Serum Antibodies Against Desipramine as a Possible Cause for Thrombocytopenia

By Eliezer A. Rachmilewitz, R. Ben Dawson, Jr., and Bracha Rachmilewitz

In recent years more and more drugs have become implicated as causes of thrombocytopenia. In many instances correlations were made from clinical reports, and occasionally in vitro methods have demonstrated the presence of antibodies specific for a certain drug.1,2

In the present paper two cases were studied in which in vitro methods suggested that thrombocytopenia was induced by desipramine (Pertofrane®). The drug manufacturers have received reports on the occurrence of purpura in one patient taking desipramine and in 23 taking imipramine (Tofranil®).3 The two drugs are considered together because imipramine is metabolized in vivo to desipramine, and owes its pharmacologic activities to this demethylated metabolite.4 Platelet counts were done in 10 of the 23 patients who developed purpura while taking imipramine. Thrombocytopenia was noted in eight. No additional studies were done on these patients. To our knowledge, thrombocytopenia has not been proved to be associated with the use of desipramine.

Case Reports

Case 1. B.S.

A sixty year old, white married woman entered the New England Medical Center Hospitals on August 4, 1966 because of postprandial mid-epigastric pain. She had received the following medications daily: for one year, digoxin 0.25 mg. and hydrochlorothiazide 50 mg.; for four months, one iron tablet (Ferrosequel®); for two weeks, desipramine 25–50 mg.

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Physical examination was negative except for many scattered ecchymotic areas and petechiae on both arms. The liver and spleen were not palpable and no lymphadenopathy was detected.

Laboratory data included hemoglobin 12.8 Gm. per cent, hematocrit 38 per cent, white cell count 9,000 per cu. mm. with a normal differential count, and a reticulocyte count of 1.2 per cent. The platelet count on August 11 was 44,000 per cu. mm. Serum iron was 94 micrograms per cent. The Duke bleeding time was 4 1/2 minutes, Lee-White clotting time 9 minutes, and prothrombin time 15 seconds (85 per cent of normal). Tourniquet test was +4 positive. Liver function tests (BSP, SGPT and LDH) and serum protein electrophoresis were normal. Lupus preparation and rheumatoid factor were negative. A bone marrow biopsy was hypercellular in certain areas, and showed adequate numbers of normal megakaryocytes and normal maturation of all cells. A cholecystogram revealed multiple small stones.

Upon admission, only desipramine and iron were discontinued. No new petechiae or ecchymoses developed. Over 14 days the platelet count increased from 44,000 to 105,000 per cu. mm. with no therapy except digoxin and hydrochlorothiazide. Since the platelet response was thought to be inadequate, splenectomy was performed in addition to cholecystectomy on August 25. The spleen was slightly enlarged, weighing 220 Gm. Histologic examination was unremarkable.

The patient's postoperative course was uneventful. On the eleventh day after surgery the platelet count had risen to 775,000 per cu. mm. On that day serum and platelets were tested for the possibility of drug-induced thrombocytopenia. All drugs the patient had been taking were used in the tests.

Case 2. G.S.

A seventy year old, married man of Italian extraction entered the New England Medical Center Hospitals on September 1, 1966 for evaluation of thrombocytopenia. A month before, he had started taking desipramine 125 mg. daily. After 3 weeks of therapy, a routine blood count had revealed hemoglobin 12 Gm. per cent, hematocrit 38 per cent, white cell count 4,900 per cu. mm., differential count normal, and platelet count 66,000 per cu. mm. Desipramine was discontinued one week before hospitalization.

The patient had a history of malaria contracted at age 23 and successfully treated. A slight anemia, present for many years, had not responded to hematinics. Physical examination was normal except for enlarged spleen and liver, 4 and 6 cm. below the left and right costal margins.

