TRANSFUSION MEDICINE UPDATE

Institute For Transfusion Medicine June, 1996

LOW MOLECULAR WEIGHT HEPARIN

Franklin A. Bontempo, M.D., Medical Director and Andrea Cortese Hassett, Ph.D., Scientific Director, Coagulation Laboratory, The Institute For Transfusion Medicine, Pittsburgh, PA

Introduction: The development of low molecular weight heparin (LMWH) represents a significant advance in the care of some patients requiring anticoagulant therapy. LMWH probably has a stronger antithrombotic effect and a lesser anticoagulant effect than standard unfractionated heparin (UFH) and does not usually require monitoring. LMWH may also allow more patients to be treated out of the hospital for uncomplicated thrombotic events.

Biochemical Differences in UFH and LMWH: Standard UFH is a heterogeneous mixture of polysaccharides ranging in molecular weight from 3,000 to 30,000 daltons. LMWHs are fragments of commercial grade heparin produced by either chemical or enzymatic depolymerization, a process that yields chains with mean molecular weights of 4,000 to 6,000 daltons. The longer chain UFH exerts its anticoagulant effect through its interaction with antithrombin (AT) inhibiting both thrombin and the active form of Factor X (Factor Xa). The shorter chain LMWH is unable to simultaneously bind to antithrombin and thrombin resulting in the preferential inactivation of Factor Xa only.

Low molecular weight heparin has several potential and demonstrated clinical advantages to standard heparin. First, LMWH may result in fewer bleeding complications due to a less pronounced effect on platelet function and vascular permeability. Second it may be more effective as an anticoagulant, because unlike standard heparin, it can inactivate platelet-bound factor Xa and resist inhibition by platelet factor 4, which is released during clotting. Third LMWH has more favorable bioavailability and pharmacokinetics. It is completely absorbed, has a longer plasma half-life (2- 4 times that of UFH) and binds less readily to plasma proteins, macrophages, and endothelial cells, resulting in a more stable and predictable anticoagulant response than UFH. Thus LMWH can be given subcutaneously, in one or two standard doses per day without monitoring. Neither LMWH nor standard UFH crosses the placenta.

Clinical Advantages Of LMWH: LMWHs have been evaluated in a number of randomized clinical trials and have been shown to be safe and effective anticoagulants.

Prophylactic Use: The greatest experience by far has been obtained in the prevention of venous thrombosis in high risk patients. In general surgery, LMWH is at least as effective in DVT prevention as UFH; overall, bleeding complications are similar except for a slight increase in post-operative wound hematomas with LMWH. In orthopedic surgery, most studies show that LMWH, given subcutaneously post-operatively is superior to UFH for hip surgery and is as effective as warfarin without the need to monitor the level of anticoagulation.

Treatment Of Established Thromboses: LMWHs have been compared with standard UFH for the treatment of established venous thrombosis in a number of large studies. Overall, LMWH showed greater efficacy in reduction of thrombus size than standard UFH. Two recent well-designed trials have clearly shown that LMWH followed by warfarin in out-patients was equivalent to treatment of in patients with UFH and warfarin for uncomplicated, out-of-hospital acquired deep venous thrombosis (DVT). These studies may lead to routine treatment of many patients with DVT as outpatients.

Heparin-Induced Thrombocytopenia (HIT): Initially it was hoped that the use of LMWHs would not be complicated by HIT, however this expectation has not been realized. Although HIT probably occurs twice as often with UFH as with LMWH, properly designed clinical studies have not been investigated. Unfortunately, once HIT is present, switching to LMWH is unlikely to result in a resolution of this complication and is not recommended.

Monitoring: Because of the reliability of the dose response of LMWH, standard prophylactic doses of LMWH and outpatient treatment of uncomplicated DVT do not usually require monitoring. When treating patients with complicated venous thrombosis, i.e. those with liver disease, thrombocytopenia, other coagulation disorders, or a high risk of falling, monitoring should be done using the anti-factor Xa assay. These patients should be kept within the therapeutic range of 0.3 - 0.7 anti-Xa IU/mL. Since LMWH does not inhibit thrombin, the APTT is not prolonged and cannot be used for monitoring.

Dosing: Numerous LMWH are available worldwide and each should be considered distinct drugs. Two LMWH have been released in the U.S., Enoxaparin and Fragmin. For surgical patients the prophylactic dose for Enoxaparin is 30 mg subcutaneously BID, usually given 12-24 hours post-operatively. For patients with established clots, the dose for Enoxaparin is 1 mg/kg subcutaneously BID.

Fragmin has primarily been evaluated for prophylaxis in general surgery at a dose of 2500 units subcutaneously once per day because of its longer half-life.

Disadvantages Of LMWH: The greatest disadvantage of LMWH is its high cost relative to UFH. Less frequent dosing and monitoring along with the possibility of outpatient dosing must be taken into account when cost is considered.

References:

Hirsh, J. and Levine, M.N. Blood 1992; 1-17.

Colwell, C.W. et al. J Bone Joint Surg. 1994; 3-14.

Levine, M. et al. N Eng J Med 1996; 677-681.

Leclerc, J.R. et al. An Int Med 1996; 619-626.

Copies of Transfusion Medicine Update can be obtained by calling Deborah Small at (412) 622-7254; or by e-mail: dsmall@itxm.org.■

For your interest, this monthly TMU now appears on the internet at the following address: "http://www.rla.org/html/update.html"

Central Blood Bank's User's Guide to Products and Services has been revised and updated. The Guide is a comprehensive reference containing important information on blood components, commercial products, special donations and procedures, apheresis, laboratory and clinical services, and the product management and testing policies of CBB. Please contact Barbara Adams (412) 456-1909, if you are interested in receiving a copy.