Heparin-Induced Thrombocytopenia

Stephen Lanzarotti, MD[a,*], John A. Weigelt, MD, DVM[b]

KEYWORDS

- Heparin-induced thrombocytopenia • Thrombosis • Platelets • PF-4
- Direct thrombin inhibitor

KEY POINTS

- Heparin-induced thrombocytopenia is an immune process, triggered by the administration of a heparin molecule, which binds to a platelet-specific protein—platelet factor 4.
- The antigenic complex of heparin–PF4 induces an immunoglobulin response, which binds the antigen as well as platelets, contributing to both thrombocytopenia and thrombosis.
- Diagnosing the condition requires clinical suspicion, platelet count monitoring, and identification of the causative antibody.
- Treatment involves stopping all heparin administration and starting alternative anticoagulation therapy.

INTRODUCTION

Anticoagulation therapy in the hospital is widespread and many patients will be exposed to heparin at some time during their hospitalization. Proper medication use requires an understanding of the medication's indications and side effects. The purpose of this article is to review heparin-induced thrombocytopenia (HIT), which is a commonly misunderstood complication from heparin-therapy.

Thrombosis related to heparin administration has been described for almost as long as heparin has been used in the clinical setting. Heparin was discovered in the 1930s at Johns Hopkins Hospital and found widespread clinical use as an anticoagulant in the early 1950s. In 1959, Dr Rodger E. Weismann described a series of 10 patients who developed thromboses after heparin administration. An immunologic cause for the thrombosis was suggested as early as 1964 by Dr Brooke Roberts at the University

Stephen Lanzarotti, MD, has nothing to disclose. Stephen Lanzarotti, MD, has received no funding for the production of this article.

[a] Evansville Surgical Associates, St. Mary's Hospital, 520 Mary Street Suite 520, Evansville, IN 47710, USA; [b] Division of Trauma and Critical Care, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA
* Corresponding author.
E-mail address: stephen.lanzarotti@stmarys.org

Surg Clin N Am 92 (2012) 1559–1572
http://dx.doi.org/10.1016/j.suc.2012.08.015 **surgical.theclinics.com**
0039-6109/12/$ – see front matter

of Pennsylvania. Once platelet counts became available in the 1970s, the association between the thrombosis and thrombocytopenia became evident.[1] Dr Glen R. Rhodes described HIT as a distinct clinical entity and identified the associated antibody.[2] HIT is still prevalent today, but misdiagnosis of the syndrome, as well as misunderstanding of the disease process contributes to its continuing morbidity for the hospitalized patient.

The purpose of this article is to review HIT, especially its pathophysiology, diagnostic challenges, and therapeutic options. This article also discusses the current recommendations for surveillance of HIT, as well as special clinical circumstances relating to the disease. At the end of this article, three patient scenarios are presented to allow the reader to evaluate their understanding of the disease in regard to clinical situations.

PATHOPHYSIOLOGY

There are two described entities relating to HIT. HIT type I is a nonimmunogenic phenomenon, in which a self-limited thrombocytopenia occurs and spontaneously normalizes. There are no thrombotic complications and there is no need to stop heparin. It is also referred to as heparin-associated thrombocytopenia. There are no long-term effects from this form.[3,4]

HIT type II is an immune process, triggered by the administration of a heparin molecule that binds to a platelet-specific protein called platelet factor 4 (PF-4). The antigenic complex of heparin–PF-4 induces an IgG response that can bind both the antigen and platelets, contributing to thrombocytopenia and thrombosis. When there is an associated thrombosis, the disease may be called heparin-induced thrombocytopenia with thrombosis (HITT). Diagnosing the condition requires clinical suspicion, platelet count monitoring, and identification of the causative antibody. Treatment involves stopping all heparin-administration and starting alternative anticoagulation therapy as necessary.[3,4] HIT Type II is the entity discussed in this article.

The Antigen

One portion of the antigen is the heparin molecule itself. Unfractionated heparin (UFH) is a large, heavily sulfated glycosaminoglycan with a strong negative charge. It exists as a polymer with a molecular weight ranging from 3 kDa to 30 kDa, with a median range of 15 kDa. Heparin acts as a cofactor with antithrombin III to inhibit several coagulation factors, but has its strongest effect against thrombin (activated factor II) and somewhat less activity against activated factor X. There are several factors that effect heparin's metabolism, specifically its route of administration, dose concentration, and its ability to bind nonselectively to endothelium. Heparin is broken down in the circulation, as well as being excreted by the kidney. UFH is produced in two forms: one from bovine lung tissue and the other from porcine gut tissue. The bovine form has been shown to produce a higher incidence of HIT.[5] UFH is given subcutaneously or intravenously for either prophylaxis or therapeutic reasons.

Low-molecular-weight heparin (LMWH) is derived from UFH, and consists of shorter chains with a molecular weight between 2 and 9 kDa, with an average of 5 kDa. It has greater therapeutic activity against activated factor X than thrombin. It is only given by the subcutaneous route and can be used either prophylactically or therapeutically. Renal excretion is linear and not dose dependent.

UFH's size and sulfation to saccharide ratio makes it an ideal antigen. Heparin itself is not antigenic because it shares a similar biochemical makeup to that of heparan sulfate, a proteoglycan that is normally found throughout the body. Heparin is one determinant in the antigenic complex that initiates the disease process. In order for