Heparin induced thrombocytopenia

Contemporary therapeutic approaches in light of the new oral anticoagulants

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Keywords
HIT, DOAC

Summary
Heparin induced thrombocytopenia (HIT) is a prothrombotic syndrome initiated by platelet-activating auto-antibodies with potentially devastating complications. Once the diagnosis of HIT is suspected, discontinuation of heparin and treatment with an alternative anticoagulant are mandatory. While established drugs for HIT are no longer available, parenteral factor Xa inhibitors, thrombin inhibitors and perhaps the direct oral anticoagulants provide additional treatment options. The aim of this review was to highlight the current clinical aspects regarding HIT focusing on the role of novel medications.

Schlüsselwörter
HIT, DOAC

Zusammenfassung
Die Heparin-induzierte Thrombopenie (HIT) ist eine prothrombotische Erkrankung, die durch thrombozytenaktivierende Autoantikörper hervorgerufen wird und fatale Komplikationen auslösen kann. Bei Verdacht auf eine HIT muss Heparin abgesetzt und ein anderes Antikoagulanz gegeben werden. Es gibt zwar keine ausdrücklichen Arzneimittel gegen HIT mehr, aber parenteral verabreichte Faktor-Xa-Inhibitoren, Thrombinhemmer und möglicherweise direkte orale Antikoagulanzien können weitere Therapieoptionen sein. Diese Übersicht soll die aktuellen klinischen Aspekte von HIT mit Schwerpunkt auf der Rolle der neuen Arzneimittel darlegen.

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Heparin-induzierte Thrombopenie
Zeitgemäße Therapien unter Berücksichtigung neuer Antikoagulanzien
Hämostaseologie 2015;35: 372–375
http://dx.doi.org/10.5482/HAMO-15-04-0013
received: April 7, 2015
accepted in revised form: August 12, 2015
epub ahead of print: August 24,, 2015

Heparin induced thrombocytopenia (HIT) is a drug mediated adverse reaction and a potentially life threatening complication with a mortality rate as high as 20%, unless timely diagnosed and managed, related to heparin treatment. HIT results from an autoantibody directed against the complex of endogenous platelet factor 4 (PF4) and heparin that activates platelets and can cause catastrophic arterial and venous thrombosis.

> Typically it occurs in up to 5% of patients exposed to heparin for more than four days regardless of type, dose, schedule or route of administration (1–5).

Risk factors for HIT (6, 7) include

- unfractionated rather than low molecular weight heparin (LMWH),
- high heparin doses,
- female gender,
- surgery and
- old age.

Clinically, albeit thrombosis might be the presenting finding in almost 25% of patients, overall thrombosis occurs in up to 50% with venous thrombi exceeding arterial ones (5). Conversely, the most common manifestation of HIT often preceding thrombosis, is thrombocytopenia occurring in 85 to 90% of individuals with a typical platelet count drop of > 50% from baseline. However, bleeding complications are rare presumably due to the prothrombotic nature of HIT rather than the moderate thrombocytopenia (8, 9). Hence, the need of an anticoagulant to protect from thrombosis is paramount.

All sources of heparin have to be discontinued immediately even with only a presumptive diagnosis of HIT type II. A non-heparin anticoagulant should be administered instead in order to reduce the risk of thrombosis, except in situations of high risk of bleeding.

In this context, we performed an extended review of the literature using PubMed database to explore the role of contemporary therapeutic armamentarium including parenteral factor Xa inhibitors and direct thrombin inhibitors (DTI) in light of the potential of direct-acting oral anticoagulants (DOACs) since there are little data on the efficacy in this setting.

Diagnostic evaluation

The most common scenarios raising the possibility of HIT involve prior heparin (unfractionated or LMWH) exposure within the preceding 5 to 10 days and prolonged treatment with LMWH. Improved recognition and early intervention has the potential to prevent thrombotic events which are the major cause of mor-

Tab. 1 Characteristics of the most important currently used agents for HIT and the new oral anticoagulants

anticoagulants		type	indications	administration	dosing	monitoring
factor Xa and thrombin inhibitors	fondaparinux	indirect factor Xa inhibitor	prophylaxis and treatment of VTE	subcutaneously	once daily 5–10 mg	no
	bivalirudin	direct thrombin inhibitor	patients with/at risk of HIT undergoing PCI	intravenous, continuous infusion	0.15 mg/kg/h	aPTT 1.5–2.5
	argatroban		prophylaxis or treatment of HIT		2 µg/kg/min	aPTT 1.5–3
direct oral anti-coagulants	dabigatran		prophylaxis and treatment of VTE, AF	per os	twice daily 150 mg	no
	rivaroxaban	direct factor Xa inhibitor			once daily 20 mg	
	apixaban				twice daily 5 mg	

AF: atrial fibrillation; HIT: heparin induced thrombopenia; PCI: percutaneous coronary intervention; VTE: vein thromboembolism

bidity and mortality in patients with HIT (4).

