North East Essex Medicines Management Guidelines for The Management of Heparin-induced Thrombocytopenia at CHUFT

Introduction

Heparin- induced thrombocytopenia (HIT) is a transient hypercoaguable state caused by heparin induced, antibody mediated platelet activation. Failure to diagnose and treat this condition appropriately may lead to life-threatening venous and/or arterial thromboses.

Incidence

The frequency of HIT is greater in surgical than medical patients, and more common with unfractionated heparin (UFH) than low molecular weight heparin (LMWH).

In orthopaedic patients given sub-cutaneous prophylactic heparin, the incidence is around 5% with UFH and 0.5% with LMWH. In medical patients given either therapeutic or prophylactic doses of UFH or LMWH, HIT is said to occur in 0.7% of patients. The risk in obstetric patients is very low, with platelet monitoring only being necessary for those on treatment doses of heparin.

Clinical presentation

When HIT develops, the platelet count typically begins to fall 5-10 days after starting heparin. This may occur more rapidly in patients who have been previously exposed to heparin within the last 3 months. It may occasionally occur develop after 10 days, but onset is very rare after 15 days of exposure.

The platelet count usually falls by >50% with a median nadir of 55 x 10^9/l. Severe thrombocytopenia (platelets <15 x10^9/l) is rare. Skin lesions at the injection site can be a presenting feature as can new thrombotic episodes.

Monitoring for HIT

The following recommendations are made for patients at CHUFT receiving heparin:

- All patients receiving heparin of any sort should have an FBC performed on the day of starting treatment.
- Patients exposed to heparin within the last 100 days should have their platelet count checked 24hrs after starting heparin once again.
- Patients receiving UFH should have an FBC on alternate days from day 4 to day 14 or until heparin has been stopped
- Medical, obstetric and surgical patients being given LMWH do not need routine platelet monitoring for HIT.
- Obstetric patients on therapeutic doses of LMWH should have an FBC performed between day 5 and 7.

Diagnosis of HIT

If HIT is suspected, the on-call haematologist should be contacted to decide whether there is a case for further investigation. An assessment based on 4 clinical categories will help determine the pre-test probability of HIT. The scoring system used is documented below:

	Points (0, 1 or 2 for each of four categories: maximum possible score = 8)		
	2	**1**	**0**
Thrombocytopenia	> 50% fall or platelet nadir 20–100 × 10^9 per l	30–50% fall or platelet nadir 10–19 × 10^9 per l	fall <30% or platelet nadir <10 × 10^9 per l
Timing* of platelet count fall or other sequelae	Clear onset between days 5 and 10; or less than 1 d (if heparin exposure within past 100 d)	Consistent with immunisation but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other causes for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present
Pre-test probability score: 6–8 = high; 4–5 = intermediate; 0–3 = low.			
*First day of immunising heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 d more until an arbitrary threshold that defines thrombocytopenia is passed.			

The definitive test to look for heparin-PF4 antibodies is performed at the platelet reference laboratory in Bristol. Turnaround time is 5 working days, but a more urgent result may be possible if clinically indicated.

A 10ml EDTA and a 10ml serum sample should be sent to the blood transfusion laboratory with the appropriate request card (also available from blood bank).

A positive result should be documented clearly both in the patient's notes and on the front cover and blood bank will issue the patient with an appropriate antibody card to carry with them.

Treatment of HIT

If on assessment, the pre-test probability of HIT is high, the heparin should be stopped and an alternative agent introduced. This can be reassessed with the results from the laboratory investigations, but failure to anticoagulate adequately at this stage will put the patient at high risk of thromboses.

At CHUFT, argatroban is now the recommended first line agent for treatment of HIT. Danaparoid sodium is an alternative drug, with details discussed below. Lepirudin is no longer available in the UK. Bleeding is unusual in untreated HIT and platelet transfusions, which could increase the risk of thrombotic risk for the patient, are relatively contra-indicated. Any anti-platelet agents the patient is taking at this time should be ceased and NSAIDs should be avoided.

Argatroban (Exembol®)

This is a synthetic direct thrombin inhibitor which is mostly metabolised by the liver so renal impairment does not affect the dosing. It has a short half-life (about 50minutes) and is monitored by the APTT. Sufficient time should be allowed for the effects of the heparin on the aPTT to decrease before starting argatroban treatment (about 1 -2 hours).

- A baseline APTT is needed before starting treatment.

- The initial vial concentration is 250mg in 2.5mls which needs to be diluted in 250ml NaCl 0.9% or glucose 5% to give a concentration of 1mg/ml. The solution must be mixed by repeated inversion of the diluent bag for one minute.
- Starting adult dose is 2µg/kg/min. If moderate hepatic impairment or patient is critically ill, starting dose should be 0.5µg/kg/min.
- Target APTT is 1.5-3.0 x baseline APTT, BUT not exceeding 100sec
- APTT should be checked 2 hours after infusion commenced and adjusted until the steady state APTT is within the desired range.

