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HEPARIN-INDUCED THROMBOCYTOPENIA IN THE CARDIAC PATIENT: 10 POINTS TO HELP THE PHYSICIAN

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Case 1:

A 65-year-old man underwent triple coronary artery bypass surgery. Postoperative atrial fibrillation lengthened his ICU stay. On postoperative day 6, it was noted that the platelet count, which had begun to rise from a postoperative nadir of 105,000, had fallen again to 90,000. The cardiologist indicated suspicion of heparin-induced thrombocytopenia (HIT); he stopped all heparin and ordered a heparin antibody test. Platelets were 98,000 the next day when the cardiologist wrote, "I am considering calling Hematology, but they would likely anticoagulate the patient; his stool guaiac is positive, so I will hold off consultation." The next morning, the patient had a pulseless, cool, and cyanotic right arm. On arrival, the hematologist found the patient confused, with a tender abdomen and absent bowel sounds. In spite of initiation of a direct thrombin inhibitor, the patient expired of bowel necrosis and sepsis within a few days.

Case 2:

A 42-year-old physician with episodic supraventricular tachycardia had an outpatient ablation procedure. Two weeks later he presented with a swollen painful leg, with Doppler showing complete thrombotic occlusion of the common femoral, popliteal, and superficial femoral veins. Platelet count was 165,000 before procedure, 111,000 on representation, and 66,000 after intravenous heparin infusion was started. Shortness of breath and documented pulmonary embolus ensued. When a heparin antibody test ordered 5 days after admission came back very strongly positive, a direct thrombin inhibitor was begun. The patient demanded transfer to our hospital. His subsequent course was benign, including transition to warfarin and discontinuation of anticoagulants after 6 months.

Introduction

Heparin-induced thrombocytopenia (HIT) is arguably the most important adverse drug reaction encountered in hospitals today, given its frequency and its devastating complications. The disorder is steeped in paradoxes, not the least of which is that an immune reaction which lowers the platelet count rarely causes bleeding but rather is associated with an extreme risk for arterial and venous thromboses.[1] It is especially important for cardiologists and cardiovascular surgeons to be knowledgeable about HIT since it is common in their patients and responsible for many of their unfavorable outcomes. Particular challenges are faced in making the diagnosis of HIT in cardiac patients as illustrated by these cases, and these will be revisited. This paper highlights 10 aspects of HIT that heart specialists should become familiar with to avoid disastrous complications in their patients (Table 1).

HIT is common in cardiac patients.

Heparin use is ubiquitous in hospitals. We were among the first to report that even tiny amounts of heparin used to flush indwelling vascular catheters can initiate or promulgate HIT.[2, 3] The incidence of HIT varies with the dose of heparin, type of heparin (10 times more common with unfractionated than low-molecular-weight heparin) and, interestingly, with the clinical situation: HIT frequency is higher in surgical than in medical patients and highest with cardiovascular and orthopedic surgery.[4] Patients undergoing "on-pump" heart surgery are at high risk for HIT due to the high doses of unfractionated heparin required, the release of platelet

Table 1. HIT Do's and Don'ts in Cardiac Patients

DO:

- Consider HIT when exposed patient has fall in platelets or new thrombosis
- If moderate or strong suspicion (timing, thrombocytopenia, thrombosis, no other causes):
  - Stop all heparin exposures
  - Begin alternative anticoagulant
  - Order heparin-platelet antibody test
  - Consider Hematology consultation

DO NOT:

- Order test when HIT diagnosis does not fit
- Wait on test results if suspicion is moderate or strong
- Believe patient must have HIT if ELISA test is "positive" (especially if low titer)
- Begin warfarin or place IVC filter

REMEMBER:

- Platelets normally low in first 3 days after pump surgery
- IABPs and LVADs cause thrombocytopenia
- High prevalence of heparin-PF4 antibodies in cardiac patients, but few have HIT

factor 4 (PF4) from battered platelets, and the inflammatory milieu. HIT has been estimated to complicate 1–3% of cardiovascular surgeries, with 0.5% in a recent prospective study.[5] These ranges correspond with our experience at The Methodist Hospital. Ten years ago, we saw about 100 cases of HIT annually, two-thirds from cardiac surgery (from more than 3,000 pump cases). Despite national and local downturns in cardiac surgery, we still encounter 3-dozen HIT cases a year. As in Case 2 above, HIT does occur in cardiology outside of surgical settings, but this is less common.

