The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

◀ Previous Volume 332:1374-1376 May 18, 1995 Number 20 Next ▶

Heparin-Induced Thrombocytopenia and Thrombosis

Heparin-induced thrombocytopenia and associated thrombotic events, relatively common side effects of heparin therapy, can cause substantial morbidity and mortality. Typically, these conditions occur after about five days of therapy, but they can appear sooner in patients previously treated with heparin. Thrombocytopenia in itself rarely poses a threat to affected patients, but disorders associated with it, which include deep venous thrombosis, disseminated intravascular coagulation, pulmonary embolism, cerebral thrombosis, myocardial infarction, and ischemic injury to the legs or arms, can produce severe morbidity and mortality. In order to prevent these complications, it has become standard medical practice to monitor platelet counts in patients receiving heparin for any extended period.

For many years there was no satisfactory explanation for the occurrence of thrombocytopenia and seemingly paradoxical thrombosis in some patients receiving heparin therapy. Attempts to detect antibodies with platelet-binding assays generally yielded negative or equivocal results. However, serum from patients with heparin-induced thrombocytopenia contained IgG that, in the presence of small amounts of heparin, activated normal platelets and caused them to aggregate and release the contents of their granules, including serotonin.[1,2] Because this process was inhibited by large amounts of heparin and could be blocked by monoclonal antibodies against the platelets' Fc receptors, it was thought for some time that the antibodies were specific for heparin and reacted with it to form immune complexes that, in turn, triggered platelet activation and caused thrombocytopenia. No formation of the postulated immune complexes could be convincingly demonstrated in vitro, however, and this hypothesis failed to explain the associated thrombosis satisfactorily.

Recent reports from several laboratories have added important new insights into the pathogenesis of heparin-induced thrombocytopenia.[3,4,5,6] The key observation made by each group is that the platelet-activating antibodies are specific not for heparin but for complexes formed between heparin and platelet factor 4, a heparin-binding protein normally found in the alpha granules of platelets. Visentin et al. showed that the antibodies, which can be either IgG or IgM, also react with endothelial cells coated with platelet factor 4.[3] This effect appears to be due to heparin-like molecules (glycosaminoglycans) on the endothelial-cell surface that, like heparin, can bind platelet factor 4 to form complexes for which antibody is specific. This finding suggests a mechanism of antibody-mediated vascular injury that could predispose a patient to thrombosis or disseminated intravascular coagulation when challenged with heparin. This suggested mechanism is shown in Figure 1.

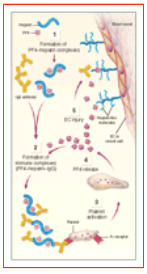

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Figure 1. Proposed Explanation for the Presence of Both Thrombocytopenia and Thrombosis in Heparin-Sensitive Patients Who Are Treated with Heparin.

According to Visentin et al.,[3] injected heparin reacts with platelet factor 4 (PF4) that is normally present on the surface of endothelial cells or released in small quantities from circulating platelets to form PF4–heparin complexes (1). Specific IgG antibodies react with these conjugates to form immune complexes (2) that bind to Fc receptors on circulating platelets. Fc-mediated platelet activation (3) releases PF4 from alpha granules in platelets (4). Newly released PF4 binds to additional heparin, and the antibody forms more immune complexes, establishing a cycle of platelet activation. PF4 released in excess of the amount that can be neutralized by available heparin binds to heparin-like molecules (glycosaminoglycans) on the surface of endothelial cells (EC) to provide targets for antibody binding. This process leads to immune-mediated EC injury (5) and heightens the risk of thrombosis and disseminated intravascular coagulation.

About 5 to 10 percent of patients treated with standard unfractionated heparin have thrombocytopenia (defined as a platelet count below 150,000 per cubic millimeter), and a substantial fraction of them have thromboembolism.[1] Recently, a new family of compounds produced by the controlled fragmentation of heparin became available for clinical use.[7] These low-molecular-weight heparins react with the regulatory protein antithrombin III to inhibit activated factor X (factor Xa), but not thrombin (factor IIa). Unfractionated heparin, by contrast, is active against both procoagulants. The therapeutic index of low-molecular-weight heparin (the potential for benefit vs. the risk of bleeding) appears to be higher than that of standard heparin.[7] Low-molecular-weight heparin is less capable than standard heparin of activating resting platelets so that they release platelet factor 4,[8] and it binds less well to platelet factor 4.[9] Considering the

importance of heparin–platelet factor 4 complexes in the pathogenesis of heparin-induced thrombocytopenia, it might therefore be expected that low-molecular-weight heparin would be less likely to cause this condition than standard heparin.

In this issue of the *Journal,* Warkentin and his colleagues decribe a prospective, controlled study addressing this very important question in patients receiving prophylactic anticoagulant therapy after hip surgery.[10] Their findings are both exciting and encouraging in that none of 330 patients treated with low-molecular-weight heparin had heparin-induced thrombocytopenia (a platelet count below 150,000 per cubic millimeter occurring at least five days after the start of heparin therapy and associated with a positive serotonin-release test). In contrast, 9 of 332 patients treated with standard heparin (2.7 percent) had heparin-induced thrombocytopenia, and 8 of them had thromboembolism. A group of 387 patients was tested for heparin-dependent antibodies regardless of their platelet count. Antibodies developed in 16 of the 205 patients treated with standard heparin (7.8 percent) but in only 4 of the 182 treated with low-molecular-weight heparin (2.2 percent). Thus, patients receiving low-molecular-weight heparin had a lower incidence of thrombocytopenia, thrombosis, and antibody formation than those receiving standard heparin.

These observations come as welcome news to physicians whose patients have had the more severe manifestations of heparin-induced thrombocytopenia, and they provide added justification for using low-molecular-weight heparin, rather than standard heparin, to prevent and treat thrombosis. It should not be expected, however, that the use of low-molecular-weight heparin will totally eliminate heparin-induced thrombocytopenia.[11] Nor should clinicians assume that low-molecular-weight heparin can be used safely in patients who have this condition as a result of treatment with standard heparin, since low-molecular-weight heparin appears fully capable of promoting platelet activation by most antibodies associated with heparin-induced thrombocytopenia.

Newly developed solid-phase assays that use complexes of heparin and platelet factor 4 as targets for the detection of heparin-induced antibodies are much more sensitive than the serotonin-release test.[3,6] Accordingly, the true incidence of antibodies induced by heparin in either the standard or the low-molecular-weight form may have been underestimated in the study by Warkentin et al. Further studies using the solid-phase assay may provide useful new information about the immunogenicity of heparin. The finding that antibodies associated with heparin-induced thrombocytopenia are specific for complexes of heparin and platelet factor 4 was unexpected, in that both these substances are normal body constituents. I await investigations of the molecular basis of this remarkable immune response with interest.

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