Malaria Treatment by Using Artemisinin in Indonesia

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ABSTRACT

Report on resistance of old malarial drug treatment (e.g., chloroquine, sulphadoxine-pyrimethamine, and quinine) in the last decade has become concerned, affecting more than 25% provinces in Indonesia. Such a situation leads to a decision made by the Department of Health through commission meetings of malarial experts or known as komisi ahli malaria (KOMLI) to change the strategy of malaria drug treatment by using ACT (artemisinin combination treatment). As a treatment for any infection, a tendency of using drug combination has a strong role against resistance and preventing resistance to primary drug. Artemisinin is a sesquiterpene lactone of anti-malaria drug which is characterized by its blood schizonticides nature to P. falciparum and P. vivax. It has been developed from an ancient Chinese traditional drug for patient with fever, which is made from an extract of Artemesia annua L (qinghao) and has been used since thousand of years ago and was found by Chinese researchers in 1971. Artemisinin has been used for mild malaria as combination drug (ACT) and for severe malaria by using intra-vena or intra-muscular artesunate, or by using artemether for intra-muscular purpose only. Patients with malaria should have their blood slides to be examined on day 2, 3, and day 7, 14, 21, and 28. Patients who are not hospitalized and could not return on day 2 (48 hours following the initial treatment), may return on day 3. For those who got early or late treatment failure, another treatment should be provided. Treatment failure shall be defined in two criteria which are early and late treatment failure.

The treatment for each patients with severe malaria should be performed as general treatment, symptomatic treatment, administration of anti-malaria drug, and treatment on complication.

Key words: malaria treatment, artemisin, anti-malaria drug.

INTRODUCTION

The development of drug resistance in malaria treatment against conventional drug such as chloroquine has reached beyond tolerance and called for new strategy in malaria treatment. Report on resistance of old malarial drug treatment (e.g. chloroquine, sulphadoxine-pyrimethamine, and quinine) in the last decade has become concerned, affecting more than 25% provinces in Indonesia. Such a situation leads to a decision made by the Department of Health through commission meetings of malarial experts or known as komisi ahli malaria (KOMLI) to change the strategy of malaria drug treatment by using ACT (artemisinin combination treatment). It is consistent with recommendation made by the World Health Organization (WHO) including a global malarial drug treatment change into utilization of ACT. As a treatment for any infection, a tendency of using drug combination has a strong role against resistance and preventing resistance to primary drug. Artemisinin has been used for mild malaria as combination drug (ACT) and for severe malaria by using intra-vena or intra-muscular artesunate, or by using artemether for intra-muscular purpose only.

ARTESININ AS ANTI-MALARIA DRUG

Artemisinin is a sesquiterpene lactone of anti-malaria drug which is characterized by its blood schizonticides nature to P. falciparum and P. vivax. It has been developed from an ancient Chinese traditional drug for patient with fever, which is made from an extract of Artemesia annua L (qinghao) and has been used since thousands of years ago and was found by Chinese researchers in 1971. Artemisinin has potential abilities to:

- Rapidly reducing parasite load in blood
- Rapidly eliminating the symptoms
• Effectively works against multi-drug resistant parasites and all stages of parasites from early to mature stages, which are sequestrized in capillary blood.
• Reducing gametocyte stage, and inhibiting the transmission.
• Until recently, no resistance has been reported
• Have a minimum side effects

Artemisinin derivates for oral use are artemisinin, artesunate, artemether and dihydro-artemisinin. The injection preparations include artemether (im), arteether (im), artesunate (i.v/i.m); in suppository preparations are artemether, artesinin, artesunate, dihydro-artemisinin. No clinical data have been developed for artemisinin use in pregnancy, either for mutagenic or teratogenic events. However, administration of artemisinin is only recommended for the 2nd and 3rd trimester and no recommendation has been made for the 1st trimester. Due to the short half-life of artemisinin (2 hr), then the ideal combination would be artemisinin and other drugs that have long half-life and have not developed any resistance. Such combination of drugs should be packed in a fixed dose combination (FDC). It is recommended to increase drug compliance.

