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Case Report
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Delayed Treatment Response in Pediatric Malaria with Atovaquone-Proguanil

Walter Dehority[1], Andrew Renuart[2] and Rolando M Viani[3,4]*

[1]Department of Pediatrics, The University of New Mexico, USA

[2]Department of Pediatric Anesthesiolgy, University of Pennsylvania Health System, USA

[3]Department of Pediatrics, University of California San Diego, USA

[4]Department of Pediatrics, Rady Children's Hospital San Diego and AbbVie, USA

Abstract

Atovaquone-Proguanil (AP) is frequently utilized for treatment of *P. falciparum* malaria. Independent of resistance, however delayed treatment responses and treatment failures may occur. We describe a case of delayed treatment response with AP in a 4-year-old child with *P. falciparum* infection, highlighting the limitations of this drug for the treatment of malaria.

Keywords: *Plasmodium falciparum*; Atovaquone-proguanil; Pediatric; Treatment; Malaria

Introduction

In 2015, an estimated 214 million new cases of malaria occurred worldwide, resulting in approximately 438,000 deaths (with 70% occurring in children under 5 years of age) [1]. In the United States, imported malaria reached a 40-year high with 1,925 reported cases in 2011 [2]. Seventy-three percent of cases diagnosed in the United States were acquired in Africa, with the majority due to *P. falciparum* [2]. Atovaquone-proguanil (AP) is a well-tolerated treatment for uncomplicated *P. falciparum* malaria, and is often used as first-line therapy in many countries. In this report, we describe a case of delayed treatment response to AP therapy in a child with *P. falciparum* malaria potentially related to poor bioavailability secondary to inadequate oral intake during treatment and slow schizontocidal activity of the drug.

Case Presentation

During December 2013, a 4-year old Somali male residing in San Diego presented to an urgent care facility with a complaint of nightly fevers, fatigue and cough for 7 days. He was febrile to 41.6°C and was subsequently transferred to Rady Children's Hospital in San Diego. The patient was born and raised in a refugee camp in Kakuma (Northwestern Kenya), and arrived in San Diego fourteen days prior to presentation. On examination, he was febrile at 39.2°C, with a blood pressure of 101/50 mm Hg, a respiratory rate of 22 breaths per minute and a heart rate of 125 beats per minute. He was alert and responsive. His sclerae were non-icteric. His liver and spleen were palpable 3 cm below the costal margin. His admission white blood cell count was 6,800 cells/μL with an associated microcytic anemia of 8.7 g/dL and thrombocytopenia of 86,000 cells/μL. His total bilirubin was elevated at 1.2 mg/dL. A blood culture was collected and the patient received a dose of ceftriaxone for possible sepsis. A blood smear revealed *P. falciparum* with a parasitemia of 0.6%. He was hospitalized and started on AP (250 mg/100 mg) by mouth daily for three days. He received his first dose at 13:00 on hospital day 1 (Figure 1: Hour 16). After 24 hours, his parasitemia had increased to 2.3%. Overnight on hospital day 2 he was febrile to 38.3°C and his parasitemia increased to 3.0% after his second dose of AP. On the night of hospital day 2, a number of hypotensive episodes resulted in a transfer to the Pediatric Intensive Care Unit (PICU). Given worsening anemia, the patient received a transfusion of packed red blood cells on the morning of hospital day 3. Following the transfusion, his parasitemia decreased to 0.7%, but he remained persistently febrile to 39.5°C. The patient received his final dose of AP that afternoon; however, given concern for a delayed treatment response to AP and the severity of his continuing illness, it was decided to further treat him with artemether-lumefantrine (AL). Since admission, the patient demonstrated poor oral intake resulting in a concern of low atovaquone absorption. Therefore a blood sample for atovaquone plasma concentration assayed by high performance liquid chromatography (NMS Laboratory, Willow Grove, PA) was collected 2 hours after the dose on the third day. He received 2 tablets of AL (20 mg/120 mg) at 0, 8, 24, 36,

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Correspondence:
Walter Dehority, Department of Pediatrics, Division of Infectious Diseases, The University of New Mexico, MSC10 5590, Albuquerque, NM 87131-0001, USA, Tel: (505) 272-6891; Fax: (505) 272-4549; E-mail: WDehority@salud.unm.edu

