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Intravenous Artesunate for Severe Malaria

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Abstract

OBJECTIVE: To review the pharmacodynamics and pharmacotherapeutic use of intravenous (IV) artesunate for the treatment of severe malaria.

DATA SOURCES: Literature retrieval was accessed through PubMed (1999 to March 2010) and Medline (1996 to March 2010) and the Centers for Disease Control and Prevention (CDC) using the search terms artemisinin, artesunate, malaria, and severe malaria. In addition, reference citations from publications identified were reviewed.

STUDY SELECTION AND DATA EXTRACTION: All articles in English identified from the data sources were reviewed. Focus was placed on postmarketing trials examining the safety and efficacy of artesunate in comparison to other regimens.

DATA SYNTHESIS: The treatment of severe malaria requires prompt, safe, and effective intravenous antimalarials. Many oral and intravenous agents are available worldwide for the treatment of malaria; however, quinindine has been the only option for parenteral therapy in the US. Furthermore, lack of this product's availability and an adverse safety profile has created a treatment option gap. Recently, IV artesunate was approved by the FDA for investigational drug use and distribution by the CDC. Three major studies regarding the use of IV artesunate are reviewed in addition to the World Health Organization's malaria treatment guidelines. While there are no published head-to-head trials of IV artesunate versus IV quinidine for severe malaria, several international studies comparing intravenous quinine and artesunate conclude that artesunate has the highest treatment success with lower adverse events. In addition, other literature is reviewed regarding counterfeit and other issues associated with artesunate.

CONCLUSION: Artesunate, a new antimalarial currently available through the CDC, appears to be highly effective, better tolerated than quinidine, and not hampered by accessibility issues. If it

were to be FDA approved and commercially available, it would be the preferred agent for the treatment of severe malaria in the United States

KEY WORDS: artesunate, artemisinin, severe malaria

Introduction

Malaria, caused by a protozoan transmitted by *Anopheles* mosquitoes, is endemic in over 100 countries, which are visited by more than 125 million international travelers, 64 million of them from the U.S., each year.[1] Nearly 250 million cases and 1 million deaths are reported annually around the world.[2] In the United States, approximately 1,500 cases of malaria are imported each year, of which nearly two-thirds are caused by *Plasmodium falciparum* (85% of cases from Africa).[3] While mortality was low in the 2007 CDC surveillance report, at least 57 people were classified as having severe malaria that year.

A malaria infection is categorized as severe when at least one of the following complications is present: hypotension, hypoglycemia, severe anemia, hyperparasitemia (>5% or 250,000 parasites per microliter of blood), hemoglobinuria, jaundice, acidosis, hyperthermia, neurologic involvement such as a decreased level of consciousness or seizures, acute respiratory distress syndrome, or renal failure. Parasitemia is defined as the percentage of red blood cells that are infected on a standard thin blood smear. A review of malaria among U.S. travelers from 1963 to 2001 found that 185 persons with imported malaria died.[4] Common contributors to death included lack of malaria chemoprophylaxis, delay in seeking care, misdiagnosis, and incorrect antimalarial regimens (i.e., therapy that was inappropriate for the species or region of acquisition). Severe malaria is a medical emergency requiring immediate treatment to prevent death. Uncomplicated malaria includes those who are symptomatic, but do not have severe disease or evidence of vital organ system dysfunction. The goal of the treatment of uncomplicated malaria is to eradicate the infection whereas the goal of the treatment of severe malaria is to first prevent death.

In the United States, intravenous (IV) quinidine gluconate (a diastereomer of quinine) is the only Food and Drug Administration (FDA)-approved, commercially available medicine for the treatment of severe malaria. However, it is in short supply nationally and its use is associated with cardiotoxicity and other adverse reactions such as cinchonism (i.e. tinnitus, headache, dizziness, diarrhea, and abdominal discomfort), and hypoglycemia. [5, 6,7]

The artemisinin class of antimalarials represents the newest class of medications for the treatment of uncomplicated and severe malaria. However, the only commercially available artemisinin in the United States is oral artemether (in combination with lumefantrine, brand name Coartem®), which was FDA-approved in April 2009 and is indicated for the treatment of uncomplicated *falciparum* malaria. On June 21, 2007, the FDA approved an investigational new drug (IND) protocol using IV artesunate for the treatment of severe malaria in the United States. The drug is made available by the U.S. Centers for Disease Control and Prevention (CDC) and produced by the Walter Reed Army Institute of Research. The World Health Organization (WHO) as well as the United Kingdom and Canada recommend artesunate over quinidine for treatment of severe malaria.[8-10]

