Eur J Med Res (2004) 9: 180-185

Pathophysiology, Epidemiology, Diagnosis and Treatment of Heparin-Induced Thrombocytopenia (HIT)

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Summary: Due to the widespread use of unfractionated (UFH) and low molecular weight heparins (LWH) for prophylaxis and treatment of thrombosis, heparin-induced thrombocytopenia is considered to be the most frequent (and potentially the most devastating) drug-induced thrombocytopenia. Induced by an immune response, excessive activation of platelets and endothelium cells causes massive thrombin generation and, as a result, life-threatening venous and arterial thrombotic vessel occlusion. The rate of mortality and amputation in HIT II is estimated to be 30% and 20%, respectively. The clinical course of HIT II depends highly on early therapeutic intervention consisting of immediate interruption of heparin application and, most important, of *compatible* thrombin inhibition. All measures implying a potentially procoagulant risk such as begin of oral anticoagulation or platelet substitution may result in disastrous side effects.

Key words: HIT; heparin; danaparoid; lepirudin; thrombocytopenia

Epidemiology and Pathogenesis

Two different forms of HIT are observed [1]:

In contrast to HIT type II, **HIT type I** is a non-immune response to the exposure of heparin. It is caused by direct interaction between the platelet surface and heparin leading to decreasing cAMP levels and activation threshold [2]. As a result, platelet count decreases (seldom to less than 10^9/L) due to easier stimulation and aggregation. In circumstances characterized by hyper reactive platelets (sepsis, vessel disease, trauma), even more pronounced falls in platelet count are possible [2]. Despite continuation of heparin the platelet count recovers within a few days [3, 4]. As there is no diagnostic test for this event [5, 6], HIT type I has to be diagnosed by exclusion. Unlike immune HIT, this entity is not associated with thromboembolic or other complications [6].

While HIT type I is seen most commonly in the begin of the administration of large doses of UFH [3, 4], following thrombolytic therapy or in the early postoperative period, **HIT type II** manifests with a typical delay of a few days following exposure to heparin [5, 6, 7, 8]. HIT type II occurs independent on heparin entity (UFH or LWH), dose (low-dose or high-dose) or site of application (intravenous or subcutaneous) [2]. As observed in recent prospective studies [4, 9], there are differences in the immunogenic potential among different heparin preparations. In a population of 665 orthopedeic patients post hip surgery clinical HIT was observed in 0 patients treated with enoxaparin and in 9 with UFH, respectively, while antibody formation occurred in 8% (UFH) vs. 2% (LWH) [4]. Another study including medical patients as well [9] revealed a 10-40 fold lower frequency between LWH-HIT (enoxaparin, dalteparin, nadroparin) and UFH-induced HIT, whereas clinical complications were similar. LWH-HIT can occur with a longer interval between initiation of heparin and onset of thrombocytopenia [9]. LWH-induced platelet fall can be more profound and take more time (2 weeks) to normalize than observed with UFH [9]. Caused by an immunoglobulin, usually IgG, HIT type II involves primarily the platelets and develops more and more to a thrombin dependent coagulation disorder (Fig.1.). Contrary to all other drug-induced thrombocytopenias, HIT type II is usually not associated with hemorrhagic, but rather with thrombotic complications involving both, the arterial and venous system (white clots) [2, 10]. Patients particularly suspicious for clinically manifest HIT type II are found in cardiovascular and bone surgery (2% in cardiac-UFH, 5% in orthopedic-UFH, 1% in orthopedic-LWH) [4, 11, 12], whereas the disorder is uncommon among internal patients receiving heparin (0.5%). Age peak among males is between 50 and 70 years, among females between 60 and 80 years [13].

