AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
1999

Heparin: How, When, Why and What Weight?

Low molecular weight heparin SC is starting to replace classic IV heparin therapy. Expert faculty will explain the latest details on how, when, and why we use this drug on our patients. In addition, there will be a review of disorders requiring the initiation of heparin in the emergency department.

- Recognize the latest developments in the use of low molecular weight heparin.
- Discuss the details of how, when, and why you would use this drug, as well as its complications.
- Recognize the emergent role of heparin in various thrombotic and embolic disorders.

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FACULTY

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I. Course Description

Emergency physicians diagnose and treat acute coronary syndromes and venous thrombotic disease on a regular basis. Recent advances in anticoagulation therapy have increased the potential to improve the short and long term welfare of these patients.

The clinical indications for anticoagulation will be discussed. The latest developments in selection, dosing, and combinations of the various anticoagulants will be presented. Implications for patient outcome, patient disposition and costs of health care will be described.

II. Objectives

At the conclusion of this course the participant will be able to discuss the latest developments in the use of low molecular weight heparin, describe how, when, and why to use this drug, as well as it's complications, and recognize the emergent roll of heparin in various thrombolytic and embolic disorders.

III. Course Outline

A. Introduction

Blood clot formation helps sustain life by preventing undesirable, and potentially fatal, bleeding. In the absence of trauma, under normal physiologic conditions blood components do not interact with the intact vascular endothelium. However, when blood is exposed to disrupted or abnormal vascular surfaces, a cascade of biochemical events occurs. There is a rapid deposition of platelets, red cells, white cells and fibrin which creates the initial hemostatic plug. Thrombosis is a dynamic process in which clot formation and dissolution occur essentially simultaneously. The balance between these processes determines the extent of thrombus formation.

"White thrombi" form in high pressure arteries where platelets adhere to abnormal epithelium. "Red thrombi" are loosely packed networks of erythrocytes and fibrin, with islands of platelets, primarily in the venous circulation. Antithrombin anticoagulants, such as heparin and warfarin, are the mainstays of the treatment of venous thrombosis. Antiplatelet therapies are the mainstay of treatment of arterial thromboses. Increasingly complex, and efficacious, combinations of different classes of anticoagulants are being delineated for the treatment of conditions including acute myocardial

infarction, unstable angina, atrial fibrillation, venous thrombosis, pulmonary embolism, TIA and ischemic stroke, and the prevention of thrombosis associated with surgical procedures, immobility, and percutaneous coronary intervention.

B. Abbreviations

UFH = Unfractionated heparin
LMWH = Low molecular weight heparin
NQMI = Non Q wave myocardial infarction
UA = Unstable angina
GP IIb/IIIa I= Glycoprotein IIb/IIIa inhibitor
DVT = Deep venous thrombosis
PE = Pulmonary embolism
PCI = Percutaneous coronary intervention

C. Clinical Indications for Emergency Anticoagulation

1. DVT and PE

Heparin (UFH or, preferably, LMWH [Enoxaparin]) is the mainstay of pharmacologic treatment for DVT and hemodynamically stable patients with PE. Unstable patients with PE should be considered for thrombolytic therapy in addition to heparin therapy or for emergency thrombolectomy.

Oral warfarin should be started on hospital day 1. Heparin should be continued for 4-5 days (until warfarin therapy has resulted in a PT approximately 1.5 times control or an INR of 2-3.)

2. Coronary syndromes

a. Angina

Aspirin po or pr, at least 81mg, if allergic may give ADP platelets receptor inhibitor (ticlopidine or clopidogrel).

b. Unstable Angina

Heparin for 48 hours in addition to aspirin.

c. Acute Myocardial Infarction

There is reasonable evidence that heparin increases vessel patency when selective thrombolytic agents (i.e. tPA) are given.

d. Percutaneous coronary intervention (PCI)

All patients who are being directed from the emergency department to the catheterization lab

should receive both heparin and a GP IIb/IIIa inhibitor in addition to aspirin.

3. Atrial fibrillation

Patients who may have been in atrial fibrillation for more than 48 hours should be anticoagulated prior to cardioversion. Patients in chronic atrial fibrillation are usually anticoagulated because the chance of hemorrhage is outweighed by the benefits of a reduced incidence of a stroke and systemic embolization.

4. Ischemic Stroke

The efficacy of heparin is not well established and it is not recommended for routine use in patients with new, completed CVA's. Heparin therapy is considered for CVA patients who have no evidence of hemorrhage on CT if they have a minor stroke, evolving clinical signs, a stroke caused by a large vessel thrombosis, or a cardioembolic cause for their CVA.

D. Low Molecular Weight Heparin (LMWH)

1. Advantages of LMWH

LMWHs are a new class of anticoagulant that has pharmacokinetics, and biologic advantages over UFH including:

- convenient subcutaneous injection without laboratory monitoring
- lower incidence of heparin induced thrombocytopoenia.

Studies of LMWH in DVT and/ or PE have shown it to be **at least as effective as UFH** (a statistically non-significant reduction in recurrent venous thromboembolism of approximately 25%, a statistically significant improvement in venographic outcome). LMWH proved to be **safer than UFH** (a statistically significantly lower incidence of serious hemorrhage and a lower incidence of death).

(See table 1.)