Methods for Selection and Assessment of Literature

A search of PubMed (1999 to March 2010) and Medline (1996 to March 2010) was performed using the key words artesunate, artemisinin, malaria, and severe malaria to identify clinical trials and review articles of artesunate in the English language. Focus was placed on postmarketing trials of the safety and efficacy of artesunate compared with other regimens, most notably quinine, for the treatment of severe malaria. The references of the identified articles were reviewed for additional citations. In addition, the CDC's website (http://www.cdc.gov) was

searched for information on the use of artesunate in the United States and to obtain its IND protocol.

Chemistry and Pharmacology

More than 1500 years ago in China, extracts of qinghao (sweet wormwood, *Artemisia annua* L.) were discovered to have antipyretic properties; subsequent analysis found that a component of this extract, qinghaosu, had antimalarial activity. Qinghaosu, better known today as artemisinin, is the basis for the newest class of antimalarial medications. Artemisinin is a sesquiterpene lactone with an internal peroxide bridge (Figure 1).[11] One potential mechanism of action of artemisinins involves that endoperoxide bridge. It has been postulated that when artemisinins react with Fe^{2+} in the body, the peroxide bridge is cleaved producing oxygen-centered free radicals that are subsequently converted to carbon-centered free radicals, which may have direct antiparasitic activity.[11,12] Evidence also suggests anti-parasitic activity may be due to the inhibition of sarcoplasmic endoplasmic reticulum calcium ATPase (SERCA) of *P. falciparum.*[13]

Derivatives of artemisinin—including arteether, artelinate, artemether, artesunate (artesunic acid), and dihydroartemisinin—differ from the parent artemisinin by substituted groups at position 10 (Figure 1).[11] A unique feature of this class of drugs is the ability to kill all erythrocytic stages of the malaria parasite, including gametocytes involved in the transmission of malaria from person to person.[5] In addition, artemisinins inhibit parasite metabolism faster than other antimalarials and enhance spleen clearance of infected erythrocytes through reduced cytoadherence.[11]

Pharmacokinetics and Pharmacodynamics of IV Artesunate

Artesunte for intravenous administration is supplied in vials containing 110mg of the medication as a sterile dry-filled powder. It is to be reconstituted with 11ml of a sodium phosphate diluent which yields a net concentration of 10mg/ml. The resultant solution should be gently mixed for five to six minutes and must be administered within one hour. Following reconstitution, it should be pushed intravenously over one to two minutes through a 0.8 micron hydrophilic polyethersulfone filter.[7]

The dosing of IV artesunate has evolved with increased experience with the drug. The previously recommended dose of 1.2 mg/kg/day was empirically derived from the absolute bioavailability of oral artesunate (F=61%). [14-16] Over time, the dose of IV artesunate for the treatment of severe malaria was increased from the previously recommended empiric dose to 2.4 mg/kg to prevent underdosing in critically ill patients with malaria.[15-17] The 2.4 mg/kg per dose is now considered the standard of practice. After three days of therapy with IV artesunate, a majority of patients will have recovered sufficiently to tolerate and be switched to oral medications; however, for those that cannot, IV artesunate can be continued for another four days or the patient may be switched to IV doxycycline or IV clindamycin.[7]

Artesunate is a prodrug and is rapidly hydrolyzed to dihydroartemisinin (DHA), the active constituent and source of the medications antiparasitic activity, directly following administration. DHA is then subsequently metabolized by CYP2B6, CYP2C19, and CYP3A4 enzymes to inactive metabolites.[11,16,18] Furthermore, IV artesunate does not need to be dose adjusted in patients with either renal or hepatic insufficiency.[5] Artemisinins, including artesunate, are considered to be the most important antimalarial agents worldwide because of their potency (can reduce parasitemia by 10,000 fold in each asexual lifecycle), rapid

antiparasitic activity and resolution of symptoms, limited resistance in malaria parasites, and good tolerability.[5,8,11] However, their use as monotherapy is limited by extremely short half-lives of approximately 45 minutes.[11] Short courses of monotherapy result in unacceptably high rates of recrudescence and raise concerns for drug resistance. Thus, intravenous artesunate, as approved for use in the United States, should be used sequentially with a second oral medication such as atovaquone-proguanil, doxycycline, clindamycin, or mefloquine after three days of use. Oral medications should be initiated on the last day of artesunate therapy, at least four hours after the last infusion.[7]

