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Hemostasis and Thrombosis

Heparin-induced thrombocytopenia

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Abstract

Background and Objectives. **There are two types of heparin-induced thrombocytopenia (HIT). HIT I is characterized by a transitory, slight and asymptomatic reduction in platelet count, occurring in the first 1-2 days of therapy, that resolves spontaneously; in contrast, HIT II, which has an immunologic origin, is characterized by a significant thrombocytopenia generally after the fifth day of therapy that usually resolves in 5-15 days only after therapy withdrawal. HIT II is the most frequent and dangerous side-effect of heparin therapy; in fact, in spite of thrombocytopenia, it can be complicated by venous and arterial thrombosis. Therefore, the recognition of HIT II may be difficult due to the underlying thrombotic symptoms for which heparin is administered. The aim of this article is to review the most recent advances in the field and to give critical guidelines for the clinical diagnosis and treatment of HIT II.**

State of the Art. **The prevalence of HIT II, as confirmed by laboratory tests, seems to be about 2% in patients receiving unfractionated heparin (UH), while it is much lower in those receiving low molecular weight heparin (LMWH). The immunologic etiology of HIT II is largely accepted. Platelet factor 4 (PF4) displaced from endothelial heparan sulphate or directly from the platelets, binds to the heparin molecule to form an immunogenic complex. The anti-heparin/PF4 IgG immunocomplexes activate platelets and provoke an immunologic endothelial lesion with thrombocytopenia and/or thrombosis. The IgG anti-heparin/PF4 immunocomplex activates platelets mainly through binding with the FcγRIIa (CD32) receptor. The onset of thrombocytopenia is independent of the dosage, schedule and route of administration of heparin. Orthopedic and cardiovascular surgery patients receiving post-surgical prophylaxis or treatment for deep venous thrombosis are at higher risk of HIT II. Besides thrombocytopenia, cutaneous allergic manifestations and skin necrosis may be present. Hemorrhagic events are not frequent, while the major clinical complications in 30% of patients are both arterial and venous thromboses which carry a 20% mortality. The diagnosis of HIT II should be formulated on the basis of clinical criteria and *in vitro* demonstration of heparin-dependent antibodies. Functional tests, such as platelet aggregation and ^{14}C-serotonin release assay and immunologic tests, such as the search for anti-PF4/heparin complex antibodies by an ELISA method are available. If HITT II is probable, heparin must be immediately suspended and an alternative anticoagulant therapy should be initiated before resolution of thrombocytopenia and the following treatment with a vitamin K antagonist. The general opinion is to administer low molecular weight heparin (in the absence of *in vitro* cross-reactivity with the antibodies), heparinoids such as Orgaran or direct thrombin inhibitors such as hirudin.**

Perspectives. **Further studies are required to elucidate the pathogenesis of HIT II and especially to discover the clinical and immunologic factors that induce the occurrence of thrombotic complications. The best therapeutic strategy remains to be confirmed in larger clinical trials.**

Key words: heparin, thrombocytopenia, PF4, platelet, anti-heparin/PF4 antibodies, thrombosis, ELISA, HIT, UFH, LMW

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Among the known side effects of heparin therapy, thrombocytopenia is without doubt the most frequent and dangerous. There are two types of heparin-induced thrombocytopenia (HIT). HIT I is characterized by a transitory, slight and asymptomatic reduction in platelet count (rarely below 100×10^9/L), occurring the first 1-2 days of therapy, that resolves spontaneously and does not require suspension of the drug. The origin of HIT I is not yet completely understood but it is thought to be related to a phenomenon of heparin-induced platelet clumping.[1-3]

HIT II, which has an immunologic origin,[4,5] is characterized by a significant reduction in platelets (>30%) generally after the fifth day of therapy (Figure 1) that usually resolves in 5-15 days after therapy has been suspended, but in some cases may take months.[6-8] HIT II may appear earlier in patients previously exposed to heparin.[6]

Epidemiology

The real incidence of HIT II is not well defined. The reported studies are mostly retrospective, and differ regarding the characteristics of the patients, type of heparin administered, schedule, duration of therapy, definition of thrombocytopenia, and laboratory tests

