

38 Current Concepts in Management of Falciparum Malaria

Abstract: Artemisinin based Combination Therapy (ACT) is the preferred agent to treat drug resistance uncomplicated Plasmodium Falciparum (PF) Malaria. National Drug Policy on malaria has advocated Artesunate + Sulfadoxine - Pyrimethamine to be used in uncomplicated P.F. cases. For severe Falciparum malaria Artesunate has distinct survival benefit over Quinine and has been advocated to be used as the preferred agent by WHO. The maintenance dose of Artesunate has been increased from 1.2 mg to 2.4 mg/kg body weight. Quinine is the preferred agent during pregnancy. However, WHO has accepted Artesunate as preferred agent during second and third trimester of pregnancy.

Current Concepts in Management of Falciparum Malaria

Malaria is an important cause of illness and death occurring in more than 1 million cases annually in tropical countries including India.^{1,2} There are about 515 million clinical episodes of malaria worldwide, of which 25% occur in South-East Asia.³ Around 2 million laboratory confirmed cases of malaria are reported in India of which 40-50% are Plasmodium falciparum (PF) malaria. The falciparum species is spreading wider due to migration of people and alarming increase in its resistance to commonly used antimalarial drugs which is resulting in increased mortality.^{1,2} It is observed that 0.5 to 2% cases of falciparum infection go on to severe form, of which nearly 30% die even with treatment.² There is an urgent need to control the death due to PF malaria. In falciparum malaria resistance has been detected against all currently used antimalarials (Chloroquine, Amodiaquine, Mefloquine, Quinine and Sulfadoxine-pyrimethamine) except artemisinin compound.¹ Recently (2007) there are reports of suspected resistance to artemisinin derivative along the Thai-Cambodian border.⁴ For this reason the treatment of falciparum malaria is becoming difficult. Therefore WHO in 2006 has completely revised the treatment schedule of PF malaria. Following the WHO directive the revised National Drug Policy on malaria (NDP) has been issued in 2007. This present article will discuss the changes of antimalarial therapy in PF malaria in brief.

When to Change the Conventional Treatment Schedule of Falciparum Malaria

Wherever chloroquine (CQ) is effective against PF malaria CQ should be used. But if the treatment failure exceeds 10% in a geographical area the antimalarial drug used should be changed to a new antimalarial drug which must be effective in more than 95% cases.¹

Objective of Treatment

Falciparum malaria cases present as uncomplicated and or severe form (Table 1). Because most death occur in severe falciparum malaria than uncomplicated cases, the treatment objective of both types differ. In uncomplicated falciparum malaria cases, it is most important to kill the parasite promptly so that it cannot progress to severe form. Besides, it is important that the drug treatment should be able to prevent transmission and drug resistance.

In severe falciparum malaria, the prime objective is to prevent death and other objectives as mentioned earlier are of secondary importance. In pregnancy survival of the mother is the most important objective.

TREATMENT OF UNCOMPLICATED FALCIPARUM MALARIA^{1, 2,5}

Combination antimalarial therapy has been advocated to achieve the objective of enhancing the effectiveness of the drug and delaying drug resistance. Antimalarial combination therapy has been divided into two groups.

- i. Artemisinin based combination therapy (ACT)–the preferred combination.
- ii. Non-artemisinin based combination therapy (Non-ACT).

Why ACT is Preferred^{1,5}

Artemisinin group of drugs (Artesunate, Artemether, Dihydroartemisinin, Artemotil) reduced the parasite load by 10000 in each asexual cycle which is far more than other antimalarials (100 to 1000). It has a unique mechanism of action by inhibiting falciparum encoded sacroplasmic endoplasmic reticulum calcium ATPase. They act over all stages of parasite and on all species of malaria. Artemisinin group of drugs have gametocidal effect which is not there with other antimalarials except primaquine. Therefore, its use will prevent transmission.