In one pharmacokinetic study, Newton et al. found that after administration of 2.4 mg/kg of IV artesunate to 11 adult patients with severe malaria, the median plasma concentration at time zero was 338 (range 124 to 2557) nmol/L, the median half-life of artesunate was 13.2 (range 4.8 to 36.6) minutes, and the median time to undetectable drug was 30 (range 15 to 120) minutes.[16] In this same study, the median C_{max} of DHA was 6292 (range 146 to 1646) ng/mL, which was reached within 15 minutes by all patients, and the median half-life of DHA was 20.4 (range 8.4 to 52.2) minutes. Median DHA clearance was 5.6 (range 2.9 to 16.6) L/kg/hr. One patient with severe malaria died in this study with only median values for all pharmacokinetic parameters.[16]

Clinical Studies and Guidelines

Clinical studies have evaluated the safety and efficacy of artesunate in comparison to quinine in patients with severe malaria. Results from selected trials are summarized below as well as in Table 1.[19-23] A brief summary of the WHO malaria treatment guidelines as they pertain to artesunate are also included.

Newton et al. compared the safety and efficacy of IV quinine to IV artesunate in a randomized, open-labeled study involving 113 persons ≥ 15 years of age in Western Thailand with slide confirmed *P. falciparum* parasitemia of > 0.1% and that were determined to have severe malaria.[21] 42% of all patients in this study had a parasitemia level of > 10%. Pregnant women, those with contraindications to study medications, and those who received artesunate, quinine, or mefloquine in the previous 24 hours were excluded from the study. Patients in the artesunate group (n=59) received 2.4 mg/kg on entry, 1.2 mg/kg 12 hours later, and then 1.2 mg/kg/day. Patients in the quinine group (n=54) received 20 mg/kg of medication administered IV over four hours followed by 10mg infused over two hours and given three times daily. There was no mention of specifically when either artesunate or quinine was first initiated (i.e. on hospital admission or on study enrollment) by the investigators. This may have lead to delays in treatment thus impacting overall mortality rates in this study. However, when patients were able to tolerate oral medications, they were switched accordingly to either oral artesunate or oral quinine.

Overall, 17% of the patients died in this study. Death was attributable to pulmonary edema/acute respiratory distress syndrome, cardiorespiratory arrest, hypotension, oliguria, and/or gastrointestinal tract bleeding. Seven patients (12%) in the artesunate group and 12 patients (22%) in the quinine group died, RR=0.53 (0.23-1.26), p=0.22. Median time to death was also shorter in the quinine group (21 hours) than in the artesunate group (48 hours), p=0.02. In addition, the mean time for parasitic clearance in the quinine group (76 hours) was longer than in the artesunate group (62.5 hours), p=0.019. The investigators concluded that artesunate is at least as effective as quinine in the treatment of severe malaria and is likely safer, as fewer patients receiving artesunate developed hypoglycemia compared with those receiving quinine (10.2%

versus 28%, p=0.028). Despite these initial findings, however, larger trials were deemed to be needed to evaluate the benefit of artesunate in reducing mortality.

The South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT; Dondorp, et al) compared IV artesunate to IV quinine in a randomized, open-labeled, multicentered trial among 1,461 patients in Bangladesh, India, Indonesia, and Myanmar (Burma) in perhaps the largest and most definitive trial to date.[23] Patients were enrolled if they were older than two years of age, had a positive blood antigen test for *Plasmodium falciparum* histadine rich protein 2 (HRP2), and had a diagnosis of severe *P. falciparum* malaria by the attending physician. Individuals were excluded if they had received a full treatment with quinine or an artemisinin derivative for more than 24 hours before admission or had a known allergy to a study medication. Patients randomized to the artesunate group (n=730) received 2.4 mg/kg on admission and then again at 12 and 24 hours followed by daily administration of IV artesunate until oral therapy could be tolerated. Those receiving quinine (n=731) received 20 mg/kg infused over 4 hours followed by 10 mg/kg infused over 2 to 8 hours 3 times daily until oral therapy could be started. The study's primary endpoint was mortality from severe malaria.

