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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Guidelines on when to use and how to monitor intravenous unfractionated heparin in adults

Heparin remains the most widely used parenteral antithrombotic. The general adoption of low molecular weight heparin (LMWH) represents a significant therapeutic advance in terms of ease and convenience of administration. There may also be some advantages in terms of efficacy and fewer side effects. This leaflet gives guidance on when to use intravenous (IV) unfractionated heparin (UFH) for treatment of thrombosis (it does not address VTE prophylaxis where LMWH is standard practice).

When to consider using IV UFH

LMWHs have replaced UFH as the preferred option in most clinical situations. Local guidelines should be followed in specialist areas where UFH is indicated. Examples of when UFH may be considered include the following:

1. Patients who might require their anticoagulation to be stopped rapidly e.g. patients at very high risk of bleeding and those who may require urgent invasive procedures
2. Patients with unstable pulmonary embolism (PE) following treatment with alteplase

Contraindications to anticoagulation

The following substantially increase the risk of major bleeding:

- Current or recent gastrointestinal ulceration
- Presence of malignant neoplasm at high risk of bleeding
- Recent brain or spinal injury
- Recent brain, spinal or ophthalmic surgery
- Recent intracranial haemorrhage
- Known or suspected oesophageal varices
- Arteriovenous malformation
- Vascular aneurysms, major intraspinal or intracerebral vascular abnormalities
- Acute stroke (contact stroke team)

If anticoagulation is felt to be contraindicated, the patient should be discussed with Haemostasis registrar (bleep 5529) or Haematology SpR via switchboard out of hours.

Baseline tests (before treatment)

Measure APTT, Prothrombin Time (PT), platelet count, haemoglobin and potassium levels. Significantly abnormal results can be discussed with Haemostasis registrar (bleep 5529).

Dosing and administration

Unfractionated heparin dosing is unpredictable and a high percentage of patients will still have APTT results outside the desired range even with careful monitoring. The risks of this must be taken into account when deciding to use UFH rather than LMWH. UFH should be prescribed using a standardised ready-to-administer heparin preparation of 1000 units per mL (undiluted) as detailed below. Administration guidelines are available via the injectable monograph.

Loading dose: 5000 units heparin (or 10 000 units if greater than 120kg) given as a slow IV bolus over 3-5 minutes. Omission of loading dose delays effective anticoagulation**.**

Maintenance dose: Give as a continuous IV infusion, starting at 1400 units per hr (1.4 mL per hr of the 1000 units per mL solution) {or 2100 units per hr (2.1mL per hr of the 1000 units per mL solution) if greater than 120kg}. Doses should be adjusted according to APTT (table 1).

Table 1: Adjustment of continuous heparin infusion rate based on APTT using 1000 units/mL concentration
**An APTT of 45 – 70 seconds corresponds to 0.35-0.7 anti-Xa units/mL with the current laboratory reagent. It will need to be reviewed when the APTT reagent is changed.*

APTT (s)	Action
Greater than 175	stop for one hr and reduce infusion rate by 700 units/hr (0.7 mL/hr)
126 – 175	reduce infusion rate by 500 units/hr (0.5 mL/hr)
101 - 125	reduce infusion rate by 300 units/hr (0.3 mL/hr)
71 - 100	reduce infusion rate by 100 units/hr (0.1 mL/hr)
45 - 70	no change
36 - 44	increase infusion rate by 100 units/hr (0.1 mL/hr)
30 – 35	increase infusion rate by 200 units/hr (0.2 mL/hr)
Less than 30	give a 5000 unit bolus IV and increase infusion rate by 400 units/hr (0.4 mL/hr)
NB: There is no defined maximum rate of UFH. If a dose exceeds 3000 units per hour, contact haematology for advice.	

Cardiac patients: consider reducing initial infusion to 1000 units per hr (1mL per hr of the 1000 units per mL solution), where there is an increased bleeding risk such as:

- Patients receiving dual antiplatelets
- Patients post-alteplase (rt-PA, tissue-type plasminogen activator)
- Patients on heparin during intra-aortic balloon pump support
- Patients post abciximab and/or bivalirudin

Note: Patients with prosthetic heart valves requiring heparinisation prior to surgery - discuss initial heparin dose with Cardiology.

Preparation of continuous infusion

A standard volume of infusion is 25mL (i.e. 25000 units in 25mL undiluted). Once prepared the infusion should only be used for 24 hours and any remaining infusion solution discarded. The infusion rate must be accurately controlled using a syringe pump and monitored using an infusion monitoring chart. Two registered professionals must set up and check the initial and subsequent syringes and rate changes.

Monitoring APTT

The target APTT is 45 – 70 seconds*. Check APTT 4 hours after start of infusion, and adjust infusion rate according to **table 1.** Recheck APTT 6 hours after any change of dose (4 hrs if greater than 125 or less than 30 seconds) or, if no change required recheck within 24 h. **Before changing the rate of infusion, check that the initial rate was correct, the cannula is patent and tubing and infusion equipment are working appropriately.**

Target APTT and infusion rate changes must be documented appropriately. **All dose and infusion rate changes must be prescribed on the patient's drug chart before administration.**

In special circumstances and only under haematology advice, dosing might be guided by anti-Xa levels rather than APTT (appendix 1).

