Recrudescence of Falciparum Malaria Following Treatment with Halofantrine

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Introduction

In 1991, some 90 countries or areas where 42% of the world’s population resided were considered malarious and estimation of malaria mortality worldwide per year was 1.5 to 3 million1). The Ministry of Justice reported that the total number of Japanese who went abroad was as many as 11,790,699 and the number of foreigners who entered Japan for the first time was 3,251,753 in 1992. Consequently the reported annual number of imported malaria cases increased to not less than 1002), and therefore malaria is no longer considered a very rare infectious disease in Japan. Indeed, there have been a number of severe cases of malaria because of the delay in the onset of effective treatment3'4). Malaria should first be presumed if a patient complains of high fever after a visit to a tropical country. Proper diagnosis and treatment should be instituted immediately.

One of the antimalarials which has been highlighted for its effectiveness is halofantrine. This drug has been used for treatment of human malaria since 1984, and to date, clinical studies have involved more than 2500 patients in 30 countries5). Several patients successfully treated with halofantrine without any treatment failure have also been documented in Japan6)-10). However, in this paper, we discuss the first case of recrudescence of falciparum malaria following treatment with halofantrine.

Case Report

The patient was a 26-year-old Japanese male non-governmental organization volunteer working in Thailand, who had a past history of Plasmodium vivax malaria in July 1989 and Plasmodium falciparum malaria in April 1990. The clinical course of the latter infection is illustrated in Fig. 1.: P. falciparum parasites were detected in a thin blood smear at the density of 0.22% red blood cells. The indirect fluorescent antibody test (IFAT) revealed a P. falciparum antibody titer of 1:64. An in vitro drug susceptibility test revealed that the P. falciparum parasites were chloroquine resistant (50% inhibitory concentration: IC50=120 nM) but pyrimethamine susceptible (IC50=10 nM). He was successfully treated with Fansidar™ (pyrimethane 25 mg + sulfadoxine 500 mg/tab x 3). The current episodes of malaria developed after he visited Thailand from March 1 to June 12, 1993. During this period, he was on weekly quinine prophylaxis (dose unknown), and took additional self-medication of quinine during several episodes of fever, for relief of the fever and headaches. His temperature was 38°C on June 21, and 37.6°C on admission to Tokyo Metropolitan Komagome Hospital on June 23, and he had chills, a headache and general...
fatigue. He was also anemic, slightly icteric but not hepatosplenomegalic. Microscopical observation revealed *P. falciparum* parasites in a thin blood smear at 0.13% red blood cells. Two tablets each of Halfan™ (halofantrine hydrochloride 233 mg base/tab) were administered orally at 17:00 and 23:00 on June 23, and 06:00 on June 24, with the informed consent of the patient. His temperature was normal and the ring forms of the parasites had disappeared by June 25. No adverse reaction was observed after the administration of Halfan™. But in less than a month, he showed fever again; he had a headache on July 16, and on July 17 felt chills and his tempearture was 39°C. He was seen at the out-patient department of Tokyo Metropolitan Komagome Hospital on July 20 and his illness was diagnosed as recrudescence of *P. falciparum* malaria, confirmed by both microscopy and the IFAT (*P. falciparum* titer 1:256). Administration of Lariam™ (mefloquine HCl 250 mg/tab × 2, for 2 days) and Minomycin™ (minocycline 100 mg/cap × 2, for 7 days) resulted in complete remission.

**Discussion**

Halofantrine is an antimalarial drug, unrelated to existing antimalarials, effective against all species, very well tolerated, and with a simple dosage regimen. It belongs to a class of compounds, the phenanthrene-methanols, which do not share chemical structure with any other antimalarials, and is therefore particularly effective in the treatment of drug-resistant malaria. Treatment with halofantrine cleared the parasites from the blood within 7 days in more than 99% of 1315 evaluable patients with falciparum malaria, and recrudescence occurred in only 78 patients (6%). The mean parasite clearance time was 57.9 hours and the mean fever clearance time was 50.2 hours in *P. falciparum* malaria. The patient now reported was thought to have been successfully treated with Halfan™; parasites were cleared by 48 hours and the fever fell to normal in 28 hours. The patient was discharged from the hospital very soon after showing rapid symptomatic improvement. However, contrary to our expectations, recrudescence was observed on the 23rd day after Halfan™ administration was started. He had to be treated with a different antimalarial. Currently, Fansidar™ is the only antimalarial drug commercially available in Japan, and imported malaria resistant to not only chloroquine but also Fansidar™ has been on the increase. Therefore particular attention has to be focused on prompt and proper treatment with safe and suitable antimalarials. General use of halofantrine is expected in Japan; however, continuing and dedicated effort to confirm its efficacy should not be neglected.

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References


ハロファントリンによる治療後再燃を起こした熱帯熱マラリアの1例

(平成5年10月18日受付)
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要旨

我々は輸入熱帯熱マラリアの治療にハロフォン

トリンを試みた。ハロファントリンは1984年に臨

床試験が開始され、日本国内でも効果を示した症

例が報告されている。国内輸入マラリアは年間100

例以上報告されているが、入手可能なマラリア薬

は限られている。また、クロロキン及びファシダールに耐性のマラリアも報告されはじめており、有効かつ安全な治療薬の導入に特徴的な関心が

払われてしかるべきである。現在ハロファントリン

は最も注目されるべき新しい抗マラリア薬と考え

られているが、本症例ではハロファントリン治療後

再燃をきたした（国内初再燃例）。今後さらにその有

効性を例証していく必要性が強く示唆された。