PubMed: 22462806]
31. Bruneel F, Hocqueloux L, Alberti C, Wolff M, Chevret S, Bédos JP, Durand R, Le Bras J, Régnier B, Vachon F. The clinical spectrum of severe imported falciparum malaria in the intensive care unit: report of 188 cases in adults. Am J Respir Crit Care Med. 2003; 167:684–9. [PubMed: 12411286]
32. Bruneel F, Tubach F, Corne P, Megarbane B, et al. Severe Imported Malaria in Adults (SIMA) Study Group. Severe imported falciparum malaria: a cohort study in 400 critically ill adults. PLoS One. 2010; 5:e13236. doi: 10.1371/journal.pone.0013236. [PubMed: 20949045]
33. Phillips A, Bassett P, Zeki S, Newman S, Pasvol G. Risk factors for severe disease in adults with falciparum malaria. Clin Infect Dis. 2009; 48:871–8. doi: 10.1086/597258. [PubMed: 19243243]
34. Checkley AM, Smith A, Smith V, Blaze M, Bradley D, Chiodini PL, Whitty CJ. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. BMJ. 2012; 344:e2116. doi: 10.1136/bmj.e2116. [PubMed: 22454091]
35. Mühlberger N, Jelinek T, Behrens RH, et al. Age as a risk factor for severe manifestations and fatal outcome of falciparum malaria in European patients: Observations from TropNetEurop and SIMPID surveillance data. Clin Infect Dis. 2003; 36:990–995. [PubMed: 12684911]
36. Zamidei L, Durval A, Bettocchi D, Luzzio MG, Bartoloni A, Consales G. Efficacy and safety of quinine-artesunate in an HIV-positive patient with severe falciparum malaria. Minerva Anestesiol. 2010; 76:66–9. Epub 2009 Oct 7. [PubMed: 20125075]
37. Askling HH, Bruneel F, Burchard G, Castelli F, et al. European Society for Clinical Microbiology and Infectious Diseases Study Group on Clinical Parasitology. Management of imported malaria in Europe. Malar J. 2012; 11:328. doi: 10.1186/1475-2875-11-328. [PubMed: 22985344]
38. Abro AH, Ustadi AM, Abro HA, Abdou AS, Younis NJ, Akaila SI. Jaundice with hepatic dysfunction in P. falciparum malaria. J Coll Physicians Surg Pak. 2009; 19:363–6. doi: 06.2009/JCPSP.363366. [PubMed: 19486575]
39. Mishra SK, Mohanty S, Mohanty A, Das BS. Management of severe and complicated malaria. J Postgrad Med. 2006; 52:281–7. [PubMed: 17102547]
40. Shah S, Ali L, Sattar RA, Aziz T, Ansari T, Ara J. Malarial hepatopathy in falciparum malaria. J Coll Physicians Surg Pak. 2009; 19:367–70. doi: 06.2009/JCPSP.367370. [PubMed: 19486576]
41. Alves C, Chen JT, Patel N, Abrams D, et al. Extracorporeal membrane oxygenation for refractory acute respiratory distress syndrome in severe malaria. Malar J. 2013; 12:306. [PubMed: 24127739]
42. Santos LC, Abreu CF, Xerinda SM, Tavares M, Lucas R, Sarmento AC. Severe imported malaria in an intensive care unit: a review of 59 cases. Malar J. 2012; 11:96. doi: 10.1186/1475-2875-11-96. [PubMed: 22458840]

43. Abanyie FA, Arguin PM, Gutman J. State of malaria diagnostic testing at clinical laboratories in the United States, 2010: a nationwide survey. Malar J. 2011; 10:340. [PubMed: 22074250]

44. Devlin JW1, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. Crit Care Med. Jun; 2010 38(6 Suppl):S231–43. doi: 10.1097/CCM.0b013e3181de125a. [PubMed: 20502176]

45. World Health Organization Global Malaria Programme. WHO Information Note on Delayed Haemolytic Anaemia following Treatment with Artesunate. Published: 09 October 2013. Available at: http://www.who.int/malaria/publications/atoz/who_note_delayed_haemolytic_anaemia_oct13.pdf?ua=1. Accessed: 28 January 2014

