B – ARTESUNATE FOR THE TREATMENT OF SEVERE MALARIA

1. Summary statement of the proposed changes

Severe malaria is a medical emergency that requires prompt diagnosis and treatment. The mortality of untreated severe malaria is thought to be 100%. The worsening problems of drug resistance, and the limited number of drugs available mean that only the parenteral formulations of quinine and the artemisinin derivatives meet the requirements of rapid action and high efficacy required for the treatment of severe malaria.

As a consequence to this situation, WHO recommendations for the treatment of severe malaria have been recently reviewed and revised based on formal systematic reviews, comparative clinical trials, observational studies and expert opinion. (WHO (2006) Guidelines for the treatment of malaria. pp251. WHO/HTM/MAL/2006.1108).

Based on current evidence, intravenous artesunate is the recommended first choice for the treatment of severe malaria in areas of low to moderate malaria transmission, as it has been shown to be superior to quinine in that setup. However in areas of high transmission, quinine still remains an option, as there is insufficient evidence to recommend any of these antimalarials over another in severe malaria.

The risk of death for severe malaria is greatest in the first 24 h, yet in most malaria endemic countries, the transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment. During this time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended parenteral treatments before referral (unless the referral time is very short). This could be intramuscular artemether, artesunate or quinine, or a rectal formulation of artemisinin or artesunate.

In light of these recommendations, it is proposed that two formulations of artesunate are now included in the WHO Model List of Essential Medicines. Intravenous quinine and intramuscular artemether are currently included in the 14th Edition of the WHO Model list of Essential Drugs (revised March 2005).

2. WHO Focal Point for this application.

Dr P. Olumese
Global Malaria Programme

3. Organization supporting the application

Global Malaria Programme
World Health Organization
Geneva
Switzerland
4. International Nonproprietary Names (INNs) of medicines included in application.

Artesunate

5. Formulations proposed for inclusion

5.1. Injectable Artesunate

Currently available as ampoules containing 60mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution.

5.2. Artesunate Suppositoires

Currently available as rectal capsules containing 100mg or 400mg sodium artesunate

6. Whether application is requested for an individual medicine or therapeutic group.

Two formulations of the same medicine, that would be deployed in different situations

7. Public Health Relevance

7.1. Malaria as a disease burden

Malaria is an important cause of death and illness in children and adults living in tropical countries. It is estimated that 300-500 million people suffer from malaria related illness and over one million people die as a result of malaria disease. Malaria mortality has risen in recent years, probably due to increasing resistance to antimalarial drugs. If ineffective drugs are given or treatment delayed in falciparum malaria, the parasite burden increases and severe malaria ensues. A patient may progress from having minor symptoms to having severe disease within a few hours.

In areas of high and stable transmission, such as in most of Africa south of the Sahara and Oceania, young children and pregnant women are at greatest risk. In contrast, in areas of unstable malaria with low or moderate transmission such as Asia and Latin America, people of all ages are at risk.

Malaria in humans is caused by four species of Plasmodium, P.falciparum, P. vivax, P.ovale and P.malariae. P.falciparum is responsible for the majority of deaths and illness. P. vivax accounts globally for around 40% of malaria cases and is the dominant species outside tropical Africa. In most areas where P. vivax is prevalent, transmission rates are low and consequently people of all ages are at risk. P.ovale and P.malariae are less prevalent but are distributed worldwide
7.2. Definition of severe malaria

Severe malaria is a medical emergency that is not easily distinguished from other severe diseases such as severe pneumonia, meningitis and bacteraemia which require different therapies. It is defined in a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of their symptoms. The presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria:

- **Clinical manifestations:** prostration, impaired consciousness, respiratory distress (acidotic breathing), Multiple convulsions, circulatory collapse, pulmonary oedema (radiological), abnormal bleeding, jaundice, or haemoglobinuria.
- **Laboratory Tests:** severe anaemia, hypoglycaemia, acidosis, renal impairment, hyperlactataemia or hyperparasitaemia.

At the periphery, the priority requirement is the rapid recognition of the signs and symptoms of severe malaria that should lead to emergency care or referral to a higher level of care. These are a history of fever plus at least one of the following: prostration, altered consciousness, lethargy or coma; respiratory distress; severe anaemia; convulsions; inability to swallow; persistent vomiting, dark or limited urine (adults only).

7.3. Objectives of treating severe malaria

The main objective is to prevent the patient from dying, secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities.

The mortality of untreated severe malaria is thought to approach 100%. With antimalarial treatment the mortality falls to 15–20% overall, although within the broad definition are syndromes associated with mortality rates that are lower (e.g. severe anaemia) and higher (metabolic acidosis). Death from severe malaria often occurs within hours of admission to hospital or clinic, and so it is essential that therapeutic concentrations of antimalarial are achieved as soon as possible.