Clinical Presentation and Diagnosis of HIT Type II

"5T" are considered characteristic for the diagnosis of HIT type II [11]:

Thrombocytopenia: The course of platelet count is the key diagnostic criterion for HIT type II. Early diagnosis becomes possible only by frequent platelet count monitoring, beginning on day 5 of heparin application. Most important is a rapid plate-

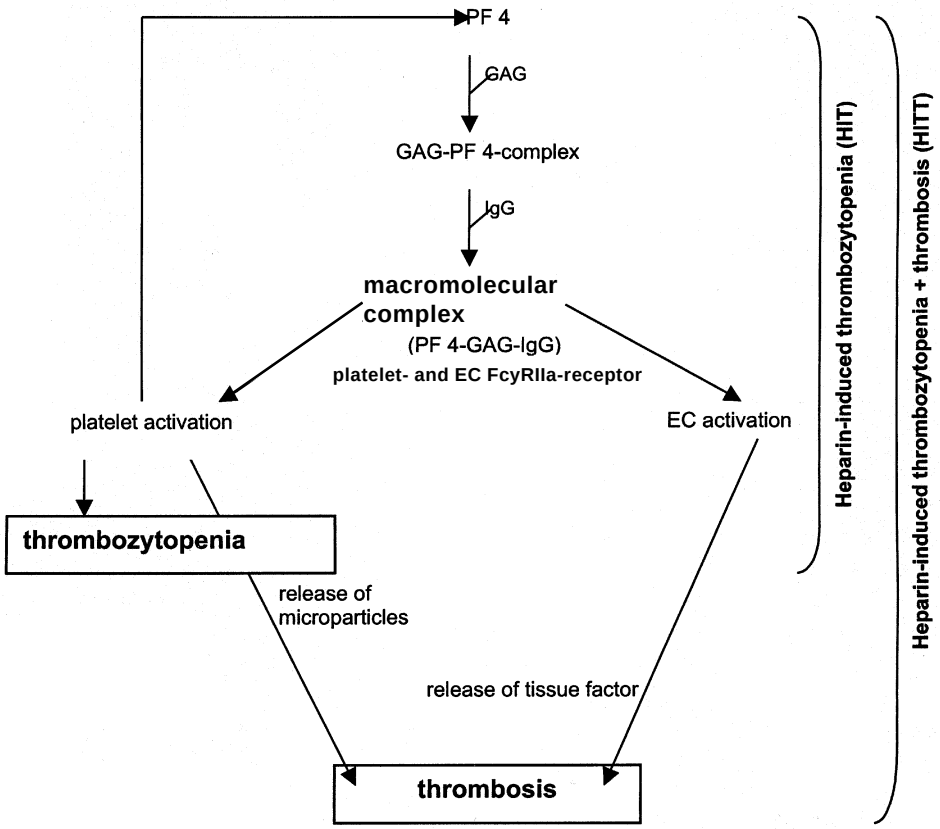

Fig.1. Pathogenesis of HIT type II: PF4, a soluble protein, is released from the platelet _ granules after activation by heparin binding or other mechanisms leading to the formation of complexes between PF4 and heparin or other high sulfated oligosaccharids (GAG) such as heparan sulfate on the EC surface. In predisposed patients antibodies (predominantly of the IgG class) are generated against these antigens leading to the formation of macromolecular complexes comprised of heparin (or other GAG), PF4 and several IgG molecules of the same specificity. These complexes are formed either in the circulation or on the platelet surface and induce platelet/EC cell activation via interaction of the IgG-Fc-moiety with the FcyRIIa-receptor. As a result, further release of granule constituents, such as PF4 occurs triggering more IgG-mediated platelet activation with platelet consumption and thrombocytopenia (circulus vitiosus) and the generation of highly procoagulant, platelet derived micro particles. These events, together with the expression of tissue factor by activated EC cause massive thrombin generation leading to further activation of platelets/EC and the coagulation cascade by activation of F V und F VIII (positive feedback). A 20fold increased thrombotic risk occurs. Hence, the most important therapeutic goal in HIT type II is the inhibition of thrombin by drugs with direct thrombin inhibition or anti-F Xa-activity.
PF 4 = Platelet factor 4, GAG = glykosaminoglykanes, EC = endothelial cell, IgG = Immuno globulin G

let fall [14] of more than 50% of the highest initial value (before use of heparin) [6], rarely to less than 30-50x109/L [2]. However, in circumstances with autonomous or reactive thrombocytosis, values of even more than 100 x 109/L can be observed [7, 13, 15].

