Case Report/Relato de Caso

Subdoses of primaquine in overweight patients and malaria *vivax* relapses: report of two cases in the Federal District, Brazil

Subdoses de primaquina associadas a recaídas de malária *vivax* em pacientes com peso elevado: relato de dois casos no Distrito Federal

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ABSTRACT

Two cases of malaria by *Plasmodium vivax* relapsed after treatment with drugs in doses recommended by the Ministry of Health are presented. Both patients were overweight and were followed in the Federal District, an area considered free from vector transmission of the disease. Radical cure was obtained after medication with the same drugs in weight proportional doses.

Key-words: Vivax malaria. Primaquine. Relapses.

RESUMO

São apresentados dois casos de pacientes com malária por *Plasmodium vivax* que apresentaram recaídas após tratamento com medicamentos em doses indicadas pelo Ministério da Saúde. Ambos os pacientes tinham pesos elevados e foram acompanhados no Distrito Federal, área considerada sem transmissão vetorial da doença. A cura radical foi obtida após medicação em dose proporcional ao peso corpóreo dos pacientes.

Palavras-chaves: Malária vivax. Primaquina. Recaídas.

INTRODUCTION

It is common practice in Brazil to treat malaria with drug in doses that are based on age groups instead of patient weight. However, this can lead to insufficient quantities of drug delivery and hence to clinical relapses that may erroneously be confused with drug resistance or reinfection. This study reports two patients with relapses of malaria caused by *Plasmodium vivax*. Both patients weighed over 70kg and were initially treated with standard-dose regimens of antimalarial agents based on age group.

CASE REPORT

Case 1

A 51 year-old male businessman with a body mass index (BMI) of 32.5kg/m^2, resident in Ceilândia (DF) traveled to Ariquemes (RO) in July 2004, and on returning to DF showed symptoms of malaria. On July 22nd, 2004, a blood smear revealed *P. vivax* (+++), with 10,651 parasites/mm^3, and the patient was treated with 10 tablets of chloroquine for 3 days (4 tablets of 150mg of active base on day 1, followed by 3 tablets on days 2 and 3), supplemented with 14 tablets of primaquine for 7 days (2 tablets of 15mg per day). On March 8th, 2004, the blood smear was negative, but it became positive again on August 26th, 2004. The same initial treatment regimen was administered and follow-up blood smears on 08/30, 09/16, 9/24 and 10/18 were negative. However, on October 25th, 2004, the test became positive again, with 11,308 parasites/mm^3, and the patient was then treated with four tablets of mefloquine, 250mg (single dose) and 14 tablets of primaquine for 7 days (2 tablets 15mg daily). Five successive blood smears were negative, but in December 15th, 2004, the patient was positive again. The first treatment regimen was reintroduced, followed by two tablets of chloroquine weekly administered for 90 days. The ten following blood smears were negative until April 28th, 2005, when the test became positive once again and the patient was treated with 10 tablets of chloroquine for 3 days followed by 14 tablets of primaquine for 14 days. Six successive blood smears were negative; however, on July 14th, 2005, parasitemia reappeared. A new treatment regimen was administered with 10 tablets of chloroquine for 3 days, followed by 21 tablets of primaquine for 21 days, and treatment was continued with 2 tablets of chloroquine weekly administered for 90 days. Since then, eleven blood smears performed up to January 1st, 2006 were negative. Throughout the monitoring period, the patient remained in the Federal District, an area not considered endemic for malaria.

Case 2

A 51 year-old male lawyer, farmer and artist, residing in Lago Sul (DF) and whose BMI was 30.4 kg/m^2, traveled to Sao Felix do Xingu (MT) in early September 2004. On September 9th, 2004, when he was in Palmas (TO), he was diagnosed with vivax malaria and standard treatment was proposed with 10 tablets of chloroquine for 3 days (4 tablets of 150mg of active base on day 1, followed by 3 tablets on days 2 and 3), supplemented with 14 tablets of primaquine for 7 days (2 tablets of 15mg per day). Returning to Brasília, he presented malaria relapse in 10/20 and was treated with the previous regimen. The following blood smears were negative, but parasitemia recurred on December 21st, 2004 and the patient was treated with four tablets of mefloquine and 14 tablets of primaquine for 7 days. The following five blood smears were negative; however, the test was positive on February 17th, 2005 and the patient was treated with the same regimen of antimalarial drugs, followed by two tablets of chloroquine weekly administered for 90 days. The following blood smears in February, March and April were negative. However, the patient proved positive parasitemia again in September 16th, 2005.

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Once more, the patient was treated with 10 tablets of chloroquine for 3 days followed by one tablet of primaquine daily administered for 21 days, continuing treatment with 2 tablets of chloroquine weekly administered for 90 days. The last eight blood smears, up to January 6th, 2006, were negative.

DISCUSSION

Numerous factors can interfere with the efficacy of antimalarial drugs, including certain factors related to the host (drug absorption, adherence to treatment, reinfection, immunity impairment, pharmacogenetic factors), the parasite (drug resistance), or even to correctly indicated treatment (deterioration of the drug quality, subtherapeutic doses)[1]. In both cases reported here, first-order factors were rejected due to the absence of clinical malabsorption indicators, such as diarrhea, vomiting and gastrointestinal alterations; lack of adherence was excluded, since administration of the drugs was supervised by Health Department staff; reinfection was unlikely to have occurred due to the permanence of patients after diagnostic confirmation within the Federal District, an area considered free from vectorial transmission; the patients did not present clinical evidence of immune impairment; though the possibility that pharmacogenetic factors might have contributed to the failure of standard dose treatment could not be excluded.

Primaquine enhances the effect of chloroquine against asexual forms and prevents relapses by eliminating hypnozoite forms[2,3]. A dose of 30mg/d for adults for seven days was more effective than 15mg/d for the same period[4]. The development of hepatic resistance to asexual forms of *P. vivax* to primaquine[5] is an emerging public health problem, since association of primaquine and chloroquine remains first line treatment of vivax malaria. In these reported cases, it was possible to exclude drug resistance and regional strains of the parasite with different response to primaquine[6], because of the successful response to the second attempt at treatment with the same drugs. Chemical deterioration of the administered drug is unlikely, because its quality is assured by the Ministry of Health and by appropriate storage conditions.

Uncomplicated vivax malaria is treated in Brazil with standard doses of drugs according to age group. Longer regimens with the same total dose of primaquine have shown lower risk of relapse[7]. In the cases reported here, the doses chosen were those recommended for patients weighing 50kg or greater, which appears to be insufficient. While several studies have shown the deleterious effect of malnutrition on malaria infection, sometimes determining growth restriction of children in endemic areas, sometimes worsening the prognosis of the disease[8], the relationship between malaria and obesity is poorly defined. The antimalarial treatment of obese patients based on doses equivalent to those of patients weighing 50kg has proven to be subtherapeutic. In order to correct this failure, the treatment standards established by the Ministry of Health already include recommendations to correct the dose of antimalarial drugs for patients over 70kg[9]. In cases of malaria recurrence, a 50% to 100% increase in the initial dose of primaquine is recommended[10].

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