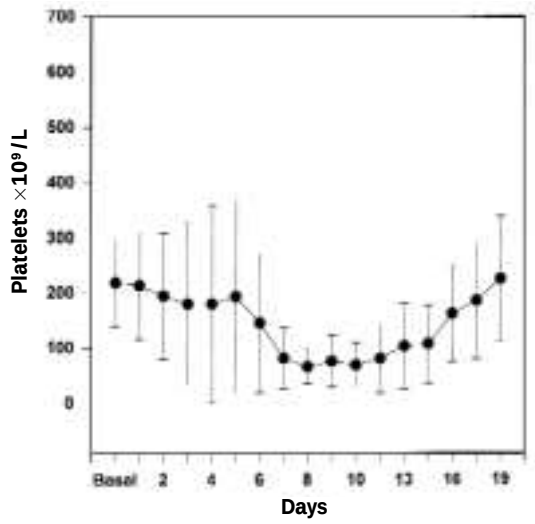

Figure 1. Platelet counts in 32 patients with heparin-induced thrombocytopenia (HIT II). The y-axis represents the platelet count as the mean ± SD of available data and the x-axis the days after onset of heparin therapy. Heparin was withdrawn at different times from the patients.

employed for diagnostic confirmation[7,9,10] (Table 1). In the studies in which the diagnosis was clinical, there are important differences in the definition of thrombocytopenia: in some studies, the threshold value was 150×10^9/L,[11-17] while in others, it was 100×10^9/L;[18,19-30] and in yet others a percentage fall was used as the reference.[31] A relationship between the incidence of HIT II (defined only on a clinical basis), and dosage and type of UFH used emerged from the study by Warkentin in 1990;[32] the incidence was about 5% for therapeutic doses of bovine UFH, and 1% for porcine UFH, while it was less than 1% with prophylactic doses of porcine heparin. In this series, the incidence of secondary thrombotic complications was about 20%. In a later review of prospective clinical trials, the HIT II incidence varied from 1 to 30% in patients treated with high doses of intravenous heparin, while it was less than 2% in patients administered low doses of subcutaneous heparin.[7]

Schmitt and Adelman[10] reviewed[23] randomized or cohort prospective studies for a total of 2,160 patients in order to evaluate the prevalence of HIT related to the frequency with which platelet count was verified. This analysis confirmed that the incidence of HIT was overestimated in studies that did not include a *repeatedly abnormal platelet count*. The cumulative incidence of HIT II in studies that employed *a reproducibly lowered platelet count* was 2.9% for bovine UFH, and 1% for porcine UFH, 1.7% for i.v. administration and 0% for s.c. administration. Although those differences do not reach statistical significance, they speak in favor of porcine heparin and s.c. administration of low doses.

Our retrospective study[33] disclosed a higher incidence. In fact, independently of the route of administration, 6% of our patients had a clinical score suggestive of HIT II and a 30% incidence of thrombotic complications, in line with other literature reports.[6,8] However, using more selective clinical criteria, the percent incidence lowered to 3% and the diagnosis was confirmed by the presence of heparin-dependent antibodies only in a portion of patients (Table 1).

On the other hand, Kappers-Klunne *et al.*[34] reported a particularly low (0.3%) incidence of HIT in 558 cardiologic and neurologic patients treated with i.v. heparin. In their study, both functional and immunologic tests were used for laboratory confirmation of the clinical diagnosis.

Anecdotal reports describe HIT II induced by LMWH,[35,36] but clinical studies indicated that LMWH is associated with a lower incidence of thrombocytopenic and thrombotic complications than UFH.[37]

A recent double-blind randomized study compared UFH administered subcutaneously with LMWH in 655 patients undergoing orthopedic surgery. In this study the clinical diagnosis of HIT II was confirmed by means of the ^{14}C-serotonin release test.[37] HIT II was documented in 2.7% of the patients treated with s.c. UFH, and in none of the patients receiving LMWH ($p = 0.0018$); thrombotic complications were also more frequent in the former (88.9%) group than the latter (17.8%; $p<0.001$). Independently of HIT II presence, in a subgroup of patients more UFH-treated than LMWH-treated patients had a positive functional test (7.8 vs 2.2%, $p = 0.02$); thrombotic episodes, however, were more frequent in the patients who developed HIT II than in those with only a positive functional test.