Laboratory data on admission included hemoglobin 12.4 Gm. per cent, red blood cell count 5.69 million per cu. mm., hematocrit 40 per cent, and reticulocyte count 3.3 per cent. The platelet count on admission was 100,000 per cu. mm.; white cell count 6,900 per cu. mm. with a normal differential count. Serum iron and total iron binding capacity were 120 and 340 micrograms per cent respectively. Morphology of the red cells showed hypochromia and basophilic stippling. Hemoglobin electrophoresis showed 5.2 per cent fetal hemoglobin (normal control, less than 2 per cent). The serum bilirubin was 0.2 and 1.0 mg. per cent, direct and indirect, respectively. Serum protein electrophoresis and liver function tests were normal. Prothrombin time was 14.5 seconds (100 per cent), Coombs' test was negative. Bone marrow showed normoblastic erythroid hyperplasia, a slight increase in plasma cells, and normal megakaryocytes.

During hospitalization the patient remained asymptomatic and received no medication, and the platelet count remained 100,000 per cu. mm. A diagnosis of thalassemia trait was made. Serum and platelets were tested for the possibility of desipramine-induced thrombocytopenia.

METHODS

Demonstration of Antibodies

For detection of antibodies, three different types of tests were done using serum and platelets from both patients and normal controls.
Barium sulfate indirect agglutination test. This test, modified from Gilboa-Garber and Nelken, was performed on serum using desipramine, and for Patient 1, also with digoxin, hydrochlorothiazide and Ferrosequel. BaSO₄, 0.2 ml. of 3.5 per cent suspension in normal saline, was added to 0.2 ml. of several concentrations of the drug (antigen) in saline. After mixing, the tubes were observed for nonspecific agglutination of BaSO₄ particles. The highest concentration of drug not causing agglutination is the optimal concentration for coating the particles. Coating was done by mixing equal volumes of the optimal concentration of drug solution with the BaSO₄ suspension, allowing the mixture to stand at room temperature with occasional shaking, for 20 minutes. The coated particles were then washed twice with saline and resuspended to the original volume in saline containing 4 per cent normal rabbit serum (NRS) which had been inactivated at 56°C and adsorbed with washed human red blood cells. Two drops of this suspension were added to 0.2 ml. of serial dilutions of the serum to be tested for antibodies. The serum dilutions were done in saline containing 4 per cent NSR. The concentration of 8 mg. desipramine per 1 ml. was found to be optimal for coating the BaSO₄ particles. Results were read after 90 and 120 minutes.

Serum from normal adults was tested as described above, and the following additional controls were used with patients and normal sera:

a. Saline 0.2 ml. with 4 per cent NRS and uncoated barium sulfate suspension (absence of antigen-drug and antibody-serum).

b. Saline 0.2 ml. with 4 per cent NRS and coated barium sulfate suspension (presence of antigen-drug, absence of antibody-serum).

c. Each sample of tested serum, patients and normal, 0.2 ml. (diluted 1:5), and uncoated barium sulfate suspension (absence of antigen-drug, presence of antibody-serum).

Clot retraction inhibition test. This test was done by adding 0.2 ml. of heat-inactivated serum from each patient to 0.9 ml. of normal human platelet-rich plasma, containing 150,000 platelets per cu. mm. The platelet-rich plasma was prepared from 10 ml. fresh venous blood drawn into a polyethylene syringe containing 1 ml. of 1 per cent Na₂ EDTA-triton solution. Then 0.5 ml. of the drug solution (0.2 mg./ml. normal saline) and two units of thrombin were added and the mixture was observed for clot retraction. Higher concentrations of the drug resulted in delayed and incomplete clot retraction in the controls (normal serum or saline) and were therefore not used. The addition of calcium was not necessary for clot retraction to occur with normal serum or saline when Na₂ EDTA-triton was used to prepare the platelet-rich plasma. However calcium is necessary for clot retraction if Na₂ EDTA without triton is used. The reason for this difference, presumably due to triton, is not known. Although trace amounts of calcium are present in the Na₂ EDTA-triton, the quantity of calcium present is not sufficient for normal clot retraction in Na₂ EDTA without triton.