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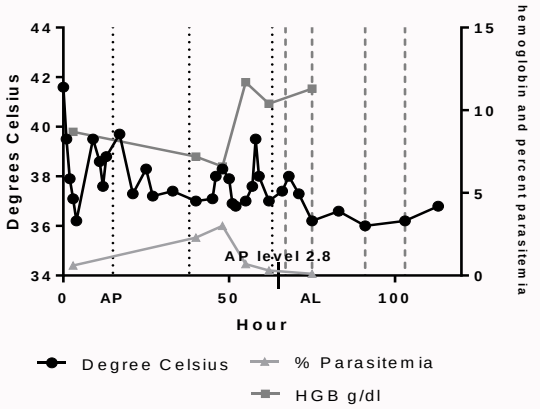

Figure 1: Clinical course of the patient. Temperature in Celsius is referenced to the left vertical axis. Measured hemoglobin in g/dl and % parasitemia is referenced on the right vertical axis. The patient remained intermittently febrile until artemether-lumefantrine started at hour 68. The patient's parasitemia continued to rise until he was transfused, after which it declined from 3.0% to 0.7%. The patient had a further decline in parasitemia to 0.3% prior to the first dose of artemether-lumefantrine. Doses of atovaquone-proguanil are labeled AP and shown with a dotted line, and doses of artemether-lumefantrine are labeled AL and shown with a dashed line. The plasma atovaquone steady state concentration was taken at hour 65 and is shown with a tick at 2.5 µg/ml.

48 and 60 hours, starting at 16:00 on hospital day 3. Soon after his first dose of AL, his fever began to improve significantly (Figure 1), as did the patient's appetite. His parasitemia decreased to 0.2% on the afternoon of hospital day 3 and to 0.1% on the morning of hospital day 4. His blood culture was sterile and ceftriaxone was discontinued. He was transferred out of the PICU on hospital day 4. The day 3 atovaquone plasma concentration was 2.8 µg/mL. He was discharged on hospital day 5 to complete his final dose of AL. Within 48 hours and at 4 weeks post-discharge, he was asymptomatic.

Discussion

AP is frequently utilized in the United States and other countries for the treatment of uncomplicated *P. falciparum* malaria. As such, it is recommended as a first-line treatment option for uncomplicated malaria in children by the American Academy of Pediatrics [3]. However, as a therapeutic option, the drug has many limitations. Treatment failures with AP may occur with sub-optimal dosing or impaired bioavailability, re-infection, or mutations predisposing to resistance (in codon 268 of the *cytochrome b* gene) [4]. In addition, the relatively slow schizontocidal activity of the drug may lead to delayed treatment responses and early treatment failures [5]. Delayed clearance of parasitemia in malaria-infected African children has been documented with AP, with up to one-third of children still parasitemic after 3 days of therapy [5]. Atovaquone is a highly lipophilic drug that is poorly absorbed unless administered with fatty food, which may increase blood concentrations up to five-fold [6]. Our patient had poor oral intake, which may have predisposed to sub-therapeutic levels of atovaquone and subsequent clinical failure or a delayed response to treatment. The specific concentration of atovaquone required for effective therapy of *P. falciparum* infection is also not well described, and failures have been reported with no evidence of resistance in the setting of presumed therapeutic levels [7]. Recently a case of early treatment failure was described without any known mutations in the *cytochrome b* gene with presumed therapeutic plasma drug concentrations in a 45-year-old male from the Ivory Coast [7]. Similar to our patient, this patient developed worsening parasitemia despite completing 3 days of AP, and improved only after quinine and doxycycline were administered. A failure of AP prophylaxis has been previously reported in a 28-year-old woman travelling to Ghana to visit friends and relatives, who took AP with water on an empty stomach, with concern that she did not achieve adequate treatment concentrations [8]. Our patient had documented hyporexia and limited oral intake, which may also have led to ineffective drug concentrations. AP treatment failure due to the emergence of *P. falciparum* with a Tyr268Ser resistance mutation in the *cytochrome b* gene results in late recrudescence (3-4 weeks post-treatment), which was not seen in our patient [4]. Unfortunately, the sample for genetic characterization was lost so it was not possible to completely exclude an atovaquone resistant strain in our patient. However, a 2015 report found that only 2.0% of 277 *P. falciparum* strains analyzed from Kenya carried this mutation, and only 1.3% of isolates over a 5-year period possessed high-level resistance to AP (IC_{50}>1,121 nM) [9].

Conclusion

We describe a case of a delayed treatment response with the use of AP for the treatment of *P. falciparum* malaria. With the high morbidity and mortality associated with *P. falciparum* malaria and the relative frequency with which AP is utilized in many countries, an awareness of the potential limitations of this drug is critical. The lack of validated concentrations of the drug required for effective therapy, delays in obtaining results from resistance testing, poor absorption in hyporexic patients and slow schizontocidal action all may lead to early or late treatment failures. Alternative therapies, such as artemisin-based compounds, may be a more attractive option if available.

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