Chlorpropamide-induced thrombocytopenia

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Summary
Thrombocytopenia is a rare complication of chlorpropamide therapy. An immunological mechanism is generally held responsible, but has never previously been proved. In the present case the existence of such a mechanism has been established.

Case report
The patient was an obese, 64-year-old Asian woman with newly-diagnosed diabetes. She was treated with a combination of metformin 850 mg b.d., chlorpropamide 500 mg daily and dietary carbohydrate restriction. Two weeks after treatment was started she developed haemorrhagic bullae in her mouth and extensive purpura on her limbs and trunk. She had taken no drugs other than metformin and chlorpropamide.

The platelet count was less than 10 × 10⁹/l, haemoglobin 14.0 g/dl, white cell count 4.2 × 10⁹/l and the blood film showed normal red cells. Tests for faecal occult blood were positive and there was microscopic haematuria. Serum fibrin degeneration products were not detected and the bone marrow was morphologically normal.

Oral hypoglycaemic therapy was discontinued and prednisolone begun. The platelet count steadily increased (see Fig. 1) and prednisolone was withdrawn after 14 days. At this stage, metformin was restarted and continued for 8 days without adversely affecting the platelet count which ultimately rose to 190 × 10⁹/l.

Methods
Blood samples were taken from the patient 1 week and 3 weeks after the onset of purpura. A further sample was obtained immediately before discharge from hospital some 4 weeks after purpura developed.

The samples were allowed to clot and the sera separated and stored at −20°C. Samples from three normal donors were collected and processed in a similar manner. Each serum, test and control, with and without chlorpropamide, was tested for evidence of drug-dependent platelet antibodies.

Inhibition of clot retraction
The delayed test of Shulman et al. (1964) utilizing normal platelet-rich plasma and incorporating magnesium chloride was modified by including an aliquot of drug solution in the reaction mixture. An equivalent volume of distilled water replaced the drug in the control series.

Anti-human globulin (AHG) consumption test
The test was performed according to Steffen (1960) modified in this laboratory in order to assess chlorpropamide involvement in a platelet 'anti-platelet' system.
Results

Results of clot retraction inhibition studies were inconclusive. The AHG consumption test showed a consumption of recovered AHG of two titre steps when the reaction mixture consisted of the patient’s serum, chlorpropamide and platelets. The same serum showed no consumption of AHG when distilled water or metformin replaced chlorpropamide. The normal control series, with and without the drug, showed no AHG consumption. Serum taken at 1 week was positive, at 3 weeks less so and the final specimen negative.

Discussion

The occurrence of profound thrombocytopenia complicating chlorpropamide therapy is a well recognized albeit rare phenomenon. De Gruchy noted eleven cases in the 5 years up to 1973 (De Gruchy, 1975) during which time the annual number of prescriptions for chlorpropamide in the U.K. alone exceeded half a million (Harris, 1971). Although it has been assumed that an immunological mechanism lies behind the thrombocytopenia, no in vitro demonstration of antibody has been made in such a case.

The mechanism by which thrombocytopenia arose was presumably peripheral in so far as the bone marrow contained plentiful megakaryocytes. However, the data presented do not distinguish between the possible immunological reactions which may have been responsible.

In general, it is thought (Miescher, 1973) that, rather than the drug forming an antigen in combination with the platelet, the antigen consists of a drug (hapten) plus protein binder. Antibody reacts with this combined antigen to form immune complexes which damage platelets, consuming complement in the process. The damaged platelets (the innocent bystanders) are removed by the reticuloendothelial system.

The place of steroid therapy is uncertain in such cases and withdrawal of all other drugs is clearly the most important therapeutic manoeuvre.

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