Platelet agglutination test. Platelet suspensions were prepared according to Nelken et al. and all tubes and syringes used were siliconized glass or polyethylene. After centrifugation the sedimented platelets were washed and resuspended in saline-EDTA-triton solution to a final concentration of 200,000 per cu. mm.; 0.02 ml. of platelet suspension and 0.02 ml. of the drug solution (8 mg./ml.) were added to 0.2 ml. of the test serum. The tubes were left at room temperature for 40 minutes and then centrifuged for 1 minute at 3,000 r.p.m. and the platelets were gently resuspended and examined under the phase-contrast microscope. 4+ agglutination was recorded when only large clumps of platelets were seen. If a few free platelets were also present, it was 3+. When free platelets were spread homogenously in the field with small clumps among them, 1+ agglutination was recorded. Other details and controls used are summarized in Table 2.

Characterization of the Antibody

Antibodies were characterized by four different procedures:

1. Sucrose-gradient ultracentrifugation of whole serum by a method modified from
Fig. 1.—Indirect barium sulfate agglutination test. The first four tubes, L to R, (serum of patient 2, dilution 1:16 to 1:128) show irregular clumping and agglutination of the BaSO_{4} particles coated with desipramine. Tubes 5 (saline control with coated particles) and 6 (patient’s serum, 1:1 dilution, with uncoated particles), show homogenous sedimentation of the BaSO_{4} particles.

Fudenberg et al. A sample of each fraction obtained was tested against desipramine-coated barium sulfate particles.

2. Reduction of immunoglobulins with 2-mercaptoethanol was done with the density gradient fractions which caused agglutination of the drug-coated barium sulfate particles. The fractions thus treated were then tested against desipramine-coated barium sulfate particles.

3. Immunoelectrophoresis was done by testing similar density gradient fractions against anti-human serum.

4. Ouchterlony micromethod was performed with each fraction which agglutinated the drug-coated barium sulfate particles using specific antisera (IgM, IgA and IgG).

**RESULTS**

**Demonstration of Antibodies**

**Indirect barium sulfate agglutination test.** Positive agglutination was recorded when definite irregular clumps could be seen in the desipramine-coated barium sulfate sediment and the supernatant became clear. When the tube remained opalescent and the coated particles sedimented uniformly as a regular compact circle, a negative result was recorded (Fig. 1). As shown in Table 1, the sera from both patients gave positive agglutination in all dilutions through 1:256. Normal human serum gave no agglutination in any dilution. All additional controls were negative. The serum of Patient 1, tested with the three other medications she had taken, showed no agglutination.

Repeated tests showed a decrease in antibody titers from 1:256 to 1:32 for Patient 1, and from 1:256 to 1:16 for Patient 2. Patient 1 had no detectable antibody when her serum was tested 17 months later.

**Clot retraction inhibition test.** In the presence of each patient’s serum with desipramine, clot retraction failed to occur (Fig. 2). When desipramine was omitted, clot retraction was prompt. There was no inhibition of clot retraction when the serum of Patient 1 was tested with hydrochlorothiazide. Serum obtained 17 months later failed to inhibit clot retraction with desipramine. A repeat test on serum taken from Patient 2, five months after the drug was stopped, still showed complete inhibition of clot retraction with desipramine. The controls with normal human serum or saline showed prompt retraction with and without desipramine. On each occasion the tests were repeated several times giving the same results.

*All sera obtained from Hyland Laboratories, Los Angeles, California.*
Table 1.—Anti-body Demonstration by BaSO₄ Agglutination *

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<th>1:16</th>
<th>1:32</th>
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*Positive agglutination marked ++++ is the greatest possible reaction; +++ is moderately strong agglutination.
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Fig. 2.—Clot retraction inhibition test with desipramine. Tubes 1 and 2, L to R, with serum of patients 1 and 2, show no clot retraction. Tubes 3 (normal human serum) and 4 (patient's serum without desipramine) show normal clot retraction.

