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SAFETY AND EFFICACY OF ARTEMISININ AND ITS DERIVATIVES IN THE TREATMENT OF SEVERE *P. FALCIPARUM* MALARIA INFECTION: A REVIEW

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SUMMARY

Malaria is a protozoal disease caused by the protozoa plasmodium. *P.falciparum* and *P. vivax* cause the significant majority of malaria infections. *P. falciparum*, which causes most of the severe cases and deaths, is generally found in tropical regions, such as sub-Saharan Africa and Southeast Asia, as well as in the Western Pacific and in countries sharing the Amazon rainforest. In 2000, malaria caused 350 to 500 million clinical episodes annually and resulted in over one million deaths, most of which affect children under 5 years old in sub-Saharan Africa. Severe malaria is most commonly caused by infection with *Plasmodium falciparum*, although *P. vivax* and *P. knowlesi* can also cause severe disease. The risk is increased if treatment of an uncomplicated attack of malaria caused by these parasites is delayed. Severe malaria is a medical emergency and may rapidly progress to death without prompt and appropriate treatment. Malaria infections may cause vital organ dysfunction and death. Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction. Nearly all deaths from severe malaria result from infections with P. falciparum. The mortality of untreated severe malaria (particularly cerebral malaria) is thought to approach 100%. With prompt, effective antimalarial treatment and supportive care the mortality falls to 15–20% overall. Until recently, the standard treatment of severe malaria was intravenous quinine. Frequent adverse effects, however, and reports of limited clinical efficacy in some *falciparum* malaraia–endemic areas preclude its usefulness. Currently different studies have recognized the effectiveness of artemisinin and its derivatives for treatment of severe malaria and recommended them as 1st line options for the treatment of the

disease. Based on these recommendations and the findings of different studies this review also concludes artemisinins specially IV artesunate is more safe and efficacious for treatment of severe *p. falciparum* malaria both in adults and children and recommends the ministry of health and regional health offices to facilitate availability and utilization of these drugs for the disease.

KEY WORDS: Artemisinin; Plasmodium falciparum; malaria infection; artesunate; and Plasmodium.

INTRODUCTION

Malaria is a protozoal disease caused by the protozoa plasmodium. Five species of the genus *Plasmodium* cause nearly all malarial infections in humans. These are *P. falciparum, P. vivax, P. ovale, P. malariae,* and in Southeast Asia the monkey malaria parasite *P. knowlesi*. Almost all deaths are caused by falciparum malaria. Human infection begins when a female anopheline mosquito inoculates plasmodial *sporozoites* from its salivary gland during a blood meal (Breman, 2012).

P. falciparum and *P. vivax* cause the significant majority of malaria infections. *P. falciparum,* which causes most of the severe cases and deaths, is generally found in tropical regions, such as Sub-Saharan Africa and Southeast Asia, as well as in the Western Pacific and in countries sharing the Amazon rainforest. *P. vivax* generally is common in most of Asia (especially Southeast Asia) and the Eastern Mediterranean, and in most endemic countries of the Americas. *P. malariae* and *P. ovale* contribute to only a small number of malaria infections. *P. ovale* is found in Africa and sporadically in Southeast Asia and the Western Pacifi. *P. malariae* has a similar geographical distribution to *P. falciparum* but its incidence is patchy and is probably underestimated (RollBackMalariaPartnership, 2014).

In 2000, malaria caused 350 to 500 million clinical episodes annually and resulted in over one million deaths, most of which affect children under 5 years old in sub-Saharan Africa. Malaria is the fifth cause of death from infectious diseases worldwide (after respiratory infections, Human Immunodeficiency Virus/Acquired Immune Deficiency syndrome (HIV/AIDs), diarrheal diseases, and tuberculosis) and the second in Africa, after HIV/AIDS. Recent estimates show that as many as 3.3 billion people live in areas at risk of malaria in 109 countries or territories. In addition to its health toll, malaria puts a heavy economic burden on endemic countries and contributes to the cycle of poverty people face in many

countries. For example, it is estimated to have in Africa alone contemporaneous costs of at least US$12 billion per year in direct losses (e.g. illness, treatment, premature death), but many times more than that in lost economic growth (RollBackMalariaPartnership, 2014).

Falciparum malaria remains a major cause of morbidity and mortality worldwide. The annual clinical caseload may well be over 500 million, leading to between 1 and 3 million deaths, mainly among young children(Snow RW, 2005). About 90% of all malaria deaths in the world today occur in Africa south of the Sahara. This is because the majority of infections in Africa are caused by *P. falciparum*, the most dangerous of the four human malaria parasites. It is also because the most effective malaria vector – the mosquito *Anopheles gambiae* – is the most widespread in Africa and the most difficult to control. An estimated one million people in Africa die from malaria each year and most of these are children under 5 years old(WHO, 2002). In all malaria-endemic countries in Africa, 25–40% of all outpatient clinic visits are for malaria (with most diagnosis made clinically). In these same countries, between 20% and 50% of all hospital admissions are a consequence of malaria. With high case-fatality rates due to late presentation, inadequate management, and unavailability or stock-outs of effective drugs, malaria is also a major contributor to deaths among hospital inpatients(organization, 2004).

It is estimated that three-fourths of the land of Ethiopia below 2000 meters is malarious with two-thirds of the country's population at risk. This makes malaria the number one health problem in Ethiopia with an average of 5 million cases a year and 9.5 million cases per year between 2001 and 2005. The disease causes 70,000 deaths each year and accountant for 17% of outpatient visits to health institutions. It also accounts for 15% of hospital admissions and 29% of inpatient deaths - a figure considered to be too low given that more than a third of the country's population does not have access to health services (AynalemAdugna).

