Cerebral Venous Thrombosis Due to Heparin-Induced Thrombocytopenia

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A patient with polycythemia vera who was treated with heparin for superficial septic thrombophlebitis developed heparin-induced thrombocytopenia and cerebral venous thrombosis with superior sagittal sinus occlusion 11 days after the institution of heparin therapy. We suggest that the severe thrombotic response to the heparin-induced platelet disorder in this patient occurred because the polycythemia vera and the purulent infection enhanced the thrombophilia caused by heparin-induced thrombocytopenia. This condition can be avoided in most instances if heparin is used for no longer than 5 days. (Stroke 1990;21:1503–1505)

Used extensively for the treatment and prevention of venous thrombosis, heparin is an effective and relatively safe anticoagulant, but undesirable effects are sometimes associated with its use. Heparin may precipitate hemorrhage and paradoxically has been associated with thrombosis, which can be due to heparin-induced thrombocytopenia. This condition can be accompanied by arterial or venous thrombosis, which may occasionally have disastrous consequences. We describe a patient with polycythemia vera who developed cerebral venous thrombosis associated with heparin-induced thrombocytopenia.

Case Report

A 63-year-old woman was admitted to the University of Wisconsin Hospital on May 19, 1988, with the diagnosis of superficial septic thrombophlebitis of the right leg. Polycythemia vera had been diagnosed 4 years earlier, at which time she had 10,900 leukocytes/mm³, 5.8×10⁶ erythrocytes/mm³, 584,000 platelets/mm³, a hemoglobin concentration of 17.1 g/100 ml, and a hematocrit of 51%. She was initially treated with P-32; thereafter, her hematocrit was maintained at approximately 40% with phlebotomies.

On admission in May of 1988, her temperature was 37.3°C. Her erythrocyte count was 5.3×10⁶/mm³, her leukocyte count was 17,500/mm³, and her platelet count was 687,000/mm³. Her hemoglobin concentration was 17.1 g/100 ml, and her hematocrit was 51%. She was initially treated with P-32; thereafter, her hematocrit was maintained at approximately 40% with phlebotomies.

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both upper extremities. The next day, a CT scan showed hemorrhages in the left occipitoparietal and right parietal areas. Her aphasia cleared within a week, but she continued to have painful flexion posturing of the upper extremities. Her grip was strong bilaterally, but the rest of her upper extremities remained weak. Her face showed only minimal weakness on the right side. The flaccid paralysis of her right leg and spastic paresis of her left leg persisted. Her platelet count gradually increased, returning to the pretreatment level 6 days after the withdrawal of heparin.

Tests for heparin-induced platelet aggregation and heparin-induced serotonin release were done 12 days after heparin withdrawal; they were negative. The patient eventually made an excellent recovery. When last examined in January of 1990, the only residual abnormalities were pathologically brisk reflexes and a right extensor plantar response.

Discussion

Cerebral venous thrombosis has been associated with many congenital and acquired hypercoagulable states. Included in this long list are thrombocytosis, polycthemia vera, and remote infections. There are at least two types of heparin-induced thrombocytopenia. Type I consists of a transient decrease in the number of platelets 1–5 days after the introduction of heparin; this type of heparin-induced thrombocytopenia is usually mild and harmless and is thought to be due to reversible clumping of platelets caused by a direct effect of heparin. In Type II heparin-induced thrombocytopenia there is a persistent depression of the platelet count beginning 3–22 days after the introduction of heparin, with the average onset at about 9 days. Of the 31 patients with Type II heparin-induced thrombocytopenia reviewed by Ansell and Deykin, the onset was ≥6 days after the initiation of heparin therapy in all but two patients. With previous heparin exposure, the phenomenon may be observed within hours to 3 days after the reintroduction of heparin.

Most studies suggest that heparin-induced thrombocytopenia is mediated by antibodies contained in the IgG portion of the serum against a heparin–platelet membrane complex, but the mechanism of the thrombosis that occurs in some patients is not clear. Tests to confirm the diagnosis of heparin-induced thrombocytopenia should be carried out promptly, but the clinical decision must be made before the results become available. The occurrence of thrombocytopenia in patients receiving heparin should be assumed to be due to the heparin, which should be discontinued forthwith. Warkentin and Kelton recommend the following steps in such patients: The platelet count should be rechecked, and blood films should be reexamined to exclude pseudothrombocytopenia. Blood samples should be cultured to look for bacteremia, and medications that could cause thrombocytopenia should be identified and replaced.

The concentration of platelet-associated IgG is elevated in all patients with drug-induced thrombocytopenia, including that induced by heparin, and therefore the specificity of this test is too low to be helpful. The test devised by Sheridan et al measures the heparin-dependent release of [14C]serotonin at low (therapeutic) and high heparin concentrations. When the test is positive, [14C]serotonin is released by low but not high heparin concentrations. This test is diagnostic for heparin-induced thrombocytopenia and should be used to confirm the diagnosis. Unfortunately, this test was not done in our patient until 12 days after the withdrawal of heparin. Approximately 10% of patients treated with heparin develop thrombocytopenia, and of those approximately 10% develop thromboembolic disease. Thus, the incidence of thromboembolic disease due to heparin-induced thrombocytopenia in patients treated with heparin may be as high as 1%. Many studies emphasize that arterial more often than venous embolism is associated with heparin-induced thrombocytopenia. Steroids do not affect the platelet count, which rises to normal spontaneously within 5 days after the withdrawal of heparin.

Cerebral venous thrombosis due to heparin-induced thrombocytopenia has been reported on three previous occasions. No details were given in one fatal case; in the other two cases, heparin-induced thrombocytopenia was associated with the presence of significant hypercoagulable states, that is, the puerperium with deep-vein thrombosis and the third trimester of pregnancy with deep-vein thrombosis, which necessitated the use of heparin. Our patient had two potentially thrombophilic conditions that can cause cerebral venous thrombosis: infection and polycythemia vera. Although her hematocrit was within normal limits, she had a mild thrombocytosis (521,000–687,000 platelets/mm³), which could have contributed to a thrombotic tendency.

Most cases of heparin-induced thrombocytopenia could be avoided if heparin were used for brief periods. Warfarin should be started with heparin, and heparin should be discontinued when adequate prothrombin times have been achieved. All cases of thromboembolic disease in patients who were not previously exposed to heparin occurred ≥6 days after the beginning of heparin, and by that time therapeutic prothrombin times should have been achieved.

It is generally agreed that heparin is indicated for the treatment of cerebral venous thrombosis, but this treatment is not available to patients with heparin-induced thrombocytopenia since prompt withdrawal of heparin is imperative. Warfarin or antiplatelet agents can be considered, but once hemorrhages have developed all anticoagulants become hazardous. The intravenous administration of immunoglobulin, plasmapheresis together with aspirin and dextran, and ancolod (a defibrinating agent), as well as low-molecular-weight heparin have been suggested for the management of thrombosis in
patients with heparin-induced thrombocytopenia. Corticosteroids should not be used as they do not influence the platelet count or the edema associated with cerebral venous thrombosis and may aggravate thrombophilia by inhibiting normal fibrinolysis. Thrombolytic agents have been employed in the treatment of cerebral venous thrombosis with encouraging results, and their use was considered in our patient but decided against because of the presence of hemorrhages. Phenobarbital coma with cerebrospinal fluid drainage has been used successfully in the management of such patients.

References
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