Table 1. Prevalence of heparin-induced thrombocytopenia (HIT II) in patients treated with intravenous and subcutaneous unfractionated (UF) heparin in a group of patients treated in Padua.

Patients	*Type of heparin*	*Mean daily dose (IU±SD) in HIT patients*	*Days of therapy*	*% Prevalence of HIT Clinical score ≥ 4*	*Prevalence of HIT Clinical score ≥ 4 + IgG/IgM anti PF4/heparin*
212	All patients	–	–	7/212 (3.3)	3/208 (1.4)
130	UF i.v. (retrospective study)	28,000±4,550	8.3±3	4/130 (3)	2/128 (1.5)*
82	UF s.c. (retrospective study)	22,000±6,472	16.8±4.1	3/82 (3.6)	1/80 (1.2)*

**Test for IgG/IgM anti PF4/heparin complex were performed in only 3 of 7 patients with clinical diagnosis of HITII by ELISA (ref. #33).*

In conclusion, the frequency of laboratory confirmed HIT II seems to be about 2% in patients receiving UFH while it is much lower in those who receive LMWH.

Pathogenesis

The immunologic etiology of HIT II is now largely accepted.[6,38] The immunologic basis of HIT II was first advanced by Rhodes who showed that the IgG fraction from the serum of patients with HIT caused *in vitro* platelet aggregation in the presence of therapeutic amounts of heparin.[39] It was also reported that immunoglobulin-heparin complexes formed only in the presence of platelets.[40] The pro-aggregating effect of heparin depends on the degree of sulphation and the molecular weight[41-43] and is mediated by the release of platelet α-granules.[44] Several platelet proteins were proposed as the putative receptors of heparin-dependent antibodies,[45] and PF4 was identified as the main co-factor.[46] The antibody is not exclusively specific for the heparin/PF4 complex, but also binds to complexes made up of PF4 and other glycosaminoglycans (GAGs), based on the degree of sulphation and the length of the polysaccharide.[41-43]

The PF4/heparin ratio appears to be critical for the constitution of the multimolecular antigenic complex, with an optimal PF4:heparin ratio ranging from 4-6:1.[43,47-49] The most accredited pathogenic model at present is the following (Figure 2). At therapeutic concentrations, ranging from 0.1 to 1.0 U/mL, heparin displaces PF4 from endothelial heparan sulphate, or releases it directly from the platelets; PF4 bind to a heparin molecule, and the soluble complex becomes immunogenic; the anti-heparin/PF4 antibodies activate the platelets, and provoke an immu-

