Prolongation of the QT Interval Observed in a Japanese Patient with Vivax Malaria Following Treatment with Halofantrine

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Introduction

In 1992, some 90 countries or territories where 42% of the world's population resided were considered malarious and estimation of deaths from malaria worldwide per year were in the order of 1.4 of 2.8 million¹⁾. The higher the number of Japanese who go abroad becomes (the total number in 1994 was 13,578,934: Records of Statistical Division of the Ministry of Justice), the greater is the risk of their contracting malaria. Indeed, the reported annual number of imported malaria cases increased to not less than 100²⁾. Now, malaria should first be presumed if a patient complains of a high fever after a visit to a tropical country. And the importance of instituting prompt diagnosis and proper treatment should also be stressed.

One of the antimalarials which has been highlighted for its effectiveness is halofantrine. This drug has been used for treatment of human malaria since 1984³⁾, and to date clinical trials have involved about 3.4 million patients in more than 30 countries (personal communication). Several patients successfully treated with halofantrine without any treatment failure have also been documented in Japan^{4)~8)}. However, in 1993, a clinical study involving 400 patients on the Thai-Burmese border revealed cardiac effects of antimalarial treatment with halofantrine, including one sudden death after the treatment⁹⁾. There have also been some spontaneous reports of serious ventricular dysrhythmias with prolongation of the QT intervals, rarely associated with death^{10)~12)}. The pharmaceutical company producing Halfan[®] has reported 8 cardiac arrests, leading to 6 deaths, when a higher dose than recommended was used, there was recent or concomitant treatment with mefloquine, there was pre-existing prolongation of the QT interval or the patient had a thiamine deficiency. Finally, the World Health Organization (WHO) announced a "drug alert" on halofantrine advising a change in recommendations for its use¹³⁾. In the present paper, we discuss the first Japanese vivax malaria patient whose QT interval was prolonged after treatment with halofantrine.

Case Report

The patient was a 22-year-old Japanese male college student, who was in India and Thailand

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from July 23 to August 31, 1994. He complained of fever (40°C) with watery diarrhoea on September 8, and was admitted to National Nishi-Saitama Chuo Hospital on the following day. He was then suspected of contracting dysentery and was treated with an antibiotic. Although he recovered from his diarrhoea soon after the drug therapy, he was still showing fever, chills and sweating every other day. Non-steroidal anti-inflammatory drugs (NSAID) were vainly administered on September 10, 14, 16, and 18, until *Plasmodium (P.) vivax* was detected in his peripheral blood smear by microscopical observation at a parasitemia of 0.5% of red blood cells. Antibody titration by the indirect fluorescent antibody test (IFAT) also supported the diagnosis (anti-*P. vivax* antigen titer=1:1024, anti-*P. falciparum* antigen titer=1:4, on Sept. 18). Two tablets each of Halfan® (halofantrine hydrochloride 233 mg base/tab) were administered orally at 12:00, 18:00 and 24:00 on September 20, with the informed consent of the patient. The clinical course of *P. vivax* parasitemia, body temperature, hematological data, and IFAT titers is shown in Fig. 1. His temperature became normal within 9 hours of the first administration of 2 tablets of Halfan® (21:00 on September 20), and *P. vivax* parasites had disappeared by September 23. He was then treated with primaquine (15 mg/day for 14 days), and no relapse occurred after the treatment. Hematological recovery was already noted on September 26, and the patient was discharged from the hospital on October 3.

The patient was monitored by electrocardiography (ECG) from one day before Halfan® administration (Sept. 19) until the day of his discharge (Oct. 3). Although he seemed to be successfully treated without any complaints of side effects of the drug, cardiac effects of halofantrine were recognized on the ECG. The QT interval was observed to be prolonged on September 21 and 22 (0.52 sec.) (Fig. 2), and became normal by September 26 (0.40 sec.) (Fig. 3). Sporadic arrhythmia was also detected on September 21. However, the QRS interval was unaffected by the drug.

Fig. 1 Clinical course of the disease

Fig. 2 The patient's electrocardiogram on September 21

Fig. 3 The patient's electrocardiogram on September 26

Discussion

Halofantrine is an antimalarial drug which is effective against all species of *Plasmodium*, very well tolerated, and has 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 falciparum malaria³⁾. Although resistance of vivax malaria to chloroquine has occurred only occasionally so far, it is now firmly established in the island of New Guinea (Indonesia and Papua New Guinea)^{14,15)}. Therefore, it has to be taken into consideration that Halfan[®] can be the drug of first choice even for patients who have contracted vivax malaria. In *P. vivax* malaria, the mean parasite clearance time was 62 hours and the mean fever clearance time was 42 hours after treatment by Halfan[®]. The patient reported here was apparently thought to have been successfully treated; parasites were cleared by 69 hours and the fever fell to normal in 9 hours, without any signs or symptoms of the side effects of the drug. However, ECG revealed by dysrhythmias with prolongation of the QT intervals following treatment with Halfan[®]. These ECG changes were reported to be brought about by the increased myocardial concentrations of halofantrine or its biologically active metabolite⁹⁾, but not associated with desbutylhalofantrine (one of the metabolites of halofantrine)¹²⁾. And the fact that these effects are similar to those of quinine¹⁶⁾ suggests caution in treating patients previously administered quinine (or vice versa)¹²⁾. In accordance with advice from the pharmaceutical company, WHO announced a drug alert for halofantrine¹³⁾ to reduce the cardiac effects of the drug to a minimum: a) It is contraindicated in patients with a family history of congenital QT prolongation. b) It is not recommended for usage in combination with drugs or clinical conditions known to prolong the QT interval or in patients who may suffer from thiamine deficiency. c) It should not be administered to patients with severe

electrolyte imbalance. d) The treatment should not exceed the recommended total dosage of 24 mg/kg given as 8 mg/kg 3 times at 6-hour intervals. e) It should be administered on an empty stomach (i.e. not given in association with food). f) It should only be used as emergency self-medication for presumptive therapy in those patients known to have normal QT intervals. Abiding by the conditions mentioned above, we experienced the first case of vivax malaria in a Japanese patient who showed abnormal ECG findings following treatment with halofantrine. Further careful studies on individual Japanese patients to confirm its efficacy or tolerance should be required, before halofantrine is generally used in Japan.

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ハロファントリンによる治療後、心電図上に一過性のQT時間 延長が認められた三日熱マラリア日本人症例

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要 旨

ハロファントリンは1984年よりマラリアの臨床治験が開始され、本邦においてもその優れた有効性が報告されてきている。しかしながら1993年より、本薬剤投与後の心電図上のQT時間延長を伴う心筋に対する重篤な障害が諸外国において報告されだした。われわれは三日熱マラリアの22歳の

日本人男性に、患者への説明とその同意を得てハロファントリンを投与したところ、自覚的な副作用は認められることなく患者は治癒に至ったが、薬剤投与後2日目、3日目に心電図上にQT時間の延長を一過性に認めた。本報告はハロファントリンの副作用と考えられる心電図上の変化を、日本人で初めて確認した症例と考えられる。