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Dr. Rice discloses that he serves on the speakers' bureaus of Berlex, GlaxoSmithKline, Sanofi-Aventis, and The Medicines Company; has received research support from GlaxoSmithKline; and has received consultation fees from Berlex, GlaxoSmithKline, and The Medicines Company.

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Special REPORT

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Heparin-Induced Thrombocytopenia Keys to Recognition and Management

NEEDS STATEMENT

Heparin-induced thrombocytopenia (HIT) is a potentially life- and limb-threatening reaction to heparin that affects up to 5% of patients exposed to the drug. It has been estimated that heparin is given to more than 12 million people per year, meaning HIT can affect up to 600,000 patients yearly. Late recognition continues to be a problem that leads to patient morbidity and mortality. Clinicians must be familiar with the clinical features that establish suspicion of HIT; heparin must be stopped and alternative anticoagulant therapy initiated upon clinical


suspicion of HIT, without waiting for confirmation from laboratory tests. The direct thrombin inhibitors argatroban and lepirudin are approved by the FDA for the treatment of HIT. This report presents guidelines for the use of these and other agents; keys to preventing, diagnosing, and managing the condition; and introductory case studies that elucidate the need for immediate detection and treatment of HIT. It is intended to encourage clinicians to be highly vigilant in identifying and avoiding this dangerous complication.

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LEARNING OBJECTIVES

At the completion of this activity, participants should be able to:

- 1 Discuss the incidence, epidemiology, and clinical features of HIT.
- 2 Summarize key measures in the diagnosis, treatment, and prevention of HIT.
- 3 Review and compare the pharmacologic properties, dosing, and administration of alternative anticoagulants.

TARGET AUDIENCE

This educational program is intended for physicians and pharmacists involved or interested in the prevention and treatment of HIT.

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ESTIMATED TIME OF COMPLETION

This activity should take approximately 1 hour to complete.

METHOD OF PARTICIPATION

There are no fees for participating and receiving credit for this activity. The participant should, in order, read the objectives and monograph and answer the multiple-choice post-test. Participation is available online at CMEZone.com. Enter the project number "SR528" in the keyword field to directly access this activity and receive instantaneous participation. Or, complete the answer sheet with registration and evaluation on page 8 and mail to: Attn: Distance Education, Continuing Education Office, Colleges of Pharmacy and Medicine, University of Kentucky, 1 Quality St, 6th Fl, Lexington, KY 40507-1428. Certificates will be mailed to participants in approximately four weeks after receipt of the mailed or faxed submissions. This credit is valid through March 31, 2007.

Case Studies

Case 1.¹ A young woman with posterior pituitary involvement by Langerhans' cell histiocytosis begins outpatient chemotherapy with 2-chlorodeoxyadenosine given by 7-day continuous intravenous infusion. Her chart indicates that each day, as her syringe is filled with drug and attached via a battery-powered pump to her intravenous port, the line is flushed with heparin. On day 9 (2 days post-chemotherapy), she is admitted with severe pleuritic chest pain and dyspnea. Her platelet count has fallen to 50,000/cu mm (from 170,000/cu mm), thought to be secondary to chemotherapy (but her leukocyte count has not fallen at all). After 2 days on morphine, a chest CT scan reveals bilateral pulmonary emboli. Low molecular weight heparin (LMWH) is begun, and the platelet count falls within hours to 19,000/cu mm. Severe pain and swelling of both arms, headache, and facial swelling promptly ensue. On transfer to a tertiary hospital, all heparin is stopped and a direct thrombin inhibitor (DTI) is begun. Imaging reveals near-complete superior vena cava thrombosis, bilateral subclavian thromboses, and bilateral pulmonary emboli with a large embolus in the right main pulmonary artery. Serology for heparin-induced thrombocytopenia (HIT) antibody is strongly positive. All signs and symptoms resolve after 8 days of DTI therapy transitioned to warfarin.

Case 2.² A middle-aged woman suffers a flare of inflammatory bowel disease. Ten days into her hospitalization, her platelet count plunges from 306,000/cu mm to 28,000/cu mm. Nursing notes reveal heparin flushes to her central venous catheter, and these are stopped. An enzyme-linked immunosorbent assay (ELISA) for HIT antibodies returns strongly positive. Over several days, platelets rise back to normal. Her bowel symptoms have also improved, and hospital discharge is contemplated. An oral antibiotic is started for cough and possible lung infiltrate (vs atelectasis). Abruptly, one evening, she suffers severe dyspnea, pleuritic pain, hemoptysis, and severe left leg pain and swelling. A hematologist is called and initiates DTI therapy for multiple pulmonary emboli, extensive deep vein thrombosis (DVT), and impending venous gangrene. Oxygenation remains unsatisfactory on a non-rebreather mask, and an echocardiogram shows acute pulmonary hypertension with severe right ventricular dysfunction. Catheter-directed and systemic thrombolytic therapies are attempted, as well as mechanical pulmonary embolectomy, but the patient succumbs.