In 2006, WHO has recommended ACT as follows:
• Artesunate + Amodiaquine (Artesediaquine, Arsuamoon)
• Artesunate + Sulphadoxine-pyrimethamine
• Artesunate + Mefloquine
• Artemether - Lumezantrine (Coartem)

In Indonesia, 3 types of ACT recently been used, they are:
• Combination of Dihydroartemisinin – Piperaquine
• Combination of Artemether – Lumezantrine
• Combination of Artesunate + Amodiaquine.

**DRUG TREATMENT FOR MILD MALARIA OR WITHOUT COMPLICATION**

Radical drug treatment for malaria *Falciparum/ Vivax* (diagnosed with microscopy) includes an alternative ACT combination, i.e.:

**First Line Treatment**

The first line drugs are dihydroartemisinin + piperaquine (DHP). The combination is selected to overcome failure of the previous combination such as: artesunate + amodiaquine. The dose coverage is seen on Table 1.

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### Table 1. Dose of DHP treatment in malaria falciparum

<table>
<thead>
<tr>
<th>Day</th>
<th>Type of drug</th>
<th>Amount of tablet for age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Single dose</td>
</tr>
<tr>
<td></td>
<td>DHP</td>
<td>¾</td>
</tr>
<tr>
<td></td>
<td>Falc: H1</td>
<td>Primaquine</td>
</tr>
<tr>
<td></td>
<td>Vivax: H1-14</td>
<td>Primaquine</td>
</tr>
</tbody>
</table>

Dihydroartemisinin : 2-4 mg/kg BW; BW > 60 Kg; BW < 60 Kg
Piperaquine : 16-32 mg/kg BW
Primaquine : 0.75 mg/kg BW

### Table 2. Combination of Quinine + Doxycycline/Tetracycline/ Clindamycin (when the ACT fails)

<table>
<thead>
<tr>
<th>Day</th>
<th>Type of drug</th>
<th>Amount of tablet according to the age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Single dose</td>
</tr>
<tr>
<td>1</td>
<td>Quinine</td>
<td>*)</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Fal : Primaquine</td>
<td>-</td>
</tr>
<tr>
<td>2 - 7</td>
<td>Quinine</td>
<td>*)</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Tetracycline dose</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Clindamycin dose</td>
<td>--</td>
</tr>
<tr>
<td>1-14</td>
<td>Vivax : Primaquine</td>
<td>--</td>
</tr>
</tbody>
</table>
When alternative of ACT fails, WHO has recommended another ACT which has higher efficacy (there are 3 ACT alternatives), or using combination of Quinine + Doxycycline + Primaquine or Quinine + Tetracycline + Primaquine. One tablet of Doxycycline = 100 mg, dose 3-5 mg/kg BW once daily for 7 days, and tetracycline 250 mg or 500 mg, dose 4 mg/kg BW by 4 times a day. For pregnant women and children under 11 years of age, it is prohibited to use doxycycline/tetracycline, and it should be substituted with clindamycin 10 mg/kg BW, twice daily for 7 days. The policy of the Indonesian Department of Health indicates that when the ACT has failed, then the combination of quinine and tetracycline/clindamycin is recommended as described on Table 2.

Primaquine should not be given to babies, pregnant women, and patients with G6PD deficiency. Doses are described based on body weight. A single dose of Primaquine 0.75 mg/kg BW is given for treatment of Plasmodium falciparum. While the dose for treatment of Plasmodium vivax is 0.25 mg/kg BW or 1 x 1 tablet for adults on day 1 to 14. Doxycycline or tetracycline or clindamycin are given on day 1 to 7 depending on drug availability and its indication.

## An Alternative Treatment

As first line or drug for fail treatment, is the combination of Artemether-lumefantrine (Coartem). As a fixed dose combination, it can be used for malaria *falciparum* and *vivax*. A study in Papua demonstrated that there is less response to *P. vivax* compared to other combination. Therefore, it is not recommended as anti-malaria drug for malaria vivax. When it is applied for malaria vivax, the regimen may be combined with doxycycline or tetracycline or clindamycin to increase sensitivity. The dose of coartem is described on Table 3.

