Heparin and heparin-induced thrombocytopenia

Heparin is a widely used drug - just about any health worker will deal with patients on the drug.

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Heparin is one of the most widely used drugs. It is used routinely for treatment and thromboprophylaxis in a broad spectrum of conditions including venous thromboembolism, atrial fibrillation, acute coronary syndromes, peripheral vascular disease and to maintain the patency of indwelling catheters and extracorporeal circuits. Heparin is one of the most frequently prescribed medications in the USA, where 12 million patients receive the drug annually.[1]

Thus clinicians and health care workers in virtually every branch of medicine may deal with patients who have received heparin in one of its forms. What follows is an overview of heparin and other rapidly acting anticoagulants. The discussion covers their pharmacology and addresses a serious complication of heparin therapy, namely heparin-induced thrombocytopenia (HIT).

Pharmacology

Unfractionated heparin (UFH), derived from porcine intestine or bovine lung, is the prototype of a rapidly acting anticoagulant and has been used for over 60 years to arrest or prevent thrombus growth. It is a heterogenous mix of mucopolysaccharides with molecular weight varying from 3 000 to 30 000 Da which bind to and enhance the effect of the natural anticoagulant antithrombin III (AT).[2] Heparin thus decreases available thrombin and other activated clotting factors (Xa, IXa, XIa, XIIa) effectively 'switching off' the clotting cascade. Fig. 1 depicts the coagulation cascade. It has a rapid onset of action and is readily reversible, although it is highly protein bound, requiring careful laboratory monitoring of the activated partial thromboplastin time (aPTT). When administered at full intravenous dose, the aPTT should be kept at 1.5 - 2.5 the control value.[3] UFH may also be given subcutaneously at fixed dose for prophylaxis and treatment.

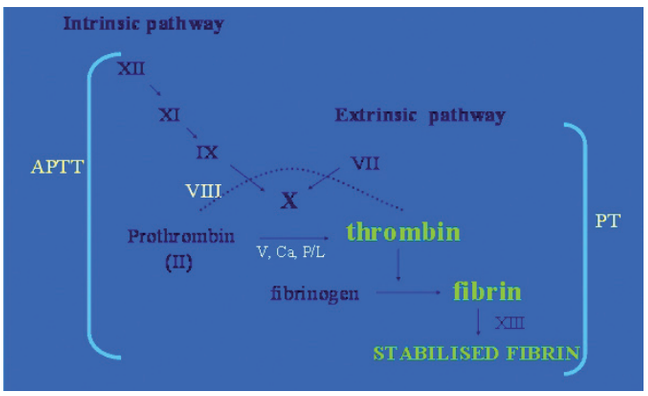

Fig. 1. Simplified coagulation cascade for interpretation of in vitro *testing.*

The low molecular weight heparins (LMWH), e.g. enoxaparin (Clexane), with average molecular weights of 5 000 Da, are manufactured from UFH and have superior dose-response relationships because of fewer nonspecific reactions with plasma proteins. They have high subcutaneous bioavailability (~90%) and allow fixed daily dosing according to body weight. In addition, they have less bleeding for a given antithrombotic effect and are at least as effective as UFH.[3] Their use does not generally require monitoring and they are cleared renally. LMWH have less antithrombin activity than UFH and more inhibition of Xa.[2] Different LMWH products vary in relative inhibition of factor Xa: thrombin. LMWH can be given in therapeutic or prophylactic doses, but unlike UFH they cannot be fully neutralised by protamine. Thus if patients have high bleeding risks or if rapid reversal may be required, UFH is a safer option. Overall costs with LMWH are cheaper than intravenous UFH, because inpatient therapy with careful monitoring of aPTT is not required. Thus LMWH have allowed uncomplicated deep vein thrombosis (DVT) to be treated on an outpatient basis.

LMWH levels cannot be monitored by the aPTT, but require a specialised anti-Xa assay, which is currently available at Johannesburg Hospital Haematology Laboratory (tel (011) 488-3068). Monitoring is only required in special circumstances such as pregnancy, renal failure and obesity.[4] See Table I for a comparison of unfractionated heparin and LMWH.

Fondaparinux (Arixtra) is a novel anticoagulant which takes the evolution of heparin even further. It is an indirect factor Xa inhibitor which does not cross-react with HIT antibodies.[5] Fondaparinux has shown to be at least as effective as LMWH in the treatment of venous thromboembolism and for thrombopophylaxis in a wide range of circumstances.[6] Like LMWH, Fondaparinux has high biovailability, does not usually require monitoring and is administered subcutaneously. Importantly, Fondaparinux is not reversed by protamine sulphate.[6] Fondaparinux is not yet commercially available for use in South Africa.