Possible HIT should run through your mind whenever a patient exposed to heparin has a fall in platelet count or a new blood clot.

HIT onset occurs 5 to 12 days after the initiation of heparin, with platelets abruptly falling more than 50% in the great majority. Half of affected patients will have a new blood clot as a presenting manifestation.[6] Most often this is deep vein thrombosis (DVT) with or without pulmonary emboli, but also common are stroke, myocardial infarction, limb thromboses (potentially leading to amputations), and acute occlusions of coronary bypass grafts. HIT should register high on the differential in patients presenting with unusual clots such as mesenteric thrombosis (Case 1), cerebral sinus thrombosis, and bilateral hemorrhagic adrenal necrosis (a microthrombotic process).[7]

You need to understand the disease — when it is likely to occur and when it is not.

A stable dialysis patient chronically exposed to heparin who develops fever and thrombocytopenia does not have HIT; the thrombocytopenia is due to sepsis. Clinicians may use scoring systems to help them judge the clinical probability of HIT.[8,9] A simple tool, the "4 T's," awards points for whether the fall in platelets is typical, whether it occurs with expected timing, whether thrombotic complications emerge contemporaneously, and, importantly, whether there are likely alternative explanations for thrombocytopenia. Common causes of iatrogenic thrombocytopenia are sepsis and certain medications (e.g., vancomycin, other antibiotics, H2-blockers).[10] Cardiac surgery itself causes platelets to fall by about 50%, with nadir 2 to 3 days post-op, secondary to "dilution" and shortened survival of damaged platelets.[11] Intra-aortic balloon pumps, left ventricular assist devices, and some cardiac medications are established causes of thrombocytopenia.

Cardiac physicians must be vigilant for alternative temporal scenarios. We were first to describe delayed-onset HIT, in which patients off heparin for more than 3 days (typically at home for a week or two) present with thrombosis, usually mild thrombocytopenia, and heparin-PF4 antibodies in very high titer (when they are measured).[12, 13] This increasingly recognized phenomenon has been seen mainly after heart surgery. If not suspected and a heparin is administered, morbidity and mortality are high. Case 2 was fortunate not to suffer clinical deterioration. Rapid-onset HIT is an alternative scenario in which patients exposed to heparin within the last month or two have preformed antibodies and develop HIT almost immediately on re-exposure, sometimes manifested as acute cardiorespiratory collapse.[14, 15]

On moderate suspicion of HIT, begin an alternative anticoagulant immediately.

HIT is an extreme hypercoagulable state in which 50% of patients will develop new thromboses, often devastating or fatal, in the absence of effective alternative anticoagulation.[6] Risk is highest in the first days after the platelets fall. *You can't just stop heparin*, the mistake made in Case 1; in fact, do not wait on results of serologic testing if clinical suspicion is moderately strong.[16] As awareness of HIT has increased, we see fewer patients in whom the diagnosis was not suspected. The message that needs to get out now is the mandate for immediate alternative anticoagulation even with isolated HIT (no new clot).

Alternative anticoagulants FDA-approved for HIT are the direct thrombin inhibitors, argatroban and lepirudin. We have published our favorable experience with argatroban and with off-label use of the direct thrombin inhibitor bivalirudin.[17, 18] Fondaparinux, a subcutaneous factor Xa inhibitor, is receiving increased off-label use for less-sick HIT patients, limited by renal clearance, long half-life, and other issues. Newer anticoagulants such as desirudin[19] and the oral thrombin and factor X inhibitors are likely to find future roles in HIT treatment and prevention.