Overall, 19% of the patients in this trial died; mortality was significantly lower in the artesunate group (15%) than in the quinine group (22%), OR=0.60 (0.45 to 0.79), p=0.0002. Reduction in mortality occurred primarily after the first 24 to 48 hours after treatment began which indicates that prompt treatment of severe malaria is vitally important. There was a statistically significant reduction in mortality associated with artesunate in adults (16% versus 24%, P < 0.0005) but not in children (5% versus 11%, P=0.15). The small number of children enrolled (n=202) may have contributed to this study's inability to detect a statistically significant

difference; however, this does not rule out a potentially clinically significant effect of artesunate when used in children.

Patients with parasitemia > 10% on admission (defined as hyperparasitemia by the study investigators) had a greater reduction in mortality with artesunate as compared to non-hyperparasitemic patients, OR=0.34 (0.17 to 0.69), p=0.001. The calculated number needed to treat (NNT) to save one life with artesunate ranged from 11.1 to 20.2. Among surviving patients, the incidence of hypoglycemia was greater in the quinine group (3%) than in the artesunate group (<1%), p=0.009. Based on these results, the investigators suggest that artesunate should be the drug of choice to treat severe malaria in adults. A statistically significant effect was not observed in children and therefore the same conclusion could not be reached as in adults; however, the drug did show benefit in this population.

In a 2007 Cochrane review, Jones et al. conducted a systematic literature review to evaluate the use of artesunate versus quinine for the treatment of severe malaria.[24] Six randomized controlled trials were identified (Anh 1989, Hien 1992, Anh 1995, Phuong 1997, Newton 2003, and Dondorp 2005) for a total enrollment of 1,938 individuals (1,664 adults and 274 children) with severe malaria as determined by study investigators. Phuong, et al. were the only investigators to enroll only children; they randomized treatment to either artemisinin suppositories, IM artesunate, or IV quinine.[22] All six studies were conducted in Asia (Bangladesh, Myanmar, India, Indonesia, Thailand, and Vietnam); the primary outcome measure was mortality from severe malaria. From their review of these trials, the authors concluded that artesunate was superior to quinine in reducing death from severe malaria (RR 0.62, 0.51-0.75). Furthermore, the authors stated that artesunate should be the drug of choice for the treatment of

severe malaria in adults; however, the same conclusion could not be reached for children as a significant benefit with artesunate treatment could not be found similar to the SEAQUMAT trial.

According to the 2005 WHO malaria treatment guidelines, IV artesunate is the drug of choice for the treatment of severe malaria in adults. However, there is insufficient data to recommend the use of artesunate over other agents for the treatment of severe malaria in children.[8] This recommendation is based largely on the results of SEAQUAMAT which showed a statistically significant treatment benefit with artesunate in adults but not in children.[23]

Adverse Reactions

Artemisinin derivatives, including artesunate, have been used to treat cases of malaria worldwide with few reported severe adverse reactions. Compared with quinine and quinidine, they are considered less toxic and have fewer side effects.[7,25,26] While formal human toxicity data are limited, evidence and surveillance data suggest that this medication class is safe to use in adults and children.[7] Furthermore, reports of severe allergic reactions are rare, although a small number of patients (approximate risk of 1 in 3,000 patients) have had a urticarial rash with additional symptoms such as hypotension, pruritis, edema, dyspnea.[21,27] Common adverse reactions to IV artesunate include dizziness, nausea, vomiting, anorexia, diarrhea, transient reticulocytopenia, and a bitter or metallic taste during infusion; however, discerning between adverse effects and symptoms from severe malaria may be difficult.[7,21,25,28] At doses of 6mg/kg, elevations in ALT and BUN have been observed and at doses of 15mg/kg, bradycardia may occur.[7]

Precautions and Contraindications

Intravenous artesunate is considered to be widely tolerated by almost all patients at recommended dosages.[7] Concerns have been raised however regarding its potential to interfere

with normal cardiac conduction since high intramuscular doses of other artemisinin derivates (e.g. artemether and artemotil) have caused QT prolongation in animal models which raise the concern of a class effect.

