

Pediatric Pharmacotherapy

A Monthly Newsletter for Health Care Professionals
Children's Medical Center at the University of Virginia

Volume 3 Number 6

June 1997

Using Low-Molecular-Weight Heparins in Infants and Children Marcia L. Buck, Pharm.D.

The medication we know as heparin is actually a heterogeneous mixture of polysaccharides derived from beef or pork livers. Although the exact mechanism for heparin's antithrombotic properties is not known, it is believed to act by binding to antithrombin III. The heparin-antithrombin III complex inhibits the activity of numerous enzymes in the clotting cascade, including factors II_a (thrombin), IX_a, X_a, XI_a, and XII_a.¹⁻⁵ In addition, heparin induces release of other endogenous antithrombotic substances, such as tissue factor pathway inhibitor and tissue plasminogen activator.³

Low-molecular weight heparins (LMWHs) are fragments of conventional porcine-derived heparin. These products were developed in an effort to provide more selective inhibition of enzyme function and reduce adverse effects. Fragmentation of heparin produces products which maintain activity against factor X_a and release antithrombotic factors, but have significantly less activity against factor II_a.¹⁻³ As a result, treatment with LMWHs provides antithrombotic effects with less anticoagulant effect, lessening the risk of hemorrhage.

Products Available

There are currently three LMWH products on the market in the United States: enoxaparin (Lovenox[®]; Rhone-Poulenc Rorer), dalteparin (Fragmin[®]; Pharmacia&Upjohn), and ardeparin (Normiflo[®]; Wyeth-Ayerst).^{2,6,7} Several more LMWHs are under investigation. The LMWHs differ in pharmacologic activity (degree of anti-II_a and anti-X_a effect) and pharmacokinetic properties (Table 1).^{2,3} Clinicians should be aware that LMWH products are **not** interchangeable.

Table 1. Comparison of heparin and LMWHs

<i>Drug</i>	<i>Average MW^a (mol)</i>	<i>Anti-X_a: Anti-II_a Ratio</i>	<i>Half-life (min)</i>
heparin	15,000	1:1	30-180
enoxaparin	4,500	2.7:1	180-360
dalteparin	5,000	2.0:1	180-300
ardeparin	6,000	2.0:1	200

^a molecular weight

Enoxaparin

In 1993, enoxaparin became the first LMWH available in the United States. It has achieved widespread use for the prevention of deep vein thrombosis (DVT) and its complications following surgery. Several clinical trials have demonstrated substantial cost savings when LMWHs have been compared to heparin therapy, based on a reduction in hospitalization and laboratory monitoring costs.⁸

Enoxaparin is administered by subcutaneous injection. The recommended adult dose is 30 to 40 mg given twice daily. It is available in prefilled syringes, designed to allow patient self-administration at home.

Dalteparin

Dalteparin was approved by the Food and Drug Administration (FDA) in 1995. Compared to enoxaparin, it offers a longer elimination half-life than enoxaparin, allowing once daily dosing. Like enoxaparin, dalteparin is administered subcutaneously, using prefilled syringes. The dose, however, is based on units of anti-X_a activity. The recommended adult dose for dalteparin is 2,500 to 5,000 anti-factor X_a units given once daily.²

Like enoxaparin, dalteparin has been studied in a variety of patient populations. In addition to

prophylaxis for DVT following surgery, these agents have been studied in patients at risk for thrombosis due to hemodialysis, coronary artery disease, stroke, spinal cord injury, or severe trauma. LMWHs also been shown to be effective in treating established thromboses.¹⁻⁵

When comparing the rate of thrombosis development or complications, LMWHs have demonstrated similar efficacy as heparin and significantly better results than placebo in controlled clinical studies. At this time, there are no clinical trials directly comparing enoxaparin and dalteparin.

Ardeparin

Ardeparin is the newest of the LMWHs, having been approved by the FDA on May 23, 1997. Unlike the other agents in this class, it is dosed based on patient weight. The recommended adult dose is 50 anti-X_a units/kg administered every 12 hours.⁶

Use of LMWHs in Infants and Children

Few studies have been performed in the pediatric population. In 1991, Broyer and colleagues⁹ studied the efficacy of enoxaparin in preventing thrombosis in children following renal transplantation. Of the 42 children studied, only one patient (1.5%) developed thrombosis. The authors compared this to a rate of 12.3% among untreated historical controls.