The burden of malaria has been increasing in Ethiopia due to a combination of large population movements, increasing large scale epidemics, mixed infections of *P. vivax* and *P. falciparum*, increasing parasite resistance to malaria drugs, vector resistance to insecticides, low coverage of malaria prevention services, and general poverty. Outpatient consultations, inpatient admissions and all in-patient deaths have risen by 21-23% over the last five years. Ethiopian adults, unlike their counterparts in more endemic areas, have relatively little protective immunity and are also vulnerable to malaria. Epidemics, which traditionally occur every five to eight years, are a hallmark of malaria in Ethiopia. The epidemic of 1950 is

estimated to have caused 3 million cases and resulted in 150,000 deaths. Unstable and largely unpredictable malaria epidemiology makes surveillance, information management and logistics for vector control and pharmaceuticals of paramount importance. *P.vivax* and *p. falciparum* comprise 40% and 60% of malaria infections respectively (President'sMalariaInitiative, 2008).

Severe and complicated P. falciparum malaria

Clinical features

Severe malaria is most commonly caused by infection with *Plasmodium falciparum*, although *P. vivax* and *P. knowlesi* can also cause severe disease. The risk is increased if treatment of an uncomplicated attack of malaria caused by these parasites is delayed. Recognizing and promptly treating uncomplicated malaria is therefore of vital importance. Sometimes, however, especially in children, severe *P. falciparum* malaria may develop so rapidly that early treatment of uncomplicated malaria is not feasible (WHO, 2012).

Whilst the majority of cases of malaria worldwide are mild and can be treated with oral drugs, a minority, mainly because of delays in diagnosis or treatment, may develop complicated, life threatening disease requiring parenteral therapy(Pasvol, 2005). Of all cases of falciparum malaria, around 10% can be classified as severe, among which the mortality is 10% (i.e. 1% of all cases) but may rise to as high as 50%. Any form of complicated or severe malaria must therefore be regarded as a life-threatening medical emergency (Pasvol, 2005)
Severe malaria is a medical emergency and may rapidly progress to death without prompt and appropriate treatment. The main objective of the treatment of severe malaria is to prevent the patient from dying; prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities are secondary objectives (malariasite, 2014).

The presentation of uncomplicated *P. falciparum* malaria is highly variable and mimics that of many other diseases. Although fever is common, it is often intermittent and may even be absent in some cases. The fever is typically irregular initially and commonly associated with chills. True rigors are unusual in acute falciparum malaria. The patient commonly complains of fever, headache, aches and pains elsewhere in the body and occasionally abdominal pain and diarrhea. In a young child, there may be irritability, refusal to eat and vomiting. On physical examination, fever may be the only sign. In some patients, the liver and spleen are palpable. This clinical presentation is usually indistinguishable clinically from those of

influenza and a variety of other common causes of fever. Unless the condition is diagnosed and treated promptly, a patient with falciparum malaria may deteriorate rapidly.(WHO, 2012) Malaria infections may cause vital organ dysfunction and death. Severe malaria is defined by clinical or laboratory evidence of vital organ dysfunction. Nearly all deaths from severe malaria result from infections with *P. falciparum*. Strict definitions of severe malaria have been published for epidemiological and research purposes, but, in practice, there should be a low threshold for starting parenteral treatment in any patient about whom a health care worker is concerned. Even if some of the laboratory measures are not available immediately, this should not delay the start of intensive treatment. A general overview of the features of severe malaria is shown in table below. Note that these manifestations can occur singly or, more commonly, in combination in the same patient.(WHO, 2012).

Table 1: clinical features of severe malaria

✓ Impaired consciousness (including unrousable coma); ✓ Prostration, i.e. generalized weakness so that the patient is unable to sit, stand or walk without assistance; ✓ Multiple convulsions: more than two episodes within 24h; ✓ Deep breathing and respiratory distress (acidotic breathing); ✓ Acute pulmonary oedema and acute respiratory distress syndrome; ✓ Circulatory collapse or shock, systolic blood pressure < 80mm Hg in adults and < 50mm Hg in children; ✓ Acute kidney injury; ✓ Clinical jaundice plus evidence of other vital organ dysfunction; and ✓ Abnormal bleeding.

The following table also indicates signs and symptoms of severe malaria in adults and in children (WHO, 2012).

Table 2: signs and symptoms of severe malaria

Sign or symptom	**Adult**	**Children**
Duration of illness	5–7 days	Shorter (1–2 days)
Respiratory distress/ deep breathing (acidosis)	Common	Common
Convulsions	Common (12%)	Very common (30%)
Posturing(decorticate/decerebrate and opisthotonic rigidity)	Uncommon	Common
Prostration/obtundation	Common	Common
Resolution of coma	2–4 days	Faster (1–2 days)
Neurological sequelae after cerebral malaria	Uncommon (1%)	Common (5-30%)
Jaundice	Common	Uncommon
Hypoglycaemia	Less common	Common
Metabolic acidosis	Common	Common

Pulmonary oedema	Uncommon	Rare
Renal failure	Common	Rare
CSF opening pressure	Usually normal	Usually raised
Bleeding/clotting disturbances	Up to 10%	Rare
Invasive bacterial infection (co infection)	Uncommon (<5%)	Common (10%)

Treatment of Severe and complicated *P. falciparum* malaria

The mortality of untreated severe malaria (particularly cerebral malaria) is thought to approach 100%. With prompt, effective antimalarial treatment and supportive care the mortality falls to 15–20% overall. Therefore, the main objective is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescence (WHO, 2010, Malariasite, 2014).

Any patient with complicated or severe falciparum malaria must be considered as a medical emergency and managed at the highest possible level of clinical care appropriate to the clinical setting, often an intensive therapy unit (Planche T, 2005).

Treatment of severe malaria includes administration of parentral antimalarials and other supportive measures for the complications of severe malaria like cerebral malaria, convulsion, respiratory distress, acidosis, hypoglycemia, acute lung injury and others (Pasvol, 2005).