Scope of the Problem

Thromboembolic disorders rank among the most common causes of morbidity and mortality. Heparin has been our most trusted weapon against these disorders for well over half a century, literally saving the lives and limbs of millions of patients. However, among the paradoxes of HIT (Table 1) is that a common adverse reaction to this drug may also cost many thousands of lives and limbs each year. It might be thought that every physician and pharmacist would be very familiar with HIT; after all, the reaction is quite common, the consequences are dire, it can be prevented and effectively treated, it is iatrogenic, and it is a major cause of malpractice litigation. Yet, 50 years after a series of heparin-related thromboses was published, and 30 years after surgeons at the University of Missouri delineated the clinical features of HIT, many practitioners using heparin remain unaware of the problem or cannot recognize it when it occurs. Some progress has been made, but this subject continues to receive surprisingly scant attention in medical curriculae and standard textbooks of pharmacy, medicine, cardiology, vascular medicine, pulmonary/critical care, and other specialties.

The theme of this report is that there is a great need to increase awareness of HIT among doctors and pharmacists, and they must keep up-to-date on emerging developments in prevention, detection, diagnosis, and treatment. Delayed recognition (Case 1) continues to result in high rates of morbidity and mortality. HIT must be considered whenever platelets fall in a hospitalized patient or

Table 1. Paradoxes of HIT

- Heparin has been the most powerful anticoagulant of the 20th century, saving uncountable patients their lives and limbs; yet heparin also produces the most extreme of hypercoagulable disorders, yearly costing many thousands their lives and limbs.
- HIT, an immune reaction to an anticoagulant that lowers platelet count, rarely causes bleeding; it causes thromboses, and platelet transfusions are generally contraindicated.
- Health professionals should be extremely knowledgeable about a reaction that is common, often catastrophic, preventable, treatable, iatrogenic, and a major source of litigation; yet textbooks and medical curriculae pay HIT little attention, and the prevailing lack of awareness is shocking.

whenever such a patient suffers a new thrombosis. As progress is made in increasing awareness, the next frontier may be to stress to caregivers that patients in this extreme hypercoagulable state require immediate intervention with an alternative anticoagulant (Case 2).

Epidemiology and Incidence

HIT will occur in 3% to 5% of patients given therapeutic intravenous unfractionated heparin for problems such as DVT or unstable angina.³ The incidence is somewhat less with lower doses of unfractionated heparin, but even minuscule amounts used to flush catheters or that leach from heparin-coated central catheters may cause the full-blown syndrome in 0.5% of patients exposed.⁴ Flushes may also promulgate the syndrome, increasing complications in those previously sensitized.⁵ LMWHs cause HIT only 10% as often as unfractionated heparin does,^{6,7} and this should be an important consideration in the initial choice of an anticoagulant drug (see Prevention, page 6). However, given the millions of patients who receive LMWHs each year, it is not surprising that many patients with HIT have exclusively received low molecular weight agents. Once a patient has HIT, LMWHs are contraindicated⁸ (Case 1) because they almost always cross-react with HIT antibodies (the in vitro cross-reaction rate is nearly 100%, thus presenting the risk for in vivo cross-reaction).

Cardiovascular surgery and orthopedic surgery patients are more prone to develop HIT than medical or obstetric patients, demonstrating that clinical factors influence the likelihood of the syndrome.⁹ Prevailing dictums that HIT is rare in cancer patients, dialysis patients, or pediatric patients generally have fallen by the wayside as such patients are more thoroughly evaluated. Genetic thrombophilias do not predispose someone to HIT, platelet polymorphisms do not have clinical predictive power, and there seems to be a slightly greater risk for females exposed to heparin. Thus, the only factors that have some value in predicting who will develop HIT are (1) how much and what kind of heparin is given, and (2) the reason for which heparin is given (eg, orthopedic surgery or cardiovascular surgery). It is worth stressing, though, that even a minuscule incidental exposure to heparin can sometimes result in catastrophic problems. Patients who have had previous HIT (>4 months prior) usually do not develop HIT again if they are re-exposed to heparin,¹⁰ although taking a chance on such a re-exposure is rarely justified.