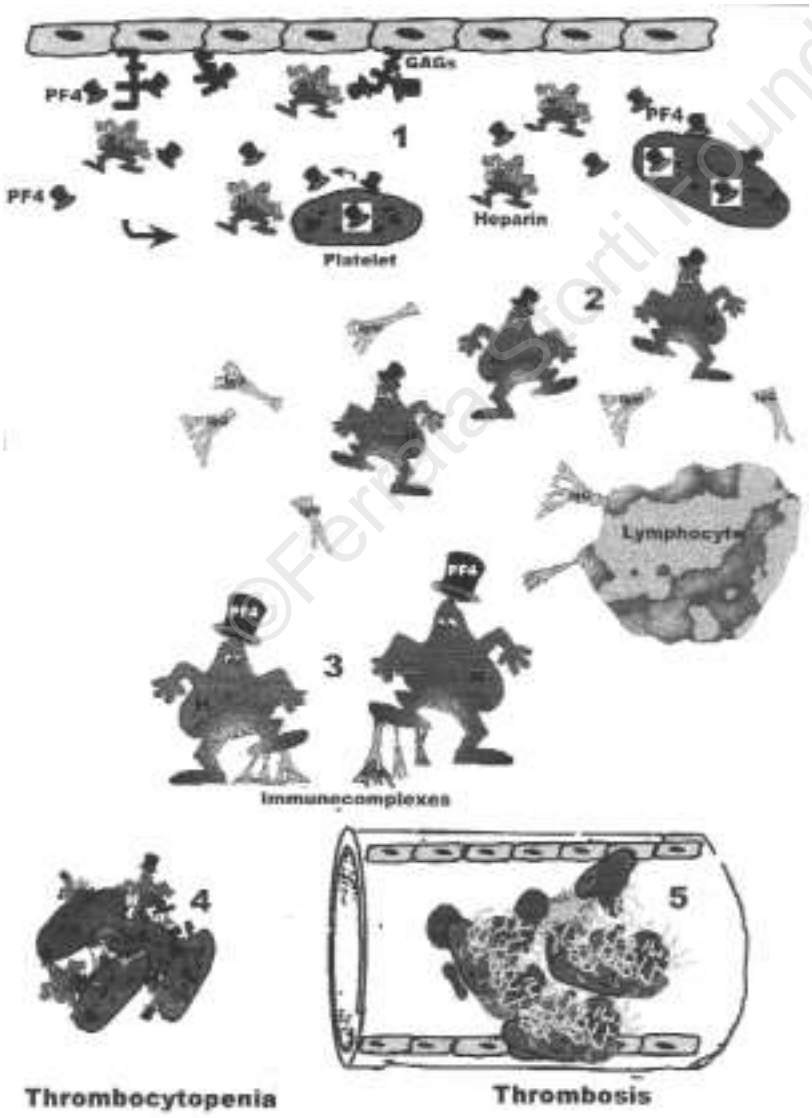

Figure 2. Pathogenic model of heparin-induced thrombocytopenia (HIT II) and thrombosis.
1) Administration of heparin induces a release of PF4 from glycosaminoglycans of endothelial layer and from the platelet pool.
2) The formation of PF4-heparin complex is a target for the production of antibodies (IgG and IgM) by the B-lymphocytes depending on the antigenicity of the complex (molar ratio, sulphation grade) and from the immune system of the patient.
3) Formation of immune complexes (antibodies bound to PF4/heparin complex).
4) Immunocomplexes bind to platelets (FcγRIIa ?, passive immunoabsorption ?) and to the endothelium, or antibodies directly bound to PF4/heparin complex on platelet and endothelial surface, cause platelet activation, microangiopathic thrombocytopenia and endothelial cell injury. Platelet activation, thrombin generation and endothelium injury associated with vessel cofactors (pre-existing thrombosis, atherosclerosis, surgery or others ?) induce the venous and arterial thromboses.

nomediated endothelial lesion,[4,6,38,49,50] with thrombocytopenia and/or thrombosis. The immunocomplex activates the platelets mainly through the bond with the FcγRIIa (CD32) receptor.[51-53] Indeed, platelet activation is blocked by both the monoclonal antibody (IV.3) specific for the FcgRIIa receptor,[49,54] and the $F(ab')_2$ fractions from patients with HIT II.[54, 55] The arginine/histidine polymorphism in position 131 of the FcγRIIa receptor influences platelet reactivity to the immunocomplexes;[53] in particular, the His/His phenotype is more reactive to IgG_2. Nonetheless, while some studies have demonstrated a greater prevalence of HIT II and thrombotic complications in subjects with the His/His phenotype;[56] others have not confirmed these findings.[57]

Other data are consistent with the hypothesis that heparin/PF4 complexes bind directly to the platelets and that these are the target for the $F(ab')_2$ fraction of antibody.[58]

However, how the anti-PF4/heparin antibodies cause thrombosis is less clear. In general, type IgG_2 anti-heparin antibodies are not particularly more frequent than the other subclasses in patients with HIT II,[59] and IgM and IgA, which are not able to bind to FcyRIIa are also present in significant percentages in these patients.[60-63] These findings suggest that the mechanism of platelet activation may occur independently of the FcyRIIa receptor for IgG. Moreover, the antibody isotype tends to modify in relation to the duration of treatment.[48, 59-62] The antibodies are still detectable in patient serum for about 4-6 weeks, although cases of even longer antibody persistence have been described.[6,33]

