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 sulphonamethoxazole.

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.

Subjects and methods

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 myelogenous leukaemia was treated with aggressive chemotherapy (daunorubicin, cytarabine, thioguanine, and cyclophosphamide) and total body irradiation, and given platelet transfusions because of myelogenous leukaemia.

Case 2—A 20-year-old man received a bone marrow transplant for severe aplastic anaemia, and because of deep thrombocytopoenia he was given platelet transfusions. The platelets survived poorly during two periods of six days in which he received co-trimoxazole (2 tablets twice daily) for a staphylococcal infection. After stopping the drug survival of the donor platelets became normal.

Case 3—A 52-year-old woman was being treated for staphylococcal spondylodiscitis. Because of penicillin allergy (fever and neutropenia) co-trimoxazole 3 tablets twice daily was instituted. On about the 10th day of treatment neutropenia (20 x 10⁹ granulocytes/l (20 mm³)) and thrombocytopenia (100 x 10⁹ platelets/l (100 000 mm³)) were found. After withdrawing co-trimoxazole there was a slow recovery.

Controls—Five hospital inpatients with normal platelet counts taking co-trimoxazole for various infections and 10 healthy blood donors served as controls.

Methods

Platelet survival—Usually preparations from four different donors containing an average of 150 x 10⁹ platelets were transfused. In the absence of immunological destruction this would be expected to increase the circulating platelet count by 20-30 x 10⁹/l (20 000-30 000/mm³) one hour after transfusion (in an adult of about 70 kg). Survival of transfused platelets was regarded as poor when the increase was less than 10 x 10⁹/l.

Isolation of platelets—EDTA blood (1 part 3%, sodium EDTA and 9 parts blood) was centrifuged for five minutes at 150 g. The upper layer of plasma containing the platelets was washed three times with phosphate-buffered saline containing 0·3%, sodium EDTA, and a 1 x 10¹⁰/ml suspension was made in this same medium.

Indirect immunofluorescence—Sera from the patients and controls were tested against platelets from healthy donors. Two drops of platelet suspension were incubated with two drops of test serum for 30 minutes at room temperature. The platelets were then washed three times and the preparations examined by immunofluorescence microscopy.

Direct immunofluorescence—Platelets from case 2 were tested by direct immunofluorescence. Two drops of platelet suspension were incubated with two drops of TRITC-labelled goat-antihuman IgG(Fc) (Nordic Pharmaceuticals, Tilburg) for 30 minutes at room temperature. The platelets were then washed three times and the preparations examined by immunofluorescence microscopy.

Results

In the indirect immunofluorescence tests sera from all three patients were found to contain antibodies against platelets incubated with co-trimoxazole. These antibodies were directed against the trimethoprim component only (table).

During co-trimoxazole treatment in case 2 the patient's platelets were tested by direct and indirect immunofluorescence with his own serum; both tests were positive regardless of whether the platelets had been incubated with co-trimoxazole. 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.
Drug-induced immune thrombocytopenia has been shown for several other drugs. The best known examples are quinine and quinidine,\(^1\)\(^2\) but allylisopropylacarbamides\(^3\); sulphafurazole, diazepam, and phenytoin\(^1\); and rifampicin\(^1\) 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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ONE HUNDRED YEARS AGO During the last two months, there have been many cases of scarlet fever among the boys at Eton. As is well known, the boys are distributed in the town in the various houses of the tutors and dames. When a case of scarlet fever or other infectious fever appears in a house, the rule is for the tutor to send a circular to the parents of the boys in that particular house informing them of the fact that there is fever in it, and giving them the option of at once removing the boys or of allowing them to remain. If a second case occur in the same house, a second circular is at once addressed to the parents advising them of this. This, as far as it goes, is satisfactory; not so the rule, as we understand it, of the head master, which docs not merely regard as sore-throat, and therefore left at large. The isolation of doubtful cases is doubly useful; it prevents the further spread of infection. Such an inspection takes place at many large public schools—among them, we believe, Marlborough, Westminster, and Rugby. (British Medical Journal, 1879.)