## ACT

ACT used as the third alternative is Artesunate + Amodiaquine (1 tablet artesunate 50 mg and 1 tablet amodiaquine 200 mg (~ 153 mg base)). Artesunate dose is 4 mg/kg BW/day for 3 days and amodiaquine dose is 10 mg/kg BW/day for 3 days (Table 4).

Artesiaqune is the first ACT drug implemented by Department of Health in malaria program, particularly in Puskesmas (public health center) and state public hospital; while the drug available in private pharmacy is Arsuaon. Having 2 years of its implementation,
fail treatment of artesunate + amodiaquine was reported quite high, such as in Papua, Lampung, and North Sulawesi or in the areas where the chloroquine failure is quiet high. The area with chloroquine resistance is also predictably resistant to amodiaquine (cross resistancy).

Combination of other ACT which have been investigated are:

- artesunate - pyronaridine
- artesunate - chlorproguanil-dapsone (Lapdap plus®)
- dihydroartemisinin - piperaquine - trimetoprim (Artecom®)
- dihydroartemisinin - piperaquine - trimetoprim - primaquine (CV8)
- dihydroartemysinine + naphthoquine

In the future, the ACT should be developed with pediatric formula, ACT suppositories and ACT fixed dose combination.

FOLLOW – UP OF MALARIA DRUG THERAPY

Patients with malaria should have their blood slides to be examined on day 2, 3, and day 7, 14, 21, and 28. Patients who are not hospitalized and could not return on day 2 (48 hours following the initial treatment), may return on day 3. For those who got early or late treatment failure, another treatment should be provided. Treatment failure shall be defined when there is one of the following criteria (WHO, 2003):11

a. Early treatment failure: is defined as the development of one or more of these conditions in the first 3 days as follows:
   - Parasitemia with severe clinical complication of malaria on day 1, 2, 3
   - Parasitemia on day 2 is greater than day 0
   - Parasitemia in day 3 (>25% from day 0)
   - Parasitemia in day 3 shows positive result and axilla temperature > 37.5°C

b. Late treatment failure: is defined as the development of one or more of the following conditions between day 4 to day 28, and is divided into 2 sub groups:
   - Late clinical and parasitological failure (LCF):
     - Parasitemia (the same species as day 0) with complication of severe malaria after day 3.
     - Axilla temperature ≥ 37.5°C with parasitemia between day 4 to day 28.
   - Late parasitological failure (LPF):
     - Parasitemia is found (the same species with the day 0) on day 7 to day 28 without increased a xilla temperature (<37.5 ° C).

When blood slide is negative and the symptom persist, the symptomatic treatment should be given. It is not considered as a treatment failure.

THE ISSUES OF USING ACT IN INDONESIA

Since the resistance of malaria has been developed globally and nationally, the commission of malaria experts meeting in 2009 has taken new strategy of malaria treatment in Indonesia. The decision was taken on the new drug recommendation for malaria, which is the combination of dihydroartemysinine-piperaquine as the program of the Department of Health. In addition, other combinations have been deployed, including the combination of Artemeter-Lumefantrine for private sector program in the form of FDC (fixed dose combination), which makes drug administration easier and increasing the patients’ compliance. Another combination of the ACT is artesunate + amodiaquine, which is arranged in malaria program by the Department of Health through Puskesmas (public health center) or state public hospital. The most issue is drug availability, i.e. lack of drug supply to be accessed by doctors when they found malaria case, particularly in a big city or other areas where malaria case is not endemic and only as an imported case. Another issue is lack of training on definitive diagnosis of malaria for the laboratory staffs, and lack of training for doctors to manage malaria cases.