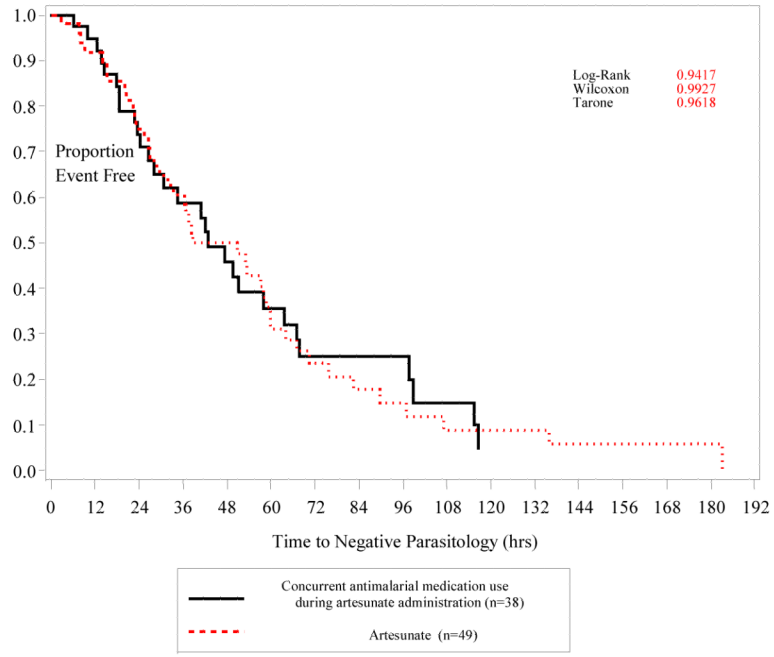

Figure 1.

Time to Negative Parasitology (Kaplan-Meier Survival Analysis) in Evaluable Patients Who Received Artesunate Plus Concomitant Antimalarial Medications vs. Patients Who Received Artesunate Alone

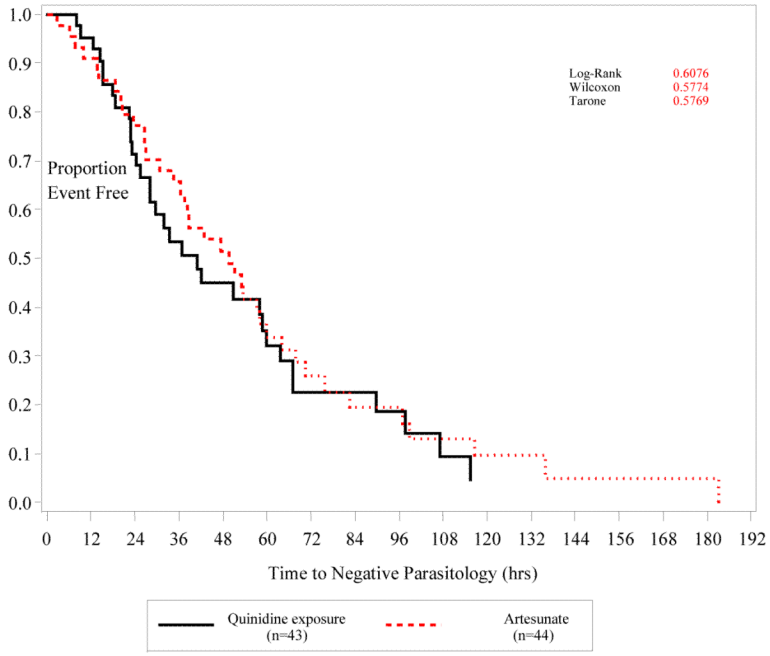

Figure 2.

Time to Negative Parasitology (Kaplan-Meier Survival Analysis) in Evaluable Patients with Quinidine Exposure vs. Patients Who Received Artesunate without Quinidine Exposure