Pathophysiology

Heparin binds to platelet factor 4 (PF4) released from platelet alpha granules. The PF4 is modified in such a way that, in some patients, it is recognized as a new antigen, mounting a humoral

immune response. The antibody/heparin-modified PF4 forms macromolecular complexes on the platelet surface and causes intense platelet activation via the platelet Fc receptors. An extreme degree of platelet microparticle generation is evident, which leads to activation of the coagulation protein cascade and thrombin production. Additionally, the antibodies against heparin–PF4 cross-react with endogenous glycosaminoglycans on endothelial surfaces, causing endothelial activation and injury. Some studies also indicate a role for monocyte procoagulant activity. The most intense of thrombotic diatheses are produced by platelet activation, thrombin generation, and endothelial perturbation.¹¹ A visual depiction of the pathophysiology of HIT is presented in the Figure.¹²

In many patients exposed to heparin, there may be an early, mild, transient, and benign fall in platelet count that is not immune-mediated—a phenomenon that has been called *type 1 HIT*.¹³ Platelets generally fall by less than 30% and will recover even if heparin is continued. In many cases, it is likely that such a mild, transient fall in platelet count has nothing to do with heparin exposure. Immune-mediated, life-threatening, “real HIT” has been called *type 2 HIT*. This terminology needs to be eliminated because it misleads clinicians into thinking that some cases of true HIT are benign and do not need treatment.

Clinical Features

The clinical features of the syndrome, repeatedly described in the late 1970s, continue to be witnessed again and again.^{14,15} Platelets fall 5 to 12 days after initial heparin exposure. In 30% to 50% of patients, this is accompanied by new, potentially deadly, venous or arterial thromboses; for example, the initial DVT worsens with new pulmonary emboli or the coronary artery bypass grafts clot producing infarction and arrhythmia. In patients with isolated HIT (no new clot upon onset of HIT), a new thrombosis can be anticipated in 23% to 52% whether or not heparin is promptly discontinued,^{8,16-18} unless an alternative anticoagulant is expeditiously initiated. The fall in platelet count is greater than 50% from baseline

in more than 90% of patients, but in most, the absolute nadir of platelets is only moderately decreased (median approximately 60,000/cu mm).¹⁸

It is easy to see how a mild degree of thrombocytopenia can be overlooked or thought to be unimportant in patients in the ICU (where a majority of cases are encountered), but this is often the only clue to the diagnosis of HIT—and the sole opportunity to intervene before a thrombosis occurs. In about 10% of patients with HIT, the nadir platelet count remains above the lower limit of normal; however, these are patients who had elevated platelet counts before heparin was given, so they have still experienced an abrupt fall in platelets. In 10% to 20% of patients, platelets may be 20,000/cu mm or lower (although as low as 5,000/cu mm is extremely rare); yet remarkably, these patients rarely show any bleeding manifestations. In fact, those with the lowest platelet counts have been found to have the highest risk for complicating thromboses.¹⁸ Therefore, rather than being a contraindication, these low counts indicate a dire need for alternative anticoagulation.

In patients who have received heparin in the past few months and may be presensitized, there may be *rapid-onset HIT* in less than 5 days—sometimes within minutes.¹⁰ Re-exposing such patients to heparin has occasionally produced severe systemic reactions including cardiovascular collapse.¹⁹ Another alternative clinical scenario is *delayed-onset HIT*, which was first described just 3 or 4 years ago but is now widely recognized.^{20,21} Most often, these patients have returned home after a benign hospitalization that included heparin exposure. They return to the hospital 1 or 2 weeks later (rarely, up to 5 or 6 weeks later) with a new clot and often, but not always, with mildly decreased platelet counts. In the past, these patients usually have been given heparin for the new thrombus, which invariably makes platelets fall further and often produces clinical worsening or death. These patients invariably have a very high HIT antibody titer. Recent educational efforts emphasize that the diagnosis of delayed-onset HIT should be considered in recently hospitalized patients who return with thromboembolic phenomena, and the use of an alternative anticoagulant should be considered until a diagnosis becomes clear.

