

Immune Thrombocytopenia Due to Antazoline (Antistina®)

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Antazoline (Antistina®)-induced thrombocytopenic purpura occurring on three occasions in a 21-year-old woman is reported. After withdrawal of the drug she recovered promptly. *In vitro* investigation demonstrated the presence of an antibody in serum, which in association with antazoline caused complement fixation when added to test platelets. Also platelet agglutinins could be detected in the patient's serum when antazoline was added. The reactions were drug specific and they could still be demonstrated 9 months after the last exposure to the drug.

Key words: antazoline; Antistina®; immune thrombocytopenia; side-effect; thrombocyte agglutinins.

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CLINICAL ASPECTS

The diagnosis of drug-induced immune thrombocytopenia is often difficult to establish. Provocation tests offer risks of harmful bleedings and should be avoided. The present study demonstrates a case with severe thrombocytopenic episodes due to antazoline (Antistina®) hypersensitivity. The diagnosis was confirmed by *in vitro* investigations detecting an antibody in serum which in association with antazoline elicited complement fixation when added to test platelets. Also agglutinins could be detected. These tests are highly specific but are at present limited to research laboratories. In thrombocytopenic purpura the possibility of drug-induced immune thrombocytopenia should be kept in mind.

Unexpected bleeding tendency often causes great anxiety, sending patients hurriedly to seek medical care. Thrombocytopenia is sometimes the cause, and this diagnosis is easily established by a platelet count or by an assessment of platelet numbers on a peripheral blood smear. If the patient has taken any medication, drug-induced thrombocytopenia should be suspected. In recent years reports of an association between thrombocytopenia and drugs have increased markedly. Drugs may produce thrombocytopenic purpura by three mechanisms: 1) bone marrow hypoplasia or aplasia; 2) direct thrombocytic toxicity; and 3) immune-related platelet destruction (7).

While thrombocytopenia is a well-known side effect of a large number of commonly used drugs, e.g. quinine, quinidine, gold salts, phenylbutazone, etc. (3, 7), only few reports of antazoline (Antistina®)-induced thrombocytopenia have appeared (1, 2).

CASE REPORT

The patient was a 21-year-old woman. She had never been pregnant or received any blood transfusions. Since early childhood she had each summer in June been troubled with sneezing, stuffy nose and red, itching eyes. Previously she had taken antazoline tablets during

periods with hay fever, followed by relief of the symptoms. In June 1978 she developed suggilations and petecchial elements on the body and extremities and was taken in ward. The day before she had taken antazoline 200 mg as tablets. At admission the thrombocyte count was $1 \times 10^9/l$, the leucocyte count $6.8 \times 10^9/l$ and the differential count was normal. The haemoglobin concentration in blood was 9.0 mmol/l. Bone marrow aspirate showed a well-differentiated cell distribution and there were many megacaryocytes with platelet production present. Treatment with oral prednisone was started and after 2 days the thrombocyte count was normal. After 2 weeks the prednisone treatment was stopped. Her hay fever re-appeared and she took 1 tablet of 100 mg antazoline. After 2 to 3 h she again developed universal thrombocytopenic purpura and felt sick. The thrombocyte count was decreased to $9 \times 10^9/l$ and treatment with corticosteroids was started immediately. In 3 days the thrombocyte count normalized. She did not take antazoline until April 1979, at which time she was on holiday in Italy. A few hours after the medication she again developed thrombocytopenic purpura. Again she was treated with prednisone and the thrombocyte count normalized quickly. On this occasion the association between the thrombocytopenia and the drug was detected, and she has never since had antazoline.

In vivo investigation

Skin prick test showed highly positive reactions towards birch (*Betula pendula*) and timothy grass (*Phleum pratense*) pollens. Inhalation challenge with timothy pollen was positive with a fall in peak expiratory flow from 480 l/min to 200 l/min after 15 min. During this challenge venous blood was examined every hour for 6 h and again 24 h later and the thrombocyte count was normal in all samples.