Timing of thrombocytopenia: The platelet count characteristically begins to fall 5 to 10 days after the begin of exposure to heparin [2, 6, 16], uncommonly thereafter [6]. Due to this characteristic delay of onset, platelet fall associated with HIT type II crosses the normally observed increase in platelet count 2 to 3 days after surgery (Fig.2.). Platelet fall together with thromboembolic events can occur immediately (rapid onset) when heparin was used during the last 100 days and/or HIT-II-IgG is detectable in the patient's serum (sensitized patient) [16]. These events are often accompanied by fever or skin reactions located at the injection site [11]. Sometimes, platelet fall follows a period of "heparin-resistance" caused by heparin-neutralizing factors such as PF4 [2, 6].

Thrombosis: Contrary to other drug-induced thrombocytopenias, purpura and bleeding are rarely observed in HIT type II [6, 16, 17]. Conversely, even in face of extreme platelet count nadirs ($5x10^9$/L), thrombotic events such as pulmonary embolism [7, 18] and deep vein thrombosis, particular of the lower limb [2, 16], are characteristic for HIT. A severely thrombocytopenic patient who is lacking bleeding signs is highly suspicious of having developed HIT type II [19]. Thromboembolic events often occur simultaneously with the platelet fall [2], but may also be observed thereafter. It is important to emphasize, that, following prospective investigations, more

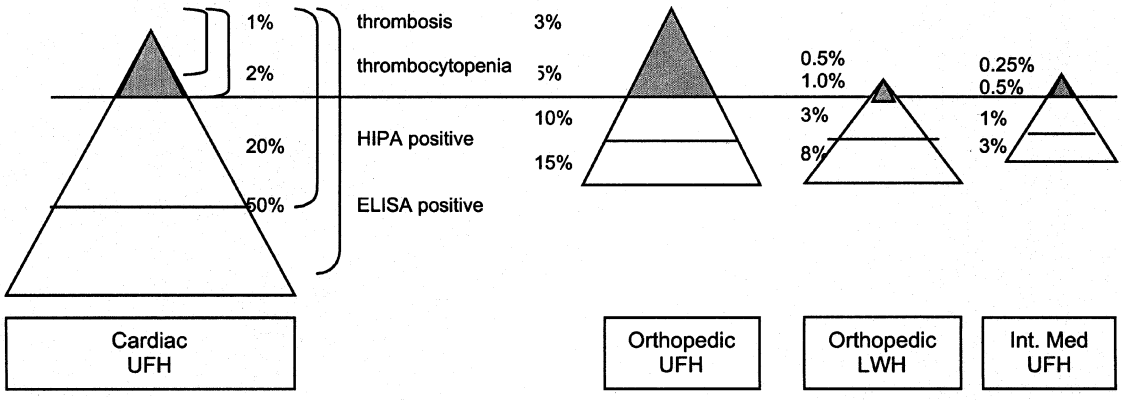

Fig.2. Frequency of HIT antibody detection (size of iceberg) and clinical HIT (peak of iceberg) among different patient populations [11]. The cardiac-UFH iceberg is about 3 times larger than the orthopedic-UFH iceberg (50 vs. 15% frequency of HIT antibody formation). The UFH-iceberg is larger than the LWH-iceberg (15 vs. 8%). HIT associated thrombosis is most common in orthopedic-UFH patients, even though HIT antibody formation is most common in cardiac-UFH patients; thrombosis is more frequent in orthopedic-LWH patients than in medical-UFH patients (0.5 vs. 0.25%).
UFH = unfractionated heparin, LWH = low molecular weight heparin; modified to [11]

than 50% of serologically confirmed and "uncomplicated" HIT patients appear to be at high thrombotic risk for the next 30 days [7, 20]. Arterial thrombosis (most commonly in the large vessels of the lower limb, cardiac, mesenterial or cerebral vessels) is observed mostly in case of too late diagnosis, when heparin application is continued despite the presence of platelet count fall and/or venous thrombosis [2]. Today, Addison crisis associated with HIT type II induced bilateral adrenal hemorrhagic infarction [21, 22] is the most common cause of acute adrenal failure in hospitalized patients [6].