Massicotte and coworkers conducted a dose finding study of enoxaparin in 25 children, ranging from newborn to 17 years.¹⁰ All patients had previously been treated with heparin. Twenty-three of the children were given 1 mg/kg every 12 hours subcutaneously for treatment of established thromboses. The two remaining children had congenital heart disease and were given enoxaparin as prophylaxis at half the above dose.

Dosages were adjusted to maintain an anti-Xa level between 0.5 and 1.0 units/ml, measured four hours post-dose. The patients less than two months of age required dose escalation to an average of 1.64 mg/kg. The remaining older infants and children did not require dosage adjustment. The median length of therapy was 14 days; however, three of the children were treated for more than 2 months. There were no new thrombotic events during treatment with enoxaparin. Two patients with previously diagnosed gastrointestinal ulcers bled during treatment and required transfusion.¹⁰

Enoxaparin has also been used successfully to prevent clot formation in children undergoing hemodialysis and in patients following liver transplantation.¹¹⁻¹³

At UVA, enoxaparin has been used for the prevention of deep vein thrombosis in non-ambulatory children following severe trauma or spinal cord injury, prevention of thrombosis in children receiving chemotherapy, and for treatment of coronary thrombosis in a premature neonate.

Dalteparin use has been reported in two publications.^{14,15} In 1993, Fijnvandraat and coworkers reported the results of a small crossover, blinded, dose finding study of dalteparin in six children receiving hemodialysis.¹⁴ The children ranged between 8 and 16 years of age. A dosage regimen consisting of a bolus of 24 units/kg followed by an infusion of 15 units/kg/hr throughout dialysis prevented clot formation without causing bleeding complications.

In a letter to the editor in *Lancet*, Dzumhur and colleagues described the use of dalteparin in a neonate with DVT following cardiac catheterization at two weeks of age.¹⁵ These authors used a dosage of 100 units/kg given subcutaneously twice daily for two days, then changed the regimen to 200 units/kg given once daily. The patient was treated for one week in the hospital and discharged. Therapy was continued for a total of 12 weeks, with an ultrasound of the leg at that time demonstrating elimination of the clot.

Adverse Effects

The primary advantage of the LMWHs is the reduced incidence of hemorrhage compared with heparin. In a comparison trial following hip replacement, 4% of the enoxaparin-treated patients experienced a major bleeding episode, defined as a decrease in hemoglobin by > 2 g/dl or a transfusion. This was the same rate as in the placebo group. Six percent of patients treated with heparin had a major bleeding episode.²

For dalteparin, the incidence of post-operative transfusions following abdominal surgery was 5.7% versus 7.9% with heparin therapy adjusted by partial thromboplastin time (aPTT) values.²

Hemorrhagic complications with LMWHs should be treated with a slow injection of 1% protamine sulfate. To neutralize the anticoagulant effect, 1

mg of protamine should be administered for every 1 mg of enoxaparin or 100 units of dalteparin that were given. If needed, a second injection of protamine may be given using half of the initial dose. Clinicians should keep in mind, however, that the anti-factor X_a activity of these agents is never fully neutralized by this treatment. Administration of exogenous blood products may be required.^{2,4}

All LMWHs have also been associated with the development of thrombocytopenia. Heparin is reported to cause thrombocytopenia in up to 30% of patients treated. The incidence of this adverse effect appears to be approximately one to two percent in patients treated with LMWHs, although the true incidence may change as more patients are treated.²

Patients with a history of heparin-induced thrombocytopenia may be at greater risk when treated with LMWHs and should be closely monitored. In a case report from France, an infant who developed thrombocytopenia while being treated with heparin demonstrated the same response to treatment with nadroparin, a LMWH available in Europe. Platelet aggregation tests were positive for both drugs.¹⁶

