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**Apparent Drug Failure Following Artesunate Treatment
of *Plasmodium falciparum* Malaria in Sokoto, Nigeria:
Three Case Reports**

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Abstract: Three cases of uncomplicated *Plasmodium falciparum* malaria in Sokoto, Nigeria, between June and July 2006, apparently failed treatment with artesunate monotherapy. Two of the cases fulfilled the World Health Organization's criteria for low grade resistance level while one case fulfilled the criteria for high grade resistance. Use of artesunate monotherapy and improper use among the population may likely quicken the pace of the emerging resistance to the drug amongst the local strains of the parasites.

Key words: Malaria, artesunate, treatment, drug failure, Nigeria

INTRODUCTION

Despite control and treatment efforts, malaria is still one of the most important parasitic diseases of man. In Nigeria, malaria is endemic and accounts for 50 and 25% of out-patients' consultation and hospital admissions respectively (Federal Ministry of Health, 2005). The predominant causative agent is *Plasmodium falciparum* (Umar and Hassan, 2002). The malaria problem has been exacerbated by chloroquine resistant parasite strains which have been reported from all parts of the country (Salako and Aderounmi, 1987; Ezedinachi, 1996; Olanrewaju and Johnson, 2001; FMOH, 2005) and has resulted in increased morbidity and mortality (Olanrewaju and Johnson, 2001).

A cornerstone of policies to reduce malaria associated morbidity and mortality is early diagnosis and prompt effective therapy. Recently, artemisinin-based therapies have emerged as effective alternatives to chloroquine, hitherto the most widely used antimalarial drug in Africa. Nigeria adopted artemisinin-based combination therapy for the first line treatment of uncomplicated malaria in 2005. This policy change was greeted with enthusiasm and artemisinin-based antimalarials started to become available in government owned health institutions and privately owned pharmacy stores and doctors resorted to the use of these drugs whose superiority over chloroquine and sulfadoxine/pyrimethamine started coming to the fore.

Artesunate is a blood schizontocide active on the intra-erythrocytic stages of the malaria parasites (De vries and Dien, 1996). The susceptibility of *P. falciparum* to artemisinin has been well-established *in vivo* and its effectiveness in the treatment of *falciparum* malaria has been well documented (White *et al.*, 1992; Elhassan *et al.*, 1993). As yet there have been no reports of artemisinin-resistant malaria from Nigeria (FMOH, 2005). Within a year and half of the adoption and widespread use of artesunate especially in urban areas cases of artesunate resistance are starting to emerge in Sokoto, Nigeria. Three cases are described below.

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CASE REPORTS

Two of the cases presented at the Usmanu Danfodiyo University Health Centre, Dundaye, permanent site of the university on June 6, 2006 (case one) and July 10, 2006 (case two). The other case presented at the City Campus Health Centre, temporary site of the university on July 13, 2006 (case three). All the patients were male adults and presented with the typical signs and symptoms of malaria and Widal test was performed to rule out typhoid fever. Widal test and blood culture were negative in all the three cases. All the patients gave their informed consent for treatment and follow-up. The study was approved by the Management and the Ethical Committee of the Health centre of the University. All the cases were treated with oral artesunate® (Mekophar Pharmaceuticals, Nopalka, Vietnam) 3.0 mg kg⁻¹ body weight on day one and 1.5 mg kg⁻¹ body weight daily for five days. The initial doses were taken under the supervision of one of the investigators (Dr. Jiya, FWACP). Molecular genotyping of Merozoite surface proteins (MSP1 and MSP 2) genes of the pre-treatment and post-treatment (recrudescence) parasite samples revealed identical patterns, warranting the conclusion that there were no new infections.

Case One

A 49-year old man presented with fever (axillary temperature 39°C), joint pains, headache and rigours. Thin film revealed the presence of *P. falciparum* infection (12,480 asexual stages μL⁻¹, quantitative buffy coat, QBC™ method, Becton-Dickinson, U.S.A.). Haematocrit was 39% and leucocyte count 3.9×10⁹ L⁻¹. The fever subsided six hours after the initial dose of artesunate and the joint pains improved significantly. On day five, the patient presented with recurrence of fever, body pains and fatigue. Blood films and QBC test confirmed *P. falciparum* (4,040 asexual stages μL⁻¹). Late treatment failure was suspected and treatment was commenced with oral Amodiaquine (10 mg kg⁻¹ body weight) day 1 and 2 and 5 mg kg⁻¹ body weight on day 3. The patient symptoms resolved 48 h after, was aparasitaemic and remained so on days 14 and 28.

