Unfractionated Heparin and Low-molecular-weight Heparin

Thrombosis Canada
Thrombose Canada

Target Audience: All Canadian health care professionals.

Objective:

To aid practitioners in prescribing unfractionated heparin and low-molecular-weight heparins to patients.

Abbreviations:

ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	antithrombin
CBC	complete blood count
HIT	heparin-induced thrombocytopenia
INR	international normalized ratio
IV	intravenous
LMWH	low-molecular-weight heparin
MI	myocardial infarction
PT	prothrombin time
TNK	tenecteplase
tPA	tissue plasminogen activator
UFH	unfractionated heparin
U	units
VTE	venous thromboembolism

Mechanism of Action:

Unfractionated heparin (UFH) acts as an anticoagulant by forming a complex with antithrombin (AT) catalysing the inhibition of several activated blood coagulation factors: thrombin (factor IIa), factor IXa, Xa, XIa and XIIa. This prevents fibrin formation and inhibits thrombin-induced activation of platelets and factors V, VIII, and XI. Smaller heparin chains (< 18 saccharide U) are too short to bind to AT and thrombin simultaneously but can inactivate factor Xa by binding to AT alone.

Low-molecular-weight heparins (LMWHs) are derived from UFH by chemical or enzymatic depolymerization and have reduced inhibitory activity against thrombin (factor IIa) relative to factor Xa. LMWHs have more predictable pharmacokinetic properties compared with UFH which allows LMWHs to be administered in fixed doses and without the need for dose adjustment based on laboratory monitoring.

INDICATION:

a) treatment of venous thromboembolism (VTE) (see DVT Treatment and PE guides)

b) prophylaxis of VTE (see Thrombophrophylaxis: Medical, Thromboprophylaxis: Orthopedic, Thromboprophylaxis: Surgical guides)

c) acute coronary syndromes

d) for patients with cardiovascular disease, following or preceding angioplasty, coronary artery bypass surgery, thrombolysis, or peripheral vascular surgery

e) prevention of clotting during dialysis and surgical procedures

Special populations:

a) bridging during temporary warfarin interruption (see Warfarin Peri-Operative guide)

b) atrial fibrillation anterior wall myocardial infarction (MI)

c) intracardiac thrombus

d) systemic arterial embolism

e) selected stroke syndromes

f) cervical artery dissection

g) anticoagulation in patients with renal insufficiency

DOSING (UFH):

a) VTE prophylaxis: 5000 U subcutaneously q8h-q12h.

b) VTE treatment for hospitalized patients: IV bolus 5,000 U followed by a rate of at least 1,300 U/hour **OR** an 80 U/kg IV bolus followed by a rate of 18 U/kg/hour.

c) VTE treatment for non-hospitalized patients: 17,500 U subcutaneously q12h or 250 U/kg subcutaneously q12h with the initial dose being 333 U/kg.

d) Acute coronary syndromes (for intermediate and high-risk unstable angina, non-ST segment elevation MI): IV bolus 60-70 U/kg (maximum 5000 U) followed by 12-15 U/kg/hour (maximum 1000 U/hour).

e) For ST segment elevation MI patients who have received fibrinolytic agents (e.g. tissue plasminogen activator [tPA], tenecteplase [TNK]) in conjunction with heparin: IV bolus 60 U/kg (maximum 4000 U) followed by a rate of 12 U/kg/hour (maximum 1000 U per hour).

DOSING (LMWH):

Dosing of LMWH depends on the drug used. In Canada, the three commonly used LMWHs are dalteparin (Fragmin™), enoxaparin (Lovenox™) and tinzaparin (Innohep™).

a) VTE prophylaxis:
    a. Dalteparin: 5,000 U daily (OD)
    b. Enoxaparin: 40 mg OD or 30 mg twice daily (BID)
    c. Tinzaparin: 4,500 U OD

b) VTE treatment:
    a. Dalteparin: 200 U/kg OD or 100 U/kg BID
    b. Enoxaparin: 1.5 mg/kg OD or 1 mg/kg BID
    c. Tinzaparin: 175 U/kg OD

c) Acute coronary syndromes (for intermediate and high-risk unstable angina, non-ST segment elevation MI):
    a. Enoxaparin: 1 mg/kg BID
    b. Dalteparin: 100 U/kg BID

d) For ST segment elevation MI patients:
    a. Enoxaparin: 1 mg/kg BID

MONITORING:

The use of a heparin dosing nomogram is encouraged because it helps achieve and maintain the activated thromboplastin time (aPTT) in the therapeutic range efficiently. The aPTT is used to monitor the effects of heparin treatment. However, aPTT reagents vary in their sensitivity to heparin; therefore, your laboratory should establish a therapeutic range locally. A reasonable estimate of an adequate therapeutic effect would be achieved by an aPTT ratio of 1.5-2.5 times control corresponding to a factor Xa level of 0.35-0.70 U/mL. Inadequate heparin therapy in the initial 24-48 hours of treatment predisposes to recurrent venous thromboembolism.

