Anticoagulant therapy monitoring (2)

Unfractionated Heparin monitoring

Unfractionated heparin (UFH) is a heterogeneous mix of polysaccharide chains of variable molecular weight. One-third of the chains have a pentasaccharide pattern that has a strong binding affinity to Antithrombin.
Molecular weight: 2,000 to 40,000 Dalton (average: 15,000).

They are used for both therapeutic and prophylactic therapy

- **Limitation:**
  - Short half-life, dose-dependent
  - Non-specific binding
  - Random dose-response effect
  - Major bleeding risk
- **Sample collection and treatment:**
  - A standardised protocol should be followed for the collection and processing of the samples.
  - Collection: tube containing an anticoagulant - sodium citrate 0.105/0.109 M or CTAD (Citrate, Theophylline, Adenosine, Dipyridamole).
  - Centrifugation within an hour of collection.
  - Stability at +20°C: 2 hours in a citrate tube or 4 hours in a CTAD tube
- **Assays:**
  - **aPTT**
    - Widely used for monitoring UFH treatment but sensitive to certain coagulation abnormalities (deficiency or specific coagulation disorders, lupus anticoagulant) and to certain drugs such as vitamin K antagonists (during heparin-VKA therapy switch) or thrombolytic drugs

Note: Therapeutic ranges may vary between reagents

- **Anti-Xa activity:** standardised measurement using an international standard (see Tables 1 and 2)
- **Platelet count:** for the detection of heparin-induced thrombocytopenia (HIT)
  - HIT, Type II :
    - Immunoallergic reaction to the drug
    - Up to 3% of treated patients[1]
    - Generally occurs after the 5th day of treatment
    - Severe thrombocytopenia, followed by life-threatening thrombotic complications

- **Antithrombin (AT):** for the exclusion of antithrombin deficiency in the case of heparin resistance.

Low Molecular Weight Heparin (LMWH) monitoring

● **Low Molecular Weight Heparin** is obtained by enzymatic or chemical depolymerisation of unfractionated heparin.
Molecular weight: 2.000 to 12.000 Daltons (mean: 5.000 Da)

● **Anticoagulant profile:**
- Ratio of anti-factor Xa / anti-factor IIa activity:
  - UFH: 1:1
  - LMWH: 2 to 5:1 (and more for same LMWH preparation)

● **Advantages:**
- More predictable anticoagulant response
- Better bioavailability at low doses
- Non-dose-dependent clearance
- Longer half-life

● **Tests:**
- The result of global coagulation tests (aPTT) are not correlated with the anti-coagulant activity of LMWH
- The only tests currently available are those that specifically measure anti-Xa activity in plasma
- An international standard for LMWH is available
- Anti-Xa activity for LMWH dose adjustment should be assayed at least 48 hours after the initial injection (curative treatment)
- Monitoring is not necessary during prophylactic treatment (except in the event of renal impairement, weight gain, bleeding or thrombosis risk)
- Monitoring is particularly recommended in children and elderly subjects
- Platelet count should be measured:
  - within the first 24h of treatment
  - thereafter, twice weekly throughout treatment.

Bibliography:
- (1) Treatment and Prevention of Heparin-Induced Thrombocytopenia. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Linkins L.A., Dans A.L., Moores L.K., Bona R., Davidson B.L., Schulman S., Crowther M. Chest, 2012; 141: 495S-530S
- Parenteral anticoagulants. Antithrombotic Therapy and Prevention of Thrombosis. 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. Garcia D.A., Bagin T.P. Witz J., Samama M.M. Chest, 2012; 141: e24S-e43S

Table 1 : Unfractionated heparin: curative therapeutic range

ADMINISTRATION MODE	SAMPLING	Curative treatment	
		aPTT Ratio* patient/reference	Anti-Xa activity
continuous intravenous infusion	any time after fourth hour of treatment	1.5-3.5 times	0.3 to 0.7 IU/mL
discontinuous subcutaneous or intravenous infusion	at the midpoint between 2 injections	1.5-3.5 times	0.3 to 0.7 IU/mL

Tableau 2 : Unfractionated Heparin: preventive therapeutic range

ADMINISTRATION MODE	SAMPLING	Preventive treatment	
		aPTT Ratio* patient/reference	Anti-Xa activity
subcutaneous or intravenous infusion	at the midpoint between 2 injections	1.2-1.3 times	0.1 to 0.2 IU/mL

*The extent of aPTT prolongation differs between reagent.
It is recommended that every laboratory establish their own aPTT therapeutic range according to their own operating procedure

Table 3: Heparin derivatives (LMWH and fondaparinux) available in France at curative doses in 2012 - (1, 16, 18)

Product	Indications	Dosage	Peak anti-Xa activity		APTT prolongation (if measured)
			Mean values[1] m±sd	Overdose threshold[2]	
LMWH: twice-daily injection regimen: *sample taken at peak activity, 3 to 4 h after injection*					
LOVENOX® (INN enoxaparin)	DVT with or without PE Acute coronary syndrome	100 IU/kg/12h (1 mg/kg/12h)	1.20 ± 0.17 IU/mL	ND	Moderate prolongation
FRAGMINE® (INN dalteparin)	Established DVT Unstable angina Non-Q-wave myocardial infarction	100 to 120 IU/kg/12h	0.6 ± 0.25 IU/mL	1.0 IU/mL	Moderate prolongation
FRAXIPARINE® (INN nadroparin)		85 IU/kg/12h	1.0 ± 0.2 IU/mL	ND	Moderate prolongation
LMWH: once-daily injection regimen: *sample taken at peak activity, 4 to 6 h after injection*					
INNOHEP® (INN tinzaparin)	Established DVT Non-serious PE	175 IU/kg/24h	0.87 ± 0.15 IU/mL	< 1.5 IU/mL	Prolongation
FRAXODI® (INN nadroparin)	Established DVT	171 IU/kg/24h	1.34 ± 0.15 IU/mL	< 1.8 IU/mL	Moderate prolongation
Fondaparinux: once-daily injection regimen: *sample taken at peak activity, 2 to 3 h after injection*					
ARIXTRA® (INN fondaparinux)	Established DVT Non-serious PE	7.5 mg/24h[3]	1.41 µg/mL	ND	No prolongation
ARIXTRA® (INN fondaparinux)	Acute coronary syndrome	2.5 mg/24h	0.45 µg/mL	ND	No prolongation

IU = International Units

DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism

INN: International Nonproprietary Name

[1]NB: mean values measured in subjects receiving treatment with each LMWH;

[2]Threshold values above which dose reduction can be considered;

[3]For patients weighing between 50 and 100 kg; 5 mg/24h for patients weighing < 50 kg; 10 mg/24h for patients weighing > 100 kg