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Extracorporeal Circulation in a Patient with Heparin-induced Thrombocytopenia

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Heparin-induced thrombocytopenia may occur after two to 15 days of heparin therapy. It has been reported after iv and subcutaneous administration with various heparin preparations and is not dose dependent. Effective management requires cessation of heparin therapy, administration of platelet antiaggregating drugs, and, when indicated, the use of another form of anticoagulation. When patients with heparin-induced thrombocytopenia are rechallenged with heparin within 12 months of the initial event, recurrent thrombocytopenia and/or thrombosis may occur.[1–3] Alternatively, reinstitution of heparin therapy within 4 months after the initial event has been performed without a decrease in platelets.[3] We report a patient with heparin-induced thrombocytopenia, documented by aggregation testing,[4] who required myocardial revascularization. The patient received heparin during coronary artery bypass 14 days after the initial thrombocytopenia had resolved and while aggregation tests indicated the persistence of a heparin-induced antiplatelet antibody.

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REPORT OF A CASE

A 57-year-old man was referred for evaluation of unstable angina pectoris. On admission he was given beta-adrenergic receptor blockers, calcium channel blockers, nitrates, and prophylactic subcutaneous beef lung heparin (Upjohn) 5,000 units every 8 h. Platelet count on admission was 300,000/mm^3. Prothrombin time and partial thromboplastin time were normal, and there was no splenomegaly. On the fourth hospital day, cardiac catheterization documented severe triple-vessel coronary artery disease. Subcutaneous heparin therapy was continued.

On the eighth hospital day, an acute inferior myocardial infarction was documented, intraaortic balloon pump (IABP) assist was begun, and a temporary transvenous pacemaker inserted to manage an associated atrioventricular conduction abnormality. Heparin anticoagulation was increased with beef lung heparin (Upjohn), 7,600 units iv, followed by a continuous iv infusion of 600 units of heparin per hour. The infusion rate subsequently was increased to 1,000 units per hour due to inadequate anticoagulation. A platelet count 6.5 h after starting iv heparin was 56,000/mm^3, and heparin was discontinued. Warfarin then was used for anticoagulation. The platelet count decreased to 32,000/mm^3 14 h after the heparin was discontinued. During this time the fibrinogen was 404 mg/dl, and fibrin degradation products were increased at 50 units. Platelet aggregation testing was positive with both beef and porcine heparin. Heparin was deleted from all solutions used to irrigate vascular cannuli.

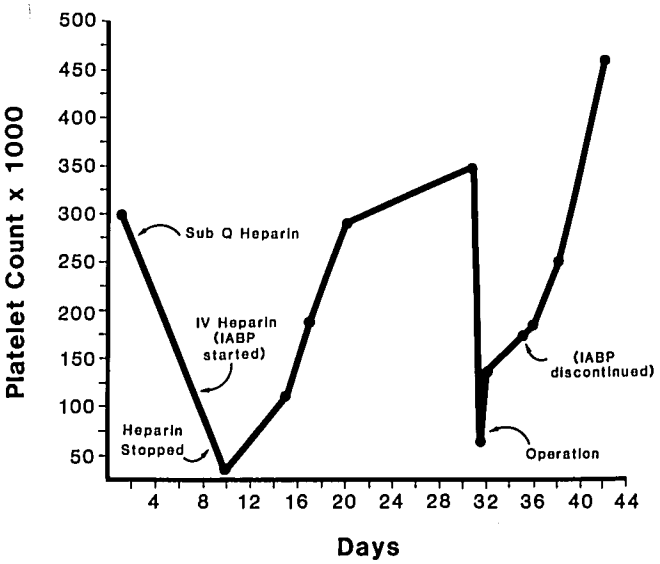

FIG. 1. Platelet counts *versus* hospital stay. Platelet count at time of hospital admission was 300,000/mm^3. Subcutaneous heparin was begun on the second day, myocardial infarction was documented the eighth day, and intraaortic balloon pump assist (IABP) was begun; subcutaneous heparin was discontinued and therapeutic intravenous heparin was begun. Heparin resistance occurred, platelet count decreased, and platelet aggregation tests indicated the presence of a heparin-induced antiplatelet antibody. Heparin was discontinued 6½ h later, platelet count reached its nadir 14 h after heparin was discontinued, and platelet count rose while IABP assist was continued. Although thrombocytopenia occurred intraoperatively and during the first postoperative day, normal platelet counts were present afterwards.

Multiple attempts to wean the patient from the IABP were unsuccessful due to angina pectoris and reduced cardiac output. Repeat cardiac catheterization documented that the previously partial occlusion of the right coronary artery had become complete. Four days prior to coronary artery bypass operation, the patient was treated with dipyridamole 75 mg three times each day and 325 mg aspirin twice each day in attempt to diminish platelet aggregation, thrombocytopenia, and potential hemorrhage with the institution of heparin required during extracorporeal circulation. The aspirin and warfarin were discontinued 2 days prior to operation, and the dipyridamole was decreased to 25 mg three times per day on the day prior to surgery. Preoperative laboratory values included a platelet count of 351,000/mm^3, a prothrombin time of 19.8 s (control of 11.1 s), prothrombin and proconvertin time of 20%, and fibrin degradation products of less than 10 units. Platelet aggregation testing *in vitro* with beef and porcine heparin still indicated the presence of a heparin-induced antiplatelet antibody.