Monitoring should include a baseline complete blood count (CBC) (including platelet count), prothombin time (PT) and aPTT, and then aPTT every 6 hours until a therapeutic range is achieved, then daily. Periodic monitoring of platelet count every 2-3 days is advised.

Laboratory monitoring is not required typically in patients who are receiving LMWHs. There may be special situations, for example, patients with moderate to severe renal insufficiency, pregnancy or patients at extremes of body weight (e.g. <45 kg, >120 kg) where laboratory monitoring with

factor Xa levels may be warranted. Laboratory monitoring of LMWHs should be done in consultation with a specialist.

ADVERSE EFFECTS:

a) Bleeding is the most common adverse effect of UFH and LMWHs.

b) Heparin-induced thrombocytopenia (HIT): Immune-mediated platelet activation has been reported in up to 5% of patients who receive UFH. It may be associated with life-threatening or fatal arterial or venous thrombosis. Onset is generally between 5 and 10 days after commencing therapy, unless there has been a recent exposure to heparin, in which case HIT can occur earlier. Should it occur, stop all sources of heparin, and alternative anticoagulants such as argatroban, danaparoid or lepirudin should be considered. HIT can occur in patients who are receiving LMWHs but is much less frequent than in patients who are receiving UFH.

c) Osteoporosis is a serious but less common side-effect associated with prolonged use of high doses of UFH. Three months of UFH treatment at a moderate dose (20,000 U/24 hours) will most likely not be associated with clinically-significant osteoporosis.

d) Hyperkalemia is a rare complication of UFH and is due to aldosterone suppression.

e) Increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with no evidence of clinical liver dysfunction may occur in patients who receive UFH or LMWHs. The significance is unknown. Transaminase values return to normal within 15-30 days.

PERI-PROCEDURAL MANAGEMENT:

Stop heparin 4-6 hours prior to procedure, if possible.

BLEEDING MANAGEMENT OR EMERGENCY SURGERY:

UFH and LMWHs should be stopped in case of major or serious bleeding. When reversal is required, protamine sulfate should be used to reverse the anticoagulant effect. Protamine 1 mg reverses 100 U of UFH, and the usual initial dose is 25-50 mg by slow intravenous infusion over 15-20 minutes due to the risk of anaphylactoid reactions. Protamine can be used in patients who have received LMWHs but is less effective to reverse the anticoagulant effect of these drugs.

SPECIAL CONSIDERATIONS:

Overlap with Warfarin

In most cases, warfarin can be started on the same day as UFH or LMWH (with the exception of HIT where warfarin would be delayed until the platelet count recovered). Warfarin and UFH or

LMWH should overlap for at least 5 days and until the international normalized ratio (INR) value is within therapeutic range for 2 consecutive days before heparin is discontinued.

Pregnancy

UFH is used for the management of thromboembolism during pregnancy although it has been largely replaced by LMWH. Consultation with a specialist is advised. Therapeutic heparin can be achieved by subcutaneous injections twice daily (see Thromboprophylaxis: Pregnancy guide). Peri-partum management of anticoagulation requires advanced planning. Secondary prevention in the post-partum period can be achieved with warfarin, subcutaneous heparin or LMWH and is recommended for at least 6 weeks after delivery. Women can breastfeed while being treated with heparin therapy.

PEDIATRICS:

In children, studies have demonstrated age-dependent dosing of heparin. Therapeutic UFH is titrated to achieve a target anti-Xa range of 0.35-0.7 U/mL or an aPTT range that correlates to this anti-Xa range or to a protamine titration range of 0.2-0.4 U/mL. If UFH boluses are used to initiate therapy, the bolus should be no greater than 75-100 U/kg, and boluses should be withheld or reduced if there are significant bleeding risks. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

REFERENCES:

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