Patient monitoring

Monitor patient for signs of bleeding. Platelet counts should be measured on alternate days from days 4-14 of therapy (see below). Potassium should also be monitored regularly, especially if therapy exceeds 7 days.

Adverse effects

- haemorrhage
- thrombocytopenia (see below)
- hyperkalaemia (see below)
- osteoporosis
- alopecia with prolonged use

- hypersensitivity reactions (including urticaria, angioedema and anaphylaxis)

Hyperkalaemia
Inhibition of aldosterone secretion by heparin can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium or those taking potassium-sparing drugs seem to be more susceptible. The risk appears to increase with duration of therapy and it is recommended that the potassium concentration should be measured in patients at risk of hyperkalaemia before starting heparin and monitored regularly thereafter, particularly if heparin is to be continued for longer than 7 days.

Heparin-induced thrombocytopenia (HIT)
Clinically important HIT is immune-mediated and does not usually develop until 5–10 days after starting heparin therapy unless the patient has been exposed to heparin before. HIT can be complicated by thrombosis. All patients who are to receive heparin should have a platelet count on the day of starting treatment. For patients previously exposed to heparin in the last 100 days, obtain a platelet count 24 hrs after starting heparin. For all other patients alternate day platelet counts should be performed from days 4 to 14 of therapy. Signs of HIT include a 50% reduction of platelet count, thrombosis, or skin allergy. If HIT is strongly suspected or confirmed, heparin should be stopped and an alternative anticoagulant should be given. Contact the on-call haematology registrar for advice and refer to local guidelines.

Overdose/Reversal
In an emergency the anticoagulant effect of heparin can be inhibited by protamine sulphate. One mg of protamine sulphate inhibits the effect of 100 units of heparin – usually the maximum dose is 50 mg given by slow IV injection (rate not exceeding 5mg per minute). Re-check APTT after reversal and discuss with the Haematology if still abnormal or if the patient is still bleeding.

Heparin and surgery In patients with normal renal function intravenous UFH can be stopped 6 hours before surgery to allow coagulation to return to normal.

Heparin and intramuscular injections
Intramuscular injections should be avoided in patients receiving anticoagulants, except for adrenaline for severe anaphylaxis.

Switching from UFH to LMWH
The half-life of UFH is dose-dependent and approximately 45-60 mins unless renal function is severely impaired. If patients are to be switched from IV UFH to subcutaneous LMWH, the UFH infusion should be stopped approximately 4 hours before the first dose of LMWH is due (providing patient's renal function is normal and last APTT result is within accepted UFH range i.e. 45-70 seconds).

Safe Medication Practice for prescribing Heparin Infusions

- A Powerplan is available to support electronic prescribers
- A Quick Reference Guide for prescribing and administration is available
- Target APTT should be documented
- Always use standard heparin infusion concentration of 1000 units per 1mL
- The prescription must state
  - ✓ Heparin dose in units for bolus dose
  - ✓ Heparin infusion rate in mL per hour
  - ✓ Infusion volume
  - ✓ Route
  - ✓ Time for next APTT
- Infusion rate changes must be prescribed by doctor.
- Infusion must be changed every 24 hrs

References

1. Kitchen, S et al. (2014) Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology. Br J Haematol 166; 830-841.
2. Sweetman SC (Ed). Martindale: The Complete Drug Reference. 37th Ed, Pharmaceutical Press; London 2011
3. Trissel L.A. Handbook on injectable Drugs. 16th Edition, American Society of Health-System Pharmacists Inc; Bethesda 2011
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Appendix 1: Monitoring UFH IV infusion with anti-Xa levels

Anti-Xa levels can be used for dose adjustment of infusion rates but are more expensive than standard APTT testing. However, in certain complex cases, they may be preferred to APTT levels. The anti-Xa levels should only be used instead of APTT for monitoring UFH infusion following haematology advice. The following table provides guidance for dose adjustment in these circumstances:

Anti-Xa (units/ml)	Action
Two consecutive results greater than 1.3	stop for one hr and reduce infusion rate by 700 units/hr (0.7 mL/hr)
Greater than 1.3	reduce infusion rate by 500 units/hr (0.5 mL/hr)
1.11-1.3	reduce infusion rate by 300 units/hr (0.3 mL/hr)
0.71-1.1	reduce infusion rate by 100 units/hr (0.1 mL/hr)
0.35-0.7	no change
0.20-0.34	increase infusion rate by 100 units/hr (0.1 mL/hr)
Less than 0.2	increase infusion rate by 200 units/hr (0.2 mL/hr)
Two consecutive results less than 0.2	give a 5000 unit bolus IV and increase infusion rate by 400 units/hr (0.4 mL/hr)