The patient was premedicated with morphine sulfate 12 mg and glycopyrrolate 0.2 mg before he arrived in the operating room. Induction of anesthesia was accomplished without incident using diazepam/fentanyl/O_2. Maintenance of anesthesia was provided using a high-dose fentanyl–oxygen technique. Blood samples were obtained for measurement of the platelet count immediately before heparin infusion, 2 min postinfusion, immediately before infusion of protamine sulfate, 2 min postprotamine sulfate infusion, 24 h postoperatively daily for the next 4 days (fig. 1).

Porcine intestinal heparin (Wyeth), 25,000 units (3 mg/kg body weight), was administered iv for anticoagulation; 5,000 units of porcine heparin was added to the pump prime; and cardiopulmonary bypass was established at 2 l/min per M^2. An activated coagulation time (ACT) was monitored every 30 min during cardiopulmonary bypass. The ACT was consistently greater than 1,000 s. Total heparin administered was 30,000 units. Cardiopulmonary bypass was instituted, and a four-vessel aortocoronary artery saphenous vein bypass graft procedure was performed. Weaning the patient from cardiopulmonary bypass required cardiotonic support with dopamine, atrioventricular sequential pacing, and intraaortic balloon pump assist. At the conclusion of bypass, the heparin was antagonized with protamine sulfate 300 mg given intravenously with correction of the ACT to baseline.

The platelet count fell from 351,000/mm^3 to 150,000/mm^3 with heparin administration and fell subsequently to 62,000/mm^3 after instituting extracorporeal circulation. After heparin reversal with protamine sulfate, 12 units of platelets were given, and the platelet count immediately after arrival in the Intensive Care Unit was 107,000/mm^3. (fig. 1) Platelet aggregation with heparin was present interoperatively and during the first postoperative day.

Postoperative chest tube drainage was greater than usual (average 125 ml/h). Seventeen hours postoperatively, a return to the operating room became necessary to remove mediastinal blood clots, which were causing progressive cardiac tamponade. Platelet count was 59,000/mm^3. Six units of platelets were given. Hemostasis was accomplished, and the patient was returned to the intensive care unit in stable condition. He continued to improve, and on the third postoperative day the IABP was removed. The remainder of his postoperative course was uncomplicated, and his platelet count was 460,000/mm^3 on the twelfth postoperative day, when he was discharged from the hospital. Although platelet aggregation with heparin was present 12 days postoperatively, testing with beef and porcine heparin 46 days postoperatively did not reveal platelet aggregation.

DISCUSSION

Heparin-induced thrombocytopenia is an uncommon but well-documented complication of heparin therapy, with reported incidence of approximately 0.6% of patients receiving heparin.[4] It usually occurs two to 15 days after heparin therapy has been initiated and is probably due to an immunologic mechanism with the formation of heparin-dependent platelet-associated IgG antibody.[5] Complications include varying degrees of thrombocytopenia, venous and arterial thromboses, limb gangrene, pulmonary embolism, and bleeding. Heparin-induced thrombocytopenia should be suspected when a patient develops increasing heparin requirements (heparin resistance), a decreasing platelet count (less than 100,000/mm^3), and thrombosis or emboli while receiving heparin therapy.[4] To our knowledge, the use of heparin in a patient with documented heparin-induced thrombocytopenia undergoing coronary artery bypass surgery using extracorporeal circulation has not been reported.

Since heparin is the usual anticoagulant used during extracorporeal circulation, the necessity for coronary artery bypass grafting in this patient presented a hazard. Several alternatives were considered. Profound hemodilution, used in conjunction with deep hypothermia to provide adequate organ protection, theoretically can be

used to decrease clot formation during extracorporeal circulation. Warfarin can give effective anticoagulation for extracorporeal circulation, but the difficulty with rapid reversal of anticoagulation with this drug may be a problem. Prostacyclin (prostaglandin I_2), the major product of the cyclo-oxygenase cascade in the walls of the arteries and veins, potentially prevents platelet aggregation by stimulation of adenylate cyclase, hence causing increased cyclic AMP.[6] Prostacyclin has been used instead of heparin as the sole antithrombotic agent in hemodialysis.[7,8] A potentially serious drawback of prostacylcin administration is hypotension secondary to vasodilatation. After eliminating each of the above possibilities, heparin was chosen as the anticoagulation agent. Although the patient's plasma demonstrated reactivity to both beef and porcine heparin, porcine intestinal heparin was used, since the patient had been sensitized with beef lung heparin.

Platelets not only aggregate in the presence of heparin and interrupted endothelium, but they also aggregate in the presence of artificial surfaces. Platelets are activated in the extracorporeal system either by contact with the foreign surfaces, by release of ADP from hemolyzed red blood cells, or by the absence of prostacyclin in the artificial surfaces.[6,9] Several studies have demonstrated that the addition of dipyridamole to the blood prime reduced microaggregate formation in the pump oxygenator.[9–11] Dipyridamole was given preoperatively in attempt to decrease platelet aggregation when heparin was given. The mortality and morbidity associated with heparin-induced thrombocytopenia at our institution appear to be related directly to the consequences and management of arterial thromboembolism, pulmonary embolism, myocardial infarction, and/or significant hemorrhage. Perhaps platelet aggregation from the heparin-induced antiplatelet antibody contributed to this patient's total right coronary artery occlusion and acute inferior myocardial infarction preoperatively.

Although general assumptions cannot be made based on a single experience, it appears that, when absolutely necessary, heparin may be used in some individuals with recent heparin-induced antibody for anticoagulation during extracorporeal circulation. Preoperative preparation with platelet inhibitory drugs may be efficacious in reducing platelet aggregation. Although significant thrombocytopenia occurred and hemostasis was less secure than usual in the patient reported, no other untoward sequelae occurred.

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