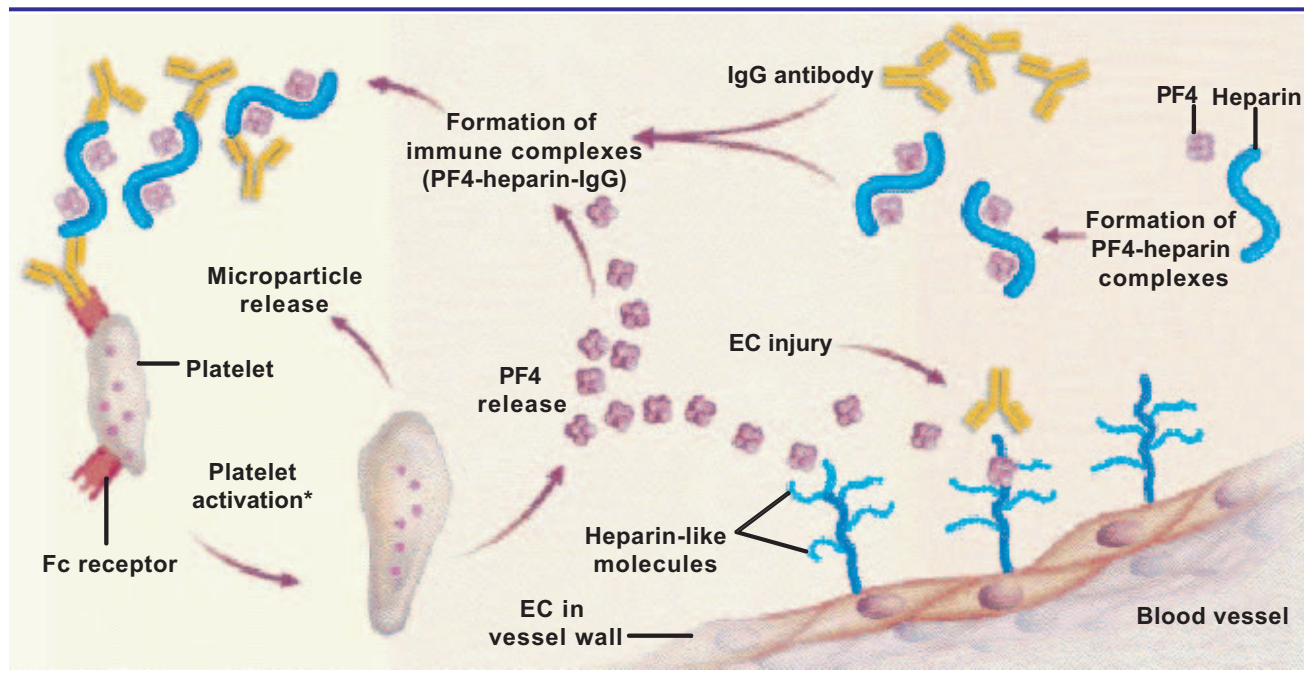


Figure. The pathophysiology of heparin-induced thrombocytopenia and thrombosis.¹²

*Places patient at greater risk for primary thrombotic problem.

EC, endothelial cell; IgG, immunoglobulin G; PF4, platelet factor 4

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While DVT and pulmonary embolism are the most common complications of HIT, arterial thromboemboli involving the heart, brain, and limbs may also occur. Furthermore, extensive venous thromboses can cause venous limb gangrene.²² Less common but well-associated complications include hemorrhagic adrenal necrosis, cerebral venous sinus thromboses, and skin necrosis mainly at subcutaneous injection sites.^{1,15}

Diagnosis

Key points regarding the diagnosis of HIT are outlined in Table 2. The initial diagnosis must be made based on clinical features, the main one being a substantial fall in platelet count at an appropriate time after heparin exposure. The diagnosis must also be considered whenever a patient exposed to heparin develops a new or worsening thrombosis. Clinical suspicion of HIT is greatly strengthened if alternative explanations for the fall in platelets appear to be unlikely or can be ruled out. HIT is among the 2 or 3 most common causes of thrombocytopenia in the hospital setting; other common causes include sepsis (with or without disseminated intravascular coagulation), other drugs (eg, antibiotics, H₂-blockers), surgery (especially with extracorporeal membrane oxygenators), and certain devices (eg, intra-aortic balloons). The keys to diagnosing HIT and preventing adverse events are awareness and alertness, and practitioners must maintain a high degree of vigilance to detect this syndrome.

When HIT is suspected, a confirmatory serologic test should be requested, but action should not be delayed by awaiting test results. All currently utilized tests have significant limitations.²³ The serotonin release assay is relatively sensitive and specific, but it is technically challenging and rarely available on a real-time basis. Aggregation assays using washed platelets may perform consistently in the best hands, but their poor standardization can produce divergent results. Currently, the most widely used tests are commercially available ELISA assays for the heparin–PF4 antibody, because they are standardized, reproducible, and easily performed in a short time. Another strength of the ELISA is its sensitivity (close to 99%), although this often causes false-positive results. The degree of positivity (antibody titer) can be telling, but as with any test, results must be interpreted in the clinical context incorporating judgment of the pre-test probability.^{9,23}