Additional uncertainties regarding the above pathogenic scheme also emerged from an experimental model in the mouse, in which the development of autoantibodies against the heparin/PF4 complex induced a picture of thrombocytopenia, but not of thrombosis.[63] From a pathogenic point of view, it is thus likely that a state of platelet and endothelial preactivation, and probably other, currently still unidentified features of the patients contribute to the thrombotic phenomena.[6,50,64,65]

Symptoms and clinical presentation

The onset of thrombocytopenia is independent of the type of heparin, dosage, schedule and route of administration.[18] The entity of thrombocytopenia usually varies from 50 to 100×10^9 platelets/L,[7] but severe cases are frequent.[66] There is no gender predominance;[9] elderly patients undergoing post-surgical prophylaxis or treatment for deep venous thrombosis,[66,68] orthopedic and cardiovascular surgery[8] seem to be at higher risk. In more than 60% of the cases there are other concomitant prothrombotic factors such as diabetes, neoplasm, cardiac insufficiency, systemic lupus erythematosus, antiphospholipid syndrome, infections, or trauma. Besides the thrombocytopenia, cutaneous allergic manifestations and skin necrosis may be present.[68] Hemorrhagic events are not frequent, while the major clinical complications in 30% of patients are both arterial and venous thromboses which carry a 20% mortality. The thrombotic event is frequently a worsening of thrombosis for which the heparin was administered, or may be a new thromboembolic complication,[8,9,32,67] thrombotic complications may appear even in the absence of thrombocytopenia.[69] Arterial thromboses were the first event to be associated with HIT;[39,70] nonetheless, at present, the prevalence of arterial and venous thrombotic complications is considered to be similar.[71] Arterial thrombosis seem to be more frequent in patients with cardiovascular disease,[66] and venous complications in patients undergoing post-surgical prophylaxis.[8,9,66] The most common arterial complications are thromboses of the large vessels with gangrene and limb amputation, stroke, myocardial infarction, and cardiac thrombosis.[4,5,32,66] Venous complications are deep venous thromboses, pulmonary embolism, thrombosis of the cerebral venous sinus, and closure of arterial-venous fistula in dialyzed patients; disseminated intravascular coagulation and hemorrhagic adrenal necrosis have been documented only occasionally.[4-7,32]

Diagnosis

It is commonly held that heparin-induced thrombocytopenia is still underdiagnosed. During heparin therapy, platelet counts must be checked regularly, at least twice weekly, especially in patients receiving treatment for more than 4 days, or who show resistance to heparin, or treatment-related skin manifestations. Once thrombocytopenia is confirmed, the diagnosis of HIT II should be formulated on the basis of clinical criteria, and the *in vitro* demonstration of heparin-dependent anti-platelet antibodies.[5,7] Nonetheless, the diagnosis is still only clinical in more than 20% of the cases.[71] Various score systems have been proposed to evaluate the clinical probability of HIT II.[72,73] These systems are based on the severity of the thrombocytopenia, the recovery following drug withdrawal, onset of thrombotic complications, and the exclusion of other causes of thrombocytopenia. A score less than 3 makes a diagnosis of HIT II improbable, from 4-6 makes it possible, and greater than 6 highly makes it probable (Table 2).[73]

Functional tests, such as platelet aggregation (PAT), ^{14}C-serotonin release (SRA), and heparin-induced platelet activation (HIPA), and immunologic tests, such as the search for anti PF4/heparin antibodies by an ELISA method are available to demonstrate heparin-dependent antibodies (Table 3).

Among the functional tests, SRA is the reference procedure.[72] This test is based on the capacity of heparin-dependent antibodies to induce platelet release of ^{14}C-serotonin. The serum from a patient with HIT II is incubated, in the presence of therapeutic heparin concentrations (0.1-1.0 U/mL), with washed donor platelets labeled with ^{14}C-serotonin. If heparin-dependent activating factors are present, ^{14}C-serotonin is released from the platelets while, in the presence of higher heparin concentrations (10-100 U/mL), release is inhibited. This method, however, has several disadvantages: it requires the use of radioactivity, the result is highly dependent on the characteristics of the donor platelets,[74] and the procedure itself is relatively time-consuming. Clearly, a test that is able to provide results within a few hours would be more useful from a clinical point of view.[5,7,32]

The platelet aggregation test, which utilizes the same principle as SRA, is able to furnish quicker

Table 2. Clinical score for the diagnosis of heparin-induced thrombocytopenia (HIT II).

