Heparin-induced thrombocytopenia: a frequent complication after cardiac surgery.

Summary

Thrombocytopenia is a common problem in cardiovascular patients, and heparin-induced thrombocytopenia (HIT) is therefore frequently suspected. Unfractionated heparin during cardiopulmonary bypass is particularly immunogenic as 25% to 50% of post-cardiac surgery patients develop heparin-dependent antibodies but only 1 to 3% will develop HIT. These antibodies recognize a ‘self protein’, platelet factor 4 (PF4), bound to heparin. Antibodies associated with a high risk of HIT are mainly IgG1 which strongly activate platelets and coagulation, thereby causing thrombocytopenia and thrombosis. A biphasic evolution of platelet count with a secondary decrease after a previous increase following CPB or non-recovery of thrombocytopenia within 6 days post-operatively always requires screening for HIT antibodies. Both functional (platelet activation tests) and immunologic assays (antigen assays) are necessary in every patient to establish the diagnosis of HIT. When the clinical probability of HIT is high, the first requirement is to discontinue heparin, without waiting for results of laboratory investigations. An alternative anticoagulant such as danaparoid sodium (Orgaran®) or lepirudin (Refludan®) must then be administered since heparin withdrawal alone is insufficient to control the prothrombotic state associated with HIT. The risk of HIT will probably soon decrease due to the wider use of fondaparinux, which does not interact in vitro with PF4, but it could remain significant in patients undergoing cardiac surgery with CPB.

Résumé

La thrombopénie induite par l’héparine : une complication fréquente après chirurgie cardiaque.

La thrombopénie est un problème fréquent chez les patients atteints de maladies cardiovasculaires, et la thrombopénie induite par l’héparine (T IH) est donc fréquemment suspectée. L’héparine non-fractionnée utilisée durant la circulation extra-corporelle est particulièrement immunogène, puisque 25 à 50 % des patients développent des anticorps héparino-dépendantes après chirurgie cardiaque, mais seulement 1 % à 3 % développeront une T IH. Ces anticorps reconnaissent une protéine appartenant au sujet, le PF4 (platelet factor 4), lié à l’héparine. Les anticorps associés à un risque élevé de T IH sont essentiellement des IgG1, activant fortement les plaquettes et la coagulation, causant ainsi une thrombopénie et la thrombose. Une évolution biphasique de la numération plaquettaire avec une décru secondaire après une augmentation après CEC et la non-résolution d’une thrombopénie dans les 6 jours post-opératoires nécessitent toujours de détecter les anticorps de T IH. Les tests fonctionnels (tests d’activation plaquettaire) et immunologiques (tests antigéniques) sont tous deux nécessaires pour faire le diagnostic de T IH. Lorsque la probabilité clinique d’une T IH est élevée, la première étape nécessaire est l’arrêt de l’héparine, sans attendre les résultats des investigations biologiques. Un anticoagulant alternatif telle que la danaparoid sodium (Orgaran®) ou la lépirudine (Refludan®) doit être administré car l’arrêt seul de l’héparine ne suffit pas contrôler l’état prothrombotique associé à T IH. Le risque de T IH va probablement diminuer bientôt, grâce à une utilisation plus large du fondaparinux, n’interagissant pas in vitro avec le PF4, mais ce risque persistera pour les patients bénéficiant de la chirurgie cardiaque sous circulation extra-corporelle.

INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a severe disease characterised by thrombocytopenia and a high risk for venous or arterial thrombosis. HIT is defined as a clinicopathological syndrome, and its diagnosis should therefore always be based upon: (a) the occurrence
of one or more HIT-associated clinical events, and (b) the detection of antibodies in patient serum or plasma (table I) [1-3]. A fall in platelet count during heparin therapy is the most common feature of this syndrome, which more frequently occurs with unfractionated heparin (UFH), affecting about 1% of patients) than with low molecular weight heparin (LMWH) [4, 5]. However, a recent study reported that 0.8% of patients treated with LMWH had developed HIT [6]. The risk of HIT with UFH is also lower in medical contexts (less than 1%) than in cardiac and orthopedic surgery patients (3 to 5%) [7]. We focus in this review, on the diagnosis and management of patients with suspected HIT after cardiac surgery.

WHY CARDIAC SURGERY IS ASSOCIATED WITH A HIGH RISK OF HIT?

HIT is an immune thrombocytopenia due to the development of IgG antibodies specific to heparin-modified platelet factor 4 (PF4) [8] (fig. 1). Heparin binds to PF4, and this interaction is easier with UFH that contains longer chains with a higher degree of sulphation compared to LMWH [9, 10]. UFH is therefore more likely to cause HIT than LMWH since shorter heparin fragments are less effective in bridging PF4 tetramers. The platelet count typically falls 5 to 10 days after the initiation of heparin when HIT occurs [11]. However, a rapid fall in platelet count can also occur in patients developing antibodies to PF4 after recent previous heparin treatment. Occasionally, thrombocytopenia occurs only after heparin has been withdrawn, corresponding to ‘delayed onset HIT’ [11].