Two classes of drugs are currently available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, arthemether, artemotil). Although there are few areas where chloroquine is still effective, parenteral chloroquine is no longer recommended for the treatment of severe malaria because of widespread resistance (Malariasite, 2014).

Parenteral antimalarial treatment should be started as soon as possible. Artesunate, given by either IV or IM injection, is the agent of choice; it is simple to administer, safe, and rapidly effective. If artesunate is unavailable and artemether, quinine, or quinidine is used, an initial loading dose must be given so that therapeutic concentrations are reached as soon as possible. Both quinine and quinidine will cause dangerous hypotension if injected rapidly; when given IV, they must be administered carefully by rate-controlled infusion only. If this approach is not possible, quinine may be given by deep IM injections into the anterior thigh. The optimal therapeutic range for quinine and quinidine in severe malaria is not known with certainty, but total plasma concentrations of 8–15 mg/L for quinine and 3.5–8.0 mg/L for quinidine are

effective and do not cause serious toxicity. The systemic clearance and apparent volume of distribution of these alkaloids are markedly reduced and plasma protein binding is increased in severe malaria, so that the blood concentrations attained with a given dose are higher. If the patient remains seriously ill or in acute renal failure for >2 days, maintenance doses of quinine or quinidine should be reduced by 30–50% to prevent toxic accumulation of the drug. The initial doses should never be reduced. If one of the artemisinin derivatives is given, dose reductions are unnecessary, even in renal failure. Exchange transfusion may be considered for severely ill patients, although the precise indications for this procedure have not been agreed upon. It has been recommended that—if safe and feasible—exchange should be considered for patients with severe malaria, but there is no clear evidence that this measure is beneficial, particularly if artesunate is used. The role of prophylactic anticonvulsants in children is also uncertain. If respiratory support is not available, then a full loading dose of phenobarbital (20 mg/kg) to prevent convulsions should not be given as it may cause respiratory arrest (Breman, 2012, Pasvol, 2005, WHO, 2012).

Table 3: Antimalarial treatment regimens in severe malaria(Pasvol, 2005)

Drug	Dose	Comments
Quinine dihydrochloride	10 mg (salt) kg^{-1} by infusion over 4 h in 500 mls 5% dextrose, every 8h until parasites less than 1% and the patient can take by mouth, then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days	Can induce hypoglycaemia and cardiac arrhythmias. A loading dose 20 mg over 4h in 500 mls 5% dextrose should be given to young otherwise healthy patients and where hyperparasitaemia cannot be treated by exchange transfusion. Special caution should be taken when used in the elderly and those with underlying cardiovascular disease. The loading dose should not be given to patients who have received quinine,quinidine or mefloquine in the previous 24 h
Quinine dihydrochloride (rapid loading dose)	7mg (salt) per kg by infusion pump over 30 min followed immediately by 10 mg kg−1 over 4h in 5% dextrose every 8h until the parasitaemia is less than 1% and the patient can take by mouth- then quinine sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days	As above
Quinidine gluconate	24mg quinidine salt per kg (equivalent to 15mg kg−1 base) infused over 4 h followed by 12mg kg−1 salt(7.5 mg base) over 4 h every 8-hourly until parasites less than 1% and the patient can take by mouth. Then quinine	In an emergency and in the USA where quinine may not always be available. The same precautions as outlined above with quinine apply.

	sulphate 600 mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days	
Quinidine gluconate (continuous infusion)	10mg kg^{-1} salt (equivalent to 6.25mg base per kg) infused over 2h followed by a continuous infusion of 0.02 mg kg−1/min^{-1} salt (0.0125 mg base kg^{-1} min^{-1} quinidine) until parasites less than 1% and the patient can take by mouth. Then quinine sulphate 600mg three times a day orally until parasites have cleared, then doxycycline 200 mg daily orally for 7 days	In an emergency and in the USA where quinine may not always be available. The same precautions as outlined above with quinine apply
Artesunate	2.4mg kg^{-1} IV followed at the same dose at 12 and 24 h; then once daily (usual adult dose 120 mg daily for 6 days) until patient able to take artesunate (2 mg kg^{-1} per day by mouth) to complete 7 days. Then doxycycline 200mg or clindamycin daily by mouth for 7 days	Can be given IV as it is water soluble. Also requires doxycycline as recrudescences are common
Artemether (artemisinin) derivative]	3.2mg kg^{-1} IM on the first day, followed by 1.6mg kg −1 daily (usual adult dose 160mg followed by 80mg daily for 6 days) until parasites cleared and the patient can take by mouth. Then doxycycline 200 mg or clindamycin daily orally for 7 days	Alternative to quinine. Usually IM. Requires doxycycline as recrudescences are common
Doxycycline	200 mg daily orally for 7 days (Adult)	To be used in conjunction with quinine /quinidine after parasite clearance and the patient can take by mouth
Clindamycin	450 mg three times a day orally for 7 days (Adult)	To be used in conjunction with quinine/quinidine after parasite clearance and the patient can take by mouth

Pharmacology of artemisinin and its derivatives

History

Artemisinin is a sesquiterpene lactone endoperoxide derived from the weed *qing hao* (*Artemisia annua*), also called *sweet wormwood* or *annual wormwood.* The Chinese have ascribed medicinal value to this plant for more than 2000 years (Goldberg, 2011).

The antimalarial properties of the traditional Chinese medicine qinghaosu (artemisinin) were discovered by Chinese scientists in 1971 who performed low temperature ethyl ether extractions of *Artemesia annua*. In a research effort, apparently prompted by the requests of Ho Chi Minh to Zhou En Lai for antimalarial drugs to protect his Vietnamese troops, the

scientists identified the active antimalarial principle, characterized its physicochemical properties, conducted in vitro, animal, and human studies, and synthesized derivatives of the more potent dihydroartemisinin (DHA). Artemisinin was first announced to the rest of the world in 1979. At first, biological chemists were puzzled by the apparent stability of the hitherto unknown 15-carbon (sesquiterpene) peroxide structure. A full chemical synthesis was reported 4 years later and the compound remains too expensive for commercialization (N.J.White, 2008).