HIT is commonly encountered after heart surgery, perhaps due to the massive doses of heparin used and the large amounts of PF4 released, but making the diagnosis in that clinical context involves special challenges that deserve mention. For example, platelets nor-

mally fall after cardiac surgery “on pump”; these patients often have preoperative heparin exposure, which can make it difficult to ascertain when sensitization may have occurred; and these patients are frequently exposed to other drugs (eg, IIb/IIIa inhibitors) and devices (eg, balloon pumps) that can cause thrombocytopenia. Recent studies have clarified platelet count trends that should create suspicion for HIT: most often, a secondary fall of platelets 5 to 10 days postoperatively; alternatively (with presensitization), an exaggerated early postoperative decline without recovery.²⁴⁻²⁶ Tests for heparin antibodies have high rates of positivity after heart surgery—about 50% in several studies using ELISA—but only 5% of the positive patients actually develop the clinical syndrome. We are learning that antibody titer can be important in distinguishing which serologically “positive” patients are likely to have the clinical syndrome.^{9,23} (Recent studies suggest that the presence of HIT antibodies in these patients may correlate with poor outcomes, even in the absence of HIT.²³)

Anticipating the next section on treatment, a common clinical problem is the patient requiring heart surgery who has suffered HIT in the past. For remote HIT and present negative serology, there is consensus that brief exposure to unfractionated heparin during surgery on pump is the best course,⁸ owing to well-established dosing protocols using activated clotting time monitoring and the predictable rapid reversibility of effects with protamine. It is not clear whether IIb/IIIa inhibitors²⁷ or the postoperative use of alternative anticoagulants add protection. With active or subacute HIT and positive serology, the course of action is less clear due to the dangers of bleeding and clotting associated with alternative anticoagulants used on pump (although some trials have had favorable experience with bivalirudin; see further discussion of bivalirudin, page 5).²⁸

Treatment

When HIT is suspected, it has been demonstrated repeatedly that solely stopping heparin is inadequate because there remains an extreme risk for potentially deadly thromboemboli (Case 2).¹⁶⁻¹⁸ Anecdotal reports and clinical experience with several cases suggest that inferior vena cava (IVC) filters should be avoided because they serve as a nidus for worsening thromboses.¹⁷ LMWHs are contraindicated once HIT has emerged⁸ (Case 1). Warfarin exerts its effects on the short-lived natural anticoagulant protein C before it impacts the procoagulants prothrombin and factor X; therefore, warfarin can exacerbate any acute thrombotic diathesis. In the extreme hypercoagulable milieu of HIT, warfarin has produced venous limb gangrene and central skin necrosis, especially when used early, unopposed, or in excess.^{22,29} When the diagnosis of HIT is suspected, all heparin exposure must be stopped (recognizing that some may be occult) and an alternative anticoagulant initiated immediately.⁹ Descriptions of, and dosing guidelines for, potential alternative anticoagulants are shown in Table 3.

Based on European studies that show significant reduction in the composite end point of new thromboemboli, limb amputation, and death compared with historical controls, the DTI lepirudin became the first FDA-approved drug for HIT.^{30,31} The design of the trials is instructive: For suspected HIT, heparin was stopped and lepirudin was not initiated until serologic confirmation; while waiting for serology, patients experienced new complications at a rate of 6% per day. Lepirudin is given by intravenous infusion, it has a half-life of 80 minutes, and the dose is adjusted by aPTT monitoring. Approved doses quoted in the package insert are excessive for many patients; boluses should be used only for the most acute active thromboses, and an initial infusion rate of 0.1 mg/kg per hour is appropriate for most patients.³² An important limitation is the renal clearance of lepirudin, and the drug should be avoided in patients with renal insufficiency because of possible prolonged, excessive effects. Antibodies to lepirudin form in 44% to 74% of treated patients; while they are usually clinically insignificant, they do sometimes prolong drug clearance and rarely are associated with anaphylactoid reactions on re-exposure.^{30,33,34}

Table 2. Diagnosis of HIT

- The keys to diagnosis, and to averting catastrophe, are *awareness, alertness, and vigilance*.
- Remember that HIT can occur with any form of heparin, by any route of administration, and at any dose (even a single flush).
- HIT should be considered whenever a hospitalized or recently hospitalized patient:
 - *has a fall in platelet count (usually by ≥50%), 5 to 12 days after beginning heparin exposure, with or without a new thrombotic problem.*
- Diagnosis is strengthened if other causes of thrombocytopenia are unlikely or excluded.
- Diagnosis is confirmed by a positive serologic test (especially a strong positive).
- Be alert for alternative clinical scenarios:
 - *Rapid-onset HIT:* <5 days, if patient had prior heparin exposure within the last 3 to 4 months
 - *Delayed-onset HIT:* ≥5 days and up to a few weeks after stopping heparin

