CASE REPORT

# Successful Treatment of Imported Cerebral Malaria with Artesunate-Mefloquine Combination Therapy

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Treatment of cerebral malaria with intravenous quinine is frequently associated with life-threatening cardiotoxicity. We report a case of imported cerebral malaria successfully treated with artesunate-mefloquine combination therapy. The 27-year-old woman presented with fever, sudden onset of binocular blindness and altered consciousness 10 days after a short stay in Indonesia. Hyperparasitemia with *Plasmodium falciparum* and *P. vivax* in more than 5% of red blood cells was demonstrated on peripheral blood smear. She was admitted to the intensive care unit due to shock, jaundice and acute renal failure. Because of a shortage of intravenous quinine, intravenous artesunate was given as an alternative. Her condition stabilized on the 3rd day of therapy, with resolution of fever and disappearance of parasitemia. Consolidation therapy with oral mefloquine and primaquine was then given to prevent recrudescence and relapse. The only adverse event associated with artesunate was transient reticulocytopenia, which resolved after discontinuation of therapy. Her vision completely recovered, along with renal and liver function. [*J Formos Med Assoc* 2006;105(1):86–89]

**Key Words:** artesunate, cerebral malaria, combination therapy, mefloquine

Although endemic malaria was successfully eradicated in 1965, there are still 40–50 cases of imported malaria annually in Taiwan.[1–5] With the worldwide spread of chloroquine-resistant *Plasmodium falciparum* since the late 1980s and the consequent increased risk of malaria death,[6,7] treatment of cerebral malaria presents a continuing challenge. Intravenous quinine has been the standard therapy for cerebral malaria caused by chloroquine-resistant *P. falciparum* in Taiwan since 1992. However, its use is frequently associated with life-threatening cardiotoxicity, including pulmonary edema, myocardial suppression, hypotension, and frank shock.[5] Such toxicities may be as hazardous as the disease itself. In contrast, artemisinin-based combination therapy (ACT), recommended by the World Health Organization (WHO) as first-line treatment for malaria since 2001,[8] is generally well tolerated and has many advantages relating to the unique properties and mode of action of the artemisinin component.[9] The use of ACT to treat severe malaria caused by chloroquine-resistant *P. falciparum* remains extremely limited in Taiwan. Here, we report a case of imported cerebral malaria successfully treated with artesunate-mefloquine combination therapy.



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**Received:** December 7, 2004
**Revised:** January 6, 2005
**Accepted:** April 12, 2005

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## Case Report

A 27-year-old Indonesian woman was admitted to our emergency department because of sudden onset of binocular blindness after a 2-day history of fever, chills and intermittent vision loss. She had been a domestic worker in Taipei for the past 2 years. Ten days before the onset of symptoms, she had returned to Jakarta, Indonesia, and stayed there for 8 days. She denied any raw food intake, visiting places other than Jakarta, or mosquito bite exposure during her stay in Indonesia. She had no previous diagnosis of malaria, and her other past medical history was unremarkable.

At the emergency department, the patient was alert and oriented. Her pulse rate was 102 bpm, blood pressure was 107/60 mmHg, respiratory rate was 18/min, and body temperature was 36.1° C. The conjunctiva was not pale, but the sclera was icteric. The pupil sizes were equal, and light reflexes were preserved. Her facial expression was symmetrical, and eye movement was full. No sinus tenderness, nuchal rigidity or lymphadenopathy was found. Examination revealed no abnormality in the chest, heart or abdomen. The extremities were freely movable, and there was no rash, purpura or petechiae. Visual acuity was hand waving at 10 cm. Ophthalmoscopic and neurologic findings were normal.

Initial laboratory studies showed hemoglobin 12.4 g/dL, hematocrit 36.1%, leukocyte count 6920/μL, platelet count 140,000/μL, lactate dehydrogenase 1634 U/L, aspartate transaminase 73.0 U/L, total bilirubin 3.85 mg/dL, direct bilirubin 2.8 mg/dL, blood urea nitrogen (BUN) 40.8 mg/dL, and creatinine 1.11 mg/dL. Urinalysis was positive for protein, urobilinogen, bilirubin and nitrite. Computed tomography of the head without administration of contrast medium revealed no hemorrhage or infarction but showed mild brain swelling.

