Agranulocytosis during malaria prophylaxis with Maloprim (pyrimethamine and dapsone)

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Summary

A case of agranulocytosis during malaria prophylaxis with Maloprim (pyrimethamine and dapsone) is described. At the recommended dose of one tablet weekly this is apparently a rare occurrence but highlights one of the hazards in a changing climate of malarial prophylaxis in which the use of Maloprim is increasing.

KEY WORDS: malaria, pyrimethamine and dapsone, agranulocytosis.

Introduction

The increasing emergence of chloroquine-resistant *Plasmodium falciparum* strains has led to a change in the pattern of prescribing for malaria prophylaxis. Two combination agents, Maloprim (pyrimethamine 12.5 mg and dapsone 100 mg) and Fansidar (pyrimethamine 25 mg and sulfadoxine 500 mg) are now recommended for use in chloroquine-resistant *P. falciparum* areas (Communicable Disease Report 52, 1982). We describe a case of agranulocytosis which occurred in association with Maloprim.

Case report

A 52-year-old man presented to his general practitioner within a few days of returning from a holiday in New Zealand. He had suffered general malaise for 5 days, sore throat and perianal tenderness for 3 days, and fever with rigors, nausea, diarrhoea and cough for 48 hr. A blood count revealed his haemoglobin to be 13.7 g/dl, white cell count $0.27 \times 10^9/l$ and platelets $333 \times 10^9/l$. No granulocytes could be seen on the blood film.

The patient was admitted to hospital within hours

of the blood test. He was severely prostrated, febrile and had a spreading perianal cellulitis. In addition he had marked pharyngitis and an inflamed area in the second toe cleft of the left foot. There was right-sided pneumonia and abdominal distension associated with paralytic ileus. Blood cultures subsequently grew *Escherichia coli* and a β -haemolytic streptococcus of Lancefield group B. Bone marrow aspirate revealed an absence of granulocytes and suppression of erythropoiesis but preservation of megakaryopoiesis. Abnormal laboratory findings included moderately raised bilirubin and liver enzyme concentrations.

The patient was nursed in protective isolation. He was treated initially with intravenous gentamicin, cefuroxime and metranidazole. In the light of the antibiotic sensitivities of the cultured organisms these were later changed to netilmicin, cefotaxime and benzyl penicillin. He received oral nystatin and chlorhexidine washes to the whole body. Folic acid supplements were given but steroids were not used. The patient remained severely ill for several days. From the second day antibiotic therapy was supplemented with daily granulocyte transfusions (consisting of buffy coat preparations from ten donors on each occasion). Seven days after admission his white cell count was still very low but he began to improve clinically and his fever settled. A repeat bone marrow aspiration on the following day showed early return of granulocyte activity. Thereafter he improved steadily over the next 2 weeks. His granulocyte count increased to supranormal levels associated with localization and early resolution of the cellulitic areas.

The only drug taken by the patient within months of admission was Maloprim, which he had been prescribed as antimalarial prophylaxis during his visit to New Zealand, travelling via Abu Dhabi, Singapore and Malaysia. He had taken a dose of one

tablet weekly for 8 weeks, the last tablet 5 days before entry to hospital.

Discussion

There has been considerable debate concerning prophylaxis against malaria in areas of *P. falciparum* chloroquine-resistance (Bruce-Chwatt, 1982; Onori, 1982). With increasing use of the combination preparations Maloprim and Fansidar reports of serious adverse reactions to these agents are appearing. Several reports of serious reactions to Fansidar (pyrimethamine-sulfadoxine) have been published recently, (Olsen, Loft and Christensen, 1982; Whitfield, 1982). These have been of a similar nature to the reactions observed with other sulphonamide-containing preparations particularly when formulated with an additional inhibitor of folate metabolism. With regard to agranulocytosis, the relative importance of pyrimethamine, an antifolate agent capable of causing megaloblastic anaemia, is debatable. Maloprim contains a reduced amount of pyrimethamine compared to Fansidar but dapsone is known to cause agranulocytosis on occasion. Nevertheless we have found only one report of this serious side effect in a patient who had been taking Maloprim at the manufacturer's recommended once-weekly dosage but who was also receiving other drugs and who died within 48 hr of admission (Rée, 1983). Herbertson and Robson (1983) observed a case of severe neutropenia in a patient who had been taking what was thought to be Maloprim once a week as prophylaxis against malaria but the nature of the preparation could not be confirmed. Other reports of agranulocytosis associated with Maloprim have been in patients taking a higher dose of one tablet twice a

week which may significantly increase the incidence of this reaction (Friman *et al.*, 1983; Whitehead and Geary, 1983).

Our case occurred in the United Kingdom following the patient's visit to New Zealand. Maloprim had been taken at the recommended dosage of one tablet weekly simply to cover passage through malarious areas in transit. With increasing use of the drug more cases such as ours can be expected and are likely to further fuel the debate concerning the safety of effective malarial prophylaxis.

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