HIT is diagnosed by integrating clinical features and laboratory testing since neither of these alone is sufficient. However, a possible diagnosis of HIT must often be made purely on clinical findings and platelet counts until the results of HIT antibody testing are available. The diagnosis of HIT is confirmed by either a positive ELISA with an optical density (OD) >2.00 or a positive functional assay for HIT antibodies (10).

Clinical scores such as the 4T score or the HIT Expert Probability Score are often used to risk stratify patients. The 4T's score as proposed by the American Society of Hematology (ASH) is an easy to use diagnostic tool that quantifies the clinical findings associated with HIT. It is implemented to estimate the likelihood of HIT based on readily available clinical data, including the degree of thrombocytopenia, timing of platelet count drop, presence of thrombosis and absence of other causes of thrombocytopenia. If the 4 T's score is low probability, HIT antibody testing is not pursued because the risk of HIT is exceedingly low (11, 12).

Management of HIT

In case of a presumptive or definite diagnosis of HIT, all types of heparin should be discontinued. Moreover, it has been estimated that the majority of the thrombotic events occur more than 24 hours after the cessation of heparin. Thus, patients who develop HIT will have an ongoing need for anticoagulation due to the increased risk of thrombosis associated with HIT and possibly for the condition for which heparin was originally administered (13).

Current therapeutic assay

Fondaparinux (Arixtra) is a chemically synthesized factor Xa inhibitor that does not interact with PF4, does not activate platelets and therefore plays an essential role in the treatment and prevention of HIT. It is administered subcutaneously (5 to 10 mg/day; ▶Tab. 1) without the need for regular monitoring. Nevertheless, periodic checking of renal function is recommended for patients taking the drug for prolonged period. The long half life of fondaparinux (17 hours), its renal elimination and the lack of an antidote are important considerations when using this agent. Data derived from small observational studies have described the safety and efficacy of fondaparinux in patients with confirmed HIT (14, 15). Intriguingly, more recent data indicate that similarly to LMWH, fondaparinux might cause HIT in patients with preexisting HIT antibodies (16, 17).

Bivalirudin (Angiox – in Europe, Angiomax – in the US) is an intravenous (iv) DTI that provides effective thrombin inhibition to prevent thrombosis and thrombin-mediated platelet effects. It is approved for anticoagulation in patients with HIT undergoing cardiovascular transcatheter interventions and cardiac bypass surgery. The recommended initial dose of bivalirudin for HIT is approximately 0.15 mg/kg per hour adjusted to achieve an active partial thrompoplastin time (aPPT) of 1.5 to 2.5 times baseline (▶Tab. 1). Reduced doses in patients with liver, renal or combined liver and renal failure have been successfully used and are shown in the table (8, 18–20).

Similarly to bivalirudin, **argatroban** is a parenteral small molecule direct thrombin inhibitor with a half life of 24 minutes with drug plasma concentrations reaching steady state within 1–3 hours. Because of its hepatic metabolism, it may be used in patients with renal dysfunction. Its effect is monitored by the aPTT and after discontinuation, aPTT returns to normal within two hours. In patients with normal liver function the standard starting dose is 2 µg/kg per minute by continuous intravenous infusion, adjusted to maintain the aPTT at 1.5 to 3 times baseline, not to exceed 100 seconds (▶Tab. 1). It can substantially increase international normalized ratio (INR), thus complicating the transition to oral warfarin (21, 22).

Since argatroban is mostly metabolized in the liver, dose adjustment is required in the presence of hepatic dysfunction. Lower starting doses of argatroban might be also appropriate in critically ill patients with multiple organ dysfunction and HIT. However, dose adjustment is not required in the presence of isolated renal impairment. Published trials using argatroban in patients with HIT showed superior efficacy of argatroban in reducing subsequent thrombotic events and death rate due to thrombosis with no increased bleeding risk (23, 24).

Other agents

Warfarin the most widely used vitamin K antagonist (VKA) is not considered to be the first anticoagulant choice in patients with HIT since it may increase the risk of venous complications. In particular, in patients with acute HIT, VKAs can induce venous limb gangrene because of VKA-induced protein C depletion (9). Therefore, it is essential to postpone this therapy until the platelet count has recovered ideally to a stable plateau at least to 150 × 10^9/l, since platelet recovery resembles a marker that HIT is under control. On these terms, warfarin can be used as bridging for continued oral anticoagulation. There should be a minimum of five days of overlapping therapy before the alternative anticoagulant is discontinued. Warfarin must be monitored by the international normalized ratio (INR). The target range for anticoagulation should be an INR between 2.0 and 3.0 (25).