In 1985, the Journal of Traditional Chinese Medicine described the satisfactory efficacy of *qinghaosu* suppositories in 100 patients with *P. falciparum* malaria, 4 of whom had cerebral malaria. *Qinghaosu* (artemisinin) derivatives were soon recognised as having powerful antimalarial activity and a variety of formulations have since been developed (Melba Gomes, 2008).

Trials reporting efficacy in both uncomplicated and severe malaria soon followed, but progress thereafter was slow. Instead of accepting the compounds the Chinese had developed, the World Health Organization Special Program for Research and Training in Tropical Diseases (TDR), the pharmaceutical industry, and the U.S. Army elected to develop their own compounds. Time and money was wasted developing artemotil (arteether), the ethyl ether of dihydroartemisinin(DHA), an oil-based formulation for IM injection, which the Chinese scientists had discarded earlier in favor of the almost identical artemether (the methyl ether of DHA)(N.J.White, 2008).

Chemistry and Pharmacokinetics

The chemical structure of artemisinin is quite different from all previously known antimalarials. Their structure contains a sesquiterpene lactone with a peroxy linkage, which is a novel type different from all other antimalarial drugs currently available(Chen, 2014, Rosenthal, 2012). The presence of the peroxide bridge is essential for artemisinins antimalarial activity as a reduced form of the compound, deoxyartemisinin, lacks the antimalarial activity(Klayman, 1985, Woerdenbag, 1994).

Artemisinin has a poor bioavailability limiting its effectiveness and it is insoluble and can only be used orally. Analogs have been synthesized to increase solubility and improve antimalarial efficacy. The most important of these analogs are artesunate (water-soluble; useful for oral, IV, IM, and rectal administration), artemether (lipid-soluble; useful for oral,

IM, and rectal administration), and DHA (water-soluble; useful for oral administration).(Rosenthal, 2012, Sangkuhl).

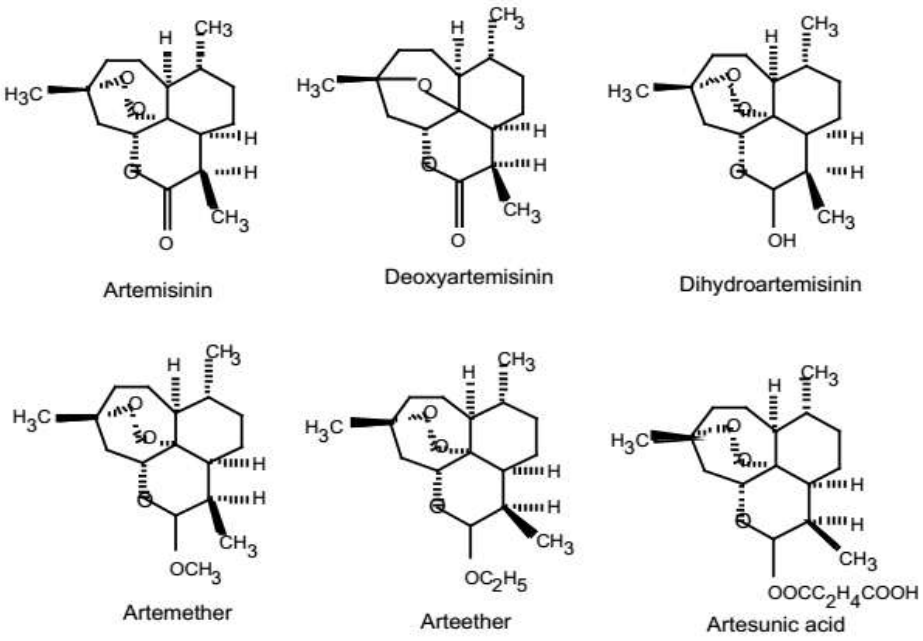

Figure 1: Molecular structures of artemisinin and its related compounds

In general, disposition of the artemisinins is incompletely understood. Absorption after oral dosing typically is 30% or less. Peak plasma levels occur within minutes of artesunate administration and at 2 to 6 hours after artemether administration. These drugs are not highly bound to plasma proteins, although the linkage may be covalent. Both artesunate and arthemether are converted extensively to DHA, which provides much of their antimalarial activity and has a plasma half-life of just 1 to 2 hours; its major urinary metabolite is a glucuronide (Goldberg, 2011).

Artemisinin is eliminated by metabolic biotransformation, predominantly by CYP 2B6, to inactive metabolites. The artemisinins specially artemisinin and artesunate are weak inducers of some important drug-metabolizing enzymes and on repeated dosing they augment their own clearance enhancing the clearance by up to five fold. After oral or parenteral administration, artemether, artemotil, and artesunate are all converted back rapidly to DHA in vivo, which is then eliminated by glucuronidation with an elimination half-life of ~1 hour, both in healthy volunteers and in patients with malaria(Goldberg, 2011, N.J.White, 2008).

A study conducted to evaluate Pharmacokinetic of IV artesunate in adults concluded IV artesunate can provide much higher peak concentrations of the drug when compared to

concentrations achieved with oral therapy; this may be crucial for the rapid elimination of parasites in patients with severe malaria (Qigui Li, 2014).