Argatroban, a synthetic arginine-derived DTI, is the other FDA-approved drug for HIT.³⁵ Its approval was based on prospective, historical-controlled, multicenter studies showing significant reduction of the same composite end point of new thromboemboli, limb amputation, and death.³⁶ The drug has a half-life of 45 minutes, is hepatically cleared, is given by intravenous infusion, and is monitored by aPTT. Recent data reconfirm its efficacy, particularly in preventing new thromboemboli. Like lepirudin, data show that lower doses (0.5-1.0 mcg/kg/min) than those described in the package insert are optimal for most patients.³⁷ Argatroban exerts more effect on the prothrombin time international normalized ratio than do other DTIs, so inexperienced clinicians are referred to algorithms for effective transition to warfarin.³⁸ Major bleeding complications were not seen more often in argatroban-treated patients (6.9%) than in historical controls,³⁶ with only 4% requiring transfusion in a recent series.³⁷

Bivalirudin, a modified hirudin DTI, is FDA-approved for use in

patients undergoing percutaneous coronary intervention or percutaneous transluminal coronary angioplasty.³⁹ It has been used off-label for HIT in small case series.^{2,40} Its pharmacologic properties—a half-life of 25 minutes with clearance mainly by plasma proteases—may offer advantages, particularly in patients with both renal and hepatic impairment. Fondaparinux is an indirect factor Xa inhibitor that does not cross-react with HIT antibodies, unlike its larger cousins the LMWHs. It is FDA-approved for the prophylaxis and treatment of venous thromboembolic disease. Fondaparinux has recently been used off-label for HIT, although its long half-life and renal clearance are problematic in the sickest patients.^{41,42}

Danaparoid, a low molecular weight heparinoid, shares the disadvantages of a 24-hour half-life and renal clearance, and it sometimes cross-reacts in vitro with HIT antibodies.⁴³ It has been used effectively for HIT in other countries but is no longer available in the United States.⁴⁴ Experimental oral DTIs are in clinical

Table 3. Potential Alternative Anticoagulants for HIT*

	Lepirudin	Argatroban	Bivalirudin	Fondaparinux	Danaparoid [†]
Mechanism	DTI	DTI	DTI	Indirect Xa inhibitor	Indirect Xa and IIa inhibitor (mainly Xa)
Approved uses	HIT	HIT; PCI	PCI	Prophylaxis and Rx VTE	Orthopedic prophylaxis
Route	I.V. infusion	I.V. infusion	I.V. infusion	SQ	SQ (or I.V.)
Half-life	80 min	45 min	25 min	20 h	24 h
Clearance	Renal	Hepatic	Plasma proteases; renal, 20%	Renal	Renal
Monitoring	aPTT	aPTT	aPTT	Anti-Xa [‡]	Anti-Xa [‡]
Approved initial dose[§]	0.4 mg/kg bolus, then 0.15 mg/kg/h	For HIT: 2 mcg/kg/min	For PCI: 1 mg/kg bolus, then 2.5 mg/kg/h x 4 h, then 0.2 mg/kg/h	Prophylaxis: 2.5 mg/d Rx: 7.5 mg/d	Prophylaxis: 750 units SQ bid or tid
Recommended HIT dose[¶]	No bolus; 0.1 mg/kg/h ³²	1 mcg/kg/min ³⁷	0.1 mg/kg/h ^{2,40}	2.5-7.5 mg/d ^{42#}	Up to 2,500 units I.V. bolus, then 400 units/h x 4 h, then 300 units/h x 4 h ^{**}
Total daily dose^{††}	168 mg	101 mg	168 mg	2.5-7.5 mg	8,500 units
Special problems	Antibodies may prolong clearance and rarely cause anaphylaxis	Greater effect on PT INR (especially with warfarin transition)	Off-label use; limited data in HIT	Long half-life; difficult to monitor; off-label use; limited data	No longer available in United States; HIT antibody cross-reactivity; long half-life; difficult to monitor; low-dose failures ⁴³

* Based on product prescribing information unless otherwise noted.

† Approved for HIT in other countries.

‡ May not require routine monitoring. Anti-Xa assays based on titration curves with the drug of interest.

§ Assumes normal renal and hepatic function.

|| Adjust for unusually high or low body weight.

¶ Based on average dose requirements in recent studies. Therapy should be individualized (ie, begin higher dose with acute thrombotic diathesis; adjust for organ dysfunction).

Dose for HIT not well established.

** Various dosing recommendations, but none well established. See: Chong BH, Magnani HN. Danaparoid for the treatment of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-induced Thrombocytopenia*. 3rd ed. New York, NY: Marcel Dekker; 2004:371-396.