Clinical features	*Score (Sheridan[72])*	*(Greinacher[73])*
Decrease in platelet count between 30-40%	+1	+1
Decrease in platelet count > 50%	–	+2
Decrease in platelet count after 5 days of therapy	–	+2
Arterial or venous thrombosis	+1	+2
Cutaneous reaction	–	+2
Characteristic acute arterial thrombosis	+4	–
Characteristic arterial thrombosis with prothrombotic cofactors	+2	–
Venous thrombosis	+2	–
Previous thrombosis	–	–1
Other causes of thrombocytopenia (infection, drug, chemotherapy etc)	0 (drug) –2 (others)	–1
Exclusion of other causes of thrombocytopenia	+4	–
Improvement in platelet count after heparin withdrawal	+2	+2
Lack of improvement in platelets after heparin withdrawal	–2	–
Improvement in platelet count during heparin continuation	–2	–
Improvement of thrombocytopenia after re-exposure		
Heparin withdrawal and relapse after re-exposure	+4	–
HIT II unlikely	< 4	0-3
HIT II probable	4-6	4-6
HIT II definite or highly probable	> 6	> 6

results more quickly.[54] This test measures the aggregation induced in a platelet-rich plasma sample by the serum under study in the presence of therapeutic concentrations of heparin. While this method is widely used due to its relative simplicity, the results nonetheless vary considerably more than those reported for SRA in relation to the different heparin concentrations, and donor platelet variability.[5,7,32]

The HIPA test on microplate demonstrates greater reliability and correlation with the SRA.[75] This test is based on the visual evaluation of the aggregation of washed platelets in a magnetically shaken microplate.

Other functional tests have recently been suggested, such as the adenosine nucleotide release assay,[76] or the binding of annexin V to platelet membrane anionic phospholipids, utilizing flow cytometry.[77] However, as these tests also employ donor platelets, they too depend on the variability of these platelets. Another recent test employs a solid-phase adherence method to demonstrate heparin-dependent antibody.[78]

Regardless of the method used in the functional tests, the selection of the donor platelets is crucial.[74] The use of washed platelets, rather than platelet-rich plasma improves sensitivity because there care be a platelet over-reactivity in response to heparin not due to the presence of antibodies. Under these conditions, the sensitivity of the PAT and SRA methods reaches 88 and 94%, respectively.[4,5,7,32,79]

Following the demonstration that heparin-dependent antibodies are mainly directed against the heparin/PF4 complex,[46] the ELISA technique began to be used.[46,48,49] A well-defined ratio of heparin/PF4 complexes is stratified on microtiter plates by means of a covalent[46,48] or electrostatic[33,49] bond. The patient's serum is appropriately diluted, and then incubated with the complex; the presence of the antibodies is detected with a second antibody conjugated with peroxidase or alkaline phosphatase. Results from the

Table 3. Functional and immunologic assays for the laboratory diagnosis of heparin-induced thrombocytopenia (HIT II).

	Principle	*Advantages and disadvantages*
Functional assays		
Platelet aggregation test (PAT)	test plasma + donor PRP + heparin (low and high conc.): platelet aggregation	Advantages: easy to perform, specificity Disadvantages: variability due to the selection of platelet donors and controls
^{14}C-serotonin release assay (SRA)	test plasma + washed platelets + heparin (low and high conc.): ^{14}C-serotonin release from platelets	Advantages: sensitivity Disadvantages: use of radionuclide, selection of donors
Heparin-induced platelet activation (HIPA)	test plasma + washed platelets + heparin (low and high conc.): visual platelet agglutination under magnetic stirring	Advantages: sensitivity, easy to perform, assay of multiple samples Disadvantages: variability due to the selection of platelet donors of PRP and controls
Flow cytometric assay (FCA)	test plasma + donor PRP + heparin (low and high conc.): assay of fluorescent binding of annexin-V by flow cytometry	Advantages: easy to perform, fast Disadvantages: Selection of appropriate donors and controls, need of a flow cytometer
Immunoassays		
PF4/heparin ELISA	test plasma + PF4/heparin coated microtiter wells: assay of IgG/IgM against PF4/heparin complex by ELISA	Advantages: sensitivity, easy and fast to perform, platelet donor not required, assay of multiple samples Disadvantages: detects only antibodies against PF4/heparin