Up to five percent of patients may experience local effects, such as pain, erythema, and hematoma formation, at the site of injection. Cases of skin necrosis at the site of injection have also been documented during clinical trials.²

Allergic reactions, including anaphylaxis, have been reported in patients treated with LMWHs, but appear rare. LMWHs are contraindicated in patients with known allergies to heparin or pork products.²

It is estimated that two to four percent of patients will develop transient increases in liver transaminases while being treated with LMWHs. This reaction appears to be reversible with discontinuation of therapy. Progression to hepatic dysfunction has not been reported at this time.^{2,4}

Patient Monitoring

Unlike heparin, LMWHs have little effect on aPTT. As a result, routine monitoring of clotting factors is not required for most patients. Anti-X_a activity may be measured as a marker of antithrombotic activity for these compounds, but is not typically used for patient management. If

more intensive monitoring is desired, the anti-X_a level should be maintained between 0.5 and 1.0 units/ml for patients with an established thrombosis. This range has been shown to optimize antithrombotic activity while avoiding adverse effects. Lower levels are likely adequate for prophylaxis, but further research is necessary in the pediatric population.¹⁰

In those patients receiving high-dose therapy or those treated for more than 10 days, a complete blood count, including platelet count and hematocrit, should be evaluated periodically to identify risk factors for hemorrhage.²

Cost of Therapy

A comparison of heparin therapy versus use of a LMWH illustrates the complexity of evaluating cost data. Comparison of the cost to purchase these drugs clearly favors heparin (Table 2); however, the indirect costs involved with therapy must also be considered.¹⁷ As mentioned previously, the LMWHs have been shown to be cost effective when days of hospitalization and laboratory monitoring are considered.⁸

Table 2. Acquisition Costs based on University Health-System Consortium Data^a

<i>Drug</i>	<i>Cost per dose</i>	<i>Cost per week</i>
Heparin	\$ 0.61	\$ 12.81
Enoxaparin	\$12.11	\$168.56
Dalteparin	\$10.92	\$ 73.50

^a Data on ardeparin are not yet available

Pediatric patients gain no cost reduction from the use of smaller dosages. The prefilled (single dose) syringes do not contain preservatives, so the remaining drug must be discarded.

In summary, the LMWHs appear to offer a safer alternative to heparin therapy and the potential for outpatient management of some conditions. More research is needed to establish the role of these agents in the treatment of infants and children.

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Pharmacology Literature Review

Ketorolac Review

The use of ketorolac, a non-steroidal anti-inflammatory analgesic, is reviewed in the pediatric postoperative population. The authors discuss basic pharmacology, as well as pertinent pharmacokinetic studies, reports of adverse effects, and the clinical studies published to date. This article would be a useful addition to the files of any pediatric health care provider. Forrest JB, Heitlinger EL, Revell S. Ketorolac for postoperative pain management in children. ***Drug Safety* 1997;16:309-29.**

Treatment of Childhood Hypercholesterolemia

The author of this review discusses the problems inherent in the consensus recommendations published by several groups on this topic. The

available studies on dietary management and adjunctive therapy are reviewed, as well as the use of bile acid-binding resins and HMG CoA reductase inhibitors. Tonstad S. A rational approach to treating hypercholesterolemia in children. ***Drug Safety* 1997;16:330-41.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/6/97:

1. Calcipotriene cream and ointment (Dovonex®) were added to the formulary for the treatment of psoriasis. Calcipotriene is a synthetic analog of vitamin D₃ and regulates skin cell production.

2. Troglitazone (Rezulin®) was added to the formulary for the treatment of resistant Type II diabetes. This is a unique drug, in that it reduces serum glucose levels without increasing insulin secretion. It is restricted to use only with approval from the endocrinology service.

3. Papain-urea debriding ointment (Accuzyme®) was added to the formulary. This preparation is used for skin debridement, primarily in patients with extensive wounds or burns. It does not affect viable tissue.

4. The issue of generic substitution for carbamazepine was discussed. The committee decided that only the Tegretol® brand will be carried by the University of Virginia pharmacies. Although there are less expensive brands, there have been case reports of both subtherapeutic and supratherapeutic serum concentrations resulting from their use.

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