Cardiac surgery with cardiopulmonary bypass is a clinical situation that induces strong platelet activation, with release into the plasma of large amounts of PF4. Furthermore, most patients receive high doses of UFH during surgery, and this clinical situation is therefore extremely immunogenic. Indeed, 25% to 50% of post-cardiac surgery patients develop heparin-depen-

tant antibodies during the 5 to 10 days following surgery [12-14]. However, these antibodies strongly activate platelets and thrombin generation, causing HIT in only 1% to 3% of cardiac surgery patients, particularly if UFH is continued beyond the first post-operative days. On the other hand, it has been well demonstrated that antibodies associated with high risk of HIT are mainly IgG1, present at high titres in the plasma of patients continuously treated by UFH. A non-randomised comparison of UFH and LMWH given after cardiac surgery confirmed that HIT is more frequent with UFH than with LMWH (2.5% vs 0.5%, OR = 6, p < 0.0001) (Personal analysis from pooled data) [14-16]. Apart from the type of heparin administered, the role of other risk factors for HIT has also been investigated. FcγRIIa receptors expressed on platelets bear a His131/Arg131 polymorphism that may influence platelet activation by human IgG. This polymorphism might thus affect the risk of HIT, but no consis-

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<th>Clinical features</th>
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| Decrease in platelet count with or without any of the following clinical events | A: Platelet activation assay using washed platelets
Serotonin release assay
Heparin-induced platelet activation test |
| 1: – Venous thrombosis
– Pulmonary embolism
– Cerebral venous thrombosis
– Adrenal haemorrhagic infarction | B: Platelet aggregation test using citrated platelet-rich plasma |
| 2: Arterial thrombosis: lower limb artery thrombosis, stroke, myocardial infarction | C: Antigen assay
PF4/heparin-enzyme immunonassay (EIA)
PF4/polyvinyl sulphonate EIA
Particle gel immunonassay |
| 3: Skin lesions (at heparin injection sites)
– Skin necrosis
– Erythematous plaques | |
| 4: Acute systemic reaction after intravenous heparin bolus | |
| 5: Hypofibrinogenaemia secondary to decompensated DIC | |

Fig. 1 – Pathogenesis of HIT
Fig. 1 – La pathogénie de la TIH.
tent at-risk profile emerged from a meta-analysis [17]. FcγRIIa, another polymorphic receptor for the Fc portion of IgG, is expressed on macrophages and natural killer cells. It binds IgG₁ and IgG₃, the main subclasses of HIT antibodies, and its role has therefore also been evoked in the pathogenesis of HIT. Indeed, recent findings strongly suggest that clearance of platelets sensitised by antibodies to PF4 is increased in patients homozygous for the FcγRIIa 158V allotype, thus contributing to the development of thrombocytopenia, particularly after cardiac surgery [18].

WHEN HIT SHOULD BE SUSPECTED AFTER CARDIAC SURGERY?

Cardiopulmonary bypass is frequently responsible for transient thrombocytopenia, favoured by haemodilution and/or platelet activation resulting from the contact of blood with the extracorporeal circuit [19]. Since cardiac surgery is associated with a high risk of HIT, careful monitoring of platelet count (PC) is a critical feature of post-cardiac surgical care to provide the early diagnosis of the disease. In most cases, the PC rapidly returns to normal after cardiac surgery, reaching a value at least equal or very close to PC prior to surgery in 5 to 6 days. Two abnormal PC patterns have been defined to allow highly specific indentification of cardiac patients with pathogenic HIT antibodies [16] (fig. 2). The first PC evolution which should prompt clinicians to investigate HIT in cardiac surgery patients, is characterized by the absence of PC recovery within the first 5 days post-operatively. The second and most typical PC pattern associated with HIT is characterised by an unexpected fall in platelet count that occurs at least 5 days after surgery and is preceded by an increase in PC. Laboratory investigations for HIT antibodies must be performed for all patients presenting one of these PC patterns.

On the other hand, thrombocytopenia is also relatively common after percutaneous coronary intervention (PCI) in patients hospitalised in cardiology intensive care units [20]. However, sudden and severe thrombocytopenia within hours of PCI in a patient receiving UFH and GPIIb/IIIa antagonist is mostly due to the anti-platelet drug. Indeed, naturally occurring antibodies that react against GPIIb/IIIa in the presence of the drug are frequently present, explaining early-onset thrombocytopenia in treated patients [21].

