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What is Heparin

Heparin is an anionic mucopolysaccharide.

Heparin acts as an anticoagulation by forming a complex with antithrombin, catalysing the inhibition of several activated blood coagulation factors: XIIa, XIa, IXa, Xa and thrombin.

Heparin is most commonly used for prevention and treatment of venous and arterial thromboembolism.

Heparin's onset of action is immediate. It is most often used in acute conditions, and must be given parenterally.

Apparent Uses of Heparin Therapy

Although low molecular weight heparin has become the treatment of choice for patients with venous thromboembolism, unfractionated heparin (UFH) by continuous intravenous infusion is still commonly used in patients with massive pulmonary embolism, for patients who are unstable or may require interventional procedures or thrombolysis. Furthermore, intravenous heparin is commonly used for patients with cardiovascular disease, following angioplasty, coronary artery bypass surgery, thrombolysis or peripheral vascular surgery. Intravenous heparin is favoured in the above cases because the effect can be rapidly reversed by discontinuing the intravenous infusion or, where necessary, administering protamine sulfate.

Monitoring Heparin Therapy

Please see TIGC Establishing Therapeutic Range for Heparin clinical guide. The aPTT is used to monitor the effects of heparin treatment. aPTT reagents vary considerably in their sensitivity to heparin, therefore your laboratory should establish a therapeutic range locally. However, 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.

Practical Guidelines

Do baseline CBC, PT, aPTT, plt count

- Give IV Bolus 5,000 U infusion or 80 U/kg,
- start infusion with initial rate of at least 1,300 U/hr or 32,000 U/24 hrs, or 18 U/kg/hour
- Monitor aPTT every 6 hours until therapeutic range is achieved (refer to Establishing Therapeutic Range of Heparin).
- Thereafter monitor aPTT and platelet counts daily

Dosage Adjustments

The use of a heparin dosing nomogram is encouraged because it helps achieve and maintain the aPTT in the therapeutic range efficiently. Two examples of heparin dosing nomograms which could be used in de novo patients are shown below.

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Bolus
5,000 U is given IV followed by IV infusion.

Maintenance

IV infusion

APTT S	Rate Change ml/h	Dose Change U/24 Hep	Additional Action & Monitoring
≤45	+6	+5760	Repeat APTT in 4-6 hrs
46-54	+3	+2880	Repeat APTT in 4-6 hrs
55-85	0	0	None***
86-110	-3	-2880	Stop heparin for 1 h. Repeat APTT 4-6 hours after restarting heparin
>110	-6	-5760	Stop heparin for 1h. Repeat APTT 4-6hrs after restarting heparin
*** During the first 24hrs, repeat APTT in 4-6hrs. Thereafter, the APTT is done once daily, unless subtherapeutic.			

Adapted from Hull et al. Arch Intern Med 1992; 152: 1589-1595.

Maintenance

IV infusion – weight -based nomogram

Initial dose	80 U/Kg bolus, then 18 U/kg/hour
APTT, <35s (<1.2 x control)	80 U/Kg bolus, then 4 U/Kg/hour
APTT, 35-45s (1.2-1.5 x control)	40 U/Kg bolus, then 2 U/Kg/hour
APTT, 46-70s (1.5-2.3 x control)	No change
APTT, 71-90s (2.3-3.0 x control)	Decrease infusion rate by 2 U/Kg/hour
APTT, >90s (>3.0 x control)	Hold infusion 1 hour, then decrease infusion rate by 3 U/Kg/hour
Key: APTT: activated partial thromboplastin time; s: seconds	

Adapted from Raschke et al, Ann Intern Med 1993; 199: 874-881.

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- These nomograms do not apply to patients following thrombolysis.
- The concentration of heparin used in these nomograms was 20,000 units per 500 ml sol.
- Local modification may be necessary depending on the local aPTT reagent used.
- aPTT should be monitored every 4-6 hours during the first 24 hours, and daily thereafter unless it is sub-therapeutic.

Overlap with Warfarin

In most cases, warfarin can be started on the same day as heparin. Warfarin and heparin should overlap for at least 5 days or until the INR value is within therapeutic range for two consecutive days before heparin is discontinued.

	Heparin					
	Warfarin					
Day	0	1	2	3	4	5

Pregnancy

Heparin is still used for the management of thromboembolism during pregnancy although it has been largely replaced by LMWH. Therapeutic heparin can be achieved by subcutaneous injections twice daily. Heparin should be stopped at the first sign of labour. Secondary prevention in the post-partum period can be achieved with warfarin or SC heparin and is recommended for at least 6 weeks after delivery. Women can breast feed while being treated with warfarin therapy.

The management of pregnant women who have previously had a DVT or PE is controversial. Heparin 5,000 q12h subcutaneously or heparin adjusted to produce a heparin level of 0.1-0.2 U/ml throughout pregnancy are recommended for high risk patients. The use of LMWH will be discussed in the guideline on pregnancy.

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Adverse Effects

Bleeding is the most common adverse effect of heparin. Therapeutic doses of heparin will not affect the PT. However, if high doses of heparin are inadvertently flushed into a patient, both the PT and the aPTT will be prolonged. As an example, patients on dialysis who have up to 10,000 units of unfractionated heparin used in the catheter to maintain patency, on occasion this can be inadvertently flushed into the patient and cause significant hemorrhage. Therefore, in hospitalized patients, particularly patients in Intensive Care and on Dialysis Units, if they have unexplained hemorrhage, it is always reasonable to check the platelet count, PT and PTT. And if both PT and PTT are prolonged, it is important. If major bleeding occurs, discontinue heparin. The administration of 10-20 mg of Protamine Sulfate IV (over at least 5 minutes) may be used to neutralize heparin's effects.

With less critical bleeding, doses should be adjusted and underlying causes investigated. Osteoporosis is a serious, but less common side-effect associated with prolonged use of high doses of heparin. Three months of heparin treatment with moderate dose (20,000 U/ 24 hrs) will most likely not be associated with clinically significant osteoporosis. Thrombocytopenia – platelet count reduction is, in most cases, asymptomatic but may be associated with life-threatening or fatal arterial or venous thrombosis. Hyperkalemia is a rare complication of unfractionated heparin.

A small percentage of patients treated with heparin will develop serious thrombocytopenia. It usually begins between 4 and 7 days after commencing therapy. Should it occur, stop all sources of heparin and, if necessary, alternative treatment with Danaparoid or Lipirudin followed by warfarin may be used. Argatroban became available in 2002. Platelet count usually return to baseline within 4 days of stopping therapy.

References:

1. Bates et al. Chest 2004; 126(3): 627S-644S.
2. Hirsh et al. Chest 2004; 126(3): 188S-203S.
3. Chest 2004; 126(3): 401S-428S.
4. Hull et al. Arch Intern Med, 1992; 152: 1589-1595.
5. Raschke et al. Ann Intern Med 1993; 119: 874-881.
6. Warkentin TE, Greinacher A, et al. Chest 2004 126(3): 311S-337S