To evaluate the effect intravenous artesunate may have on cardiac conduction, Maude et al. studied the electrocardiograms (EKGs) of patients ≥ 16 years old with severe malaria on admission that were given intravenous artesunate and then again after the last dose of artesunate. Patients were initially given IV artesunate at 2.4 mg/kg, followed by 2.4 mg/kg at 12 and 24 hours and then every 24 hours thereafter. EKG's were recorded at time 0 (prior to artesunate therapy) and then at 10, 30, 60, 120, and 240 minutes following administration of artesunate. Blood pressure, heart rate, and temperature were also measured at these time points. The primary outcome in this study was a change in QTc before and after artesunate with a significant change in QTc being defined as > 500ms in an individual patient or a mean increase of > 25% in all patients. No significant change in the mean QTc was observed nor did any patient have an increase in QTc of > 25% above baseline. The investigators therefore concluded that intravenous artesunate does not have a consistent cardiovascular or electrocardiographic effect when administered.[29]

Artemisinin-induced neurotoxicity in humans has also been a concern because this side effect has been observed in animal models when either very high doses (range 25 to 250 mg/kg/day) or when the lipophilic artemisinins (e.g, artemether and arteether) have been administered. Such neurotoxic effects in laboratory animals may include auditory dysfunction, ataxia, hypersalivation, as well as deleterious effects on the brainstem.[7,25] It is important to note that these or other CNS related side effects have not been directly associated with any artemisinin, including artesunate, in humans at currently recommended doses. In addition, severe

malaria itself can cause deficits in neurological functioning; therefore, differentiating between symptoms of severe malaria and adverse drug reactions from treatment may be difficult. The only known contraindication to artesunate is a known allergic or anaphylaxic reaction to the medication.[7] While there is little known about drug-drug interactions with IV artesunate, its short half-life of less than two hours suggests this is not a significant concern.

Special Populations – Pediatrics

Children, particularly those residing in areas of high malaria transmission (e.g. Africa), are at risk for developing severe malaria due to their limited immunity from previous exposures. Despite positive findings from SEAQUAMAT in the adult population, the efficacy of artesunate for the treatment of severe malaria in the pediatric population remains to be clearly established. In SEAQUAMAT, 202 children (age < 15 years) were enrolled. While fewer died in the artesunate group than in the quinine group (5 vs. 11% respectively), the results were not statistically significant. Therefore, the authors could not conclude that artesunate was superior to quinine; however, the medication did appear to be effective in the pediatric population for the treatment of severe malaria as mortality was less in the artesunate group. It is important to note that the presentation of malaria may also differ in children than in adults and childhood mortality from malaria tends to occur within the first 24 hours after treatment initiation giving antimalarials less time to work.[23] Large-scale studies, similar to SEAQUAMAT, are therefore needed to evaluate the use and efficacy of IV artesunate in the pediatric population. One such study, AQUAMAT (an open labeled randomized comparison of injectable artesunate and quinine in children with severe falciparum malaria in Africa), is currently underway. Artesunate is available to children in the U.S. under IND protocol despite the lack of statistical evidence demonstrating superiority over quinine.

Special Populations – Pregnancy

In pregnant animals given IV artesunate, fetal resorption and abortion, cardiac malformations, and skeletal defects have been observed. There is a thus theoretical risk of artesunate causing teratogenicity in humans because of the medication's ability to cross the placenta. However, in trials conducted in Thailand, the Gambia, and Sudan that primarily involved women in their second or third trimester of pregnancy (n=2045) who were given either artesunate alone or in combination with other antimalarials found that birth weight, duration of gestation, placenta weight, and congenital abnormality rates were not statistically different than in the community.[7] While the number of pregnant women treated with artesunate remains relatively low, continuous observations will need to be made to better assess the risk of artesunate teratogenicity.

Currently, the WHO recommends the use of artesunate over quinine in pregnancy in the second and third trimesters due to higher rates of mortality versus non-pregnant adults in addition to the risk for fetal mortality and premature birth.[8] Hypoglycemia is also a common complication during these stages of pregnancy and quinine use may further cause hypoglycemia to occur. In the first trimester, the severity of hypoglycemia is not as great and the risks of using artemisinin derivatives appear to be greater; therefore, the risk of using artesunate during the first trimester of pregnancy should be weighed against the potential for complications from severe malaria. During the first trimester, the WHO advocates the use of either artesunate or quinine.[8]

