Revista da
ASSOCIAÇÃO MÉDICA BRASILEIRA
www.ramb.org.br

Original article

Heparin-induced thrombocytopenia: a review of concepts regarding a dangerous adverse drug reaction☆

Daniela Rezende Garcia Junqueira[a,b,*], *Maria das Graças Carvalho*[b], *Edson Perini*[b]

[a] *The University of Sydney, Sydney, Australia*
[b] *Centro de Estudos do Medicamento (Cemed), Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

ARTICLE INFO

Article history:
Received 27 July 2012
Accepted 4 November 2012

Keywords:
Drug toxicity
Anticoagulants
Heparin
Thrombocytopenia

ABSTRACT

Heparin is a natural agent with antithrombotic action, commercially available for therapeutic use as unfractionated heparin and low molecular weight heparin. Heparin-induced thrombocytopenia (HIT) is a serious adverse reaction to heparin that promotes antibody-mediated platelet activation. HIT is defined as a relative reduction in platelet count of 50% (even when the platelet count at its lowest level is above > 150 x 10^9/L) occurring within five to 14 days after initiation of the therapy. Thrombocytopenia is the main feature that directs the clinical suspicion of the reaction and the increased risk of thromboembolic complications is the most important and paradoxical consequence. The diagnosis is a delicate issue, and requires a combination of clinical probability and laboratory tests for the detection of platelet activation induced by HIT antibodies. The absolute risk of HIT has been estimated between 1% and 5% under treatment with unfractionated heparin, and less than 1% with low molecular weight heparin. However, high-quality evidence about the risk of HIT from randomized clinical trials is scarce. In addition, information on the frequency of HIT in developing countries is not widely available. This review aims to provide a better understanding of the key features of this reaction and updated information on its frequency to health professionals and other interested parties. Knowledge, familiarity, and access to therapeutic options for the treatment of this adverse reaction are mandatory to minimize the associated risks, improving patient safety.

Trombocitopenia induzida por heparina: revisão de conceitos de uma importante reação adversa a medicamentos

Palavras-chave:
Toxicidade de drogas
Anticoagulantes
Heparina
Trombocitopenia

RESUMO

A heparina é um agente natural com ação antitrombótica, sendo disponibilizadas para uso terapêutico a heparina não fracionada e a heparina de baixo peso molecular. A trombocitopenia induzida por heparina (TIH) é uma reação adversa grave às heparinas mediada por anticorpos que promovem ativação de plaquetas. A TIH é definida como uma redução relativa na contagem de plaquetas de 50% (mesmo se a contagem de plaquetas no seu nível mais

☆ Study conducted at the Centro de Estudos do Medicamento (Cemed), Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil.

* *Corresponding author:* Rua Camapuã 700/102, Grajaú, Belo Horizonte, MG, 30431-236, Brazil.
E-mail addresses: danijunqueira@gmail.com, daniela.junqueira@sydney.edu.au (D.R.G. Junqueira).

0104-4230
http://dx.doi.org/10.1016/j.ramb.2012.11.004

baixo estiver acima 150 x 10^9/L) que pode ocorrer no período de cinco a 14 dias após o início da terapia com o medicamento. A trombocitopenia é a principal característica que direciona a suspeita clínica da reação, sendo o aumento do risco de complicações tromboembólicas a consequência mais importante e paradoxal. O diagnóstico é uma questão delicada e requer a combinação da probabilidade clínica com testes laboratoriais para detectar a ativação plaquetária induzida pelos anticorpos da TIH. O risco absoluto de TIH tem sido estimado entre 1 e 5% no tratamento com heparina não fracionada e inferior a 1% no uso de heparina de baixo peso molecular. No entanto, evidências de alta qualidade provenientes de ensaios clínicos randomizados sobre a frequência dessa reação são escassas. Além disso, informações sobre a frequência de TIH em países em desenvolvimento não são amplamente disponíveis. Esta revisão teve como objetivo fornecer aos profissionais de saúde e demais interessados um melhor conhecimento sobre a TIH e as principais características dessa reação, bem como apresentar dados atualizados sobre a frequência da mesma. Conhecimento, familiaridade e acesso a opções terapêuticas para o tratamento dessa reação adversa são necessários para minimizar os riscos associados, melhorando a segurança do paciente.