Points to be acknowledged for using ACT are:

1. It shall only be given for those who has a positive laboratory result for malaria (at least rapid test positive), and NOT to be administered for clinical treatment of malaria (in absence of laboratory result).
2. It can be used as the first line treatment both malaria falciparum and vivax.
3. Radical treatment against gametocyte stage shall still be provided with single dose of primaquine 45 mg for *P. Falciparum* and 15 mg/day in 14 days for malaria vivax.
4. Monitoring of drug response shall be performed for 28 days, and 42 days if possible.

TREATMENT OF SEVERE MALARIA OR MALARIA WITH COMPLICATION

The treatment of severe malaria generally consists of 3 components, i.e.:12

- Specific treatment with anti-malaria chemotherapy
- Supportive treatment (including general care and symptomatic treatment).
- Treatment on the complication
For each patient with severe malaria, the following treatment should be performed:
1. General treatment
2. Symptomatic treatment
3. Administration of anti-malaria drug
4. Treatment on complication

**General/Supportive Treatment**

a. An intensive care at the ICU or referred hospital which is able to provide care on severe malaria case
b. Keep the patient air way and mouth to prevent asfixia, and supply with oxygen (O2) when required
c. Enforcing a better general condition of the patient (supplying liquid and general care).
d. Monitoring for vital signs such as: consciousness, respiration, blood pressure, temperature, and pulse in every 30 minutes.
e. When the patient had hypotension, lay the patient down in Trendenlenburg position.
f. Provide one early dose of artemeter/artesunate or quinine before referring the patient.

**Symptomatic Treatment**

a. An anti-pyretic is given to prevent hyperthermia: paracetamol 15 mg/kgBW/, provide it in every 4 hours and do warm compress
b. If the patient had convulsion, provide the patient anti-convulsant, *Adults*: diazepam 5-10 mg IV and repeatable in 15 minutes later if the convulsion persists. Do not provide it for more than 100 mg/24 hr.
c. If diazepam is not available, Phenobarbital 100 mg IM/x (for adults) for 2 times a day may be used as an alternative drug.

**Anti-malaria Treatment**

Anti-malaria drug treatment for severe malaria is different from general treatment of malaria because in severe malaria, the drug should have capacity to eliminate parasite rapidly and remains long stay in blood system in order to rapidly reduce parasitemia stage. Therefore, parenteral drugs are preferred (intravenously, per infuse/intra muscularly) which may bring rapid effect and less impact to resistance. Derivate of Artemisinin

Three types of artesiminin are used in parenteral preparation for severe malaria, such artesunate, artemether and arteether. Artesunate is more superior compared with artemether and artemotil. The SEQUAMAT study comparing artesunate with quinine HCl demonstrates that artesunate has decreased mortality rate of 34.7%. Anti-malaria Treatment in parenteral preparation:

- Artesunate injection (1 flacon = 60 mg), Dose iv 2.4 mg/kg BW/ times of administration. An intravenous administration: it is dissolved in the solution of 1 ml 5% bicarbonate and liquidated in 5-10 cc of 5% dextrose which then is injected as intravenous bolus. It is given at 0, 12, 24 hour and continuously in every 24 hour until the patient is conscious. The dose of every single use is 2.4 mg/kg BW. When the patient is conscious, then it shall be substituted with oral artesunate, i.e. tablet of 2 mg/kg BW until the day 7 and after that, it is continued by parenteral use. To prevent recrudescence, it should be combined with doxycycline 2x100 mg/day for 7 days or clindamycin 2 x 10 mg/kg BW for pregnant women/children. Adjusted dose of artesunate is not necessary when the organ failure develops. ACT drugs may be used as a continuation of parenteral drug treatment.

- Artemether i.m (1 ampul 80 mg)
  a. It is administered on the following indications:
  - No intravenous treatment/infusion is allowed
  - No bleeding manifestation (e.g., purpura, etc)
  - For severe malaria at the peripheral hospital/health center (puskesmas)
  b. Dose : Day 1 : 1.6 mg/kg BW every 12 hr, Day-2 – 5 : 1.6 mg/kg BW.