Danaparoid (Orgaran) is a heparinoid which exerts its anticoagulant effects predominantly by inhibiting factor Xa and to a much lesser degree by inhibiting thrombin that can be administered subcutaneously or intravenously. There is extensive experience using danaparoid in patients with acute HIT or a history of HIT requiring cardiopulmonary bypass surgery. After an initial iv bolus infusion of 2250 units, doses are modified according to body weight to achieve anti-factor Xa levels of 0.5 to 0.8 anti-Xa units/mL. This need to measure anti-factor Xa levels is the major disadvantage of danaparoid along with its long half-life (approximately 25 hours), its renal elimination and the absence of a reversal agent (9).

Lepirudin (Refludan), a recombinant hirudin and parenteral DTI, binds to both free and clot-bound thrombin and was shown effective in preventing new thromboses in patients with isolated HIT. Pooled analysis from three studies using lepirudin for HIT demonstrated significantly reduced mortality and thromboembolic complications but an increased risk of major bleeding compared to other agents (26).

In a non-randomized comparison study, the efficacies of therapeutic (rather than prophylactic) doses of danaparoid and lepirudin in preventing death, amputation or new thromboembolic complications in patients with HIT did not differ significantly, although the risk of bleeding appeared to be higher in patients treated with lepirudin. It is worth mentioning that both danaparoid and lepirudin are no longer available in the US merging the need for other alternatives (27).

Direct oral anticoagulants (DOACs)

Several novel orally administered agents approved for different thrombotic conditions offer an attractive alternative therapy option for HIT (▶Tab. 1). Important advantages of DOACs include lower incidence of major bleeding, convenience of use, minor drug and food interactions, wide therapeutic window and no need for laboratory monitoring (28). There are theoretical reasons why the orally active anticoagulants namely dabigatran, rivaroxaban and apixaban could be effective for patients with established HIT, although data on clinical efficacy and safety as well as clinical experience with these agents in patients with HIT are still limited.

With **lepirudin** and **danaparoid** no longer available in the US, treatment options are limited particularly in the outpatient setting and in patients with hepatic or renal dysfunction. Parenteral administration requires prolonged hospitalization, intensive monitoring and complex transitioning to warfarin. Although initial hospitalization is still necessary for the majority of patients with HIT, some of the newer options may expedite discharge with continuation of outpatient therapy. Conversely, the lack of a validated tool for monitoring these new drugs might be a disadvantage in the situation of acute HIT which is so prothrombotic that aggressive treatment is required while at the same time close monitoring is needed to avoid overdosing in these often severely ill patients.

Dabigatran (Pradaxa) is an oral DTI approved for perioperative prophylaxis of deep vein thrombosis (DVT) use in non-valvular atrial fibrillation (AF) and treatment of acute vein thromboembolism (VTE) with outcomes comparable to enoxaparin and warfarin. It has a fixed oral dose and rapid onset of action, does not require routine monitoring and does not interact with cytochrome P450 enzymes or with other food and drugs. Currently, results from a small number of patients have demonstrated the lack of interaction with PF4 antibody rendering dabigatran a potentially good treatment option for HIT (29, 30).

Apixaban (Eliquis) is an oral factor Xa inhibitor approved for prophylaxis and treatment of VTE and thromboprophylaxis of non-valvular AF, with equal outcomes to warfarin and superior to enoxaparin (31). It has a rapid onset of action and a wide therapeutic window (31). In vitro data have demonstrated that apixaban does not cross-react with preformed PF4 antibodies to cause platelet activation or aggregation (32). However, it has not yet been assessed for the treatment of patients diagnosed with HIT.

Rivaroxaban (Xarelto) is also an oral factor Xa inhibitor approved for prophylaxis and treatment of VTE and thromboprophylaxis of non-valvular AF with outcomes comparable to enoxaparin. Rivaroxaban does not cause any platelet activation in the presence of PF4 antibody therefore it has a potential utility in patients with HIT or a history of HIT. The first case series with the use of rivaroxaban in the treatment of HIT showed reassuring results in regard to thrombotic events and bleeding complications in these patients (33–36).

Conclusions

HIT is a serious condition related to heparin therapy. In patients suspected of HIT, all exposure to heparin should be eliminated immediately and a non-heparin anticoagulant should be administered. Parenteral factor Xa and thrombin inhibitors are proven to be excellent therapeutic choices. However, in outpatient setting and in patients with liver or renal dysfunction the newer orally given anticoagulants offer an emerging alternative. Inevitably, further clinical studies are anticipated to confirm the safety and efficacy of DOACs in HIT.

Conflict of interest

The authors declare that there is no conflict of interest.

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