

Case Report

Therapeutic failure after regimen with artemether-lumefantrine combination therapy: a report of three cases in Benin City, Nigeria

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Abstract

Artemisinin-based combination therapy (ACT) is recommended by the World Health Organization for the treatment of uncomplicated malaria. Currently, there appears to be a downward trend in the efficacy of ACT in some parts of sub-Saharan Africa because some patients have been positive for *Plasmodium* parasite 3 days after artemether-lumefantrine treatment. We reported three cases of possible parasite resistance to artemether-lumefantrine therapy. All subjects had complete parasite clearance when treated with other antimalarial drugs. This observation necessitates the urgent need to re-evaluate artemether-lumefantrine medication in Nigeria since it is one of the most commonly used ACT drug.

Keywords: Malaria. Nigeria. Artemether-lumefantrine. Resistance.

INTRODUCTION

Artemisinin-based combination therapy (ACT) is recommended by the World Health Organization (WHO) for the treatment of uncomplicated malaria. ACT is effective because it reduced the surge in malaria mortality from approximately 1000000 to 429,000 deaths between 2005 and 2015¹. Currently, there appears to be a downward trend in the efficacy of ACT because some patients have been positive for *Plasmodium* parasite 3 days after artemether-lumefantrine treatment in some parts of sub-Saharan Africa. Ajayi and Ukwaja reported three clinical cases of possible malaria resistance to ACT in the eastern part of Nigeria, and these data were further substantiated by Wundermann and Osiki in 2017, who reported five clinical cases in northern Nigeria.

Incomplete parasite clearance in ACT has also been noted in southern Nigeria, particularly in Edo and Delta states,

because individuals in this region showed malaria symptoms after artemether-lumefantrine treatment. However, their conditions improved after subsequent treatment with other antimalarial drugs. Thailand and Cambodia are two of the five countries where resistance to ACT has been scientifically documented. The probable reason for artemisinin resistance is k13 mutation, which increases the survival rate of the ring-stage parasite². There is a need to re-evaluate the quality of artemether-lumefantrine therapy administered to patients with malaria since this may be a contributing factor in endemic areas. Therefore, this study aimed to raise awareness that may intensify collective efforts geared toward reconnaissance of areas with *Plasmodium* parasite resistance and recrudescence after artemether-lumefantrine treatment.

CASE REPORT

Case one

A 58-year-old woman presented with a 4-day history of weakness, cold, polydipsia, cough, headache, and fever. On examination, she was febrile (++) with a temperature of 38.6°C; pulse rate was 92 beats per minute, respiration rate was 26 counts per minute, and blood pressure was 150/80 mmHg. The provisional diagnosis was malaria and upper respiratory tract

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infection. Blood sample was collected for malaria parasite test, packed cell volume (PCV) measurement, random blood sugar (RBS) test, and retroviral screening (RVS). Blood film examination revealed the presence of *Plasmodium falciparum* parasitemia (++) , PCV of 34%, RBS level of 87 mg/dL, and negative RVS. The patient was administered oral artemether-lumefantrine (Coartem, Novartis Pharma AG, Switzerland) and paracetamol (Panadol Extra, GlaxoSmithKline Consumer Nigeria Plc, Ogun State, Nigeria).

Three days after treatment, the patient returned with previously described symptoms. Repeated blood film examination showed the presence of malaria parasites (+). The patient was admitted and treated with intravenous infusion of dextrose saline infused with quinine hydrochloride (600 mg) and vitamin B complex injection 2 mL every 4 h \times 3 doses alternated with plain infusion of 5% dextrose water. The patient was also administered intravenous paracetamol (600 mg) every 8 h, ceftriaxone injection (1 g) every 12 h, and oral chlorpheniramine maleate B.P. and ammonium chloride B.P. (Coflin syrup, Vitabiotics (Nig.) Ltd, Lagos, Nigeria) 10 mL every 12 h. After 48 h, symptoms subsided, and repeated blood film examination on days 7 and 14 were negative for malaria parasitemia.

Case two

A 24-year-old man presented with a 2-day history of fever, weakness, cephalgia, and body pain. On examination, he had a temperature of 37.5°C, pulse rate of 86 beats per minute, respiration rate of 22 counts per minute, and blood pressure of 110/70 mmHg. The provisional diagnoses were malaria and typhoid fever. Blood samples were collected for film examination for malaria parasites, full blood count, and Widal test. Blood film examination revealed the presence of *P. falciparum* parasitemia (++) , white blood cell (WBC) count of 4,000/mm³, PCV of 40%, hemoglobin level of 13.3 g/dL, and normal platelet and red blood cell count. The neutrophil level was 52%, lymphocyte level 47%, basophil nil, monocytes nil, and eosinophil 1%, and Widal test was insignificant. The patient was treated with oral artemether-lumefantrine (Coartem DS), paracetamol, and multivitamin.

Four days after treatment, the patient was still febrile with headache, with temperature of 37.1°C and normal pulse and respiratory rates. Repeated blood film examination showed the presence of malaria parasites (+). The patient was admitted and treated with intravenous infusion of dextrose saline infused with quinine hydrochloride (600 mg) and vitamin B complex injection 2 mL every 4 h \times 3 doses alternated with plain infusion of 5% dextrose water. The patient was also administered intravenous paracetamol (600 mg) every 8 h. On the third day, symptoms subsided, and repeated blood film examination showed no parasites on days 7 and 28.