Platelet agglutination test. A combination of each patient's platelets with his serum gave a positive clumping (+) (Table 2). With the addition of desipramine (8 mg./ml.) the clumping became much more pronounced (4+)

Table 2.—Platelet Agglutination Test

<table>
<thead>
<tr>
<th>Serum Diluted 1:4 in Na₂EDTA Triton</th>
<th>Desipramine Suspensions (8 mg./ml.)</th>
<th>Platelet Suspension</th>
<th>Diluent: Na₂EDTA Triton</th>
<th>Platelet Agglutination</th>
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*Indicates presence in the system.
Fig. 3.—Platelet agglutination test with desipramine (Phase Microscope 1000×).
(Above) Control with normal human serum shows free platelets. (Below) Serum of patient 1 showing 3+ clumping of platelets.
Fig. 4.—Ouchterlony diffusion plate. Center hole contains IgG antiserum. Note the confluent precipitation lines between antiserum and fractions 4 and 5 from each patient, L to R, counterclockwise. The lines are more prominent with fraction 4 from each patient.

as illustrated in Figure 3. When normal human serum was tested with normal or patients' platelets, with or without the drug, no agglutination occurred. When patients' sera were tested with normal platelets in the presence of desipramine, 3+ agglutination was seen, compared to 4+ agglutination with patients' platelets. No agglutination occurred when patients' sera was tested with normal platelets without the drug.

Characterization of the Antibody

Sucrose-gradient ultracentrifugation of serum. Fractions 4 and 5, numbered from the bottom of the sucrose-gradient tubes, caused agglutination of desipramine-coated barium sulfate particles. The agglutination was 3+ in fraction 4, and 1+ in fraction 5 for both patients. The other fractions of patients' sera, and all 9 fractions of normal serum gave no agglutination.

Reduction of immunoglobulins with 2-mercaptoethanol. The same degree of agglutination was observed in fractions 4 and 5 from each patient after incubation with 2-mercaptoethanol. This indicated that the biologic
activity of the antibodies persisted in spite of the inactivation of 19S immunoglobulins.

**Immunoelectrophoresis.** Fractions 4 and 5 from each patient tested against whole human anti-serum showed distinct precipitation lines in the gamma globulin area which were more prominent in fraction 4. For each patient the location of these lines coincided with the known location of 7S immunoglobulins. No 19S globulins were detected.

**Ouchterlony micro-method.** Precipitation lines occurred only on the Ouchterlony plate which contained specific anti-IgG serum. The four lines, corresponding to fractions 4 and 5 from each patient, were confluent as shown in Figure 4. These observations demonstrate similarity between the four fractions.

**Discussion**

Since the description by Grandjean\(^1\) of purpura caused by quinine, and the later studies by Ackroyd\(^11\) on the mechanism of Sedormid purpura, several in vivo and in vitro methods have been described to implicate a specific drug as the cause of thrombocytopenia. Direct in vivo proof correlating with in vitro tests has been obtained by readministering the drug.\(^12\) However, such direct testing is not always recommended since it might be hazardous.

In the present report, agglutination using BaSO\(_4\) for detection of antibodies against desipramine was positive to a highly significant titer in each patient with thrombocytopenia. However, this was insufficient evidence to implicate the drug as the cause of the thrombocytopenia.

The clot retraction inhibition test is a simple test of platelet function which can indicate involvement of platelets in an antigen-antibody reaction. When distinctly positive as in the present report, this method may imply a high antibody titer.\(^13\) Positive results with this test have been found with quinine,\(^13\) quinidine, Dilantin\(^14\) and digitoxin.\(^15\)

It has been found that desipramine in human platelet suspensions causes inhibition of the second phase of platelet aggregation.\(^16\) This observation might be related to the delayed and incomplete retraction which occurred when the desipramine concentration in our controls was greater than 0.2 mg./ml.

