CME CREDIT

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Heparin-induced thrombocytopenia: How to manage it, how to avoid it

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ABSTRACT

Heparin therapy has two potential adverse effects: bleeding and heparin-induced thrombocytopenia (HIT). There are two types of HIT: type I is more common but less severe; type II occurs less frequently but involves severe thrombocytopenia and a high risk for thrombotic events. Treatment involves discontinuing heparin, allowing the platelet count to return to normal, and treating any thrombosis. Lepirudin (Refludan) is the only agent currently approved for the treatment of HIT-related thrombosis, but other agents may have a role in combination therapy. Prevention includes using low molecular weight heparin instead of unfractionated heparin and limiting unfractionated heparin therapy to less than 5 days.

IN ADDITION TO INCREASING the risk of bleeding, heparin therapy can cause heparin-induced thrombocytopenia (HIT) in 10% to 20% of patients.

Most patients who develop HIT have type I, a mild form that occurs within the first 4 days of heparin therapy and usually resolves without treatment. HIT type II, however, involves severe thrombocytopenia and carries a significant risk of thrombotic events if not detected and treated early. It develops in 3% to 5% of patients receiving unfractionated heparin for 5 days or more and is characterized by thrombocytopenia, thrombosis, and formation of the HIT antibody.

The following is a brief summary of the diagnosis, treatment, and prevention of this potentially severe adverse effect of heparin therapy.

HOW HIT DEVELOPS

Heparin is both anticoagulant and prothrombotic

Heparin works as an anticoagulant by activating antithrombin III, which neutralizes factors XIIa, XIa, IXa, Xa, and thrombin. However, in vitro studies show that unfractionated heparin also neutralizes the inhibition of platelet aggregation by prostacyclin, leading to platelet aggregation.

Heparin both prevents and paradoxically promotes clotting

Specific mechanisms

HIT type I is characterized by nonimmune platelet aggregation, likely due to heparin-induced stimulation of platelets, which leads to sequestration in the spleen and reticuloendothelial system. The platelet count stays above 100,000 per µL and may return to normal even if the patient continues heparin therapy. Patients are usually asymptomatic.

In HIT type II, however, the platelet count falls to 50,000 to 70,000 per µL. The HIT antibody, an immunoglobulin (Ig) G antibody, forms in response to the heparin-platelet factor 4 (PF4) antigenic complex. PF4 is a protein normally released by platelets to neutralize heparin (FIGURE 1). IgG-PF4 complexes bind to platelet Fc receptors, resulting in strong platelet activation. These complexes also bind to vascular endothelium, causing expression of tissue factor by endothelial cells, activation of the extrinsic coagulation pathway, and increased generation of thrombin—all of which accelerate the process of thrombus formation.

RISK FACTORS

The risk for HIT is higher in postoperative patients and in patients with underlying vascular endothelial cell injury (eg, atherosclerosis) or venostasis.

Unfractionated heparin is much more likely to cause HIT than low molecular weight heparin, and use of bovine heparin carries a higher risk for HIT than porcine heparin.

POTENTIAL COMPLICATIONS

HIT type II is usually seen after the first week of heparin therapy, but the range of onset can be 4 to 14 days. If the patient has been previously exposed to heparin, however, HIT type II may develop much sooner. In addition to thrombocytopenia, HIT type II carries an increased risk of deep venous thrombosis, and pulmonary embolism can occur in up to 25% of affected patients. The risk of venous gangrene of the legs, skin necrosis, and arterial events such as stroke or myocardial infarction is also high. A small percentage of patients develop disseminated intravascular coagulation. Bleeding is an uncommon complication, mainly because the thrombocytopenia is due to an underlying platelet activation syndrome.

Limiting heparin therapy to under 5 days cuts the risk of HIT

DIAGNOSIS

The diagnostic criteria for HIT type 2 are:

- Thrombocytopenia noted during heparin infusion
- Exclusion of other causes of thrombocytopenia (eg, infection, other drugs, autoimmune process)
- Thrombocytopenia resolves after stopping heparin
- HIT antibody demonstrated by laboratory tests.