Pharmacodynamics

Mechanism of action

The mechanism of action of artemisinin and its derivatives are not completely defined. The model of artemisinin action involves two steps. First, heme iron within the parasite catalyzes cleavage of the endoperoxide bridge. This is followed by rearrangement to produce a carbon-centered radical that alkylates and damages macromolecules in the parasite, likely including the ortholog of sarco/endoplasmic reticulum Ca^{2+}-ATPase(Goldberg, 2011). Alkylation of important macromolecules like heme and specific proteins, including transporters, iron-sulfur proteins and the translationally controlled tumor protein (TCTP) homolog was seen on different in vitro and in vivo studies. (Ingrid B Müller, 2010).

Antiprotozoal spectrum and resistance

The artemisinin derivatives possess several important pharmacological characteristics, including rapid onset of action, short half-life, activity against the broadest range of stages in the life cycle of the malaria parasite, and an excellent safety profile(Tanabe, 2012).

Artemisinin and its analogs are very rapidly acting blood schizonticides against all human malaria parasites but they have no effect on hepatic stages (Goldberg, 2011, Rosenthal, 2012).

Artemisinins have broad stage specificity of antimalarial action which has two therapeutic consequences; Killing young circulating ring stage parasites in P. falciparum infections results in a more rapid reduction in parasitaemia compared with other antimalarials and reduces considerably the number of parasites that mature to sequester in and block capillaries and venules. This explains the rapidity of clinical responses and the life-saving benefit in severe malaria compared with quinine (which does not stop sequestration because it kills parasites only after they have matured and adhered to vascular endothelium). Reducing gametocyte carriage by artemisininns diminishes the transmission potential of the treated infection (N.J.White, 2008).

Artemisinin and its derivatives exhibit antiparasitic activity *in vitro* against other protozoa, including *Leishmania major* and *Toxoplasma gondii*, and have been used alone or in combination in patients with schistosomiasis (Utzinger, 2003).

It is interesting to note that over the centuries there has been no documented artemisinin resistance in the treatment of malaria. Recently, however, reduced parasite susceptibility in artesunate and dihydroartemisinin treated patients was observed on the Thai–Cambodian border(Ingrid B Müller, 2010, Rick M. Fairhurst, 2012).The proportion of patients in Pailin, Cambodia, who were still parasitemic after 3 days of dihydroartemisinin–piperaquine treatment increased from 26% in 2008 to 45% in 2010. In another study, over 40% of patients in Pailin and Tasanh, Cambodia, were parasitemic after 3 days of artesunate monotherapy. Recent studies from the Thai-Myanmar border show a significant slowing of parasite clearance rates. A small proportion of the parasite population there has a similar phenotype and degree of heritability of the slow clearance phenotype as that in Western Cambodia. It is unclear at present whether this represents spread of artemisinin-resistant parasites from the original focus to the Thai-Myanmar border or the emergence of a new focus (Rick M. Fairhurst, 2012).

The proportion of patients showing a very slow rate of parasite clearance is also rapidly increased from 0.6% in 2001 to 20% in 2010 on the northwestern border of Thailand (Tanabe, 2012).

The Greater Mekong subregion is the most threatening focus of malaria in terms of antimalarial drug-based control. This area comprises six countries: Cambodia, Thailand, China's Yunnan province, Lao Peoples Democratic Republic, Myanmar, and Vietnam. *P. falciparum* isolates resistant to the conventional antimalarial drugs chloroquine, pyrimethamine, and sulfadoxine initially emerged from the Greater Mekong subregion before subsequently migrating to the African continent(Dondorp, 2009) (refe 96 of Japan Tanabe). The Thailand-Cambodia border in particular has been regarded as the most important focal point for the emergence of drug-resistant parasites. In this region, population movements were frequent and extensive due to abundant mining of precious stones/gems. These mobile populations could carry artemisinin resistant parasites to other countries where artemisinin resistance may be introduced and spread (Tanabe, 2012).

Artemisinin combination therapy

One of the major drawbacks in monotherapy with artemisinin or its derivatives is the high rate of recrudescent infections observed in several clinical studies. It has been suggested that the short half-life of artemisinin family of antimalarials and the parasite life-cycle, including generation of artemisinin insensitive stages, are among the major reasons for the inefficiency

of these drugs in clearing the parasites totally(Tanabe, 2012, Gordi, 2001). Nowadays, the general recommendation in treatment of falciparum malaria with artemisinin or one of its derivatives is a combination with another antimalarial with relatively long half-life (WHO, 2002, N.J.White, 2008, Rick M. Fairhurst, 2012, Tanabe, 2012).

Adverse drug reactions

Artemisinins are generally well tolerated at the doses used to treat malaria. (Taylor WR, 2004). No serious adverse event or severe significant toxicity was reported from the use of artemisinins according to different studies.(Mahesh N. Belhekar, 2012 , Taylor WR, 2004). The side effects from the artemisinin class of medications are similar to the symptoms of malaria: nausea, vomiting, anorexia, and dizziness. Mild blood abnormalities have also been noted. A rare but serious adverse effect is allergic reaction(Leonardi E, 2001).

Rare serious toxicities include neutropenia, anemia, hemolysis, elevated liver enzymes, and allergic reactions. Irreversible neurotoxicity has been seen in animals, but only after doses much higher than those used to treat malaria. Artemisinins have been embryotoxic in animal studies, but rates of congenital abnormalities, stillbirths, and abortions were not elevated, compared with those of controls, in women who received artemisinins during pregnancy (Rosenthal, 2012).

Artemisinin and its derivatives for treatment of severe and complicated *p. falciparum* malaria infection

WHO recommends the use of artemisinin-based combination therapies (ACTs) in order to ensure high cure rates of *P.falciparum* malaria and to reduce the spread of drug resistance. The majority of falciparum endemic countries have adopted ACT as first-line treatment and deployment of ACT in the public sector has increased exponentially(WHO, 2006). Artemisinin combination drugs recommended by WHO for treatment of uncomplicated *p.falciparum* malaria include artemether plus lumefantrine (AL), artesunate plus amodiaquine (AS+AQ), artesunate plus mefloquine (AS+MQ), artesunate plus sulfadoxine-pyrimethamine (AS+SP) and dihydroartemsinin plus piperaquine (DHA+PPQ)(organization, 2004, WHO, 2002). Based on the recommendation ACT is the main stay of therapy for treatment of uncomplicated *p. falciparum* malaria in many countries.

