Singapore Med J 1998; Vol 39(5):208-210

Treatment of Severe Falciparum Malaria with Artesunate and Mefloquine

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ABSTRACT

Aim: To study the therapeutic efficacy of low dose intravenous artesunate followed by oral mefloquine in severe falciparum malaria in Singapore.

Methodology: Retrospective review of 4 cases of severe falciparum malaria admitted for treatment in a private hospital in the first six months of this year. Patients were considered cured when no malaria parasites were detected in the blood film on discharge and remained afebrile at 28 days.

Results: This drug regimen was well tolerated, rapidly reduced parasitaemia and achieved 100% cure in all four patients.

Conclusion: Low dose intravenous artesunate followed by mefloquine was found to be well tolerated and rapidly effective in treating severe falciparum malaria contracted in Indonesia and India. There was no relapse of clinical disease in all four cases after 28 days.

Keywords: severe falciparum malaria, low dose artesunate and mefloquine, effective

INTRODUCTION

The annual mortality from malaria is estimated to be between 1 and 3 million in the world today and nearly all the deaths are due to Plasmodium falciparum. As multi-drug resistant P. falciparum is becoming an increasing problem in south-east Asia, interest has focused on artemisinin and its derivatives which has been extensively studied in China as a drug against P. falciparum[1-3]. Since then, many clinical trials using artemisinin or its derivatives, either alone or in combination with other drugs, have been carried out in China and south-east Asia. Artemisinin and its derivatives are currently the most rapidly acting of all the antimalarials in the treatment of severe and even multi-drug resistant falciparum malaria[4]. Artesunate, the water soluble hemisuccinate derivative of dihydroartemisinin, is the most rapidly acting of all the artemisinin derivatives. Combination therapy with artesunate which rapidly reduces parasitaemia and mefloquine which has a long term effect in clearing the remaining parasites, is probably the most widely studied drug regimen in the treatment of falciparum malaria[5,6].

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PATIENTS

The following is a description of four consecutive cases of severe falciparum malaria admitted for treatment in the first six months of 1997. The patients received intravenous artesunate 300 mg total dose given over 3 days followed by mefloquine 1.5g total dose given 12 hours after the last dose of artesunate. 5% dextrose saline, antipyretics, antibiotics and platelets were given as required.

A 50-year-old Canadian woman presented with a history of fever for 5 days and diarrhoea and vomiting for 2 days. At the time of the illness she was travelling in North Sumatra where she was thought to have typhoid and was given chloramphenicol. She had vaccinations for hepatitis A, typhoid and polio but was not on malaria prophylaxis.

On admission, she was afebrile but dehydrated, jaundiced and had a palpable spleen. Blood film for malaria showed P. falciparum (1%), platelet count was critically low at 23,000 and liver function tests were abnormal with a bilirubin of 10 mg/dL. Response to artesunate was dramatic with few P. falciparum seen the next day and none detected 48 hours later. She spiked a fever on the second day but the fever settled on the fifth day of treatment. On discharge 10 days later, blood film for malaria remained negative.

A 50-year-old Canadian man, husband of the above patient, was admitted with a history of fever for 5 days. He was diagnosed with malaria in North Sumatra and given paludrine and dexamethasone. Like his wife, he was not taking malaria prophylaxis but had vaccinations for hepatitis A, typhoid and DPT.

On admission he was afebrile, mildly jaundiced and had a palpable liver and spleen. Again blood film confirmed the presence of P. falciparum (about 1%). Platelet count was low – 24,000 and liver function tests were also abnormal with a bilirubin of 4.4 mg/dL.He spiked a fever of 39°C the next day. Forty-eight hours after starting treatment, no malaria parasites were detected in the blood film and his fever settled on the fifth day of treatment.

A 28-year-old Norwegian man working in Singapore since January this year presented with headache, a 3-day history of fever with sweats and dark urine on the day of admission. He had been treated for flu earlier by his company doctor. In

the past two weeks he had a history of travel to Bintan where he spent a night. In view of the short duration of stay, he had not taken any malaria prophylaxis.

When seen he looked unwell, was febrile, jaundiced and had a tachycardia. Blood film showed P. falciparum (2%). He had a platelet count of 20,000, prolonged PT and PTT, abnormal liver function tests, and urobilinogen in the urine. Parasitaemia was greatly reduced the next day and cleared 72 hours after starting treatment; but 36 hours after admission, he developed bilateral broncho-pneumonia which responded to parenteral antibiotics. As a result of his chest infection, his fever did not settle till the 8th day.

The fourth patient was a 64-year-old hypertensive Indian man who presented with a 3 – 4 day history of fever and cough. He lives in Bombay and had just arrived in Singapore 10 days earlier. When seen, he was febrile with a temperature of 38°C, very mildly icteric but otherwise well. Blood film showed a surprisingly heavy infection with P. falciparum (6%). He became afebrile 72 hours after starting treatment and parasitaemia had cleared 96 hours later.

All four patients became anaemic (haemoglobin <11.5g/dL) during treatment. The two most severely affected were the woman with a drop of 31% and the Norwegian with 26%. The latter also had chest infection and epistaxis as complications. The fourth patient despite having the greatest parasitaemia had only a slight drop of 3% of his haemoglobin.