The four laboratory tests now available for the diagnosis of HIT type II all have limitations:

- **The platelet aggregation assay** (PAA) is the most commonly used; it is highly specific, but its sensitivity is only 30% to 50%
- **The serotonin release assay** (carbon-14 SRA) is highly specific and sensitive, but it is time-consuming and requires radiolabeled material; only a few centers in the United States perform this test
- **The heparin-induced platelet aggregation assay** (HIPA) is more sensitive than the standard platelet aggregation assay but is technically demanding
- **Enzyme-linked immunosorbent assay** (ELISA) that detects IgG antibody can be fairly sensitive but not very specific.

Given these limitations, the best approach at present may be to order an ELISA and then a platelet aggregation assay for confirmation if the ELISA is positive.

PREVENTION

When possible, substituting low molecular weight heparin for unfractionated heparin and limiting unfractionated heparin treatment to less than 5 days markedly decrease the risk of HIT.

TREATMENT

When HIT type II develops, treatment starts with the immediate discontinuation of heparin. The platelet count usually normalizes within a week, although it can take several weeks.

If the patient shows evidence of HIT-related thrombosis, agents that decrease or inhibit thrombin should be considered.

Low molecular weight heparin is contraindicated in the treatment of HIT-related thrombosis because of its nearly 100% cross-reactivity with the HIT antibody and the potential risk for continued thrombosis.

Warfarin is contraindicated in the acute stage of HIT type II because it is associated with the progression of thrombosis and limb gangrene. Warfarin is safer to use once the platelet count is above 100,000 per μL, at which point the immune-modulated stimulation of platelet activity is thought to be reduced and the risk of progression of thrombosis decreases.

Danaparoid (Orgaran), used extensively in Europe and Australia, is a combination of heparan sulfate, dermatan sulfate, and chondroitin sulfate. It works via anti-factor Xa activity, without much antithrombin activity. It cross-reacts with HIT antibody with a 10%