Test for heparin-induced antibodies: Although clinical suspicion for HIT has to be confirmed immediately by laboratory testing, the clinical management must often be made prior to the availability of test results [2, 6, 19]. HIT antibodies remain detectable for 4 to 6 weeks after cessation of heparin application [2, 6]. Laboratory testing is performed either by antigen assays (ELISA) [23] or functional tests (HIPA) [24]. Unfortunately, none of them is 100% reliable for the diagnosis of HIT, thus both tests should be performed in case of clinical suspicion and negative result of one of the two tests. Despite high concordance between the two tests, some samples yield discordant results [6]. The reason is, that, sometimes (5%), HIT type II can be caused by alternate mechanisms (IgA or IgM instead of IgG as causative antibodies [6], heparin-PF4-related chemokine complexes instead of heparin-PF4-complexes as causative antigens [25]) which fail to be detected by common laboratory tests [2]. Of interest, many, particularly cardiovascular patients [26] form HIT-IgG without developing further complications such as thrombocytopenia or thrombosis [11] (iceberg model, Fig.3.).

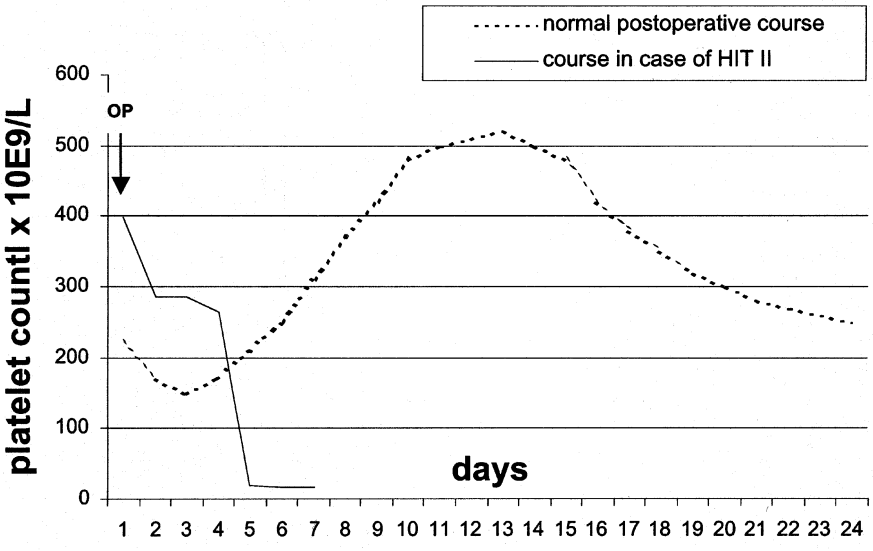

Fig.3. Postoperative course of platelet count after exposure to heparin. Difference between a „normal" patient and a „HIT type II patient" [11]. Normally, after a postoperative nadir due to blood loss and hemodilution, platelet count increases from the 2nd to 3rd day [29] and reaches normal values after a short hyperreactive peak period. Due to the typical delay of a few days after exposure to heparin the fall of platelet count associated with HIT type II crosses the normal postoperative period of platelet count increase.

While antibody formation depends on molecular weight, degree of sulfation (UFH > LWH) [27] and duration of antigen exposition [2], the patient dependent variables causing adverse events are not entirely known. Different antibody-subgroups and titers [28], polymorphisms of platelet FcyRIIa-receptor, level of platelet activation [14, 29], additional drugs and the immunologic state (e.g. autoimmune disease) [11] may modulate the risk of HIT-associated thrombosis in sensitized patients. Furthermore, it has been observed that diseased or injured vessels (e.g. use of intravascular catheters, tumors, inflammation, sepsis, postoperative venous stasis) increase the thrombotic risk in serologically confirmed HIT type II patients [16, 30]. Today, laboratory testing for HIT type II is highly specific and sensitive [6, 31, 32], but of low positive predictive value for the development of clinically-manifest HIT [2, 6].