††Based on 70-kg person receiving average dose. (Average daily cost of therapy can be estimated multiplying this amount by the price per milligram, considering also vial size and wastage.)

aPTT, partial thromboplastin time; DTI, direct thrombin inhibitor; INR, international normalized ratio; PCI, percutaneous coronary intervention; PT, prothrombin time; VTE, venous thromboembolism

The Pharmacist's Role in the Management of HIT

Commentary by Ann K. Wittkowsky, PharmD, CACP, FASHP, FCCP

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Dr. Rice outlines emerging strategies in the prevention, diagnosis, and treatment of heparin-induced thrombocytopenia. Pharmacists can play a vital role in each of these areas of medical care.

It is obviously not possible to avoid the use of heparin products when they are necessary for the prevention and treatment of venous and arterial thromboembolism. However, recognition of the differential incidence of HIT associated with unfractionated heparin versus low molecular weight heparins, and the lack of HIT associated with fondaparinux, may be helpful in selecting one agent over another in certain clinical situations. In addition, healthcare systems should move toward heparin-free locks and flushes for intravenous and intra-arterial lines. Heparin-free hemodialysis systems are a recent and promising trend.

It is also critical to realize that in patients with confirmed HIT, simply

discontinuing heparin products is not sufficient to prevent thromboembolic complications. Since over 50% of patients with HIT will develop thrombosis despite discontinuation of heparin, DTI therapy should be initiated in all patients with highly suspected (once other causes of thrombocytopenia have been ruled out) and/or confirmed HIT. Pharmacists should be aware of the pharmacokinetic and pharmacodynamic differences among the various DTIs, and they should assist in the selection, dosing, and monitoring of these agents. Transition to warfarin is complicated by the impact of the DTIs on the international normalized ratio, and by the risk of venous gangrene and warfarin-induced skin necrosis if oral anticoagulation is not managed carefully. These problems also represent roles for pharmacists in the management of HIT.

Finally, pharmacists should be part of multidisciplinary teams that are charged with the development of healthcare system-specific guidelines for the prevention, diagnosis, and treatment of HIT. A systematic approach to the management of this potentially devastating adverse drug reaction is imperative to "save lives and limbs," as so pointedly described by Dr. Rice.

development, and hopefully they will find a place in HIT therapy in the near future. Although none of these alternative anticoagulants have specific antidotes, the short half-lives of some agents rarely make this an issue. If bleeding complications arise, the use of recombinant factor VIIa may have value.

Alternative anticoagulant therapy should be continued in full therapeutic doses until the HIT has "cooled off," meaning platelet recovery to near normal levels (at least 100,000/cu mm) and no new thromboses in several days. At that time, it is safe to cautiously introduce warfarin with an overlap transition of ≥ 5 days. Modest warfarin dosing is prudent because overshooting the dose is associated with thrombotic complications (owing to the effects on protein C).²² Most patients with HIT have an ongoing need for anticoagulation, which is why they were exposed to heparin. If a patient has a thrombotic complication from HIT, then the duration of anticoagulation should be at least 3 to 6 months, or whatever is appropriate for the type of clot encountered. In patients who had isolated HIT and heparin exposure that was incidental or for a very transient thrombotic risk, 6 weeks of anticoagulation are recommended. There are no prospective data on treatment duration, but this recommendation is based on some existing data,¹⁸ on clinical experience with delayed-onset HIT,^{20,21} and repeated experiences with patients who were not anticoagulated and present with late thromboses long after platelet recovery.

Prevention

Heparin should not be used when it is not needed; for example, heparin flushes do not maintain catheter patency better than saline for most intravenous catheters.⁴⁵ In situations where LMWHs or fondaparinux can be used with equal efficacy, these should be pre-

ferred to unfractionated heparin because of the dramatically lower incidence of HIT (or, with fondaparinux, the absence of HIT). In fact, these alternatives to unfractionated heparin are superior for a number of reasons, and they should be substituted for heparin in all but very few circumstances: mainly, in patients undergoing cardiac surgery with extracorporeal circuit, and in some fragile patients for whom it is important to be able to titrate the effect closely and possibly reverse the effect rapidly. When unfractionated heparin is used, porcine is preferred to bovine because it has been shown to induce fewer HIT antibodies.³

Another part of prevention is platelet count monitoring, to alert caregivers and to allow intervention before serious complications ensue. The American College of Chest Physicians endorses the following guidelines for platelet count monitoring: every other day until day 14 of therapy with unfractionated heparin; every other day on days 4 to 14 for postoperative patients receiving prophylactic unfractionated heparin; and every second or third day on days 4 to 14 for medical/obstetric patients receiving prophylactic unfractionated heparin, postoperative patients receiving prophylactic LMWH, and postoperative/critical care patients receiving heparin flushes.⁸

Summary

HIT is a common reaction that produces an intense prothrombotic state. Myths and misunderstandings surrounding the condition contribute to frequent dire consequences, creating a need for redoubled educational efforts. The diagnosis of HIT must be considered whenever a hospitalized or recently hospitalized patient has a fall in platelet count and/or a new thrombotic event. To avoid serious complications, caregivers must be highly vigilant, and an alternative anticoagulant must be initiated on suspicion of HIT.