ELISA method show good correlation with those from the SRA and HIPA procedures,[73,80] but comparison with PAT results is less reliable.[73,81] The method is characterized by a greater sensitivity than the functional tests,[80] and a greater reproducibility because it does not employ donor platelets; moreover, this procedure is technically easier to perform, and may reveal IgG, IgM, IgA and isotype antibodies not detectable by the functional methods. Nonetheless, it has evidenced anti-heparin/PF4 antibodies in patients who did not have heparin-associated thrombocytopenia, and in particular in patients undergoing heart surgery.[31,34,60,62,82] On the other hand, the test was negative in patients with HIT confirmed by positive functional tests.[73,80] It is possible that the complete pattern of HIT II only occurs with high antibody titers or after persistent exposure to heparin;[62,82,83] on the other hand, antigens other than the heparin/PF4 complex may be involved in the pathogenesis of HIT II.[84] That having be said, the presence of PF4/ heparin-dependent IgG seems to be related to a high clinical probability of HIT II.[33]

Evaluation of the cross-reactivity between UFH and GAGs appears to be important because of the immediate clinical effects. The rate of cross-reactivity between HIT-related antibodies and low molecular weight heparins (LMWH) or polysulphated oligosaccharides has been reported to be as high as 90% when conducting platelet aggregation or activation studies.[41,75,85] Indeed, just 8 oligosaccharide units/molecule are needed for efficient binding of PF4 to GAGs.[86] It was observed that HIT-related antibodies also bound to PF4/LMWH complexes,[33,48] however, the optimal PF4/GAGs ratio appeared to be more critical for LMWH than UFH.[33] From a clinical point of view, a different interaction between PF4 and LMWH could account for the lower incidence of HIT II in patients treated with LMWH.[37]

In general, aside from the varying sensitivity of the methods, and the lack of an accurate standardization, neither functional nor immunologic tests have proven to be predictive of the diagnosis of HIT II or of the thrombotic risk.[62,82] In any situation, therefore, and especially in the absence of a highly suggestive clinical picture, it appears more appropriate to flank the clinical diagnosis with a functional test as well as a PF4/heparin ELISA test.[47,79,80-82,87,88]

Therapy

The best therapeutic strategy for patients with HIT II is not yet clearly established but reasonable guidelines have a wide consensus (Table 4). If HIT II is clinically probable, heparin therapy must be suspended immediately even in the absence of confirmatory laboratory tests. Platelet transfusion is contraindicated because it may worsen the thrombotic picture. Anticoagulant therapy with vitamin K antagonists should be initiated at least 3 to 5 days after heparin suspension, and preferably not before resolution of the thrombocytopenia in order to avoid potential worsening of the thrombotic picture.[6] However, heparin suspension alone and substitution with dicumaroids do not prevent the onset of severe thrombotic complications in almost 50% of the patients.[8] On the basis of these disappointing results, new approaches have been proposed that include the use of LMWH, heparinoids, anticoagulating agents such as ancrod, prostaglandins such as hyloprost, hirudin and other thrombin inhibitors (argatroban). Of these various drugs, only LMWH, heparinoids, ancrod and hirudin have been used in a significant number of patients.[4-6,9,71,89,90]

Table 4. Guidelines for the treatment of heparin-induced thrombocytopenia (HITII).

1. Immediate withdrawal of heparin.
2. Platelet transfusions only in presence of severe hemorrhages.
3. First choice: anticoagulant therapy with hirudin or orgaran (if available) during the first days after heparin withdrawal followed by oral dicumaroids (preferentially after resolution of the thrombocytopenia).
4. Second choice: low molecular weight heparins (negative *in vitro* cross-reactivity test). Anti-platelet drugs; high doses of immunoglobulin and/or plasmapheresis associated with LMWH.
5. In presence of thrombotic complications: as points 3-4 plus thrombolysis, thrombectomy, filter in the inferior vena cava.
6. Patients with previous history of HITII: hirudin, orgaran; LMWH (negative *in vitro* cross-reactivity test); anti-platelets agents; LMWH plus anti-platelet agents.

