HIT: treatment easier, prevention harder

Theodore E. Warkentin  McMaster University

In this issue of Blood, Krauel and colleagues identify two potential off-label treatments (rivaroxaban, dabigatran) for heparin-induced thrombocytopenia (HIT), and also outline a HIT prevention strategy through disrupting PF4/heparin complexes with low-sulfated heparin; the former approach will be easy to implement, the latter much harder—but potentially more worthwhile.

HIT is a highly prothrombotic adverse drug reaction caused by strong platelet-activating antibodies that amplify coagulation reactions. In about half of all patients with HIT confirmed by laboratory detection of heparin-dependent, platelet-activating antibodies, the patient is found to have thrombosis at the time that of HIT diagnosis. These presenting HIT-associated thromboses include disabling stroke, critical limb ischemia, or fatal pulmonary embolism.

For more than a decade, treatment of HIT in the US has focused on parenteral administration of parenteral heparin. The studies of Krauel et al, together with a previous study by Walenga and colleagues, indicate that there is no reason why the direct thrombin inhibitors (DTIs), lepirudin and argatroban. However, these are “niche” agents that did not obtain approvals for any other non-HIT indication. Moreover, they require frequent monitoring (usually by activated partial thromboplastin time [aPTT]), cause serious bleeding (~ 1% major bleed rate per treatment day), and are expensive—not only because of drug costs but also because their parenteral administration mandates prolonged hospitalization. Recently, even their “advantage” of simple aPTT monitoring has come under scrutiny, as it has been recognized that patients with severe HIT-associated consumptive coagulopathy can fail DTI treatment due to difficulty monitoring treatment with the aPTT. This problem should not occur with agents such as fondaparinux, rivaroxaban, or dabigatran that do not require active laboratory monitoring (although they have their own drawbacks; eg, potential for accumulation in renal insufficiency).

It is also now recognized that, at most, only 10% of patients suspected of having HIT ultimately are proven to have this disorder. So, what is needed to treat HIT are easy-to-apply anticoagulant regimes effective for both HIT and non–HIT settings of thrombosis treatment and prevention. In this regard, agents such as fondaparinux, rivaroxaban, and dabigatran are likely to be welcomed by practitioners. The studies of Krauel et al, together with a previous study by Walenga and colleagues, indicate that there is no reason why the direct Xa inhibitor, rivaroxaban, should not be effective for thromboprophylaxis in patients with a history of HIT or, more provocatively, for the treatment of acute HIT itself. Krauel and colleagues further extended these studies to dabigatran, an orally active DTI now approved for the prevention of stroke in atrial fibrillation. No doubt these new agents will be tried in some patients with clinically suspected HIT, and some of this experience will be reported in the medical literature, as has occurred with fondaparinux.

“Off-label” use of approved medications is permitted, experience treating HIT with rivaroxaban and dabigatran will likely emerge quickly.

Why should we care about prevention of HIT when there are effective therapies for HIT? The answer is that HIT still harms many patients, usually as a result of serious thrombotic events that occur soon after this drug reaction begins. For example, the study described above also noted that 34 of the 52 fondaparinux-treated patients (65%) had already developed HIT-associated thrombosis before this alternative anticoagulant was started. Three of these patients (6% overall) required limb amputation; another patient (patient no. 3 in the McMaster study) had a disabling stroke (aphasia), which occurred at the very onset of the platelet count fall indicating HIT, and which therefore was unlikely to have been pre-empted by any platelet count monitoring protocol. So while fondaparinux therapy of HIT yielded “successful” outcomes (ie, platelet count recovery, no new thrombosis, infrequent major bleeding), the inescapable conclusion is that HIT will still harm
many patients in a devastating fashion before the hypercoagulability state can be controlled by an alternative anticoagulant (see figure).

Krauel et al now describe a possible prevention strategy for HIT. They report that a low-sulfated heparin, called 2-0, 3-0 desulfated heparin (ODSH), has several properties that would be expected to reduce the immunogenicity of heparin: (1) it inhibited formation of PF4/heparin complexes; (2) it disrupted PF4/heparin complexes on platelets and other cells; and (3) it inhibited HIT antibody–induced platelet activation.