Table 1

Enrollment B Criteria Shift Table by Treatment Day

Patients with This Criterion at baseline (n)	Criterion after Artesunate	Day 1 N (%)	Day 2 N (%)	Day 3 N (%)
Unable to take oral medication (n=33)	Able	6 (18)	12 (36)	15 (45)
	Unable	26 (79)	20 (61)	12 (36)
	Unknown	1 (3)	0 (0)	0 (0)
	No Observation	0 (0)	1 (3)	6 (18)
Parasitemia >5% (n=65)	Decreased	53 (82)	53 (82)	44 (68)
	Unchanged	1 (2)	0 (0)	0 (0)
	Increased	1 (2)	0 (0)	0 (0)
	Unknown	9 (14)	10 (15)	14 (22)
	No Observation	1 (2)	2 (3)	7 (11)
Impaired consciousness (N=24)	Resolved	3 (13)	8 (33)	9 (38)
	Improved	3 (13)	4 (17)	2 (8)
	Unchanged	10 (42)	4 (17)	3 (13)
	Deteriorated	2 (8)	3 (13)	0 (0)
	Unknown	6 (25)	4 (17)	4 (17)
	No Observation	0 (0)	1 (4)	6 (25)
Seizures (N=5)	Resolved	1 (20)	1 (20)	1 (20)
	Improved	3 (60)	3 (60)	3 (60)
	Unchanged	0 (0)	0 (0)	0 (0)
	Deteriorated	0 (0)	0 (0)	0 (0)
	Unknown	1 (20)	1 (20)	1 (20)
	No Observation	0 (0)	0 (0)	0 (0)
Circulatory collapse/shock (N=24)	Resolved	2 (8)	11 (46)	13 (54)
	Improved	6 (25)	2 (8)	2 (8)
	Unchanged	14 (58)	7 (29)	2 (8)
	Deteriorated	1 (4)	2 (8)	2 (8)
	Unknown	1 (4)	1 (4)	2 (8)
	No Observation	0 (0)	1 (4)	3 (13)
Pulmonary edema or ARDS (N=9)	Resolved	0 (0)	0 (0)	0 (0)
	Improved	0 (0)	1 (11)	3 (33)
	Unchanged	6 (67)	5 (56)	2 (22)
	Deteriorated	2 (22)	2 (22)	2 (22)
	Unknown	1 (11)	0 (0)	1 (11)
	No Observation	0 (0)	1 (11)	1 (11)
Acidosis (N=35)	Resolved	6 (17)	10 (29)	13 (37)
	Improved	9 (26)	9 (26)	9 (26)
	Unchanged	13 (37)	6 (17)	3 (9)
	Deteriorated	4 (11)	4 (11)	0 (0)
	Unknown	2 (6)	4 (11)	4 (11)
	No Observation	1 (3)	2 (6)	6 (17)

Table 2

Baseline Characteristics and Subsequent Clinical Course of Patients Who Expired

Patient (Gender/Age)	Medical History	Baseline Parasitemia	Enrollment Criteria B (Need for IV Treatment)	Baseline Hepatic Impairment	Cerebral Malaria Markers at Baseline	No. Doses artesunate received	Fatal AE/ Relationship to artesunate
Patient A (F/32)	Not significant	0.75% (*P vivax*)	Unable to take PO meds; Circulatory collapse; ARDS; Acidosis; DIC	Moderate	Yes	2	ARDS/ Not Related
Patient B (F/61)	Acute respiratory failure; Coma; Severe hemolytic anemia	62%	Unable to take PO meds; Impaired consciousness; Circulatory collapse; ARDS; Acidosis	Moderate	Yes	2	Multi-organ failure/ Not Related
Patient C (M/71)	Coronary artery bypass; Hypertension; Diabetes	3.4%	Unable to take PO meds; Impaired consciousness; Circulatory collapse; Acidosis	Moderate	Yes	3	Cardiac arrest/ Not Related
Patient D (M/31)	Not significant	14%	Unable to take PO meds; Impaired consciousness; Acidosis; Abnormal bleeding/DIC	Moderate	Yes	3	Brain herniation/ Not Related
Patient E (M/31)	Not significant	12%	Unable to take PO meds; Impaired consciousness; Circulatory collapse; Acidosis; Acute renal failure; Abnormal bleeding/DIC; Jaundice	Not assessed	Yes	3	Brain herniation/ Not Related
Patient F (M/54)	HIV Hypertension Hyperlipidemia Lymphedema	25.3%	Unable to take PO meds; Impaired consciousness; Jaundice	Moderate		4	Brain edema/ Not Related
Patient G (M/72)	Hypertension; Diabetes; Dyslipidemia; Hypothyroidism: Myopathy; Depression	90%	Unable to take PO meds; Impaired consciousness; Seizures; Circulatory collapse; Acidosis; Acute renal failure; Severe anemia	Severe		4	Cardiac arrest/ Not Related