Other causes for platelet fall unlikely: The clinical suspicion for HIT type II should be high, if the thrombocytopenia can not be explained otherwise (sepsis, drug intake, autoimmune or hematological diseases, etc).

Therapeutic Management of HIT Type II

The management of HIT should begin as soon as clinical symptoms are recognized. Once the clinical suspicion of HIT type II is made, heparin application should be discontinued immediately [2, 6, 19, 33]. However, recent investigations showed, that in serologically confirmed HIT II patients the only cessation of heparin is not sufficient to prevent thrombotic adverse events over the subsequent days [2, 6, 7, 34]. Induced by an immune response, the clinical effect of HIT type II is massive thrombin generation, thus the disturbance in pro-/anticoagulant balance ongoing even after heparin cessation [6]. The therapeutic management should not only refer to the interruption of antigen exposure, but also and mainly to the inhibition of thrombin. The central role of thrombin provides the rationale for *compatible* anticoagulation in HIT type II [2, 14].

In HIT type II patients LWH or oral anticoagulants such as Vitamin-K-antagonists (warfarin) are ineffective – and potentially deleterious [6, 16, 35, 36, 37, 38]. While LWH is 100% cross-reactive with HIT-IgG [2, 6], the induction of warfarin therapy increases the HIT induced disturbance of pro-/anticoagulant coagulation balance. The reason is a transient lack of protein C (shorter halftime) compared to procoagulant Vitamin-K-dependent factors (FII, FVII, FIX, FX). As a result, deep vein thrombosis may progress to venous limb gangrene making amputation inevitable [35, 36, 37].

Since HIT-IgG leads to activation of transfused platelets as well, platelet transfusion may have disastrous side effects in HIT type II, even in case of highly reduced platelet counts. Substitution of platelets should be carefully considered, better avoided [11].

The compatible anticoagulant options in HIT type II include danaparoid sodium [2, 6, 19] and recombinant hirudin (r-hirudin) [6, 39, 40] both shown to be effective in the treatment of HIT based in comparative studies.

Danaparoid sodium is a mixture of low molecular weight and low sulfated glycosaminoglycans (84% heparan sulfate, 12% dermatan sulfate, 4% chondroitin sulfate). It reduces thrombin generation predominantly by its anti-FXa-activity. Compared to common heparins, there is only a small hemorrhagic risk as antithrombin (anti-FIIa) activity is only poorly expressed [41]. Another advantage is a reduced ability of in vitro platelet activation due to its low sulfation and charge density. Clinical data were obtained including more than 750 patients ("Compassionate-Use-Program" [19]). Danaparoid sodium was effective in the majority of patients (93%) after 7 days of therapy (mean value). New thrombotic events were overcome by dose increase. Disadvantages are 10% in vitro cross-reactivity with HIT-IgG [2, 6, 19] whose clinical significance, however, appears to be less important [6, 19, 42], anticoagulant drug monitoring by anti-FXa-assays only (not always available) and lack of an antidote leading to hemorrhagic complication, when overdosed (> 2 anti-FXa units/ mL).

Advantages of r-hirudin are its potent direct antithrombin activity, the short half-life (easy to handle), its ability to inactivate clot-bound thrombin [6, 16], its lack of cross-reactivity with HIT IgG [2, 6, 43], and its possibility to be monitored by the more convenient aPTT. In clinical trials (HAT-1, HAT-2 studies) including more than 300 patients, r-hirudin was as effective as danaparoid sodium [39, 40]. Platelet count recovered within 2 to 3 days. Drawbacks are hemorrhagic complications (no effective antidote available), the need for extreme caution in patients with renal impairment, and, as foreign protein, the induction of (non neutralizing) antibodies. Severe anaphylactic reactions have been reported in 9 patients overlooking 35,000 treatment sessions [16].

Compatible anticoagulation in HIT type II should be performed for the entire duration of increased thrombotic risk recognizable by the low platelet count.

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Received: February 13, 2004 / Accepted: April 15, 2004

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