The prothrombotic effects of heparin

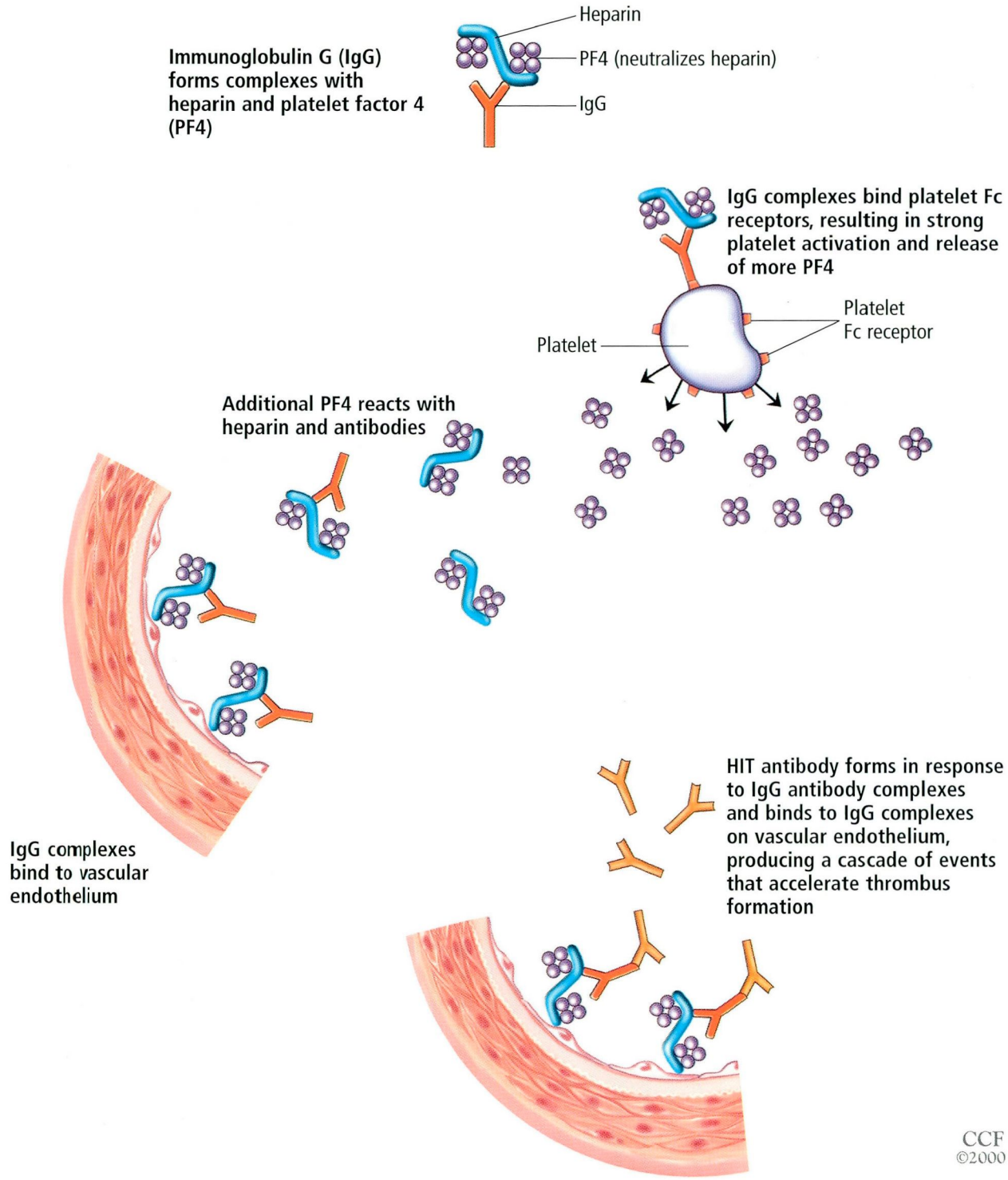

FIGURE 1

to 20% incidence rate in vitro. However, in vivo the incidence is thought to be less than 5%.

The US Food and Drug Administration (FDA) has approved danaparoid for the prophylaxis of deep venous thrombosis in patients undergoing hip replacement surgery, but it is often used off-label for the treatment of HIT. Disadvantages are its high cost, a long half-life, and the lack of a reversing agent if bleeding problems emerge.

Lepirudin (Refludan) is the only drug that is FDA-approved for the treatment of HIT-related thrombosis. Lepirudin, a recombinant hirudin derived from the salivary glands of medicinal leeches, is a potent thrombin inhibitor. Its advantages include a fairly short half-life (1.3 hours in healthy volunteers). There is no cross-reactivity to the HIT antibody, and it can be monitored by routine activated partial thromboplastin time (aPTT) tests. A disadvantage is that the drug is renally cleared, and careful titration is necessary in patients with advanced renal insufficiency. While lepirudin does not cross-react with HIT antibody, more than 50% of patients treated with lepirudin may develop anti-lepirudin antibodies. However, the clinical and biological significance of this is still undetermined.

In HIT type II, stop heparin immediately

Argatroban (Novastan) is a synthetic thrombin inhibitor with advantages similar to those seen with lepirudin. Like lepirudin, it does not cross-react with HIT antibody and has a short half-life. On the other hand, argatroban is hepatically metabolized and may be a better option in patients with advanced renal insufficiency. A disadvantage is that there is no reversing agent for bleeding complications related to its use. Argatroban may be an option for patients with previous exposure to heparin who need to undergo percutaneous coronary revascularization. Phase III clinical trials have been completed using argatroban for the treatment of thrombosis in HIT, but the results are not yet available.

Ancrod (Venacil), derived from Malayan pit viper venom, is a defibrogenating agent with a slow onset of action. It may actually increase thrombin generation, so it would not be a good choice for a patient with HIT and high thrombin levels. Ancrod carries an increased risk of disseminated intravascular coagulation and may also be associated with higher rates of warfarin-associated venous limb gangrene.

Other drugs currently under investigation as treatments for thrombosis in HIT include glycoprotein IIb/IIIa inhibitors, ticlopidine, and clopidogrel.

SUGGESTED READING

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