Two classes of medicines are available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate,

arthemether, artemotil). Parenteral chloroquine is no longer recommended for the treatment of severe malaria, because of widespread resistance(WHO, 2010). The choice of drug depends according to availability and licensing (Pasvol, 2005).

Until recently, the standard treatment of severe malaria was IV quinine. Frequent adverse effects, however, and reports of limited clinical efficacy in some falciparum malaraia–endemic areas preclude its usefulness (Kristine Mørch, 2008).

Currently different studies have recognized the effectiveness of artemisinin and its derivatives for treatment of severe malaria and recommended them as 1st line options for the treatment of the disease. Some of them are compiled as follows.

A case report entitled artesunate for the treatment of severe falciparum malaria raised a case of 35 year old American born old man presented with severe malaria and recommended IV artesunate for treatment because it has been shown to have superior efficacy and is likely to have fewer side effects and a better safety profile than IV quinidine. According to this case report IV artesunate is appropriate therapy as long as it can be acquired promptly (Rosenthal, 2008).

Another case report from Hawai‘I reported a case of a 49-year-old man presented to Tripler Army Medical Center, in February 2009 with a one-month history of fever, chills, and weight loss. The patient was travelled to multiple malaria endemic areas. The patient met criteria for severe malaria and immediately treated with IV artesunate. The patient manifested a quick and durable response to therapy. Through this report, the authors have demonstrated that IV artesunate is an efficacious and well-tolerated treatment for severe cases of *P. falciparum* malaria in Hawai‘i.(David M. Callender, 2011).

A retrospective evaluation of IV artesunate versus IV quinine in the treatment of severe falciparum malaria at center in the United Kingdom identified adults admitted to the Infectious Diseases Unit with severe falciparum malaria and treated with IV quinine (1991–2009) or IV artesunate (2009–2011). The study included out comes like adverse events, mortality, length of stay, admission to intensive care and, where data were available, parasite/fever clearance time and hypoglycaemic events. According to this study out of 167 patients, 24 received IV artesunate and 143 IV quinine. There was one potential artesunate-associated adverse event, a case of late onset haemolysis. Median length of stay (LOS) was

significantly shorter for AS (3.5 versus 5 days, P=0.017). In the artesunate group, there were no fatalities (versus five in quinine group) and fewer intensive care unit (ICU) admissions. Median parasite clearance was significantly faster in artesunate (65 versus 85 hours in quinine, P=0.0045) with no hypoglycaemic episodes (versus five in quinine). Over all the researchers found IV artesunate to be safe and effective, with shorter LOS, faster parasite and fever clearance, no fatalities or hypoglycaemic events, and fewer ICU admissions versus IV quinine and concluded IV artesunate should be first-line for treating severe *p.falciparum* in the UK(Marcus Eder, 2012).

Another case series reported the case of 9 patients who were treated with IV artesunate for treatment of severe falciparum malaria from February 2006 to May 2008 at 3 centers in Norway. Clinical and laboratory features were retrospectively obtained from the medical records. With the exception of 1 patient who had become infected while in Myanmar, all patients acquired falciparum malaria in West Africa and one of the patients was pregnant. The initial treatment consisted of IV artesunate plus doxycycline (n = 7), IV artesunate monotherapy (n = 1), or IV artesunate plus clindamycin (n = 1). The dosing of artesunate was 2.4 mg/kg at 0 h, 12 h, and 24 h and then daily thereafter. Patient 6 received a 1,200-mg loading dose of quinine before transfer to one of the study hospital. None of the patients needed exchange transfusions. No adverse effects were attributed to artesunate, and the pregnant patient delivered a healthy child at term. The parasitemia level fell below 1% in all patients within 1–2 days. Treatment was changed to oral antimalarial drugs (artemether–lumefantrine, mefloquine, proguanil–atovaquone, or quinine) within 2.1 days (mean); all patients recovered uneventfully and were discharged from the hospital within 4.2 days (mean). No episodes of recrudescence were documented posttreatment at 4 weeks follow-up; 7 patients had a negative malaria slide and 2 patients were not examined for parasites but had no clinical recrudescense at follow-up. Finally the researchers agreed that their finding supports those of several randomized controlled trials performed in Asia and indicated therapy with IV artesunate is safe, induces rapid parasite clearing, and usually results in swift clinical cure. In conclusion, the case series suggested IV artesunate as an efficacious and safe treatment option in travelers returning from West Africa with severe falciparum malaria.(Kristine Mørch, 2008).

Another study has done a retrospective analysis of 25 patients from 7 treatment centers in Europe who were admitted to a hospital for *P. falciparum* malaria, which was classified as

severe according to WHO criteria, and who received IV artesunate as the main antiparasitic therapy. Patients treated at 7 centers; 4 in Germany, and 1 each in Denmark, Sweden, and Norway, participated in the study. The researchers concluded treatment with IV artesunate in these patients was effective and induced rapid parasite clearance. According to this study patients from Europe may benefit more from treatment with artesunate than with quinine(Thomas Zoller, 2011).

A Case Report on Artesunate for Severe Acute Plasmodium falciparum Infection in a Patient with Myasthenia Gravis reported a case of severe malaria in a patient with underlying myasthenia gravis who was successfully treated with artesunate. The outcome was favorable. According to this report artesunate seems to be a good option for patients with underlying myasthenia gravis disease because they benefit from a better toxicity profile than quinine (Nathalie Dournon, 2012).

