Heparin

Unfractionated Heparin

Polyanionic mucopolysaccharide. $T_{\frac{1}{2}}$ 30min. 90% protein bound. Doesn't cross placenta. Liver met.

- Binds & potentiates antithrombin (which inhibits factors including thrombin & Xa).
- Prolongs APTT.
- Activates lipoprotein lipase

SE:

- Inadequate response
- Haemorrhage 8%
- Thrombocytopaenia 3% – HITS type 1 (self-resolving) & type 2 (worse prognosis)
- Alopaecia
- Osteoporosis

Dosing - Depends on indication. Some variation between centres. Adult values (SSWAHS):
Prophylaxis: 5000u SC bd
ACS: Loading: 50-60u/kg IV then infuse (100u/ml NS) 12u/kg/hr up to 1000u/hr
DVT/PE, AF, heart valves: Loading: 70-75u/kg IV then 18u/kg/hr up to 2100u/hr
Monitoring: check APTT daily or 6hrs after starting or a change in dose. Adjust by protocol.
APTT therapeutic range is 55-75 for ACS, 55-90 for other therapy.

Low molecular weight heparins (LMWHs e.g. tinzaparin, enoxaparin, dalteparin and bemiparin)

Produced by depolymerisation of heparin. Potent anti-Xa action, less on thrombin.
Better SC bioavailability than UFH. $T_{\frac{1}{2}}$ 3-4hr SC (2hr IV). Doesn't cross placenta. Renal elim.

SE:

- Ocal pain/bruising at injection site
- Haemorrhage 4%
- Thrombocytopaenia 2%
- Fever
- Nausea
- Confusion (rare)

Dosing

Depends on indication. Some variation between centres. Adult values (SSWAHS):
Prophylaxis: 20-40mg enoxaparin (Clexane) SC od
ACS/DVT/PE, AF, heart valves: 1.5mg SC od or 1mg/kg SC bd (up to 100mg/dose) reduced in renal impairment.

LMWH vs. UFH

- More predictable pharmacokinetics
- Higher bioavailability
- Long plasma half-life
- Easy administration
- Routine laboratory monitoring not needed
- There is less risk of haemorrhage & thrombocytopenia
- They are more effective against thrombus growth
- However slower reversal following cessation & protamine not very effective

Warfarin

Drug of choice for oral anti-thrombotic Rx.
Warfarin antagonises vitamin K dependent clotting factors (II, VII, IX, X) and Protein C & S.
~100% oral bioavailability. 97% albumin-bound. Hepatic P450 met. Not excreted in breast milk.
NB it takes 2-3 days to exert its full effect so for immediate effect heparin must be given too. Also Early reduction of factor VII & Protein C, before factor II (thrombin) → prothrombotic state (at least theoretically).

Indications and targets

Indication	INR Target Range	Duration
VTE Prophylaxis	1.5-2.5	Long term
AF	2.0-3.0	Long term
DVT/PE Rx		
• temporary risk factors	2.0-3.0	3mo
• recurrence off warfarin	2.0-3.0	6mo
• permanent risk factors	2.0-3.0	6mo
• recurrence on warfarin (add aspirin 100mg od)	3.0-4.5	Long term
Cardiac Valves		
• tilting/bileaflet	2.0-3.5	Long term
• ball/disc	2.0-4.5	Long term
Antiphospholipid syndrome	3.0-4.0	Long term

Doses

Loading 10mg (or 5mg in elderly) PO OD x 2, then 5mg and adjust to INR.

Contraindications

- Known bleeding tendency
- Liver disease or continuing alcohol abuse
- Platelets <80x10^9/l.
- Haemorrhagic stroke
- Uncontrolled severe hypertension
- Non-compliant patients
- Active peptic ulcer
- Pregnancy: oral anticoagulants are teratogenic and cross the placenta in late pregnancy.

Monitoring

Check INR daily until in therapeutic range for 2 consecutive days, then 2x/wk for 1-2wk, then weekly until stable, then every 6-12wk unless change in a patient's condition.

Complications

Haemorrhage in 10%/yr. Esp Elderly. 50% have INR in therapeutic range. Mortality 0.25%.
Skin necrosis (esp if Protein C or S deficiency) – breast, buttocks, thigh & toes.
Teratogenicity – max at 6-9wks (nasal hypoplasia, frontal bossing, cataracts, low IQ, short)
Atheromatous cholesterol embolisation (digital oschaemia). Rare.

INR & invasive procedures

Usually safe if INR<2.0. Stop warfarin 3 days prior to surgery & cover with heparin once INR below therapeutic range.

Over-anticoagulation Management

1) Therapeutic range<INR<5.0 & no bleeding: Reduce the dose or omit the next dose and resume at a 10-20% lower dose when INR approaches therapeutic range.
2) INR 5.0–9.0 & no bleeding: Cease warfarin, if bleeding risk is high, give vitamin K1 (1.0–2.0mg PO or 0.5–1.0mg IV). Measure INR within 24hrs, resume warfarin at a 10-20% lower dose once INR is therapeutic.
3) INR > 9.0 & no bleeding: Cease warfarin, give 2.5–5.0mg vitamin K1 PO or 1.0mg IV. Measure INR in 6–12 hours, resume warfarin at 20% lower dose once INR<5.0. If high risk of bleeding‡, then give the vitamin K1 IV and consider Prothrombinex-HT (heat treated II,IX & X, 25–50IU/kg) and FFP (150–300mL).

   NB. If INR overcorrected & INR<therapeutic range give enoxaparin 1.5mg/kg/day SC until INR>2.0
   ‡*Bleeding risk factors: Age>65, uncontrolled HT, CVA, PUD, IBD, platelets<50, antiplatelet Rx, NSAIDs, recent surgery, renal impairment, recent trauma, EtOH++, liver disease.*

4) If any clinically significant bleeding: Cease warfarin therapy, give 5.0–10.0mg vitamin K1 intravenously, plus Prothrombinex-HT (25–50IU/kg) and FFP (150–300mL or 10-15ml/kg if no Prothrombinex-HT), assess patient continuously until INR<5.0, and bleeding stops.

Interactions

Enhancers: EtOH, phenytoin, erythromycin, metronidazole, omeprazole, simvastatin, allopurinol, aspirin, paracetamol, TCAs, SSRIs, cranberry/grapefruit juice, flu vaccine, amiodarone.
Inhibitors: carbamazepine, chronic EtOH, rifampicin, anti-thyroid drugs, OCP & St John's Wort

Other Anticoagulants

Fondaparinux - a new synthetic factor Xa inhibitor. Long $T_{\frac{1}{2}}$ 17 hours. Used for VTE prophylaxis for patients with hip fracture or having total knee or hip replacements. ?Use in ACS.

Brodifacoum – a superwarfarin (100x more potent than warfarin). Rodentacide. Long half-life. In OD may need to take serial INR s to rule out toxicity. Rx: Vit K or FFP.

Abnormal Coagulation Tests

APTT – reflects intrinsic pathway, INR extrinsic pathway, and Bleeding Time platelet function.

High INR & APPT

- Chronic oral coagulants (warfarin)
- Severe liver disease
- DIC
- Factor X, V deficiency
- Afibrinogenaemia

High INR, normal APTT

- Oral coagulants (warfarin)
- Mild liver disease
- Malabsorption
- Factor VII deficiency

High APPT

- Heparin
- Haemophilias

High APPT & bleeding time, Normal INR

- Heparin with thrombocytopaenia
- Von Willibrand's disease

Prolonged bleeding time, normal APTT & INR

- Platelet dysfunction
- Aspirin or NSAIDs
- Uraemia