Therapeutic Issues and Controversies

Access to IV Artesunate in the United States

While IV artesunate itself is not currently approved by the FDA, it is available in the United States through the CDC under IND protocol #76,725 in collaboration with the Walter

Reed Army Institute of Research. Under this IND, IV artesunate is available only for the treatment of patients with severe malaria (see table 2 for eligibility criteria).[7]

Artesunate is available from the CDC (see www.cdc.gov/malaria for details). Depending on the time of day and distance to the treatment facility, artesunate is sent by the fastest method available including ground courier or commercial flight. Once received, artesunate should be administered as soon as possible. If during therapy a serious adverse drug reaction is experienced, it must be reported to the CDC within 24 hours by telephone and a Serious Adverse Event Report Form must also be submitted to the CDC within 10 days.[7] Currently, approximately 70 patients have been successfully treated with IV artesunate in the United States since August 2007 (CDC unpublished data).

Resistance to Artesunate

The use of IV artesunate as monotherapy for severe malaria is limited as discussed previously in the pharmacokinetics and pharmacodynamics section. While resistance to artesunate and to other artemisinin derivates appears to be minimal at present, two recent reports of P. *falciparum* resistance in Western Cambodia raise concern that resistance to this important class of medication may occur in the future.[30,31]

Counterfeit Medications

Although any type of medicine may be counterfeited, artesunate has been disproportionately targeted internationally due to the relatively higher retail price and high demand. [32,33] A counterfeit medicine is one that is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients, or with fake packaging. [34,35] Counterfeit artesunate, predominantly in Southeast

Asia, has been directly implicated in numerous deaths. [33,36] Travelers to developing countries should be discouraged from acquiring artesunate while overseas due to the high risk of receiving a counterfeit medicine. If medicines to treat malaria will likely be needed, it is preferable to fill a prescription for a reliable supply at a pharmacy in the industrialized country prior to traveling.

Dosage and Administration

Per its IND protocol, artesunate for the treatment of severe malaria should be administered intravenously at a dose of 2.4 mg/kg initially and then repeated at 12, 24, and 48 hours later for a total of four doses.[7] It is worth noting that this dosing regimen is the same as that used in SEAQUAMAT.[23] After three days of therapy, the patient should be switched to an oral antimalarial agent to ensure a curative treatment.

Summary

For years, IV quinidine has been the sole drug in the United States for the treatment of severe malaria. However, its limited availability and the need for continuous cardiac monitoring underscore the need for additional options. The artemisinin class of medications is available worldwide, has been effective for the treatment of severe malaria, yet is not routinely available in the United States. Intravenously administered arartesunate is therefore necessary to provide another treatment option for severe malaria in light of the limitations with the use of quinidine. Since artesuante is distributed only by the CDC, an FDA-approved, commercially available formulation with widespread availability would be a welcome addition to the U.S. antimalarial formulary.

Table 1: Selected Comparative Treatment Studies

Trial (Year) and Reference	Participants	Interventions	Outcomes measured	Key results for IV artesunate
Hien (1992)[19]	Severe malaria (n=79)	Artesunate 60mg IV at 0, 4, 24, and 48 hrs (n=31) Artemisinin suppositories 600mg initially and at 4 hrs, then 400mg at 24, 32, 48, and 56 hrs (n=18) Quinine 500mg IV over 4 hrs then 500mg IV Q8H until able to swallow then 500mg PO Q8H until day 14 (n=30)	• Fever clearance time • Parasite clearance time of 50% • Mortality	• Fever clearance time faster than quinine (39 vs. 78 hrs) • Faster parasite clearance than quinine (5.4 vs. 16.6 hrs) • 16.5% mortality vs. 26.7% for quinine
Phuong (1997)[22]	Age < 15 years old with severe malaria (n=109)	Artemisinin suppositories 40mg/kg initially then 20mg/kg at 4, 24, 48, and 72 hrs. (n=37) Artesunate 3mg/kg IM at	• Mortality • Number that survived with neurological sequelae • Fever clearance	• 11% mortality vs. 14% for quinine • Fever clearance time similar for artesunate and quinine (84% and