A randomized prospective study conducted in Pakistan with a view to compare efficacy regarding fever clearance, parasitaemia clearance and coma resolution between Quinine (10 milligrams per kilogram perdose diluted in 100 ml of 10 % dextrose solution for seven days) and Artemether (3.2 milligrams per kilogram per day IM on the first day and 1.6 milligrams per kilogram per day from second to fifth day of treatment) among 138 children with severe malaria indicated parasitaemia clearance was better with Artemether than Quinine. Parasitaemia clearance was 68 (98.55%) and 69 (100%) on third and fifth day respectively in Artemether group while Quinine group had 64 (92.75%) and 67 (97.1%) on third and fifth day. Between 24-72 hours the coma recovery rate for Quinine and Artemether were 49 (98%) and 41 (85.41%) respectively but after 72 hours of treatment the coma recovery remained 49 (98%) for quinine while it was 42 (87.5%) for arthemether. The rapid resolution of coma with Quinine within 24 to 72 hours and after 72 hours were statistically significant than Artemether. In conclusion the researchers said in severe paediatric malaria IV Quinine or IM Artemether therapy does not have any statistically significant difference in terms of fever clearance but Quinine has statistically significant shorter duration of coma resolution than with Artemether therapy after 24 hours of treatment(Rehman MU, 2013).

A large, randomized comparison of intravenous artesunate and quinine in 1461 patients in Asia showed a significant survival benefit with artesunate. Mortality was 22% with quinine, as compared with 15% with artesunate, a risk reduction of 34.7%. Treatment with artesunate

had a relatively mild side-effect profile; hypoglycemia was significantly more common with the use of quinine (Dondorp A, 2005).

A case report entitled Short Report: Successful Oral Therapy for Severe Falciparum Malaria: The World Health Organization Criteria Revisited reported a case of a successful treatment of severe falciparum malaria in a non-immune adult patient with 30% parasitemia treated with the 6-dose oral regimen of artemether plus lumefantrine combination therapy alone. The reporters of this case have also retrospectively searched for similar cases and have found two additional severe malaria cases, resolved uneventfully with oral regimen. Based on this finding the researchers said the 6-dose artemether plus lumefantrine combination oral regimen, which is now easily available and proved to be highly effective, could possibly allow some variations of the historic WHO guidelines, which mandate initial parenteral treatment in all forms of severe malaria for all patients, regardless of the patient's oral tolerance ability. In summary the researchers said this report might implicate the possible therapeutic option of the oral artemether-lumefantrine regimen in some forms of severe malaria despite its explicit contraindication for treating any form of severe malaria at the time of the report (Eran Kopel, 2012).

An open randomized trial conducted at Sudan and entitled Comparison of artesunate and quinine in the treatment of severe *Plasmodium falciparum* malaria assigned patients with severe malaria to either intravenous artesunate at 2.4 mg/kg at 0, 12, and 24 hours, then daily, or intravenous quinine at a 20 mg/kg loading dose, then 10 mg/kg three times a day. Fever and parasite clearance and coma resolution time were compared between the two groups. According to this study the mean of the fever clearance (10.8 *vs*. 14.0 hours, $p = 0.028$) and the parasite clearance time (16.5 *vs*. 21.7 hours, $p = 0.007$) were significantly shorter in the artesunate-treated patients. Regarding adverse drug events ten patients developed tinnitus ($p < 0.001$), and four had hypoglycemia ($p = 0.033$) following quinine infusion which were not detected in the artesunate group. One patient in the artesunate group died. Finally the researchers concluded artesunate is more effective than quinine, in terms of parasite and fever clearance time, in the treatment of *P. falciparum* malaria in eastern Sudan and no difference between artesunate and quinine in coma resolution time (Tajeldin M Abdallah, 2014).

The AQUAMAT trial is a multi-centre study conducted in African children hospitalized with severe malaria. This very large randomized controlled trial, which enrolled 5425 children < 15 years of age across Africa, showed a significant mortality reduction by 22.5% in the

artesunate group when compared to the quinine group. The incidence of convulsions, coma, and hypoglycaemia developing after hospital was also significantly reduced. Importantly there was no significant difference in the incidence of severe neurological sequelae (AQUAMAT, 2010).

A systematic review of evidence conducted to address the question: "In children with severe/complicated malaria (*population*), do Artemisinin derivatives (*intervention*), improve clinical outcome in terms of mortality, clinical recovery, parasite clearance, adverse effects, etc (*outcome*), as compared to standard parenteral quinine therapy (*comparison*)? Included a total of 10 trials. All the ten trials reviewed demonstrated comparable mortality between artemisinin derivatives and quinine irrespective of the type of derivative, route of administration, type of severe malaria (cerebral or otherwise), or methodological quality of trial. Out of the 10 trials only one trial suggested a favourable effect with artemether; the remainder showed no difference between groups. Parasite clearance time was comparable between groups in five trials. Six trials examined neurological sequelae at follow-up, and all showed comparable effect between artemisinin and quinine. Although the review does not demonstrate superior efficacy of artemisinin derivatives, comparable effect across all outcomes suggests that either therapy could be equally efficacious. According to the researcher even though artemisinins have no superior efficacy over quinine, artemisinin could have an edge for treatment of severe malaria in children because of reasons like artemisinins have simpler administration, potentially greater safety (lower risk of quinine adverse events)and quinine administration requires controlled infusion in a hospital setting (L.MATHEW, 2010).