The test is your friend, but it cannot tell you if this is HIT or not.

Serologic tests are not screening tools but are validated in the context of reasonable suspicion for HIT. Commercial ELISA kits (Enzyme-Linked ImmunoSorbent Assay) for measuring the presence of heparin-PF4 antibodies are inexpensive, reproducible, and widely available. They have 99% sensitivity, so a negative result virtually rules out HIT. The "high false positive rate" may mainly reflect a lack of interpretation of the numeric optical density (OD) result in the context of the individual case pretest probability. Some advocate confirmation of positive ELISA results with more specific platelet-activating assays such as the serotonin-release assay, but these are rarely available in real time and may be poorly reproducible from lab to lab.

ELISA OD values greater than 0.4 have traditionally been reported "positive," but Warkentin found that titers between 0.4 and 1.0 are associated with only a 0–2% chance of having platelet-activating antibodies.[20] OD results >2.0 had an 89–90% association with HIT. I support the recommendation not to append "positive" or "negative" interpretations to ELISA results but rather encourage clinicians to interpret the numerical results in the context of their patient.[21] When this is done, I do not find that further serologic testing informs clinical decision-making. This may not be good news for clinicians who prefer an easy way, a definitive test that establishes whether the disorder is present or not. Alas, HIT is like most things in medicine: there is no substitute for careful history (e.g., when did heparin exposure occur; chart platelet trends) and clinical judgment. The test alone cannot answer the question, and a "positive" test *does not mean the patient has HIT*.[5]

Over-diagnosis of HIT can harm your patients.

The need to increase awareness of HIT continues (see CATCH data below), but over-diagnosis has also emerged as a substantial problem at many medical centers.[22] Over-diagnosis is not benign: needed heart surgeries have been delayed or cancelled, transplant lists have been culled, and alternative anticoagulants have been administered to those who do not need them by those unfamiliar with them. There is a learning curve to the use of alternative anticoagulants, and FDA-approved labels may not be the best guide.[23] In the last few years, when we have been consulted for suspected HIT, most often the patient has not had it. In fact, when HIT antibodies are ordered and/or alternative anticoagulants substituted for heparin in our ICUs, we find that the clinical probability of HIT could have been judged extremely low.[24] Today it is as important as ever to have an understanding of the disease process, when to suspect HIT or not, when to order and how to interpret serologic tests, when and how to use alternative anticoagulants, and when to seek experienced help.

Diagnosing HIT in cardiac patients poses special challenges.

Thrombocytopenia is very common in cardiac patients and, regardless of cause, has been linked in multiple studies to increased complications and death. The Methodist Hospital was one of 48 U.S. hospitals that participated in the CATCH registry, which compiled data on nearly 4,000 patients who had received heparin for more than 4 days or who had become thrombocytopenic in the CCU. Thrombocytopenia occurred in one-third of the patients and was the strongest independent predictor of serious complications and death. Despite suggestive features in many cases, a shockingly small percentage had HIT considered, a test ordered, alternative anticoagulation initiated, or hematologic consultation.[25, 26]

Some special challenges in cardiology patients include prior heparin exposures (some not obvious), such as during catheterization or angina hospitalization. It may be difficult to judge when sensitization occurred; in a patient who received heparin during catheterization a week ago, the day of heart surgery could be considered day 1 or day 8 of exposure (although the intraoperative dose is most often sensitizing). Platelet counts are expected to fall 25–50% after cardiopulmonary bypass. Analysis of the platelet count pattern is the best predictor of HIT after heart surgery.[27-29] With HIT, platelets that plummet after surgery and do not recover is compatible, but the great majority will have beginning postoperative recovery and then a secondary decline (as in Case 1 above).