	Starting dose 2µg/kg/min	**Starting dose 0.5µg/kg/min**
APTT < 1.5 x baseline	Increase by 0.5µg/kg/min, repeat APTT in 2 hours	Increase by 0.1µg/kg/min, repeat APTT in 4 hours
APTT 1.5 – 3.0 x baseline	No change, repeat APTT in 2 hours. After two consecutive APTT's within target range check once a day	No change, repeat APTT in 4 hours. After two consecutive APTT's within target range check once a day
APTT > 3.0 x baseline or > 100 seconds	Stop infusion until APTT is 1.5 – 3 x baseline then restart at half the previous infusion rate, repeat APTT in 2 hours	Stop infusion until APTT is 1.5 – 3 x baseline then restart at half the previous infusion rate, repeat APTT in 4 hours

- The maximum recommended dose is 10µg/kg/min
- If the APTT becomes elevated to 3 x baseline or >100 seconds then stop infusion for 2 hours and then the APTT rechecked. Once the APTT is within the desired range restart the infusion at half the previous infusion rate. Check the APTT after 2 hours and adjust accordingly.
- Once within therapeutic range, APTT should be measured daily with adjustments made as needed.
- For advice regarding patients receiving haemodialysis and those receiving PCI please contact pharmacy.

Danaparoid sodium (Orgaran®)

This can be used as an alternative agent if argatroban is not available or cannot be used. It can be used for the treatment of HIT when renal impairment is present or considered likely to develop. Monitoring is via anti-Xa levels which should be checked daily and also before dialysis if the patient is receiving this. The target anti-Xa level is 0.5-0.8units/ml during the maintenance infusion with adjustments to dose as advised by the on-call haematology consultant.

The recommended dose of danaparoid sodium is:

- An initial IV bolus of 2500units (1250units if body weight < 55kg, 3750units if > 90kg) followed by a continuous infusion of 400units/hour for 2 hours, then 300 units/hour for 2 hours then 200 units/hour thereafter for 5 days.

For patients already requiring dialysis, a suggested dosing regime is:

- IV bolus of 3750 units (2500 if < 55kg) before 1st and 2nd dialyses
- IV bolus of 3000 units before 3rd dialysis, then according to pre-dialysis anti- Xa level:

< 0.3	3000units (2000 if <55kg)
0.3 – 0.35	2500units (1500 if <55kg)
0.35 - 0.4	2000units (1500 if <55kg)
> 0.4	0 units

Anticoagulation in a patient with a history of HIT:

Further exposure to either UFH or LMWH is not recommended in this situation and an alternative agent should be used. Fondaparinux may be considered. Patients with a diagnosis of HIT should be therapeutically anticoagulated for a period of 3 months if they have had a thrombotic complication, and for 4 weeks if not. Please contact the oncall Haematologist for further advice on restarting anticoagulation in patients that have a history of HIT.

Converting to warfarin:

Patients receiving argatroban:

Warfarin should not be commenced until the platelet count has recovered and full dose anticoagulation should be continued with argatroban until the INR has been within the therapeutic range for 2 consecutive days. There should be a minimum of a 5 day overlap between non-heparin anti-coagulants and warfarin. Argatroban affects the INR, so the INR should be ≥ 4.0 for 2 days prior to stopping the argatroban.

The INR measurement should be repeated 4 – 6 hours after stopping argatroban. IF the repeat INR is below the desired therapeutic range then the argatroban infusion should be resumed and the procedure repeated daily until the desired INR range is achieved.

For patients receiving an argatroban dose of > 2µg/kg/min the relationship between the INR on warfarin alone and the INR on warfarin and argatroban is less predictable. In this situation the dose of argatroban should temporarily be reduced to > 2µg/kg/min in order to improve the prediction of the INR on warfarin alone.

Patients receiving danaparoid sodium:

Warfarin should not be commenced until the platelet count has recovered and full dose anticoagulation should be continued with danaparoid sodium until the INR has been within the therapeutic range for 2 consecutive days. There should be a minimum of a 5 day overlap between non-heparin anti-coagulants and warfarin.

Warfarin can be given with the danaparoid sodium infusion (maximum rate 300units/hr) which can then be stopped once the INR is ≥ 1.5. If the risk of bleeding is high then:

- Stop the danaparoid sodium infusion and start danaparoid sodium 750 units SC BD. Then 24 hours later start warfarin. Continue the danaparoid sodium for 48 – 72 hours to allow the INR to reach therapeutic levels. The INR must not be taken within 5 hours of the danaparoid sodium bolus being given. OR
- Stop the danaparoid sodium infusion and start warfarin 12 hours later.

Reference: Guidelines on the diagnosis and management of heparin-induced thrombocytopenia, BCSH 2012
Danaparoid sodium SPC 23.04.15, accessed October 2015
Aratroban SPC 02.03.15, accessed October 2015