Thrombocytopenia is the central feature of HIT and PC falls between 20 – 150 G/L (median 60 G/L) within 10 to 10 days of heparin treatment in at least 85-90% of patients [22]. Spontaneous haemorrhage and petechiae are rare in HIT, even in the occasional patients with platelet counts of less than 10 G/L. Severe thrombocytopenia might also be due to disseminated intra-vascular coagulation (DIC) which occurs in only 5 – 15% of HIT patients. DIC might also be more common in cases of delayed-onset HIT since IgG-induced platelet activation is promoted in the absence of heparin anticoagulation.

HIT is associated with a high risk of thrombosis, and venous thrombosis (i.e. DVT and/or PE) complicates HIT more often than arterial occlusion [23, 24]. However, lower limb ischaemia seems to occur more frequently in patients undergoing cardiac surgery, probably favoured by arteriosclerotic lesions in some patients and vascular surgery with catheterisation. Other arterial thromboses such as ischaemic stroke and myocardial infarction have also been reported. In view of this high risk of thrombosis, it is recommended that investigations for deep-vein thrombosis such as Doppler ultrasoundography have to be performed when HIT is suspected even when no clinical symptoms are present. Skin lesions at heparin injection sites, ranging from erythematous plaques to skin necrosis, are also typical but infrequent in HIT. Acute systemic reactions following an intravenous bolus of heparin occur occasionally with various signs such as fever, chills, respiratory distress, hypertension or transient global amnesia.

**Fig. 2 – Evolution of platelet counts after cardiopulmonary bypass.**

(A) Normal change in platelet count in patients without antibodies to H-PF4.

(B, C) Platelet count patterns associated with HIT [16].

(A) Évolution normale de la numération plaquettaire sans anticorps contre H-FP4.

(B, C) Profils de numération plaquettaire associés au TIH [16].
Finally, thrombocytopenia is usual in the first hours or days following cardiac surgery and HIT might thus be suspected only in patients who had received heparin within the previous few weeks. However, HIT must be strongly suspected if the platelet count increases normally within the 6 days following surgery and then significantly decreases (variation of at least 40%), and in this situation heparin must be discontinued and replaced by an alternative anticoagulant.

The clinical likelihood of HIT can be evaluated in every patient using a scoring system such as the one recently described by T. Warkentin, known as the 4T’s (table II) [25]. This score is based on four criteria (Thrombocytopenia, Timing, Thrombosis and the absence of other explanations) and three levels of risk of HIT (low, intermediate or high) can be identified before laboratory testing. Preliminary evaluations have suggested that HIT antibodies are unlikely to be detected (< 5%) when a low score (< 3) is obtained. On the other hand, significant levels of antibodies are often present in patients (> 80%) with a high score (≥ 6). An intermediate score (4 or 5) is the most frequent situation and indicates a clinical history compatible with HIT but laboratory assays are especially useful in such cases. Apart from the 4T’s, another diagnostic score for HIT has also been proposed based on the analysis of platelet count evolution after cardiopulmonary bypass [26].

**HOW TO INTERPRET RESULTS OF LABORATORY TESTING FOR HIT ANTIBODIES AFTER CARDIAC SURGERY?**

Two categories of assays for HIT are currently available to detect heparin-dependent antibodies. One is functional and based on platelet activation (platelet aggregation test, serotonin release assay, heparin induced platelet activation), and the other is immunologic, investigating the binding of immunoglobulins to modified PF4 complexes [27, 28]. Enzyme immunoassays (or ELISA) detect IgG, IgM and IgA antibodies directed against PF4 modified by heparin (Asserachrom HPIA®, Diagnostica Stago, Asnières, France) or polyvinyl sulphonate (Test GTI, Brookfield, USA). The sensitivity of these assays for detecting clinically relevant HIT antibodies is very high, and thus a negative result is usually reliable to rule out the diagnosis of HIT [29]. However, the specificity of ELISA is fairly low since these assays also detect antibodies in about 30% to 50% of patients after cardiac surgery and most cases do not develop HIT. A particle gel immunoassay (HP/PF4-PaGIA®, Diamed, Switzerland) has recently been licensed that provides the detection of HIT antibodies in less than an hour after blood sampling, with a negative predictive value higher than 90% [30]. However, when there is a positive result with an immunologic assay, specific functional assays performed with washed platelets such as SRA or heparin-induced platelet activation test (HIPA) are always necessary to ensure the positive diagnosis of HIT in any patient, whatever the method used (ELISA or particle gel assay).