DISCUSSION

Three of the cases described had contracted their disease in Indonesia while the fourth was infected in India. Indonesia and India are not known to have quinine resistance but artesunate was chosen as the drug to treat the four cases in view of its proven rapidity of action and the fact that it is well tolerated[4] unlike quinine which causes hypoglycaemia, symptoms of cinchonism in most patients and even blackwater fever[7]. In China artemisinin and its derivatives have now replaced chloroquine and quinine in the treatment of malaria[3]. There have been reports of neurotoxicity with high doses and chronic use of the artemisinin compounds, but these data have all been from animal studies[8]. To date there is no evidence of this in man. Apart from a temporary depression of the reticulocyte count, a recent Vietnamese study using higher doses of artemisinin in children with severe malaria found no other adverse effects or toxicity[9].

Despite the rapid clearance of parasitaemia, recrudescence within one month of treatment using artemisinin or its derivatives as a monotherapy, was observed in many clinical studies[2]. However when combined with mefloquine which has a long half-life, at a dose of 25 mg/kg, cure rates were much improved[5]. Subsequent investigation by the same workers using smaller doses of artesunate (300 mg) and mefloquine (750 mg) showed the sequential regimen to be slightly less effective with a 10% recrudescent rate[10].

Various therapeutic regimens are currently recommended for the artemesinin derivatives in the treatment of falciparum malaria[11]. These regimens are largely empirical, having been derived from results of clinical studies showing treatment efficacy. As all the four patients came from countries not known to have multi-drug resistant P. falciparum, we decided to use the lower dose of artesunate (300 mg total dose) but followed by mefloquine 1.5 mg total dose. Nausea and vomiting which has been reported to be associated with the sequential combination of artesunate and mefloquine was only observed in one patient when given the first dose of mefloquine (750 mg). It might be of interest to mention that the Indian man who had quinine treatment previously found this drug combination much more pleasant and acceptable as it was free of the disturbing side-effects of quinine. He did, however, have transient mild dizziness while on mefloquine.

All four patients were considered to have severe malaria as each of them had one or more of the features of the disease[12]. The Indian with a parasitaemia of 6%, the other three with serum bilirubin ranging from 4.4 – 10 mg/dL (75 – 171 μmol/L) and one of them also had bleeding disturbance and severe broncho-pneumonia. It is interesting to note that the Indian patient despite having the most severe parasitaemia was clinically quite well compared to the other three who had only 1% – 2% parasitaemia. This is most probably due to his semi-immune state as he had two previous episodes of falciparum malaria in India in 1993 and 1994 when he was treated with quinine. The longer parasite clearance time observed in these four patients (range from 48 – 96 hours) when compared to other studies could be due to the lower dose of artesunate used in our patients.

All four patients have remained well and afebrile when contacted 28 days after their admission. Three of them had returned to their home countries soon after discharge from hospital. It appears that using a lower dose of artesunate (300 mg total dose) followed by 1.5g mefloquine is effective in treating severe falciparum malaria which is not multi-drug resistant.

REFERENCES

1. Jiang JB, Li GQ, Guo XB, Kong YC, Arnold K. Antimalarial activity of mefloquine and qinghaosu. Lancet 1982; 2:285-8.
2. Li GQ, Arnold K, GuoXB, Jian H, Fu L. Randomised comparative study of mefloquine, qinghaosu and pyrimethamine-sulfadoxine in patients with falciparum malaria. Lancet, 1984; 2:1360-1.
3. Li GQ, Guo XB, Fu LC, Jian HX, Wang XH. Clinical trials of artemisinin and its derivatives in the treatment of malaria in China. Trans R Soc Trop Med Hyg 1994; 88, Suppl 1,5-6.

4. Hien TT, White NJ. Qinghaosu. Lancet, 1993; 341:603-8.
5. Looaresuwan S, Viravan C, Vanijanota S, Wilairatana P, Suntharasamai P, Charoenlarp P et al. Randomised trial of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria. Lancet 1992; 339:821-4.
6. Win K, Than M, Thwe Y. Comparison of combinations of parental artemisinin derivatives plus oral mefloquine with intravenous quinine plus tetracycline for treating cerebral malaria. Bulletin of the WHO 1992; 70:777-82.
7. White NJ, Jong EC. Malaria diagnosis and treatment. In: Jong, McMullen, editors. The travel & tropical medicine manual. Saunders, 2nd edition 1995; 189-202.
8. Brewer TG, Peggins JO, Grate SJ, Petras JM, Levine BS, Weina PJ et al. Neurotoxicity in animals due to arteether and artemether. Trans R Soc Trop Med Hyg 1994; 88, suppl 1:33-6.
9. Cao XTP, Bethell DB, Pham TP, Ta TTM, Tran TNT, Nguyen TTH et al. Comparison of artemisinin suppositories, intramuscular artesunate and intravenous quinine for the treatment of severe childhood malaria. Tnars R Soc Trop Med Hyg 1997; 91:335-42.
10. Looaresuwan S, Viravan C, Vanijanonta S, Wilairatana P, Charoenlarp P, Canfield C & Kyle DE. Treatment of acute uncomplicated falciparum malaria with a short course of artesunate followed by mefloquine. Southeast Asian J Trop Med & Pub Health 1993; 24:230-4.
11. Looaresuwan S. Overview of clinical studies on artemisinin derivatives in Thailand. Trans R Soc Trop Med Hyg 1994, 88, Suppl 1:9-11.
12. World Health Organisation, Division of Control of Tropical Diseases. Severe and complicated malaria. Trans R Soc Trop Med Hyg 1990; 84:Suppl 2:1-65.

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