Case Two

A 52-year old man presented with fever (axillary temperature 38.5°C), malaise and nausea. He admitted being placed on chloroquine treatment for the past three days, for the same complaints, by a rural health clinic while he was at his village. Thin film revealed the presence of *P. falciparum* infection (7,680 asexual stages μL⁻¹, quantitative buffy coat, QBC™ method, Becton-Dickinson, USA). Haematocrit was 33% and leucocyte count 3.7×10⁹ L⁻¹. A day after initiation of treatment with artesunate (at our centre) the fever only slightly subsided and the malaise persisted. On the third day there was no improvement (axillary temperature 39°C, throbbing headache, parasitaemia 6,040 asexual stages μL⁻¹) and RIII resistance was suspected. Treatment was switched to oral Coartem® (artemether-lumefantrine, Novartis, USA) 4 tablets 12 hourly for 3 days, within 24 h the patient's symptoms improved remarkably and was aparasitaemic. No *P. falciparum* was detected on days 14 and 28.

Case Three

A 39-year old man presented with fever (axillary temperature 38.5°C), malaise, loss of appetite and headache. Thin film revealed the presence of *P. falciparum* infection (18,000 asexual stages μL⁻¹, quantitative buffy coat, QBC™ method, Becton-Dickinson, USA). Haematocrit was 36% and leucocyte count 3.6×10⁹ L⁻¹.

A day after initiation of treatment the fever only slightly subsided, headache and the malaise persisted. On the third day there was no improvement (temperature 39°C, throbbing headache, parasitaemia 16,280 asexual stages μL⁻¹) and treatment was switched to oral Amodiaquine

(10 mg kg⁻¹ body weight) day 1 and 2 and 5 mg kg⁻¹ body weight on day 3. The patient's symptoms resolved 48 h after, was aparasitaemic and remained so on days 14 and 28.

DISCUSSION

To our knowledge this was the first study to document cases of resistance (barring unusual pharmacokinetic profiles in the study subjects) by *P. falciparum* to artesunate (artemisinin) in Nigeria and further demonstrates the shocking capability of the parasite to develop resistance to any drug used to treat it. We were sure that the drug had been ingested by our patients as instructed and the drugs were what they were assumed to be, having passed the general drug test (data not shown). *In vitro* test for sensitivity to artesunate using *P. falciparum* isolates from the patients would have helped to confirm whether or not the failures were due to resistance. Unfortunately, such test was not possible at the time. Nosten *et al.* (1994) have reported that chloroquine resistant and susceptible *P. falciparum* parasites are equally sensitive to artesunate.

Since the dawn of antimicrobial drug era, resistance has shadowed the success of infectious disease therapy. In a 2003 Institute of Medicine Report, 'Microbial threat to health', antimicrobial resistance was noted as a paramount microbial threat of the 21st Century (Smolinski *et al.*, 2003). Resistance to artesunate monotherapy had earlier been reported from multi-drug resistant areas of Indonesia and Thailand where poor therapeutic response was associated with both five-day and seven-day treatment courses of uncomplicated *falciparum* malaria (Tjitra *et al.*, 1995; Luxemburger *et al.*, 1998). A recent report of artesunate resistance by *P. falciparum* came from Sierra Leone in West Africa (Sahr and Willoughby, 2001). The recrudescence results from the rapid elimination of the drug (White, 1997), which was not allowed to occur or the presence of the second drug (lumefantrine) with longer elimination half-life ensured effective drug levels for days thereby leading to elimination of parasites (as happened in case 2 of this study). This clearly demonstrates the superiority of combination therapy over monotherapy. It has been reported that radical cures can be achieved when artemisinins are combined with drugs such as mefloquine, sulfadoxine-pyrimethamine, or doxycycline (Looreesuwan *et al.*, 1992; Nosten *et al.*, 1994; Von Siedlein *et al.*, 2000; World Health Organization, 2005).

Widespread prescription of artesunate monotherapy, its intake in sub-optimal doses and its availability over the counter in private pharmacy may accelerate the spread of the emerging resistance to artesunate. This study provides evidence against the use of artesunate monotherapy for treatment of uncomplicated malaria and emphasizes the use of drug combinations for malaria treatment.

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