Case three

A 33-year-old man presented with history of fever, indigestion, poor appetite, and restlessness. He received amoxicillin-clavulanate potassium (Augmentin®, SmithKline Beecham Pharmaceuticals, West Sussex, UK) antibiotic one

week before presentation. On examination, he had a temperature of 37.6°C, blood pressure of 100/70 mmHg, respiratory rate of 28 counts per minute, and pulse rate of 80 beats per minute, was not pale and anicteric, and was warm to touch. Chest was clinically clear, and the abdomen was full with mild epigastric tenderness. The provisional diagnosis was peptic ulcer disease or malaria. Blood samples were collected for PCV, film examination for malaria parasites, fasting blood sugar (FBS) test, and urinalysis and a general abdominal scan were performed. Blood film examination revealed the presence of *Plasmodium falciparum* parasitemia (++) , FBS of 85 mg/dL, and PCV of 45%. Urinalysis revealed clear urine with pH 5, yellow color, and proteinuria (+). The patient was treated with oral artemether-lumefantrine (Lonart®), metronidazole (Flagyl®), amoxicillin capsule (Amoxil®), omeprazole, and multivitamin.

Three days after treatment, the patient was still febrile with temperature of 37.9°C and had poor appetite and constipation. Repeated blood film examination showed the presence of malaria parasites (+). The patient was admitted and treated with intravenous artesunate 120 mg at 0, 12, and 24 h, and paracetamol injection 600 mg every 8 h. Intravenous omeprazole, metronidazole, hyoscine butylbromide (Buscopan®) (i.m.), and ceftriaxone were also administered to the patient. Repeated blood film examination on day 7 showed no malaria parasite, and the patient's condition was significantly improved.

DISCUSSION

The WHO recommended ACT as a first-line treatment for uncomplicated malaria due to the emergence of strains of *Plasmodium falciparum* resistant to chloroquine and other antimalarial drugs³. ACT is preferable to monotherapy because the artemisinin component is fast acting and kills most parasites at the start of treatment, while the long-lasting partner kills other residual parasites. The mode of action of the ACT drug may help prevent the early emergence of parasite strain resistant to artemisinin derivatives. In sub-Saharan Africa, artemether-lumefantrine remains one of the most commonly used ACT drug for the treatment of uncomplicated *Plasmodium falciparum* malaria, and a pooled analysis showed a 28-day parasitological cure rate of 97% in malaria-endemic areas⁴.

Presently, the greatest challenge of ACT is the emergence of resistant strains of *Plasmodium falciparum*⁵. Artemisinin resistance has emerged and spread independently in some areas of mainland Southeast Asia⁶. In Africa, ACT-resistant malaria is uncommon, and one of the earliest reports on late clinical failure of ACT was on a Japanese traveler who visited Sierra Leone⁷. Suboptimal lumefantrine concentration was suggested to be responsible for the observed late clinical failure⁷. Another report showed adequate lumefantrine concentrations and suggested that the clinical failure was as a result of parasite recrudescence rather than recurrent infection⁸. Although ACT-resistant malaria is rare in Nigeria, three cases of treatment failure in ACT was reported in 2013⁹ and another two cases in 2017¹⁰.

According to the WHO classification of response to treatment¹¹, the cases in this study had early treatment failure (ETF). The cases also fulfilled the WHO definition for suspected

artemisinin resistance since there were detectable parasitemia 72 h after treatment with antimalarial drugs¹². The common availability of counterfeit drugs for the treatment of diseases, such as malaria and typhoid fever, is a major problem in Nigeria. Thus, the observed treatment failure in this study may have been caused by substandard artemether-lumefantrine combination. Aside from the possibility of counterfeit drugs causing treatment failure, ACT-resistant parasites may have played a role, as several other patients who received the same artemether-lumefantrine combination responded positively and were successfully treated. Interestingly, all studied cases showed adequate parasitological and clinical response to quinine and artesunate. Therefore, the ETF described in these patients may have been a result of ACT-resistant malaria. Epigastric tenderness associated with the digestive system presented in case 3 may be responsible for the treatment failure due to decreased absorption and increased excretion of drug, and in most cases, patients with ulcerative stomach vomit the ingested drug after oral administration. Hence, treatment with intravenous artesunate allowed parasite clearance and improvement of the patient's condition. Additionally, some vitamins, such as vitamin C and E, are known to reduce the efficacy of antimalarial drugs and may contribute to ACT failure. These vitamins may have reduced the oxidative environment in the host, thereby promoting parasite survival since the parasite is highly sensitive to free radicals. Hence, ACT failure in some of these patients may be associated with the presence of multivitamins. Proteinuria in case 3 may be an indication of renal dysfunction.

Although ACT-resistant malaria is uncommon in Nigeria, there is an urgent need for increased surveillance to monitor the spread and re-examine the efficacy and quality of ACTs. Furthermore, it is essential to re-evaluate the use of artemether-lumefantrine combination in Nigeria since it is one of the most commonly used ACT drugs.

Conflict of Interest

The authors declare that there is no conflict of interest.

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