In vitro investigation

The serum of the patient was investigated for presence of complement-fixing and agglutinating antibodies active against normal platelets as well as autologous platelets. Technical details have been described previously (5). Investigations were performed in May 1979 and January 1980, and all tests, where antazoline (100 mg in 100 ml saline) and platelets were included in the reaction mixture, were positive, while relevant controls were negative (Table 1). The only exception was that the patient's serum + antazoline resulted in a weak complement fixation, which could support the mechanism proposed by Miescher (1973) as mentioned in the discussion. The complement-fixing platelet antibodies

Table 1
Complement fixation test

Patient serum heat inactivated	Complement	Platelets 300,000/ μ l	Antazoline 1 mg %	NaCl 0.9 %	Result
40 μ l	40 μ l	40 μ l	40 μ l	0	positive
40 μ l	40 μ l	0	40 μ l	40 μ l	weakly pos.
40 μ l	40 μ l	40 μ l	0	40 μ l	negative
40 μ l	40 μ l	0	0	80 μ l	negative
0	40 μ l	0	0	120 μ l	negative
0	40 μ l	40 μ l	0	80 μ l	negative
0	40 μ l	0	40 μ l	80 μ l	negative

The amount of complement fixation was measured using sensitized sheep blood cells. The complement fixing platelet antibodies in presence of antazoline had a titre of 1:16. The varying amount of NaCl in the individual test was added in order to keep the total volume constant. Human A B serum was used as complement.

in presence of antazoline had a titre of 1:16. The serum was not anticomplementary. Investigation of thrombocyte-aggregation in September 1979 was found normal. The patient's serum did not contain lymphocytotoxic antibodies.

The positive reactions were drug-specific as negative reactions were found with two other antihistamines, difenhydramine (Anautin®) and mepyramine.

DISCUSSION

The present study demonstrates the development of antazoline-induced immune-thrombocytopenia in a young woman with hay fever. The medication with antazoline had been without problems for many years. But thereafter she developed hypersensitivity to the drug resulting in prompt thrombocytopenic purpura after exposure to small amounts of the drug. *In vitro* investigations showed an antibody in her serum, which in association with antazoline caused complement fixation when test platelets were added and weak fixation when only the patient's serum was present. Thrombocyte agglutinins could also be detected in the presence of antazoline. The reactions were drug-specific as they could not be elicited by other antihistamines. This high specificity of drug-induced immune thrombocytopenia is a characteristic feature (5).

A mechanism by which the drug is involved in the development of thrombocytopenic purpura has been proposed by Miescher (1973). The drug, acting as a hapten, becomes bound to a plasma protein and induces antibodies which then bind to the drug forming an antigen-antibody complex. This complex for unknown reasons settles on the platelets which are then removed by the reticuloendothelial system. The platelets act in this way as "innocent bystanders" (6).

Drug-induced thrombocytopenia must be considered as a dangerous condition. Even small amounts of the sensitizing drug may elicit severe thrombocytopenia (4, 8). No specific treatment is available, but it is essential to withdraw the drug immediately. There is no evi-

dence that corticosteroids will increase the platelet count in most cases of drug purpura as they may do in idiopathic thrombocytopenic purpura. However, because of their effects on vascular integrity, the bleeding diathesis may decrease (7).

While still present in serum the antibodies do not exert any effect on the platelets in the patients when the drug is avoided. But after exposure to the drug the thrombocyte count will decrease immediately. This may be dangerous to the patient, and thus a provocation test must be avoided. The present case demonstrates the possibilities of testing the serum *in vitro* in the case of drug-induced immune thrombocytopenia. However, the *in vitro* tests are limited to research laboratories, and there are still great problems in performing these tests, because of some lack of sensitivity, which may be due to less potent antibodies, or due to the fact that the antibody is directed against a drug metabolite or that the drug is insoluble in water.

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