Choosing the partner drug is very important for the success of ACT. To be effective the partner drug should be effective and long acting. The minimum duration of ACT is 3 days. In 3 days time there will be 2 asexual cycle of parasite and artemisinin drug will reduce parasite load by 10.⁸ The rest of the parasite will be killed by the long acting partner drug.

Non-ACT like Amodiaquine + Sulfadoxine-pyrimethamine is effective in some places. But it should not be used unless ACT is not available.

Available ACT and Practice Guidelines for Treatment of Uncomplicated Falciparum Malaria (Table 2)

In chloroquine resistant areas ACT is the drug of choice.^{1,2} There are 4 groups of ACT which have been recommended by WHO.

- i. Artesunate + Mefloquine (AS + MQ)
- ii. Artemether + Lumefantrine (AL)
- iii. Artesunate + Sulfadoxine-Pyrimethamine (AS + SP)
- iv. Artesunate + Amodiaquine (AS + AQ)

All the 4 ACT are equally effective. However because of intolerance of MQ by African children and resistance of SP in South-East Asia AS+MQ and AL should be preferred in South-East Asia including India but AS+SP and AS+AQ in Africa.

National Drug Policy 2007 (NDP)² has advocated AS+SP in chloroquine resistant areas. This may not be most ideal choice for the above said reason. The details of drug administration has been shown in Table 2.

Treatment of Treatment Failure Cases^{1,2}

If one group of ACT fails to cure the case or relapse occurs the following treatment should be followed *in order of preference*.¹

- i. Another ACT is the first choice.
- ii. Artesunate 2 mg/kg body weight/day once orally for 7 days + Tetracycline/Doxycycline 3.5 mg/kg body weight/day for 7 days/Clindamycin 10 mg/kg body weight/twice a day for 7 days (in pregnancy and children).
- iii. Quinine 10 mg/kg body weight/dose (max. 600 mg/dose) 8 hourly orally for 7 days + Tetracycline/Doxycycline/Clindamycin as above.

However, NDP 2007 has advocated to use quinine alone in ACT failure cases.

Treatment of Uncomplicated Falciparum Malaria during Pregnancy

As per the WHO recommendation 2006 during 1st trimester – Quinine + Clindamycin orally for 7 days is preferred. In 2nd and 3rd trimester– ACT or Artesunate + Clindamycin orally for 7 days should be used. However, as per NDP 2007 only Quinine should be used during pregnancy.

TREATMENT OF SEVERE FALCIPARUM MALARIA^{1,2}

Because of high and early mortality in severe falciparum malaria only parenteral antimalarial should be used. The available parenteral antimalarial should be used promptly even before the parasitological diagnosis is more if clinical suspicion is there. Quinine (QN), Artesunate (AS), Artemether, Artemotil (Arteether) are antimalarials available in parenteral form.

Artesunate

WHO 2006 has recommended Artesunate as the *most preferred antimalarial* in severe falciparum malaria. In a landmark randomised controlled trial (RCT) in 2005 Artesunate had 15% mortality in comparison to 22% mortality with Quinine. There was relative reduction in mortality of 34.7% with Artesunate group. There is clear evidence of survival benefit with Artesunate.⁶ In a recently published conchrane database systematic review (2007) has also endorsed Artesunate as the drug of choice for adults with severe falciparum malaria particularly if acquired in Asia.⁷ Because the maintenance dose of AS used higher in the RCT showing survival benefit of AS over Quinine and in view of pharmacodynamic and pharmacokinetic data on AS, WHO has accepted the new higher maintenance dose AS as the preferred dose of AS than the conventional dose of AS used so far (Table 3).

In spite of overwhelming evidence of superiority of AS over Quinine, the NDP 2007 has advocated Quinine as the drug of choice and Artesunate as alternative choice in severe falciparum malaria. They have advocated the conventional doses of AS and for shorter period (Table 4). It will promote drug resistance and deprive people of India of the survival benefit with AS.

Combination of Artesunate and Quinine has not resulted in any improvement in survival in comparison to Artesunate alone but increased the adverse effect.⁸ In our study there was 13% mortality with AS, 25 with QN and 31% with AS + QN. Both WHO and NDP guidelines have not advocated this combination.

