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Regular Article

Clinical characteristics and laboratory testing of patients with suspected HIT: A survey on current practice in 11 university hospitals in France

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ABSTRACT

Summary: We undertook a survey of French university hospital hematological laboratories to ascertain the clinical characteristics of patients with suspected HIT, the laboratory tests performed, and the therapeutic strategy adopted in current practice.
Methods: A standardized medical records database for patients with suspected HIT was sent to 19 laboratories. During two months, all consecutive patients for whom a biological test was performed were included.
Results: 169 patients were included, 27 (16%) patients having a final diagnosis of HIT. At the time HIT was suspected, the heparin duration and the level of thrombocytopenia were similar in HIT- positive and HIT-negative groups. The use of unfractionated heparin, a therapeutic heparin dose regimen and the presence of thrombotic complications were significantly more frequent in HIT-positive patients. When the heparin dose regimen was taken into account, only thrombotic complications under a therapeutic dose regimen were significantly increased in HIT-positive patients. Eighty-six percent of patients presented at least one alternative diagnosis of thrombocytopenia without significant difference between the two groups. Laboratory tests were performed after a mean of 0.3 days and mainly consisted of antigen assays. At the time HIT was suspected, heparin was stopped in 56 (33%) patients, being replaced mainly by danaparoid. Only three laboratories declared they usually received all the necessary clinical information to establish the likelihood of HIT.
Conclusion: In current practice in France, the clinical probability of HIT is rarely established, leading to systematic requests for laboratory HIT tests.

Introduction

Heparin-induced thrombocytopenia (HIT) is a severe adverse drug reaction caused by platelet-activating antibodies reactive against complexes between heparin and chemokine proteins, particularly platelet factor 4 (PF4). In most cases, HIT is caused by platelet-activating antibodies of the IgG class that recognize multimolecular complexes of PF4 and heparin [1,2]. IgG isotypes can be present alone or associated with IgA and/or IgM isotypes in other cases. Whether IgA and/or IgM isotypes (which, *in vitro*, do not activate platelets through FcγRIIa receptors in the presence of heparin) are pathogenic is still a matter of debate [3–5]. HIT antibodies can also sometimes be specifically directed towards other chemokines, such as interleukin-8 or neutrophil-activating peptide-2 [6]. HIT syndrome occurs at a frequency of 2.6% with unfractionated heparin (UFH) and 0.2% with low-molecular-weight heparins (LMWH) [7]. The risk of developing HIT seems to be

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lower in the medical context (less than 1%) than in patients having recently undergone cardiac or orthopedic surgery (3 to 5%) [8]. In HIT, the marked drop in platelet count typically occurs 5 to 14 days after heparin exposure, although it may occur earlier (recent prior heparin exposure) or later (treatment with LMWH) or even after discontinuation of heparin ("delayed-onset" HIT) [9,10]. The drop in platelet count relative to baseline is usually ≥ 50 % but may be less, depending on the clinical situation [9]. In view of the substantial thrombotic risk (odds ratio for thrombosis: 20 to 40), it is crucial to establish the diagnosis of HIT [9]. Clinicians should therefore consider a diagnosis of HIT whenever thrombocytopenia occurs with a temporal pattern consistent with heparin-induced immunization and/or whenever patients develop arterial or venous thrombosis while receiving heparin prophylaxis or treatment. Clinical suspicion of HIT should be confirmed by serological assays. Two types of serological assay are available for laboratory detection of HIT antibodies. Antigen assays detect the presence of antibodies directed towards PF4-heparin complexes, whereas functional assays detect heparin-dependent activation induced by these antibodies. Antigen assays are easy to perform and present good sensitivity but poor specificity in certain contexts (post-cardiac surgery), while functional assays can only be performed in specialized laboratories (^{14}C-serotonin release assay [SRA]) or present variable sensitivity (platelet aggregation test [PAT]). Faced with all these limitations related to the clinical and laboratory diagnosis of HIT, we undertook a survey of specialized coagulation laboratories in French university hospitals in order to ascertain the clinical characteristics of patients with suspected HIT, the type of laboratory tests performed and the therapeutic strategy adopted for these patients in current French practice.