A study conducted to assess efficacy and safety of rectal artemisinins for treatment of malaria pooled individual patient data from 1167 patients in 15 clinical trials of rectal artemisinin derivative therapy (artesunate, artemisinin and artemether) in order to compare the rapidity of clearance of *P.falciparum* parasitemia and the incidence of reported adverse events with each treatment. The study also included data from patients who received comparator treatment (parenteral artemisinin derivative or quinine). Primary endpoints included percentage reductions in parasitaemia at 12 and 24 hours. A parasite reduction of >90% at 24 hours was defined as parasitological success. The finding of this study said artemisinin and artesunate treatment cleared parasites more rapidly than parenteral quinine during the first 24 hours of treatment. A single higher dose of rectal artesunate treatment was five times more likely to

achieve >90% parasite reductions at 24 hours than were multiple lower doses of rectal artesunate, or a single lower dose administration of rectal artemether. With regard to safety of the drugs 2.7% (21/786) of all rectal artemisinin treated patients were thought to have had a potentially drug-related adverse event, 8.8%(69/786) a non-drug related adverse event and an additional 6.4% (54/786) had an adverse event of uncertain causality. By comparison, 27 of 67 (40.3%) reported adverse events occurring in 123 quinine-treated patients were considered drug related meaning that 22.0% (27/123) of quinine-treated patients experienced an adverse event that was considered potentially drug-related. The investigators of this study concluded artemisinin and artesunate suppositories rapidly eliminate parasites and appear to be safe. The more rapid parasite clearance of single high-dose regimens suggests that achieving immediate high drug concentrations may be the optimal strategy (Melba Gomes, 2008).

A review conducted with the objective of assessing the effects of artemisinin drugs for severe and complicated falciparum malaria in adults and children included twenty three trials of which allocation concealment was adequate in nine. Sixteen trials compared artemisinin drugs with quinine in 2653. According to this study artemisinin drugs were associated with better survival (mortality odds ratio 0.61, 95% confidence interval 0.46 to 0.82, random effects model). In trials where concealment of allocation was adequate (2261 patients), this was barely statistically significant (odds ratio 0.72, 95% CI 0.54 to 0.96, random effects model). In 1939 patients with cerebral malaria, mortality was also lower with artemisinin drugs overall (odds ratio 0.63, 95% CI 0.44 to 0.88, random effects model). The difference was not significant however when only trials reporting adequate concealment of allocation were analysed (odds ratio 0.78, 95% CI 0.55 to 1.10, random effects model) based on 1607 patients. No difference in neurological sequelae was shown. Compared with quinine, artemisinin drugs showed faster parasite clearance from the blood and similar adverse effects. Finally in this early period of investigating artemisinins for severe malaria the authors suggested artemisinin drugs are no worse than quinine in preventing death in severe or complicated malaria and said no artemisinin derivative appears to be better than the others (McIntosh H, 2000).

Another systemic review compared artemisinin derivatives versus quinine in treating severe malaria in children. Twelve trials were included (1,524 subjects) in the review. According to the finding of this study there was no difference in mortality between artemisinin derivatives and quinine. The artemisinin derivatives resolved coma faster than quinine, but when trials

with adequate concealment only were considered these differences disappeared. There was no statistically significant difference between the two groups in parasite clearance time, fever clearance time, incidence of neurological sequelae and 28th day cure rate. One trial reported significantly more local reactions at the injection site with intramuscular quinine compared to arthemether. In conclusion the researchers said there was no evidence that treatment of children with severe malaria with parenteral artemisinin derivatives was associated with lower mortality or long-term morbidity compared to parenteral quinine (George PrayGod, 2008).

A systematic review of five randomized trials comparing the efficacy of intravenous quinine with that of artesunate and one additional trial of intramuscular artesunate demonstrated the superiority of artesunate, with significant reductions in the risk of death (relative risk, 0.62), incidence of hypoglycemia, and parasite clearance time, as compared with quinine(Jones KL, 2007).

Despite the presence of different favorable studies on safety and efficacy of artemisinin and its derivatives for treatment of severe plasmodium falciparum malaria very few studies reported occurrence of delayed haemolysis more in artemisinins group than quinine. One among such studies included 16 patients who contributed sufficient data to assess the endpoint delayed haemolysis. Twelve were treated primarily with intravenous quinine – with four patients having received intrarectal artesunate as an adjunct treatment – and five patients were treated primarily with artesunate. Five cases of delayed haemolysis could be detected – two in patients treated with quinine and intrarectal artesunate and three in patients treated with artesunate. No case of delayed haemolysis was detected in patients treated with quinine alone. In conclusion the researchers said their study provided further evidence on delayed haemolysis after artesunate and underlined the importance of a standardized follow-up of patients treated with artesunate for severe malaria (Thierry Rolling, 2013).

Finally depending on findings on safety and efficacy of artemisinins for treatment of severe p.falciparum malaria different authorities have recommended these drugs for the treatment of the disease both in adults and children. Among such recommendations is the recommendation by WHO in 2010 (WHO, 2010). Also, the European surveillance network, TropNetEurope, and the Advisory Committee on Malaria Prevention in UK Travelers advocated artesunate as the first line treatment for severe falciparum malaria in travelers (T., 2005, Lalloo DG, 2007).

Conclusion and Recommendations

Even though parentral quinine was the 1st line treatment for severe malaria until recently, based on different recommendations and the findings of different studies this review concludes artemisinins specially IV artesunate is more safe and efficacious for treatment of severe *p. falciparum* malaria both in adults and children. The review also recommends the ministry of health and regional health offices to facilitate availability and utilization of these drugs for the disease.

Competing Interests

The authors declare that they have no competing interests.

Acronyms and Abbreviations

ACT - Artemisinin combination therapy; DHA- Dihydroartemisinin; HIV/AIDs - Human Immunodeficiency Virus/Acquired Immune Deficiency syndrome; IM-intramuscular; IV-intravenous; *P. falciparum -Plasmodium falciparum; P. Malariae -Plasmodium Malariae; P. Ovale-Plasmodium Ovale; P.vivax-Plasmodium vivax;* WHO-world health organization.

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