Introduction

Heparin is one of the most commonly used medications worldwide, with over one trillion units used in the United States yearly.[1] It is an anticoagulant that occurs naturally in the organism in small amounts, and whose activity is expressed through ligation to a plasma cofactor, the antithrombin, thus inactivating thrombin (factor IIa) and factors Xa, IXa, and Xia.[2] For medicinal purposes, the drug is extracted from animal mucosa (swine or bovine), and used mainly in the treatment and prophylaxis of thromboembolic disorders.

There are two types of heparin drugs available: unfractionated heparin (UFH), also called standard heparin; and low-molecular-weight heparin (LMWH). UFH is a heterogeneous mixture of glycosaminoglycans with molecular weight ranging from 3,000 to 30,000 on average. LMWH is obtained by fractionation or depolymerization of standard heparin yielding fragments, with mean molecular weight ranging from 4,500 to 5,000.[2,3] Therefore, LMWH constitutes a group of several drugs (e.g. enoxaparin, dalteparin, nadroparin, tinzaparin, etc.) differing in some extent in their pharmacokinetic properties and anticoagulant profile, since they are prepared by different methods of depolymerization. LMWH presents a more predictable dose-response relationship and an improved bioavailability after subcutaneous administration due to reduced binding to plasma proteins, macrophages, and endothelial cells, thus allowing for a fixed-dose regime.[2,4]

Among the possible adverse effects during treatment with heparin, hemorrhage is the main and best-known risk, occurring in 5% to 10% of exposed patients.[3] Another important adverse drug reaction faced by clinicians during treatment with heparin is heparin-induced thrombocytopenia (HIT), potentially the most morbid complication of heparin therapy. Formerly termed white clot syndrome or HIT type II, HIT is a type of acquired hypercoagulability syndrome caused by an immune-mediated reaction induced by the heparin compound, and commonly followed by venous or arterial thrombosis.[5–7] The first report of the association of HIT with thrombosis dates from 1958; since then, there has been a massive effort to explain this intriguing syndrome.

Purpose of the review

Considering the potential consequences of a thrombotic event, HIT is an important and life-threatening adverse drug reaction following treatment with heparin. Therefore, this study aimed to review the literature addressing key characteristics of this syndrome, its frequency, and diagnostic issues, in order to aid HIT recognition in daily clinical practice.

Pathophysiology of heparin-induced thrombocytopenia

The pathophysiology of the thrombocytopenia in HIT is still not completely understood.[8] According to the elucidated mechanism, following the administration of heparin, platelet factor 4 (PF4), a small peptide stored in platelet α-granules, is released in blood circulation due to a transient and unspecific platelet aggregation induced by direct interaction of platelets with heparin.[9] Subsequently, heparin binds to PF4 due to charge differences, thus resulting in a macromolecular complex (PF4/heparin). The formation of this complex induces a conformational change in the molecules, resulting in the formation of several neo-epitopes.[2,10,11] An immune response against these antigenic epitopes results in the production of IgG, IgM, and IgA antibodies.

The clinical importance of IgA and IgM antibodies remains uncertain, as they appear unable to cause platelet activation in the presence of heparin,[12,13] although in a few HIT cases (< 10%), only IgA or IgM antibodies to PF4/heparin are detectable.[11] The IgG antibodies react with the PF4/heparin complex, forming an immunocomplex of PF4/heparin/IgG antibodies (HIT antibodies), which has the ability to bind to platelets' surfaces through their FcγRIIa receptor, inducing platelet activation and aggregation.[14,15] The intensive platelet activation induced by HIT antibodies increases thrombin generation, thus determining a hypercoagulability state.[16,17]

Observational data regarding the prevalence of HIT in the setting of local or systemic inflammation have also raised the possibility that additional cell types are involved in the pathogenesis of thrombosis, including leukocyte-platelet