Immunological effect of co-trimoxazole on platelets

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Summary and conclusions
Diminished survival of transfused platelets occurred in two patients given co-trimoxazole, and a third patient taking this drug developed thrombocytopenia. By means of an indirect immunofluorescence assay antibodies against donor platelets coated with co-trimoxazole were found in the sera in all cases. These antibodies were directed against the trimethoprim component of co-trimoxazole and not against sulphamethoxazole.

Co-trimoxazole is a potent antimicrobial agent and is advocated for treatment and prophylaxis in leukaemia. Hence its adverse effect on platelets is of great importance.

Introduction
Co-trimoxazole (trimethoprim-sulphamethoxazole), a potent antimicrobial drug, is effective in various infections. The antimicrobial activity is due to sequential blockade of the synthesis of folic acid: sulphamethoxazole competes with para-aminobenzoic acid in the synthesis of dihydrofolate, and trimethoprim inhibits dihydrofolate reductase, the enzyme that converts dihydrofolate to tetrahydrofolate.1 Reported haematological effects of co-trimoxazole2-4 mostly concern megaloblastic transformation, which probably results from the effect of trimethoprim on dihydrofolate reductase.1 It is not clear, however, whether thrombocytopenia or neutropenia or both in the absence of megaloblastic changes are also due to trimethoprim or caused by the sulphonamide component.2-4

Two patients receiving platelet transfusions showed diminished survival of transfused platelets during treatment with co-trimoxazole, and a third patient taking the drug developed thrombocytopenia and neutropenia. We therefore used an indirect immunofluorescence assay to test sera from all three patients against donor platelets coated with co-trimoxazole were found.

Subjects and methods

Patients and controls

Case 1—A 43-year-old man, suffering a blast crisis of chronic myelogenous leukaemia was treated with aggressive chemotherapy (daunorubicin, cytarabine, thioguanine, and cyclophosphamide) and total body irradiation, and given platelet transfusions because of thrombocytopenia. He then began a nine-day course of treatment with co-trimoxazole (2 tablets twice daily) for a bacterial infection. On day 3 of this treatment poor survival of transfused platelets was observed. When the course ended survival of transfused platelets became normal.

During co-trimoxazole treatment in case 2 the patient's platelets were infused with untreated platelets and those incubated with trimethoprim-sulphamethoxazole. These antibodies were directed against the trimethoprim component only.

During co-trimoxazole treatment in case 2 the patient's platelets were transfused with untreated donor platelets and those incubated with trimethoprim-sulphamethoxazole. Four weeks after stopping co-trimoxazole direct immunofluorescence on the platelets was negative with and without co-trimoxazole incubation. Nevertheless, when the platelets were incubated with co-trimoxazole the indirect immunofluorescence test became positive, indicating that the antibody was still present in his serum.
**Discussion**

Two of our patients showed decreased survival of transfused platelets during co-trimoxazole treatment. Since co-trimoxazole is advocated for treatment of streptococcal infections and prophylaxis in leukaemia,

awareness of this side effect is of great importance. Antibodies against platelets incubated with co-trimoxazole were detected in sera from these patients and in the serum of a patient who developed thrombocytopenia while taking co-trimoxazole. We think that the thrombocytopenia in case 3 and the poor survival of donor platelets in the other patients were probably caused by these antibodies,

since after stopping the drug the survival of donor platelets became normal and the thrombocytopenia disappeared.

In vitro experiments showed that the antibodies reacted against the trimethoprim component of co-trimoxazole,

suggesting that in our patients trimethoprim was responsible for the effect on platelets and not the sulphamethoxazole component.

The positive direct immunofluorescence test in case 2 during treatment with co-trimoxazole suggests that the binding of trimethoprim and antibody to the platelets also occurs in vivo. After treatment was stopped and trimethoprim was no longer present in the circulation, the test became negative. The direct immunofluorescence test, however, remained positive after incubation of the platelets with co-trimoxazole, showing that the antibody was still present and that the patient would still be at risk if the drug was readministered. These observations suggest that platelets coated with trimethoprim serve as a neoantigen leading to antibody production.

Drug-induced immune thrombocytopenia has been shown for several other drugs. The best known examples are quinine and quinidine,

but allylisopropylacetaminibicarboxamide; sulphafurazone, dipyrazamol, and phenytoin,

and rifampicin have also been implicated. Why some patients develop these antibodies and others do not remains a subject for further study.

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**References**


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