Because of her recent travel history, a blood smear was performed to rule out malaria. Peripheral blood smears demonstrated ring form trophozoites of *P. falciparum* and *P. vivax* in red blood cells with hyperparasitemia over 5%. Sudden loss of consciousness occurred soon after her admission. Because of a shortage of intravenous quinine, intravenous artesunate (120 mg immediately, followed by 60 mg 12 and 24 hours later, and then once per day) was given as an alternative. She was then transferred to the intensive care unit. Initially, spiking fever persisted, and her consciousness level and visual acuity continued to fluctuate. Urine was black in color, and severe diarrhea was also noted. Renal function (creatinine, 1.54 mg/dL) deteriorated, and intravascular hemolysis, black water fever with progression of anemia (hemoglobin, 8.3 g/dL) and hemoglobinuria, and hypotension (80/50 mmHg) also developed. Brain magnetic resonance imaging revealed generalized increased signal at the white matter of both hemispheres on both T2 weighted and FLAIR images compatible with encephalitis.

On the 3$^{rd}$ day of intravenous artesunate treatment, parasitemia decreased to less than 0.1%. Blood smear showed no parasitemia on the 4$^{th}$ day and thereafter. The patient's clinical condition and laboratory abnormalities improved gradually under appropriate management. However, worsening anemia (hemoglobin, 5.7 g/dL) and reticulocytopenia (reticulocyte count, 0.27%) occurred on the 4$^{th}$ day of intravenous artesunate therapy. Artesunate-related reticulocytopenia was suspected, and artesunate was changed to oral mefloquine (750 mg-500 mg-250 mg every 8 hours) for 1 day as consolidation therapy followed by oral primaquine (15 mg once daily) for eradication therapy. Her anemia and reticulocytopenia improved after cessation of artesunate therapy. However, severe anemia (hemoglobin, 3.5 g/dL) developed again after 4 days of primaquine administration. Primaquine-induced hemolytic anemia due to glucose-6-phosphate dehydrogenase (G6PD) deficiency was suspected. Although G6PD level (19.41 U/g) was within normal limits, it was difficult to interpret the significance of this value soon after the episode of acute hemolysis. Anemia improved after discontinuation of primaquine. She was discharged in good condition after hospitalization for 20 days. Her vision completely recovered, along with renal and liver function.

## Discussion

As in previously reported cases of imported malaria, this patient presented with nonspecific fever patterns, thrombocytopenia, and mild hyperbilirubinemia.[5] The diagnosis was made promptly after obtaining a travel history and a blood smear examination. Her condition was complicated by cerebral malaria,[10] evidenced by the sudden onset of binocular blindness and altered consciousness at admission, along with other indicators of severe malaria including hyperparasitemia, shock, jaundice and acute renal failure.[11] Nevertheless, prompt treatment with intravenous artesunate led to a rapid clinical recovery without the risk of life-threatening cardiotoxicity frequently associated with the use of intravenous quinine. Intravenous artesunate can be a safe and effective alternative to intravenous quinine for patients suffering from life-threatening imported malaria in Taiwan.

Compared with quinine, artemisinin class compounds have many advantages in falciparum malaria treatment, such as rapid therapeutic response (reduction of the parasite biomass and resolution of symptoms), activity against multidrug-resistant *P. falciparum*, good tolerance of the drug, and reduction in gametocyte carriage (and thus having the potential to reduce transmission of malaria).[12] However, when given as a single agent, recrudescence rates are unacceptably high.[13,14] Based on the synergistic or additive potential of two drugs with different mechanisms of action, in order to improve therapeutic efficacy and to delay the emergence of resistance to the artemisinin class of compounds, the WHO endorses a policy of use of ACT.[8] The WHO has urged all countries experiencing resistance to conventional therapies, such as chloroquine, amodiaquine or sulfadoxine/pyrimethamine, to shift to one of the following regimens: (1) artemether plus lumefantrine; (2) artesunate plus amodiaquine; (3) artesunate plus sulfadoxine/pyrimethamine (SP; in areas where SP efficacy remains high); or (4) artesunate plus mefloquine.[8] In keeping with this policy, after the completion of artesunate therapy in this patient, we gave a full course of mefloquine as consolidation treatment for *P. falciparum* infection. The treatment for *P. vivax* coinfection, however, was not completed because of the development of severe hemolysis after 4 days of primaquine use.

Unlike quinine, artemisinin derivatives are generally well tolerated by patients, although there have been occasional reports of reticulocytopenia,[15] manifested as worsening anemia after resolution of fever, as experienced by our patient. Other reported adverse effects included mild gastrointestinal disturbance, dizziness, tinnitus and, rarely, neutropenia, elevated liver enzyme values, prolongation of the QT interval, bradycardia and neurotoxicity.[15–17] Although artemisinin derivatives are generally safe, it would be prudent for clinicians to monitor the possible development of the above-stated adverse drug effects during the therapeutic course.

In summary, compared to the cardiotoxic intravenous quinine regimen, artesunate-mefloquine combination regimen can be considered as an effective and safe treatment alternative for patients suffering from life-threatening imported malaria in Taiwan, as demonstrated in this case.

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