Management of severe malaria comprises four main areas: clinical assessment of the patient, specific antimalarial treatment, adjunctive therapy, and supportive care.

Optimal care for severe malaria, therefore, requires well developed diagnostic facilities and intensive care.

7.4. Specific antimalarial treatment

It is essential that antimalarial treatment in full doses is given as soon as possible in severe malaria. Two classes of drugs are currently available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine) and the artemisinin derivatives (artesunate, artemether and artemotil).
Intravenous quinine and intramuscular artemether are currently included in the 14th Edition of the WHO Model list of Essential Drugs (revised March 2005).

8. Deployment and Treatment Details

8.1. Deployment

8.1.1. Pre-referral Treatment at the periphery- Emergency treatment

The risk of death for severe malaria is greatest in the first 24 h, yet in most malaria endemic countries, the transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment. During this time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended parenteral treatments before referral (unless the referral time is very short). This could be intramuscular artemether, artesunate or quinine, or a rectal formulation of artemisinin or artesunate.

The administration of artemisinins by the rectal route as pre-referral treatment is feasible even at the community level.

There is insufficient evidence to show whether rectal artesunate is as good as intravenous or intramuscular options in the complete management of severe malaria. Pending research from current trials, the recommendation is to use artesunate or artemisinin suppositories as pre-referral treatment and to refer the patient to a facility where complete parenteral treatment with either artesunate, quinine or artemether can be instituted. If referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication, at which point a full course of the recommended ACT for uncomplicated malaria in the locality can be administered.

8.2. Recommended Treatment Schedules

8.2.1 Parenteral Artesunate

Artesunate is dispensed as a powder of artesunic acid. This is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 ml of 5% dextrose and given by intravenous injection or by intramuscular injection to the anterior thigh. The solution should be prepared freshly for each administration and should not be stored. The dosage of artesunate is as below:

Artesunate 2.4mg/kg bw i.v or i.m. given on admission (time =0), then at 12hr and 24hr, then once a day until patient is able to tolerate medication when an ACT is given.

8.2.2 Rectal Artesunate
This is indicated only as an Initial (pre-referral) treatment of severe malaria.

The appropriate single dose of artesunate given by suppository should be administered rectally as soon as the presumptive diagnosis of severe malaria is made. In the event that an artesunate suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and, especially in young children, the buttocks should be held together, for 10 min to ensure retention of the rectal dose of artesunate.

For adults: One or more artesunate suppositories inserted in the rectum, dose as indicated below. The dose should be given once and followed as soon as possible by definitive therapy for malaria.

Dosage for initial (pre-referral) treatment in adult patients

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Artesunate dose</th>
<th>Regimen (single dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>10 mg/kg body weight</td>
<td>Use appropriate no. of 100-mg rectal suppositories (see below children)</td>
</tr>
<tr>
<td>40–59</td>
<td>400 mg</td>
<td>One 400-mg suppository</td>
</tr>
<tr>
<td>60–80</td>
<td>800 mg</td>
<td>Two 400-mg suppositories</td>
</tr>
<tr>
<td>&gt;80</td>
<td>1200 mg</td>
<td>Three 400-mg suppositories</td>
</tr>
</tbody>
</table>

For children: One or more artesunate suppositories inserted in the rectum as indicated below. The dose should be given once and followed as soon as possible by definitive therapy for malaria.

Dosage for initial (pre-referral) treatment in children

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Age</th>
<th>Artesunate dose (mg)</th>
<th>Regimen (single dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–8.9</td>
<td>0–12 months</td>
<td>50</td>
<td>One 50-mg suppository</td>
</tr>
<tr>
<td>9–19</td>
<td>13–42 months</td>
<td>100</td>
<td>One 100-mg suppository</td>
</tr>
<tr>
<td>20–29</td>
<td>43–60 months</td>
<td>200</td>
<td>Two 100-mg suppositories</td>
</tr>
<tr>
<td>30–39</td>
<td>6–13 years</td>
<td>300</td>
<td>Three 100-mg suppositories</td>
</tr>
</tbody>
</table>
9. Comparative effectiveness

9.1. Comparison of intravenous artesunate with intravenous quinine

*Summary of randomized clinical trials*

No systematic reviews and only 2 randomized clinical trials have been carried out. The first trial (113 adults with severe malaria, Thailand) compared i.v. artesunate (2.4 mg/kg initially, 1.2 mg/kg 12 h later, then 1.2 mg/kg daily) with i.v. quinine (20 mg/kg initially, then 10 mg/kg every 8 h) (Newton et al., 2003). There was no significant difference between the treatments in mortality after 300 h (7/59 (12%) artesunate, 12/54 (22%) quinine, RR 0.53, 95% CI 0.23–1.26). It found that artesunate significantly improved parasite clearance time, but that there was no significant difference in fever clearance time or coma recovery time (parasite clearance time 63 h with artesunate, 76 h with quinine, P = 0.019; fever clearance time 41 h compared with 65 h, P = 0.2; coma recovery time 17 h compared with 18 h, P = 0.6).