**HOW TO TREAT HIT IN CARDIAC SURGERY PATIENTS?**

When the clinical probability of HIT is intermediate or high (e.g. 4T’s score > 4), the first urgent decision is to discontinue heparin, without waiting for laboratory assay results [28, 31]. Alternative anticoagulant treatment must be prescribed even if the thrombocytopenia is not associated with thrombotic complications. Antiplatelet agents (aspirin or clopidogrel) are ineffective in inhibiting thrombin generation induced by HIT antibodies. Other treatments (IV immunoglobulins, plasma exchange) have been proposed but they cannot replace the antithrombotic drugs which have been approved in many countries to treat HIT patients (table III). Several criteria influence the choice of drug, such as their availability, clinical features of HIT, the patient’s renal and hepatic status and the experience of the centre. Danaparoid (Orgaran®) has been approved in Europe and Canada and widely used in large populations of patients [32]. Like heparins, it is a mixture of glycosaminoglycans, and this explains the possible cross-reactivity of this drug with HIT antibodies. Its anticoagulant activity depends on its ability to inhibit factor Xa (anti Xa/anti IIa ratio > 20). Danaparoid can be administered by SC or IV injections, with

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<th>Criteria for estimating the pre-test probability of HIT: the ‘4 T’s’ according to T. Warkentin [25]</th>
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<td><strong>2</strong></td>
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<tr>
<td>Thrombocytopenia</td>
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<td>Timing of fall in platelet count or other sequelae</td>
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<td>Thrombosis or other sequelae (e.g. skin lesions)</td>
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<td>Other cause(s) of platelet fall</td>
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Pre-test probability score 6-8 = High; 4-5 = Intermediate; 0-3 = Low.
a bioavailability of almost 100%. The half-life is 24 hours for anti Xa activity and shorter (7 hours) for anti-IIa activity, explaining why IV infusion or 2 to 3 SC injections are necessary daily. Overdosage can occur in cases of renal failure, with an increased risk of bleeding.

Lepirudin (Refludan®) is the second antithrombotic agent to become available in Europe for treating HIT patients. This recombinant hirudin exerts similar biological actions to natural hirudin extracted from the salivary glands of Hirudo medicinalis, the medicinal leech. Lepirudin is thus a direct, specific and irreversible inhibitor of thrombin and does not bind to PF4, and this drug does not exhibit any cross reactivity with HIT antibodies. Lepirudin can only be administered intravenously and its elimination is also rapidly impaired in cases of renal failure, with a rapid increase in half-life from 1 to 2 hours (normal) to more than 24 – 48 hours. This explains the high risk of bleeding in any patient treated with lepirudin, particularly if the recommended dosage is administered [33]. In any case, strict laboratory monitoring is required and the usual test applied is aPTT. However, the dose-response with aPTT is not linear and overdosage can be difficult to diagnose early. Other tests such as ecarin clotting time (ECT) are therefore often recommended. Apart from bleeding, anaphylactic reactions have also been reported in patients reexposed to lepirudin. Every patient should therefore be clearly informed that he has received this drug to reduce the risk of severe adverse effects [34]. Apart from lepirudin, argatroban is another direct thrombin inhibitor used to treat HIT patients in North America, and several countries in Europe, but this drug is not available in France. However, its short half-life and its hepatobiliary excretion are two major advantages in severely ill patients with renal insufficiency [35]. Finally, fondaparinux (Arixtra®), a synthetic pentasaccharide and factor Xa inhibitor that exhibits little or no in-vitro cross-reactivity with HIT antibodies has recently been proposed to treat patients with acute HIT [36]. However, prospective trials evaluating the efficacy and safety of fondaparinux in this particular clinical situation are always mandatory.

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<th>Anticoagulant</th>
<th>Prophylactic regimen</th>
<th>Therapeutic regimen</th>
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<tr>
<td>Danaparoid: Orgaran®</td>
<td>No bolus 750 U X 3 sc (1250 U X 3 if body weight &gt; 90 Kg)</td>
<td>Bolus* 2250 U, then IV perfusion 400 U. hr⁻¹, then 300 U. hr⁻¹, then 150-200 U. hr⁻¹, monitored by anti-Xa activity (0.5 to 0.8 U anti-Xa. ml⁻¹)</td>
<td>- risk of cross reactivity - *adjust for body weight (&lt;60 Kg = 1500 U, 75 – 90 Kg = 3000 U, &gt; 90 Kg = 3750 U)</td>
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<tr>
<td>Lepirudin: Refudan®</td>
<td>Not approved</td>
<td>bolus** 0.4 mg/kg then IV infusion 0.15 mg/kg/hour monitored by aPTT (1.5 to 2.5 times baselines)</td>
<td>- *risk of anaphylactic shock after bolus (specially if reexposure) - **: risk of early overdose under discussion: bolus limited to life-threatening thrombosis, reduction of IV infusion to 0.1 mg. Kg⁻¹ per our, aPTT range 1.5 to 2 times baseline.</td>
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<tr>
<td>Argatroban: Argatroban®</td>
<td>No bolus IV infusion 2μg.Kg⁻¹.min⁻¹, monitored by aPTT (1.5 to 3 times baseline)</td>
<td>Same dosage</td>
<td>- limited experience - reversible antithrombotic effect</td>
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References