These are intriguing observations and imply that ODSH could prevent HIT if given to the appropriate patient population at the appropriate time point. As ODSH has only minimal anticoagulant effect, one approach would be to coadminister ODSH with heparin in a study of postoperative thromboprophylaxis. Antibody formation could be used as a “surrogate” marker for HIT. Most likely, ODSH would only need to be given for the first day or 2 (because HIT is believed to represent a “point immunization” syndrome related to perioperative PF4 release and surgery–associated proinflammatory factors). Indeed, the therapeutic combination of heparin and ODSH would mirror somewhat the composition of danaparoid—a mixture of both high- and low-sulfated anticoagulant glycosaminoglycans, and a compound which (to my knowledge) has never been implicated as causing HIT when given for postoperative thromboprophylaxis.

If such a proof-of-principle study was successful, definitive trials with HIT as a key study end point could be performed, also combining ODSH with intraoperative heparin use (ie, for cardiac or vascular surgery). Such studies would not be easy; the frequency of HIT is approximately 1% in situations of intra- and/or postoperative unfractionated heparin administration, and performing appropriately powered clinical trials would be challenging. But reducing the scourge of HIT is a worthwhile goal, and could have a cost-effective benefit of making an expensive anticoagulant—unfractionated heparin—much safer. Conflict-of-interest disclosure: The author has received lecture honoraria from Pfizer Canada and Sanofi–Aventis, has provided consulting services to, and/or has received research funding from, Canyon Pharmaceuticals, Gen-Probe GTI Diagnostics, GlaxoSmithKline, and Paringenix, and has provided expert witness testimony relating to heparin-induced thrombocytopenia. ■

REFERENCES

TRANSFUSION MEDICINE

Comment on Jansen et al, page 1263

Toddy for Chilled Platelets?

Cécile Kaplan INSTITUT NATIONAL DE LA TRANSFUSION SANGUINE

In this issue of Blood, Jansen and colleagues use murine models to give new insights into the possible mechanisms of clearance of transfused refrigerated platelets.1

Today, platelet transfusions are used routinely in preventing or treating hemorrhage and the demand for platelet concentrates continues to rise, mainly because of the increasing number of patients undergoing marrow suppressive therapy. The main task for blood transfusion services is to maintain an adequate supply of safe and effective platelet products. Unfortunately, because of the potential risk of bacterial contamination, platelets have a very short shelf life of 5 days stored at 20–24°C with continuous gentle agitation.2 Consequently, platelet products are often in short supply. The processes used to collect and store platelets have evolved during past years to allow storage under optimal conditions to limit physiologic alterations in the cells known as the platelet storage lesion (PSL). The PSL is associated with decreased posttransfusion survival of transfused platelets and their rapid clearance from the bloodstream. Several approaches are presently being explored with the goal of better preserving cell viability and function during platelet storage, including adjusting the storage medium3 and/or modifying the platelets themselves. The latter approach has arisen from the publications of Hoffmeister and colleagues.4

Four decades ago, Murphy et al showed that cold temperatures, which reduce the risk of bacterial growth, had deleterious effects on platelets.5 Considerable effort was subsequently expended on better understanding the phenomena underlying the metabolic and structural modifications related to cold storage to develop mitigation strategies and forestall on-going platelet shortages.

Hoffmeister et al demonstrated in 2003 that the reduced survival of short-term cold-stored platelets was because of the clustering of the von Willebrand factor (VWF) receptors at the platelet surface.6 The recognition of β-N-acetylgalosaminie (β-GlcNac) residues on clustered GPIbα by the αMβ2 integrin receptor present on hepatic macrophages (Kupffer cells) produced in vivo platelet phagocytosis in mice. Subsequently, the same group showed the role of the hepatic asialo-glycoprotein, the Ashwell-Morell receptor, in recognizing desialylated GPIbα and its importance in increased clearance of long-term refrigerated platelets.7

The article by Jansen et al here makes a novel and interesting contribution to the field. In their present study, the authors investigated the behavior of key enzymatic pathways in platelets after refrigeration, including the role
HIT: treatment easier, prevention harder

Theodore E. Warkentin