**Figure 1. Administration of artesunate**

Table 5. Anti-malaria drug for severe malaria

<table>
<thead>
<tr>
<th>Artesunate (1flacon = 60 mg artesunic acid), dissolved in 1 ml of 5% sodium bicarbonate(the solvent) to make sodium artesunate solution, then it is dissolved into 5 ml 5% dextrose to be provided by intra-venous/intra-muscular route</th>
<th>Dose 2.4 mg/kg BW is given in every 12 hr on the first day and continued at dose 2.4 mg/kg BW on the day 2 – 7/ 24 hr. No adjusted dose is necessary for patients with renal/liver dysfunction; it does not cause hypoglycemia, arrhythmia/hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether (1 flacon=80 mg)</td>
<td>Dose : 3.2 mg/kgBW i.m as a loading dose divided into 2 dose (in every 12 hr) on the first day, followed by 1.6 mg/kgBW/ 24 hr for 4 days since intramuscular route frequently has uncertain absorption. It does not cause hypoglycemic effect.</td>
</tr>
<tr>
<td>Suppositoria drugs for severe malaria</td>
<td>Artesunate (50mg/100 mg/400 mg) Dose 10 mg/kg BW administered in single dose of 400 mg for adults</td>
</tr>
<tr>
<td>Artesinin</td>
<td>Dose 10-40mg/kgBW administered at 0, 4, 12, 24, 48, and 72 hour.</td>
</tr>
<tr>
<td>Dihydroartemisinin 40 mg, 80 mg</td>
<td>Adult dose is 80 mg and it is continued as 40mg at 24 and 48 hour.</td>
</tr>
</tbody>
</table>
REFERENCES

1. ACCESS: ACT NOW. To get malaria treatment that works in Africa. Medicine Sans Frontieres; 2003.


Table 6. Treatment on complications

<table>
<thead>
<tr>
<th>Manifestations/complications</th>
<th>Early treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma (serebral malaria)</td>
<td>Maintaining oxygenation, put on the certain position, exclude other causes of coma (hypoglycemia, stroke, sepsis, diabetis comia, uremia, electrolyte disturbance), avoid unnecessary drug, perform intubation when necessary.</td>
</tr>
<tr>
<td>Hyperpirexia</td>
<td>Decrease body temperature by compress, fan, air conditioner, and antipyretic</td>
</tr>
<tr>
<td>Convulsion</td>
<td>Maintain oxygenation, provide anticonvulsant by iv/ per rectal diazepam, i.m. paraldehyde</td>
</tr>
<tr>
<td>Hypoglycemia (Gl blood &lt; 40 mg%)</td>
<td>Provide 50 ml of 40% dextrose and provide infusion of 10% dextrose until the blood sugar is stabilized, seek for other cause of hypoglycemia</td>
</tr>
<tr>
<td>Severe anemia (Hb &lt; 5 gr% or PCV &lt; 15%)</td>
<td>Provide fresh blood transfusion, investigate the cause of anemia</td>
</tr>
<tr>
<td>Acute lung edema, difficult breathing, respiration rate&gt;35x</td>
<td>Put on 45° sleeping position, oxygenation, Furosemide 40 mg iv, slow the infuse down, intubation-ventilation PEEP,</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Exclude the pre-renal kidney failure, if there is dehydration make correction; when renal kidney failure occur, give an immediate dialysis</td>
</tr>
<tr>
<td>Spontaneous bleeding/coagulopathy</td>
<td>Support with vitamin K 10 mgs/ day for 3 days; fresh blood transfusion is necessary, make sure that it is not DIC</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>Put aside/corrected for hypoglycemia, hypovolemia, septichaemia. Dialysis when necessary</td>
</tr>
<tr>
<td>Shock</td>
<td>Assure that there is no hypovolemia, find for sepsis sign, give an adequate broad spectrum antibiotics</td>
</tr>
<tr>
<td>Hyperparasitemia</td>
<td>Immediately administer an antimalaria drug (artesunate), provide exchange transfusion</td>
</tr>
</tbody>
</table>