Hirudin was the first parenteral anticoagulant used in humans in 1909,[7] and is derived from the medicinal leech. Lepirudin is recombinant hirudin, and directly inhibits clot-bound thrombin, preventing its binding to fibrinogen. It thus prevents clot formation. Lepirudin has recently become available in South Africa as an alternative anticoagulant for patients with HIT. It is administered

Table I. Unfractionated heparin versus low molecular weight heparin

	UFH	LMWH
Molecular weight	3 000 – 30 000 Da	Mean 5 000 Da
Mechanism of action	Increases antithrombin activity > anti-Xa	Greater anti-Xa: IIa activity
Mode of administration	IVI or SC	SC only
Therapeutic dose	Bolus then IVI infusion with monitoring of aPTT	Fixed dose according to body weight
Monitoring	aPTT	Usually not necessary; anti-Xa levels needed in renal failure, severe obesity, pregnancy
Reversal	Reversed with IVI protamine sulphate	Only partially reversible with protamine
Heparin-induced thrombocytopenia in those receiving therapy for ≥ 5 days	3 - 5%	< 1%

IVI = intravenous injection; SC = subcutaneous; aPTT = activated partial thromboplastin time.

by intravenous infusion with monitoring by the aPTT (as per heparin), but unlike UFH it has no antidote. Hirudin is an expensive agent and is used with special permission only. Other anticoagulants not available in the local setting include the direct thrombin antagonist, argatroban, and the heparinoid danaparoid.

Heparin-induced thrombocytopenia

Heparin therapy may lead to HIT, which is paradoxically a prothrombotic state. It is one of the commonest and most serious of immune-mediated drug reactions.[8] The diagnosis is based on a high clinical index of suspicion. Laboratory testing is available in some referral centres in South Africa. Appropriate management includes the immediate cessation of heparin therapy and the institution of appropriate alternative full-dose anticoagulation. Warfarin should not be administered in the acute setting and platelet transfusions are contraindicated.

Pathophysiology

HIT is caused by platelet-activating IgG antibodies that recognise complexes of heparin bound to a 'self' protein, platelet factor 4 (PF4). Heparin induces a conformational change in PF4 which is recognised by the antibodies.[9] The heparin/PF4/HIT-IgG complexes form on the platelet surfaces. This leads to *in vivo* platelet activation with associated thrombocytopenia and extension of existing thrombus or new venous/arterial thrombosis. Not all patients who develop the antibodies develop HIT.

Incidence

Patients of any age receiving any form of heparin via any route may develop HIT, although the incidence is higher with UFH than LMWH: 3 - 5% of patients exposed to UFH for 5 days or more develop HIT during or after treatment.[10] The incidence is much lower for LMWH (< 1%).[11] Usually HIT occurs in patients given standard-dose heparin, but can be induced by minimal heparin exposure, e.g. heparin flushes used to maintain patency of indwelling venous and arterial lines. Surgical patients, particularly cardiac and orthopaedic patients have the highest incidence of HIT.[11] The condition is rare in obstetric patients. Unfortunately HIT is often unrecognised because thrombocytopenia is common in hospitalised patients for many other reasons, e.g. sepsis or sensitisation to drugs other than heparin.

Clinical presentation

The time of onset of HIT varies according to the history of exposure. Classically the platelet count drops by > 50% from baseline between 5 and 10 days after initial exposure to UFH. However, in patients who have received heparin in the last 100 days the onset is much quicker (hours) as these patients often have pre-existing antibodies. The thrombocytopenia is typically not severe and usually is 40 - 80 x 10^9 /l.[11] Note that the platelet count may drop by 50% from baseline and still be within the normal range.

Bleeding is rare and the platelet counts typically recover within a week of ceasing heparin.

Diagnosis

If HIT is suspected, the probability of the condition should be judged on clinical grounds in the first instance. Four features are particularly helpful and a scoring system has been proposed to estimate the probability of HIT.[12] This incorporates the '4 Ts': Thrombocytopenia + Thrombosis + Timing + absence of oTher causes of thrombocytopenia (Table II).