Table 3

Most Frequently Reported Adverse Events (Occurrence ≥ 5%) by MedDRA System Organ Class and Preferred Term

System Organ Class/ Preferred Term, n(%)	Occurrence[1)]	N (%) in Safety Population (N=102)
At Least One Adverse Event	94/102 = 92.2% [85.3%, 96.0%]	94 (92)
Blood and lymphatic system disorders	75/102 = 73.5% [64.2%, 81.1%]	75 (74)
Anaemia		66 (65)
Thrombocytopenia		18 (18)
Leukocytosis		10 (10)
Lymphopenia		7 (7)
Neutropenia		5 (5)
Investigations	52/102 = 51.0% [41.4%, 60.5%]	52 (51)
Both hepatic transaminases increased or aspartate aminotransferase (AST) increased		50 (49)
Both hepatic transaminases increased		28 (27)
Aspartate aminotransferase (AST) increased		22 (22)
Respiratory, thoracic and mediastinal disorders	20/102 = 19.6% [13.1%, 28.3%]	20 (20)
Acute respiratory distress syndrome		8 (8)
Hepatobiliary disorders	17/102 = 16.7% [10.7%, 25.1%]	17 (17)
Hyperbilirubinaemia		14 (14)
Renal and urinary disorders	13/102 = 12.7% [7.6%, 20.5%]	13 (13)
Renal failure acute		10 (10)
Vascular disorders	8/102 = 7.8% [4.0%, 14.7%]	8 (8)
Gastrointestinal disorders	8/102 = 7.8% [4.0%, 14.7%]	8 (8)
Cardiac disorders	6/102 = 5.9% [2.7%, 12.3%]	6 (6)
Infections and infestations	7/102 = 6.9% [3.4%, 13.5%]	7 (7)
Metabolism and nutrition disorders	7/102 = 6.9% [3.4%, 13.5%]	7 (7)

Error! Reference source not found. Percent having at least one AE in the SOC with corresponding 2-sided exact Clopper-Pearson 95% CI in Safety analysis population. A patient was counted at most once within each system organ class and preferred term. Denominator of percentage is the number of patients in the column.

Table 4

Concomitant Medications Administered to the First 25 Patients Enrolled

Acetaminophen	Dexamethasone	Imipenem/Cilastatin	Omeprazole
Acetaminophen/Oxycodone	Dexmedetomidine	Insulin - Humalog	Ondanestron
Acetazolamide	Diphenhydramine	Insulin – Human Aspart	Oxycodone
Advair® (fluticasone/salmeterol)	Docusate Sodium	Insulin – Human Regular	Pantoprazole
Albuterol	Docusate Sodium/Senna	Insulin - NPH	Pepcid
Albuterol/Ipratropium	Dopamine	Ipratropium	Phenergan
Amlodipine	Doxycycline	Ketorolac	Phenobarbital
Amoxicillin/Clavulanate	Enoxaparin	Levalbuterol	Phenylephrine
Ampicillin	Epoprostenol	Levofloxacin	Phytonadione
Atovaquone/Proguanil	Esomeprazole	Lisinopril	Piperacillin/Tazobactam
Atropine	Etomidate	Lorazepam	Prochlorperazine
Azithromycin	Famotidine	Mefloquine	Propofol
Bisacodyl	Fentanyl	Meperidine	Quinidine
Budesonide	Fioricet	Metformin	Quinine
Bumetanide	Fluconazole	Methyprednisolone	Ranitidine
Cefalexin	Flunisolide	Metoclopramide	Senna
Cefazolin	Furosemide	Metronidazole	Simvastatin
Cefepime	Guaifenesin	Midazolam	Succinylcholine
Ceftriaxone	Haloperidol	Montelukast	Tessalon
Cefuroxime	Heparin	Morphine	Tinzaparin
Chloroquine	Hydrocodone	Moxifloxacin	Tolnaftate
Ciprofloxacin	Hydrocortisone	Nalbuphine	Trimethoprim/Sulfamethoxazole
Clindamycin	Hydromorphone	Niacin	Vancomycin
Codeine	Hydroxychloroquine	Nifedipine	Vasopressin
Darbepoetin	Ibuprofen	Norepinephrine	Zolpidem