The platelet agglutination test was strongly positive when desipramine was added to the patients' serum and platelets, but slight agglutination occurred without the drug. This last reaction might be explained by Shulman's observation that at times very low in vivo drug levels are sufficient to cause attachment of some antibody molecules to each platelet, that is, enough to sensitize the platelets for sequestration by the reticuloendothelial system and result in thrombocytopenia.\(^17\) However, application of this in vivo observation to our in vitro system is speculative. The possibility of nonspecific agglutination due to high serum prothrombin in thrombocytopenia should be considered.\(^18\) In the present cases, this seems unlikely because no agglutination occurred upon adding patients' sera to normal human platelets without desipramine.
By employing the barium sulfate agglutination test on the nine sucrose gradient fractions, it was possible to localize the presence of desipramine antibodies in fractions 4 and 5, identified as 7S immunoglobulins. It should be noted that for each patient, the biologic activity was found in the same fractions, with greater activity in fraction 4. This correlates with Shulman's findings of 7S immunoglobulins which affect platelets in purpura due to quinine and quinidine.¹⁰

By the use of specific antisera, the 7S antibodies were further characterized as IgG. It will be important to know if the 7S antibodies in other drug-induced thrombocytopenias are of the IgG type. Moreover, in determining the target cell of drug sensitization, the size, configuration, and charge of antigen-antibody complexes and of appropriate cellular sites for their adsorption are thought to be more significant than properties of the antigen alone.²⁰ Therefore, identification of these antibodies may help to associate certain drugs with a particular blood dyscrasia, and eventually, to elucidate the mechanisms involved.

The clinical courses of the two patients were not like most reported cases of drug-induced thrombocytopenia, which typically have a sudden onset, severe bleeding manifestations, and rapid recovery after withdrawal of the drug. However mild thrombocytopenia with minimal clinical manifestations has been reported after ingestion of digitoxin with demonstration of antibodies¹⁵ and also with hydrochlorothiazide.¹⁶

In Patient 1, because of the splenectomy, increases in the platelet count could not be related to the titers of antibody which decreased and finally disappeared. In Patient 2, the platelet count, after a slight initial rise did not change in spite of a significant decrease in antibody titer. This could be due to secondary hypersplenism resulting from his thalassemia trait and possibly, malaria. For these reasons a direct clinical correlation between desipramine antibodies that were demonstrated and the degree of thrombocytopenia could not be made. Although, by the use of two in vitro tests, the platelets were shown to be directly involved in the antigen-antibody reaction.

**SUMMARY**

In vitro tests were done on the serum and platelets of two patients who had thrombocytopenia while taking desipramine (Pertofrane®), the active metabolite of imipramine (Tofranil®).

The indirect agglutination test with barium sulfate demonstrated the presence of antibodies against desipramine (titer of 1:256). Follow-up studies showed decreasing antibody titers in both patients after discontinuation of the drug. By complete inhibition of clot retraction and by platelet agglutination, the platelets were shown to be involved in the antigen-antibody reaction.

The antibodies against desipramine were characterized as 7S-IgG types for both patients. The characterization of antibodies may prove to be a useful step in clarifying the mechanisms involved in drug-induced blood dyscrasias.
SUMMARIO IN INTERLINGUA

Tests in vitro esseva effectuate con le sero e le placettas de duo patientes manifestante thrombocytopenia durante un curso therapeutic de desipramina (Pertofrane®), le metabolito active de imipramina (Tofranil®).

Le test de agglutination indirecte con sulphato de barium demonstrava le presentia de anticorpore contra desipramina (con contin titro de 1:256). Studios posterior demonstrava declinante titros de anticorpore in ambe le patientes post le suspension del pharmaco.

Per medio del complete inhibition del retraction del coagulo e per medio de agglutination placchettal, il esseva monstrate que le placettas habeva un rolo in le reaction de antigeno e anticorpore.

Le anticorpore contra desipramina esseva characterisate in ambe patientes como typos 7S-IgG. Le characterisation de anticorpore promitte esser un mesura utile in le clarification del mechanismos responsabile pro dyscrasias hematologic de character pharmacogenic.

ACKNOWLEDGMENTS

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