With cardiac surgery, the circulating heparin and PF4 lead to very high rates of antibody formation. About 50% of patients develop "positive" heparin-PF4 ELISA tests (OD >0.4), but few of them actually have HIT; those who do generally have high antibody titers. Detectible heparin-PF4 antibodies may be found in 20% of patients preoperatively, but fortunately their courses may not be adversely affected despite heparin on pump.[30] An especially high prevalence of heparin-dependent antibodies has been seen in both LVAD patients and in heart transplant candidates.[31]

Special caveats: warfarin and inferior vena cava (IVC) filters

Warfarin should never be initiated "unopposed" (without effective anticoagulation on board) in any patient with active thrombosis, because activity of the short-lived natural anticoagulant protein C declines before the important longer-lived vitamin K-dependent procoagulants, factors II and X. Thus, warfarin will initially worsen a thrombotic diathesis. In the extreme hypercoagulable milieu of HIT, early unopposed warfarin is linked to venous limb gangrene and central skin necrosis.[32, 33] Higher prothrombin time international normalized ratio (INR) correlates with increased thrombotic risk, because the early INR response reflects activity of short-lived factor VII that correlates well with protein C.

The most established indications for IVC filters are failure of adequate anticoagulation or contraindication to anticoagulation in those with (or at very high risk for) DVT. HIT would seem to fit these indications on first thought, but actually the syndrome mandates aggressive alternative anticoagulation and is not a contraindication. (HIT patients with the lowest platelet counts have the highest thrombotic risk, so thrombocytopenia mandates rather than contraindicates anticoagulation.) Anecdotal reports have linked placement of the foreign-body IVC filter with severe distal thrombotic complications.[16, 33] Our recently compiled experience finds a very high rate of new thromboses when filters are placed in patients with HIT.[34]

Caring for patients with past HIT

Heparin-PF4 antibodies are transient and usually undetectable 2 to 3 months after an episode of HIT. Interestingly, the great majority of patients re-exposed to heparin at a later time do not develop recurrent HIT. That said, we have seen a couple of patients with distant HIT who developed devastating complications after re-exposure.[35] In most situations, there is no reason to risk heparin re-exposure because very suitable alternatives are available, for example, bivalirudin for percutaneous angioplasty or fondaparinux for orthopedic surgery. One situation in which unfractionated heparin offers unique advantages is on pump cardiac surgery, where dosing and monitoring protocols are well-established and rapid reversibility is achieved with protamine. With distant HIT, I concur with published guidelines on HIT diagnosis and management that endorse intraoperative unfractionated heparin on pump, avoiding postoperative heparin exposures including flushes and coated catheters.[36]

A knowledgeable hematologist can be invaluable to you.

Some of the diagnostic challenges in cardiac patients have been reviewed, including the high prevalence of heparin-PF4 antibodies, the need for proper interpretation of serologic tests in the context of pretest probabilities, the need to consider predicted platelet count falls (such as post-pump surgery), and considerations of competing causes of thrombocytopenia. When and which alternative anticoagulant to initiate, optimal dosing, and proper monitoring can be additional challenges for the inexperienced. Early consultation with a hematologist experienced in this area can be crucial to a patient's outcome.

Summary

HIT is a potentially devastating problem, common but particularly challenging to diagnose and treat in the setting of heart disease. This diagnosis needs to be considered whenever a patient who has been exposed to heparin has a significant fall in platelet count or new arterial or venous thromboses. The degree of clinical suspicion depends on whether platelet count fall is typical, timing is typical, thrombotic complications have appeared, and whether alternative explanations for thrombocytopenia are likely. Some special difficulties in dealing with cardiac patients include prior heparin exposures, expected platelet declines post-pump and with inserted devices, the high prevalence of nonplatelet-activating heparin-PF4 antibodies, and the fact that alternative temporal scenarios (delayed-onset HIT) are more common. With moderate or strong suspicion, an alternative anticoagulant should be started while serologic tests are awaited. The strength of reaction of the ELISA test must be interpreted in the clinical context to make a diagnosis of HIT. Overdiagnosis can harm the patient, so a thorough understanding of the disorder and consultation when appropriate can be life and limb saving.

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