Methods

Medical database

A standardized medical record database for patients with suspected HIT was developed by members of the French thrombosis and hemostasis expert group (Groupe d'Etude sur l'Hémostase et la Thrombose, GEHT) involved in HIT research (HIT group). This GEHT-HIT group comprises principally clinicians and biologists working in France and Switzerland. The medical record database consisted of 19 items (103 questions) including the major elements of the patient's medical or surgical history, site of current hospitalization and the main reason for this, the type and aim of heparin therapy, the changes in platelet count before and after suspected HIT, the presence or absence of thrombotic complications, the existence or not of potential alternative diagnoses of thrombocytopenia, the type of laboratory tests for HIT performed and the interval between suspicion of HIT and laboratory testing, the therapeutic strategy adopted, and the final diagnosis.

Participating centers and patients

This prospective study was proposed to 19 members of the GEHT-HIT study group each working in a specialized coagulation laboratory of a French university hospital. During two consecutive months between July and October 2007, participating members were asked to include all consecutive patients admitted to their university hospital for whom a laboratory test for HIT was performed. For each patient included, all the clinical and laboratory data obtained from the first day of hospitalization until discharge had to be recorded in the medical database.

Likelihood of HIT

In addition, the participating members were asked to specify how patient data are usually collected by their laboratory before HIT laboratory testing and how the clinical likelihood of HIT is established in their current practice.

Statistical analysis

The chi-square test or Fisher's exact test was used to compare categorical variables. Student's t-test or the median test was used to compare continuous variables. All P-values were two-tailed and differences were considered to be statistically significant at an alpha risk of ≤ 0.05.

Results

Patients

Eleven of the 19 (58%) French university hospital hematological laboratories invited agreed to participate. A total of 169 patients (99 men, 70 women) with a mean age of 65 years (range: 17-94) were included. Twenty-seven patients (16%) had a final diagnosis of HIT syndrome at the end of their hospitalization:

- In 16 cases, the diagnosis of HIT was supported by both positive antigen assays [enzyme-linked immunosorbent assay (ELISA)] and positive functional assays (PAT, SRA).
- For 10 patients, the diagnosis of HIT was supported by a strongly positive ELISA assay alone [mean optical density in the ELISA: 2.1 (range: 1.25-3.15); mean cut-off: 0.50 (range: 0.33-0.55)] (Table 1). For these 10 patients, the PAT was not performed in 2 cases and was negative in 8 cases. Five of these 8 patients presented a thrombotic complication associated with thrombocytopenia during heparin therapy. Four of the 10 patients without positive PAT presented anti-H-PF4 IgG antibodies, while the immunoglobulin classes were not identified for the other six. Among these 10 patients, five (patients 3 to 7) presented thrombocytopenia after cardiopulmonary bypass. All these patients but one (patient n°6) presented a typical abnormal platelet count pattern observed in HIT patients following cardiac surgery [11,12]. In one case, the patient (patient n°8) presented both thrombocytopenia and a thrombotic complication 2 days after heparin initiation. In fact, shortly beforehand this patient had been treated with LMWH for 7 days for a mesenteric infarct with a platelet count drop from 190 to 38 giga/L. At this time, LMWH was stopped without initiation of any other alternative antithrombotic therapy. Eight days later this patient returned to hospital for a PE with a platelet count of 241 giga/L and UFH was re introduced. Two days later, this patient presented a new platelet count drop and a new thrombotic complication.

In one case, a final diagnosis of HIT was established by the clinician despite a negative antigen assay and no functional testing. This patient received therapeutic doses of LWMH for a portal vein thrombosis in a context of essential thrombocythemia. On day five of LMWH therapy, his platelet count fell from 304 giga/L to 165 giga/L. After four additional days of LMWH, the platelet count dropped to 96 giga/L without any thrombotic complication. No evident alternative cause of this low platelet count, including hepatic failure, sepsis, or medications, was found. Two successive ELISA assays were negative and during the subsequent treatment with danaparoid for 16 days the platelet count increased up to initial values. In view of the absence of other potential causes of thrombocytopenia and the recovery of the platelet count on discontinuation of LMWH, a final diagnosis of probable HIT syndrome was made by the clinician in charge of the patient, despite the negative antigen assays. The results reported below, including the results of statistical analysis, remain the same whether or not this patient is taken into account.

Except for progressive cancer, which was more often observed in patients without a final diagnosis of HIT, the main demographic and