Artemisinin combination therapy can result in clinical failure if oral therapy is not directly observed

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Intravenous artesunate therapy is the first-line therapy for severe malaria, and is highly efficacious when used in combination with an oral partner drug such as doxycycline or atovaquone-proguanil. However, treatment failure occurs routinely with artesunate monotherapy due to the very short half-life of this drug. In North America, experience with artesunate is limited. With the pressure to discharge patients early, administration of the essential oral partner drug is often left to the discretion of the patient. Thus, treatment failure may be commonplace if nonadherence is a factor, as was observed in the case described in the present report.

Key Words: Adherence; Artesunate; Malaria; *Plasmodium falciparum*; Treatment failure

Risque d'échec clinique de la thérapie associative à l'artémisinine si le traitement oral n'est pas rigoureusement observé

L'artésunate par voie intraveineuse, le traitement de première ligne du paludisme sévère, est très efficace lorsqu'on l'utilise en association avec un médicament complémentaire par voie orale, comme la doxycycline ou l'atovaquone-proguanil. Cependant, à cause de sa très courte demi-vie, l'artésunate échoue régulièrement en monothérapie. En Amérique du Nord, on a peu d'expérience de l'artésunate. En raison des pressions exercées pour donner rapidement leur congé aux patients, l'administration essentielle du médicament complémentaire par voie orale est souvent laissée au gré du patient. L'échec thérapeutique peut être courant en cas de non-observance, comme on l'a constaté dans le présent rapport de cas.

CASE PRESENTATION

A case involving a 26-year-old woman from Sudan in the winter of 2011 is presented. During her immigration flight from Sudan via Frankfurt, Germany to Calgary, Alberta, she began to experience fevers and abdominal pain. From the airport, she presented directly to the emergency room (ER) on day 0, where she was afebrile with normal vital signs. She was diagnosed with gastroenteritis and discharged home. Over the next three days, she developed fever with chills and rigors, anorexia, vomiting, myalgias and increasing confusion. She had recently tested negative for HIV before immigration.

On day 3, she returned and was febrile (temperature 38.6°C), tachycardic, normotensive and required 5 L/min O₂ to maintain O₂ saturation. Scleral icterus and nuchal rigidity were noted. She had moderate abdominal tenderness but no peritoneal signs. Investigations revealed a hemoglobin level of 115 g/L, platelet count of 27×10⁹/L and leukocyte count of 8.3×10⁹/L. Her electrolyte, creatinine and liver transaminase levels were normal, lactate dehydrogenase level was 943 U/L and total bilirubin level was 42.75 µmol/L. She was started on empirical meningitis treatment with ceftriaxone. A lumbar puncture was deferred because of her low platelet count. Computed tomography scanning of the head was normal; a computed tomography scan of the abdomen revealed borderline hepatomegaly and splenomegaly. A set of malaria smears drawn that evening identified 2.1% *Plasmodium falciparum*. Because of her confusion and impaired level of consciousness, the patient was classified as a severe case of malaria (1). Artemisinin combination therapy is the first-line therapy in North America for severe and complicated malaria, and she was started on artesunate 2.4 mg/kg (190 mg) intravenously every 12 h, given at 0 h, 12 h, 24 h and 48 h (1). Repeat malarial smears were performed, showing an increasing parasitemia that peaked at 6.6% on day 4 but decreased to 0.3% after treatment on the same day, and was undetectable by day 5.

The patient improved cognitively and symptomatically after 48 h. She was closely monitored for hypoglycemia, acute renal failure and acute respiratory distress syndrome, but these did not manifest. After completing her course of parenteral artesunate on day 5, the patient was started on a course of atovaquone-proguanil for an additional four days. She received one dose in hospital and was then discharged on day 7 with a prescription for three more days. She was also to receive seven additional days of ceftriaxone through a home parenteral therapy program. At the time of discharge, the patient's platelet count had recovered to 130×10⁹/L and hemoglobin level had risen to 88 g/L from a nadir of 77 g/L on day 5. When seen in follow-up in the outpatient parenteral therapy clinic on day 12, she was feeling well.

On day 31 after onset of illness, the patient again presented to the ER, complaining of two weeks of fevers, chills, nausea and vomiting, and intermittent right upper quadrant abdominal pain. Her husband insisted that she had completed her course of atovaquone-proguanil. Vital signs showed a temperature of 38.9°C and tachycardia (heart rate 134 beats/min), with normal blood pressure and O₂ saturation at room air. Abdominal examination revealed tenderness to percussion and dullness over Castell's point. The rest of her examination was unremarkable. At this time, her hemoglobin level was 115 g/L, platelet count was 97×10⁹/L and leukocyte count was 7.3×10⁹/L. Electrolyte, creatinine and liver transaminase levels were normal. Bilirubin and lactate dehydrogenase levels were elevated (27.4 µmol/L and 384 U/L, respectively). Blood cultures were negative, but her malaria smears were once again positive for *P. falciparum*, with a parasitemia of 3.5%. The patient was diagnosed with recrudescence malaria and started on artesunate therapy (2.4 mg/kg intravenously every 12 h) again. Repeat malaria smears revealed a drop in parasitemia to 2.0% after 8 h and became negative in subsequent smears. She was treated for 48 h with parenteral artesunate, followed by a course of doxycycline (100 mg

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Figure 1) Clinical, pharmacological and parasitological timelines of events in patient's course. ER Emergency room; *P. falciparum* Plasmodium falciparum

orally twice per day for seven days). The patient showed marked recovery within 48 h, and insisted on leaving on day 37. When seen in follow-up on day 38, she was completing her course of doxycycline and was doing well. Figure 1 summarizes her clinical course.

In an effort to determine whether this was a treatment failure due to genetic alterations in putative markers of artemisinin resistance, molecular detection of *pfmdr1* copy number and mutations in *cytb* (malarone resistance), *pfcr1* (chloroquine resistance) and *pfmdr1* (artesunate and mefloquine resistance) were conducted (2-4). The original and recrudescence malaria specimens were analyzed using real-time polymerase chain reaction and *pfmdr1* copy number was calculated relative to the chloroquine-sensitive strain 3D7 as 0.89 and 0.93, respectively. DNA pyrosequencing confirmed the following haplotype in the recrudescence isolate: *cytb* Y268, *Pfcr1* K76, *Pfmdr1* N86Y, Y184, S1034, N1042 and D1246 (5). Further investigation of pharmacy records revealed that the patient did not fill the full atovaquone-proguanil prescription as an outpatient but did fill the doxycycline prescription. This suggests that failure of adherence to the follow-on drug was responsible for treatment failure in the present case. It is well described that the rapid-acting nature of artemisinin derivatives require a partner drug, with previous reports of up to a 50% recrudescence rate following artemisinin monotherapy (6,7). It is, therefore, likely that artesunate combination therapy was the appropriate treatment in this patient from Africa, and that adherence to the accompanying oral drug as an outpatient is critical to avoid treatment failure. Given the potentially dire outcomes of *P. falciparum* infection and, even more ominous, the spectre of widespread artemisinin resistance, measures should be taken to improve adherence, including consideration of direct observation of the administration of artemisinin derivatives and their partner drugs in settings where this is practical. Emphasizing the importance of completing the course of therapy with the patient and their caregivers should be undertaken, optimally with adequate language translation. Providing the patient with the full course of tablets rather than a prescription at discharge may minimize the barriers of finances and

transportation. Finally, close follow-up, which may include a visit at one week postdischarge to ensure adherence and another at four weeks postdischarge, is key to detecting treatment failure or recrudescence early, and to swiftly manage these situations to avoid the risk of subsequent morbidity and mortality.

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