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CME/CPE Post-test

Select the single-letter response that best answers the question or completes the sentence.

1. **Which of the following statements concerning HIT is *not* true?**
 - a. It is a drug-induced humoral immune reaction.
 - b. In the great majority of cases, the target antigen is modified PF4.
 - c. The onset is usually 5 to 12 days after beginning heparin.
 - d. The percent fall in platelet count is often very small ($\leq 30\%$).
2. **In patients receiving I.V. unfractionated heparin for DVT, what is the incidence of HIT?**
 - a. 3% to 5%
 - b. 0.5% to 1%
 - c. About 0.1%
 - d. Less than 0.1%
3. **What is the risk of HIT in patients whose only exposure to heparin was the small amounts that leached from coated central catheters?**
 - a. 3% to 5%
 - b. 0.5%
 - c. Less than 0.1%
 - d. No risk
4. **All of the following have been identified as substantially affecting the risk of HIT, *except* which?**
 - a. Dose of heparin
 - b. Source of heparin (bovine or porcine)
 - c. Genetic thrombophilic mutations
 - d. Clinical situation of patient (eg, post-orthopedic surgery)
5. **All of the following complications have been associated with HIT, *except* which?**
 - a. Venous limb gangrene
 - b. Pulmonary emboli
 - c. Increased risk of bleeding gastric ulcers
 - d. Bilateral hemorrhagic adrenal necrosis
6. **Concerning the special situation of HIT after heart surgery, which of the following is *not* true?**
 - a. Platelets may normally be moderately reduced on post-op day 2.
 - b. Intra-aortic balloon pumps commonly lower platelet counts.
 - c. ELISA antibody tests may be falsely positive in close to 50% of post-op patients.
 - d. If a patient with HIT in the distant past requires pump surgery, an alternative anticoagulant must be used.
7. **A patient is receiving prophylactic LMWH after knee surgery. On post-op day 7, the platelet count (which had been 250,000/cu mm pre-op) is found to be 80,000/cu mm. There are no signs of infection, no clinical signs of blood clots, and no other medications that are suspicious for causing thrombocytopenia. Which of the following would be the *best* course of action?**
 - a. Continue prophylaxis, and do not send HIT serology because HIT is rare with LMWH.
 - b. Stop anticoagulants and wait for the result of HIT serology.
 - c. Begin a DTI while waiting for the HIT serology result.
 - d. Stop anticoagulants, place IVC filter, and wait for HIT serology result.
8. **The physician caring for the patient in question 7 stopped anticoagulants and sent HIT serology, which came back strongly positive 3 days later. Clinical exam and Doppler ultrasound show no venous thromboses. What should be done now?**
 - a. Begin an alternative anticoagulant because of high risk for new thromboemboli.
 - b. Place IVC filter and consider an alternative anticoagulant.
 - c. Begin warfarin.
 - d. No action needs to be taken because the period of high thromboembolic risk has passed.
9. **A patient has coronary artery bypass of 4 vessels and is discharged on post-op day 7 after an uneventful course. He returns 3 days later with aphasia and right hemiparesis. MRI shows an ischemic brain infarct. Platelet count is 125,000/cu mm (200,000/cu mm when last checked on post-op day 4). Which of the following is *most likely* true?**
 - a. Emboli are emerging from intracardiac thrombi formed during surgery.
 - b. The patient is a "vasculopath" and needs immediate heparin.
 - c. HIT is very unlikely because the patient has not had heparin in days and platelets have not fallen by 50%.
 - d. The result of an ELISA for HIT antibodies is likely to return very strongly positive, and an alternative anticoagulant should be started immediately.
10. **A diabetic patient with chronic renal insufficiency is hospitalized for DVT and treated with I.V. heparin protocol. On day 7, the platelets suddenly fall to 80,000/cu mm (from 250,000/cu mm on admission). Which course of action would be *best*?**
 - a. Begin argatroban, 0.5 mcg/kg per minute.
 - b. Begin lepirudin, 0.1 mg/kg per hour.
 - c. Begin bivalirudin, 0.2 mg/kg per hour.
 - d. Begin fondaparinux, 2.5 mg SQ daily.