LMWH could represent the first therapeutic option for HIT II. The rationale behind using another type of heparin resides in the fact that with a decrease in the molecular weight and degree of sulphation, the interaction with PF4 diminishes.[86] However, the *in vitro* cross-reactivity with heparin-induced antibodies ranges from 60 to 100%.[4,75,85,91] The general opinion, therefore, is to not administer low molecular weight heparins unless the absence of cross-reactivity has been demonstrated by an *in vitro* test.[6] Nonetheless, some reports describe cases in which the use of LMWH was effective in controlling the HIT even though cross-reactivity with heparin had been evidenced.[92,93]

At present, it appears that the use of low molecular weight heparinoids and direct thrombin inhibitors is the safest and most effective therapeutic approach to HIT.[6] The major experiences reported concern danaparoid sodium (Org 10172, Orgaran), a mixture containing heparan sulphate (85%), dermatan sulphate (10%), and chondroitin sulphate (5%), whose cross-reactivity with heparin *in vitro* is less than 10%.[9,33] More than 600 patients with HIT II have been successfully treated with this drug;[9, 71,93-95] but failure of the treatment[96] or of danaparoid-induced fatal thrombotic thrombocytopenia have also been reported.[97] In particular, treatment with Orgaran resolved the thrombocytopenia in 91% of HIT patients, and significantly reduced mortality due to thrombotic complications from 28 to 5%, but not total mortality which was 20%.[9,71] Org 10172 has been approved for the treatment of HIT II in New Zealand, Denmark, Luxembourg, Belgium and Portugal, but it is marketed in only a few countries.

Direct thrombin inhibitors also have a precise indication in HIT II. Hirudin is able to inactivate circulating and subendothelium-bound thrombin without having a direct effect on platelets;[98] its use in the treatment of HIT II was evaluated mostly in Germany, where it was found to be effective.[89,99] A few patients with HIT II associated with thrombosis were successfully treated with Argatroban®, a thrombin inhibitor derived from L-arginine.[90] A small clinical trial was conducted with Ancrod®, a viper venom with anticoagulating action.[100] A further theoretical possibility, especially in patients who require prophylaxis during surgery, is the use of anti-platelet agents.[4-6] It was recently demonstrated in an *in vitro* study that c7E3, a monoclonal antagonist of glycoprotein IIb/IIIa, is able to inhibit platelet aggregation induced by the plasma of patients with HIT II, and thus might be useful especially during thrombotic complications.[101] In addition to the anticoagulants, thrombolytic agents, the insertion of filters in the inferior vein cava, embolectomy or thrombectomy are also indicated.[4-6] There are anecdotal descriptions of the use of plasmapheresis to remove immunocomplexes[102] or high doses of immunoglobulin alone[103] or associated with LMWH and Orgaran®.[93]

Conclusions

Besides idiosyncrasy, bleeding and osteoporosis were the two well-known complications of heparin therapy till about 10 years ago. The realization that platelets may interact with heparin by means of an immunologic mechanism added HIT to the list of side-effects. Physicians should be very cautious in prescribing heparin therapy. Platelet count should be carried out daily or every two days during the first 10-12 days of any cycle of heparin therapy regardless of the route of drug administration; if the patient is discharged from a hospital on UFH or LMWH, he or she should be instructed to have frequent platelet count monitoring.

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FF planned the review and was responsible for writing the paper. PMS critically read and identified the articles of potential relevance to the review. GL and GC were responsible for the clinical and laboratory diagnosis of HIT. BG collected and analyzed the data of the patients treated in Padua with heparin. AG critically reviewed the manuscript. All the authors gave their critical contribution and approved the final version of the manuscript. The authors are listed in an order reflecting their individual contribution to the article. The authors are indebted to Dr. A. Steffan for his precious realization of the figures.

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