The second randomized clinical trial (SEAQUAMAT study group, 2005) was a large multi-centre trial in Bangladesh, India, Indonesia and Burma with 1461 patients enrolled. It demonstrated that the mortality of 15% (107/730 in the artesunate group was significantly lower than the 22% (164/731) in the quinine group. An absolute reduction of 34.7% (95CI 18.5-47.6%; p=0.0002) in the artesunate group. There are however, still insufficient data for children, particularly from high transmission settings. Quinine was associated with hypoglycaemia (RR 3.2, p=0.009).

9.2. Comparison of rectal artesunate with intravenous quinine as pre-referral treatment of severe malaria.

*Summary of Randomized clinical trials*

The objective of the trials that have been conducted was to establish the safety and efficacy of rectal artesunate as pre-referral treatment where there is no access to parenteral treatment.

Comparisons between rectal artesunate and intravenous artesunate or intravenous and intramuscular quinine have been carried out to assess response in the 12 or 24 hours immediately after treatment (Krishna et al., 2001; Barnes et al., 2004). These studies included two randomized, open-label Phase II and three randomised open label Phase III trials conducted in people with moderately severe malaria, i.e. patients who could not take drugs by mouth but did not have features of severe malaria and its complications. Patients in the artesunate group in the Phase III studies were rescued if their parasitaemia did not decline to below 60% of baseline parasitaemia or if they deteriorated clinically and developed features of severe malaria, convulsions or coma within 24 hours of treatment.
Artemisinate had a superior effect on all efficacy criteria measured immediately after treatment. In children treated with artesunate, 80/87 (92%) had a parasite density lower than 60% of baseline, compared with 3/22 (14%) of those who received quinine (RR 0.09, 95% CI 0.04–0.19, \( P < 0.0001 \)). In adults, parasitaemia at 12 hours was lower than 60% of baseline in 26/27 (96%) in the artesunate group, compared with 3/8 (38%) in the quinine group. (RR 0.06, 95% CI 0.01–0.44, \( P < 0.001 \)). The differences were more significant at 24 h. Artemisinate and/or dihydroartemisinin were detected in plasma within 12 h in all adults and in 84/87 of the children.

10.1. Adverse reactions to artemisinin derivatives

Artemisinin derivatives

Artemether and artesunate are safe and remarkably well-tolerated (Ribeiro and Olliaro, 1998; Price et al., 1999). There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopaenia, elevated liver enzymes values, and ECG abnormalities, including bradycardia and prolongation of QT values. Most of the studies have not found any ECG abnormalities. The only potentially serious adverse effect reported is Type 1 hypersensitivity reactions in approximately 1 in 3000 (Leonardi et al., 2001).

The neurotoxicity observed in animals treated with artemisinin derivatives has prompted large prospective assessments in humans but no evidence of neurotoxicity has been found (Kissingier et al., 2000; van Vugt et al., 2000; Hien et al., 2003).

Evidence of deaths of embryo and morphological abnormalities in early pregnancy has been demonstrated also in animals but not in humans treated during the second and third trimesters. Artemisinin derivatives have not been evaluated in the first trimester of pregnancy in humans and therefore their use in patients with uncomplicated malaria during this period should be avoided until more information is available (WHO, 2006).

10.2.1. Comparison of intravenous artesunate with intravenous quinine.

A randomized clinical trial in Thailand found that artesunate significantly reduced hypoglycaemia compared with quinine (6/59 (10%) compared with 15/54 (28%), RR 0.37, 95% CI 0.15–0.88) (Newton et al., 2003). One person treated with artesunate developed an urticarial rash. A similar finding was obtained in the second RCT where treatment with artesunate was well tolerated, whereas quinine was associated with hypoglycaemia (relative risk 3.2, 1.3-7.8; \( p=0.009 \)) (SEQUAMAT Group, 2005).

10.2.2 Comparison of rectal artemisinin formulations with intravenous quinine.

A single administration of artesunate suppositories at a dose of 10 mg/kg was well tolerated in both children and adults. There was no significant difference in frequency of adverse events (defined as any new symptom, worsening of any existing symptom, sign or abnormal laboratory value) between treatment groups. Other than local reactions at the site of
the intramuscular quinine injection in three adult patients, the few adverse events that occurred could have been attributable to falciparum malaria or to pre-existing disease.

One randomized clinical trial in children found that artemisinin significantly reduced the risk of hypoglycaemia compared with quinine (3/30 (10%) with artemisinin, 19/30 (63%) with quinine, RR 0.16, 95% CI 0.05–0.48) (Birku et al., 1999).

11. Pharmacopoeial Standards

Standards for artemether and artesunate are included in the 5th Edition of the International Pharmacopoeia.


   See below at the of document
REFERENCES