The most common thrombotic complications are DVT and pulmonary embolism. The British Society for Haematology has produced practical, evidence-based guidelines for monitoring of platelet counts (Table III).[13]

The South African Society of Thrombosis and Haemostasis has provided guidelines for monitoring patients receiving prophylactic LMWH anticoagulation (Table IV).[4]

Laboratory tests for HIT are broadly classified into two categories – immunological assays (e.g. ELISA) which detect the antibody in the patient's serum and functional assays which detect platelet activation in the presence of heparin. The immunological assays are generally used for screening and have high negative predictive values (i.e. a negative ELISA

Table II. Algorithm to assess likelihood of HIT (the 4 Ts)[12]

	2 points	1 point	0 point
Thrombocytopenia	> 50% fall or nadir of (20 - 100) x 10^9/l (> 30% fall)	30 - 50% fall or nadir of (10 - 19) x 10^9/l	< 30% fall or nadir < 10 x 10^9/l
Timing consistent with HIT	Yes (day 5 - 10); or < day 4 (recent heparin)	Possible (> day 10)	No (< day 4)
Thrombosis	Yes	Possible/silent	No
O**T**her cuse for TP[b]	No	Possible	Likely

High probability 6 - 8 points; moderate probability 4 - 5 points; low probability 0 - 3 points.

TP[b] = thrombocytopenia.

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Table III. Recommendations for platelet count monitoring of patients on heparin treatment (British Society of Haematology)[13]

- All patients who are to receive heparin of any sort should have a platelet count performed on the day of starting treatment
- For patients who have been exposed to heparin in the last 100 days a baseline platelet count and a platelet count 24 hours after starting heparin should be obtained
- For all patients receiving unfractionated heparin, alternate-day platelet counts should be performed from days 4 to 14
- For surgical and medical patients receiving LMWH, platelet counts should be performed every 2 - 4 days from days 4 to 14
- Obstetric patients receiving treatment doses of LMWH should have platelet counts performed every 2 - 4 days from days 4 to 14. Obstetric patients receiving prophylactic LMWH are at low risk and do not need platelet monitoring
- If the platelet count falls by 50% or more and/or the patient develops new thrombosis or skin allergy between days 4 and 14 of heparin administration, heparin-induced thrombocytopenia (HIT) should be considered and a clinical assessment made
- If the pretest probability of HIT is high, heparin should be stopped and an alternative anticoagulant started in full dosage while laboratory tests are performed, unless there are significant contraindications

Table IV. Recommendations for monitoring patients on LMWH (South African Society of Thrombosis and Haemostasis 2004)[4]

- The patient's platelet count should be checked on initiation of LMWH, after 5 days, and thereafter not less than once every 3 months, while on therapy
- Anticoagulant activity is measured using an anti-Xa activity assay
- Anti-Xa measurement is only indicated in pregnancy, renal failure or in excessively obese patients in whom large doses are required
- The anti-Xa assay must be calibrated for each LMWH tested
- The anti-Xa assay is available for enoxaparin and nadroparin at Johannnesburg Hospital Haematology Laboratory, tel (011) 488-3068 or (011) 489-8552
- 5 ml citrated blood taken 3 hours after a LMWH dose is required for the assay

Target levels:

Prophylaxis target: 0.3 – 0.5 anti-Xa U/ml of blood

Therapeutic target: 0. 6 – 1.0 anti-Xa U/ml of blood

assay generally rules out HIT). However, false positives do occur and it is important to interpret the test in the appropriate clinical context.[14] Limited laboratory testing is available in the South Africa.

Management

The British Society of Haematology has provided concise practical guidelines regarding management of HIT.[13] For patients with strongly suspected HIT, heparin should be stopped and full-dose anticoagulation with an alternative anticoagulant like lepirudin commenced. Alternatives available for the treatment of HIT include danaparoid and argatroban, although neither of these are available in South Africa Platelet transfusion should NOT be given as this may exacerbate the thrombosis, and warfarin should not be used until the platelet count has recovered. Warfarin may acutely increase the prothrombotic state due to dropping the protein C (natural anticoagulant) level. Vitamin K administration is recommended if warfarin has already started and investigation for lower limb DVT is advised. Specialist consultation with an experienced tertiary haematology centre should be instituted.

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In a nutshell

- HIT is a common and serious immune-mediated drug reaction.
- Any form of heparin may cause the reaction.
- The incidence is higher with UFH (~3%) than LMWH.
- Surgical patients are at highest risk, especially those who have had orthopaedic surgery.
- The platelet count typically falls by > 50% 5 - 10 days after first exposure to heparin. This occurs sooner in patients with previous heparin exposure.
- The heparin-induced antibody complex causes platelet activation, leading to thrombosis, usually venous.
- Half of those with HIT will develop associated thrombosis which has a high mortality rate.
- A clinical scoring system ('the 4 Ts') is useful to make the diagnosis.
- Appropriate management involves promptly ceasing heparin and instituting full-dose alternative anticoagulation.
- Warfarin should NOT be given in the acute setting as it may precipitate thrombosis, and platelet transfusions should be avoided.