Table I: LMWH vs. UFH

	Unfractionated Heparin	LMWH
Molecular wt. (daltons)	15,000 - 30,000	3,000 - 9,000
Anti-Xa: Anti-thrombin	1	2 - 4
Bioavailability	~30%	~ 90%
Major hemorrhage	~ 2%	~ 1%
Cost of drug	less	more
Cost of care	more	less
Route	IV, IM, SQ	SQ
Dose	80 u/kg IV bolus then 18 u/kg/hr IV infusion	1 mg/kg SQ q12hr (enoxaparin)

Outpatient Treatment of DVT

LMWH therapy can be administered on an outpatient basis since intravenous access is not necessary and there are no blood tests to be monitored. It is important that the diagnosis be made definitively (by doppler ultrasound or venograph) and that none of the following exclusionary criteria are present.

- inability to provide a informed consent
- geographic inaccessibility
- potential for medication non-compliance
- inability to afford cost of drug
- pregnancy
- hereditary or acquired disorders
- active bleeding (PUD less than six weeks, GI, GU)
- concomitant medical problems (i.e. acute CHF, decreased creatinine clearance, increased LFT's)
- hypoxia
- suspected PE
- recent LP or spinal anesthesia

F. Conclusion

Emergent heparinization is indicated to treat DVT, PE, UA, NQMI, acute MI that is receiving thrombolytic therapy, pre-existing atrial fibrillation prior to cardioversion, and any patient requiring PCI. The major complications are related to bleeding, usually secondary to thrombocytopoenia. LMWH is now available and appears to be safer and at least as effective as UFH. Enoxaparin (1mg per kg q12 hr SQ)is approved for the treatment of UA, NQMI, and DVT with or without PE. Outpatient treatment of DVT is now possible in carefully selected cases.

Table 2:
Emergency Anticoagulation Treatment Summary

Condition	Antithrombin Rx		Antiplatelet Rx		Additional Possibilities
	UFH	LMWH	Aspirin	GP IIb/IIIa I	
DVT +/- PE	Yes: IV (80 u/kg then 18u/kg/hr)	Yes: SQ (enoxaparin 1 mg/kg q 12)	No	No	Unstable or phegmasia dolens: thrombolysis or thrombolectomy
Unstable CAD (UA or NQMI)	Yes IV (80 u/kg then 18 u/kg/hr)	Yes: SQ (enoxaparin 1mg/kg q12)	Yes: PO 2-4 x 81mg (not enteric-coated)	Yes: IV* Especially if PCI planned	Nitrates, beta-blockers Ca++ channel blockers, PCI
Acute MI (with ST elevation)	Yes: IV (80u/kg then 18u/kg/hr)	?	Yes: PO 2-4 x 81 mg (not enteric-coated)	No	Thrombolysis or PCI or CABG. Beta-blockers, ACE inhibitors
Atrial fibrillation	Consider	Consider	Yes: PO 325 mg qd	No	Warfarin, cardioversion
Ischemic CVA (neg. CT and evolving clinical signs)	Consider	?	Consider	No	Thrombolysis
PCI	Yes	Consider	?	Yes*	

* GPIIb/IIIa I doses

1) Abciximab for acute coronary syndromes, with planned PCI, 0.25 mg/kg IV bolus than 0.125 mcg/kg/min IV drip for 12 hr. Must be given with heparin.
2) Eptifibatide for acute coronary syndromes dose 180 mcg/kg IV bolus the 2 mcg/kg/min IV drip up to 72 hr.
3) Tirofban for acute coronary syndromes dose 0.4 mcg/kg/min IV for 30 min then o.l mcg/kg/min IV

IV. References

Pomes SR. Quest T. Booker G. Anticoagulation and antiplatelet therapy in emergency medicine. *Emergency Medicine Reports*. 19 (24 & 25): 257-280, 1998, Nov. 23 and Dec. 7. [Excellent review for the practicing emergency physician. SP]

Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficiency and safety of subcutaneous enoxaparin in non-Q-wave coronary events study group. *N Engl J Med* 1997; 337:447-52.

PRISM study investigators. A study of aspirin plus tirofiban versus aspirin plus heparin for unstable angina. *N Engl J Med* 1998; 228:1498-505

PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998, 339:436-43.

CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997; 349: 1429-35.

Campbell RW, Wallentin L, Verheugt FW, et al. Management strategies for a better outcome in unstable coronary artery disease. *Clin Cardiol* 1998; 21: 314-22.

Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation,* 1998; 97: 1195-206.

Yeager BF, Matheny SC. Low-molecular-weight heparin in outpatient treatment of DVT. *American Family Physician*. 59(4):945-52, 1999 Feb 15.

Purcell H, Fox KM. Current roles and future possibilities for low-molecular-weight heparins in unstable angina. *European Heart Journal*. 19 Suppl K:K18-23, 1998 Sept.

Hirsh J. Warkentin TE, Raschke R, Granger C, Ohman EM, Dalen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety.
Chest. 114(5 Suppl):489S-510S, 1998 Nov.

The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657-62.

Doroux P, A Collaborative European Multicentre Study: a randomized trial of subcutaneous low molecular weight heparin (CY216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost*. 1991;65:251-256.

Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med*. 1992; 326:975-928.

Koopman MMW. Et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996;334:682-7.

Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; 334:677-681.

Simonneau G, Sors H, Charbonnier B, Page Y, Laaban J-P, Azarian R, et al. For the THESEE Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;337:663-9.

Antman. TIMI 11B. Enoxaparin versus unfractionated heparin for unstable angina or non-Q-wave myocardial infarction: a double-blind, placebo-controlled, parallel-group, multicenter trial. Rationale, study design, and methods. Thrombolysis in Myocardial Infarction (TIMI) 11B Trial Investigators. *American Heart Journal.* 13596 Pt 3 Su):S353-60, 1998 Jun.
The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban and aspirin plus heparin for unstable angina. *N Engl J Med*, 338;21:1498-1505, May 21, 1998.