Trial (Year) and Reference	Participants	Interventions	Outcomes measured	Key results for IV artesunate
		0 then 2mg/kg IM at 12, 24, 48, and 72 hrs (n=37) Quinine 20mg/kg IV at 0 then 10mg/kg IV Q8H up to day 7 (n=35)	time • Resolution of coma • Parasite clearance time of 50% • Hypoglycemia	81%) • Parasite clearance time of 5.7 hrs for artesunate vs. 13.2 for quinine • 16% hypoglycemia vs 26% for quinine
Newton (2003)[21]	Age > 15 years old with severe malaria (n=113)	Artesunate 2.4mg/kg IV at 0 then 1.2mg/kg at 12 and at every 24 hrs until able to swallow then 12mg/kg PO Q24H over 7 days (n=59) Quinine 20mg/kg over 4 hrs followed by 10mg over 2 hrs infused three times daily until able to swallow (n=54)	• Fever clearance time • Parasite clearance time of 50% • Time to regain full conscious • Death • Hypoglycemia • Adverse effects	• Mean parasitic clearance time of 62.5 hrs for artesunate and 76 hrs for quinine • 10.2 % hypoglycemia in artesunate group vs. 28% in the quinine group • Reduced mortality in artesunate

Trial (Year) and Reference	Participants	Interventions	Outcomes measured	Key results for IV artesunate
				group vs quinine group(12% vs 22%)
Mohanty (2004)[20]	Pediatric cases with severe malaria (n=80)	Artesunate 2.4mg/kg IV at 0 then 1.2mg/kg at 6 hrs; then every 24 hrs for 5 days (n=40) Quinine 20mg/kg IV at 0, then 10mg/kg IV Q8H until able to swallow then 10mg/kg PO Q8H until day 7 (n=40)	• Fever clearance time • Parasite clearance time of 50% • Time to regain full consciousness • Death	• Time to regain full consciousness was 50 hrs in artesunate group vs 70 hrs for quinine • Fever clearance time of 43.5 hrs for artesunate and 62 hrs for qunine • Parasitic clearance time of 42 hrs for artesunate and 52 hrs for qunine • 12.5% mortality in artesunate group, 20% mortality in

Trial (Year) and Reference	Participants	Interventions	Outcomes measured	Key results for IV artesunate
				quinine group
Dondorp (SEAQUAMAT) (2005)[23]	Individuals > 2 years old with severe malaria (n=1461)	Artesunate 2.4mg/kg IV at 0, 12, and 24 hrs then 2.4mg/kg IV Q24H until able to swallow then 2mg/kg PO until day 7 (n=730) Quinine 20mg/kg infused over 4 hours followed by 10mg/kg over 2 to 8 hours three times daily (n=731)	• In hospital death • Death within 48 hrs • Death after 48 hrs • Neurological sequelae • Time to discharge • Hypoglycemia	• In hospital death 15% in artesunate group, 22% in quinine group • Death after 48 hrs was 6% in the artesunate group and 12% for the quinine group

Table 2: Qualifications to receive intravenous artesunate per investigational new drug protocol[a, b]

Category	Eligibility Criteria
Clinical and Laboratory	• Diagnosis of *P. falciparum* or other *Plasmodium* species by microscopy • Strong clinical suspicion of severe malaria without a timely and reliable microscopic diagnosis
Parenteral Therapy Required	• Inability to take oral medications • High density parasitemia of > 5% • Severe malaria

IV Artesunate Preferred	• IV artesunate more readily available than IV quinidine
	• Quinidine failure documented as parasitemia of > 10% of baseline at 48 hours after initiation
	• Quinidine intolerance defined as
	  o QRS widening by ≥ 50%
	  o QT interval > 0.6 seconds
	  o QTc interval prolonged by >25% of baseline
	  o Persistent hypotension despite IV fluids
	  o Development of quinidine ADR
	• Contraindication to quinidine defined as
	  o Allergy to quinidine or cinchona alkaloids
	  o Thrombocytopenic purpura with previous therapy
	  o AV junctional or idioventricular pacemaker (with

Category	Eligibility Criteria
	no atrial activity) o AV block o Left bundle branch block or other intraventricular conduction defects o Digitalis toxicity o Myasthenia gravis

Adapted from reference 7

a. Patients must meet at least one eligibility criteria from each category to qualify for IV artesunate therapy

b. To obtain IV artesunate, the treating physician must first call the CDC Malaria Hotline at 770-488-7788 (open from 9:00am to 5:00pm eastern time) to determine patient eligibility. After hours, clinicians may call 770-488-7100 and request to speak with a CDC Malaria Branch clinician.

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