Alternative Drug

Artemether

In several RCT Artemether is equal to QN in its effectiveness in severe falciparum malaria. However, in sub-group analysis of adult with multi system failure, there was significant

improvement of survival with Artemether than QN. Despite being oil based preparation it is given IM, its absorption is erratic. At times it takes upto 18 hours or more to reach peak concentration. Therefore, WHO has regarded it as 2nd preferred drug behind AS but above QN. NDP 2007 though has accepted it as an alternative drug the dose schedule and duration are less than that advocated by WHO (Tables 3 and 4). The NDP recommended dose schedule may result in increasing drug resistance and drug failure.

Quinine

WHO has accepted parenteral Quinine as the 3rd choice in severe falciparum malaria though NDP has taken it as first choice. Loading dose has been advocated by WHO as peak concentration reaches earlier (4 hours vs 12 hours) than without loading dose. However, RCT has not shown any survival benefit with loading dose.¹ NDP has not advocated any loading dose.

Artemotil (Arteether)^{1,2}

There is less published information of its efficacy and pharmacokinetic properties. Its absorption is erratic. At times it is undetectable even 24 hours after administration. Therefore, it is not recommended by WHO. However, NDP has mentioned it as an alternative drug.

Treatment of Severe Falciparum Malaria during Pregnancy

As per NDP parenteral Quinine is the only drug to be used during the whole period of pregnancy. Pregnancy with severe falciparum malaria has nearly 50% mortality. In view of survival benefit of AS in non-pregnant lady and no reported evidence of fetal abnormality with AS. WHO has advocated Artesunate as first choice during 2nd and 3rd trimester and Quinine in first trimester of pregnancy.

CONCLUSION

Most of the antimalarial treatment of falciparum malaria has been changed by WHO. ACT has been accepted as the preferred agent for treating uncomplicated falciparum malaria. In severe falciparum malaria Artesunate in higher doses has distinct survival advantage over Quinine and should be used as first choice, if available. In pregnancy during first trimester Quinine should be used. In 2nd and 3rd trimester WHO has advocated to use Artesunate to reduce death though NDP has advocated Quinine for the safety purposes. Treating falciparum cases as per the new guidelines will improve survival and bring back chloroquine sensitivity in future.

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MULTIPLE CHOICE QUESTIONS

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- 1. Which antimalarials have *P. falciparum* gametocidal effect?**
 - A. Quinine
 - B. Artemisinin derivative
 - C. Primaquine
 - D. Sulfadoxine-pyrimethamine
- 2. Which artemisinin based combination has been advocated by National Drug Policy-2007 to be used in uncomplicated *Falciparum* malaria?**
 - A. Artesunate + Mefloquine
 - B. Artesunate + Sulfadoxine-Pyrimethamine
 - C. Artemether + Lumefantrine
 - D. Artesunate + Amodiaquine
- 3. Which drug is preferred to treat severe *falciparum* malaria by WHO?**

A. Quinine	B. Quinidine
C. Artesunate	D. Artemether
E. Arteether	
- 4. In the case of recurrence or treatment failure in uncomplicated *P. falciparum* Malaria. Which is the best drug?**
 - A. Another ACT
 - B. Artesunate + Doxycycline for 7 days
 - C. Quinine + Doxycycline for 7 days
- 5. Which is the maintenance dose of artesunate in severe *P. falciparum* Malaria as advocated by WHO?**
 - A. 1.2 mg/kg body weight
 - B. 1.6 mg/kg body weight
 - C. 2.2 mg/kg body weight
 - D. 2.4 mg/kg body weight
- 6. Which antimalarial to be used in severe *P. falciparum* malaria with third trimester pregnancy as per WHO?**

A. Quinine	B. Artesunate
C. Artemether	D. Arteether
- 7. Which antimalarial to be used in uncomplicated severe *P. falciparum* Malaria during first trimester?**

A. Quinine	B. Artesunate
C. Arteether	D. Artemether