



Pharmacy

November/December 1997

Update

Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196

Charles E. Daniels, Ph.D.
Chief, Pharmacy Department

Editor
Karim Anton Calis, Pharm.D., M.P.H.
Coordinator, Drug Information
Service, and Endocrinology Clinical
Pharmacy Specialist
kcalis@nih.gov

Associate Editor
Amy M. Heck, Pharm.D.
Specialized Resident in Drug
Information Practice and
Pharmacotherapy
aheck@nih.gov

In This Issue

- **Danaparoid (Orgaran™): A Brief Review**
- **Clonidine Hydrochloride Injection (Duraclon®): A Brief Review**
- **Did You Know . . .**
- **Formulary Update**

Danaparoid (Orgaran™): A Brief Review

Danaparoid, a "heparinoid," was approved by the FDA in January of 1997 for prophylaxis of post-operative deep-vein thrombosis (DVT) and pulmonary embolism (PE) associated with elective hip replacement procedures. Compared to low-molecular-weight heparins (LMWH), danaparoid has been reported to cause less platelet activation and have less cross reactivity with standard heparin in causing late-onset heparin-induced thrombocytopenia/thrombosis syndrome (HITTS).

Pharmacology: Danaparoid is a mixture of glycosaminoglycans consisting of heparan sulfate (~84%), dermatan sulfate (~12%), and chondroitin sulfate (~4%) derived from porcine intestinal mucosa. It anticoagulates plasma by reducing thrombin formation (by inhibiting factor Xa) and thrombin (factor IIa) activity. The anti-Xa: anti-IIa activity ratio for danaparoid is approximately 28:1.

Pharmacokinetics: Danaparoid reaches peak plasma concentrations in four to five hours after subcutaneous administration. The estimated bioavailability of subcutaneously administered danaparoid is between 89% to 100%. Danaparoid is eliminated renally with a clearance of 0.36 L/h and a mean apparent volume of distribution of 8-9 L/kg. Doses of danaparoid have ranged between 400 to 6400 anti-Xa units per day without any correlation between plasma concentrations (0.18 - 0.44 anti-Xa units/mL) and clinical efficacy. The anti-Xa unit activity of danaparoid is not interchangeable (unit for unit) with doses of either heparin or LMWH.

Selected Clinical Studies: A European multicenter, double-blind, placebo-controlled trial evaluated danaparoid in 196 patients undergoing elective hip replacement surgery. Patients received danaparoid for 7 to 14 days post-operatively. The incidence of DVT was 15% in danaparoid-treated patients compared to 57% incidence in the placebo-treated group.

The efficacy and safety of high- and low-dose regimens of danaparoid compared to continuous intravenous infusion of unfractionated heparin was evaluated by De Valk. Two hundred and nine patients were randomly assigned to receive either 1250 units of danaparoid as an intravenous loading dose followed by 1250 units administered subcutaneously twice a day, 2000 units of danaparoid as an intravenous loading dose followed by 2000 units administered subcutaneously twice a day, or a 2500 unit intravenous loading dose of unfractionated heparin followed by a dose-adjusted continuous infusion. In the patients receiving 2000 units of danaparoid twice a day, there was a significant decrease in the incidence of recurrence or extension of thromboembolism (13%) compared to patients on continuous infusion of unfractionated heparin (28%). The incidence of major and minor bleeding events was similar in all treatment groups.

Ramakrishna and colleagues studied 15 patients with the clinical syndrome of heparin-induced thrombocytopenia/thrombosis caused by an immune response to heparin and a platelet protein. *In vitro* cross reactivity occurred between unfractionated heparin and a LMWH in 40% (6/15) of patients, whereas only two patients showed weak cross-reactivity with danaparoid. In a study by Keeling and colleagues, 11 of 12 serum samples from patients with HITTS reacted with LMWH, but there was no cross-reactivity with danaparoid in any of the cases. In another series, 230 patients with HITTS were safely treated with danaparoid instead of heparin; 93% of the patients were considered to have been successfully anticoagulated.

Independent of its role in HITTS, heparin often causes mild degrees of *in vitro* platelet activation even in normal individuals. Danaparoid, however, has been reported to have a very low propensity to initiate platelet activation. Burgess and associates compared the platelet proaggregating and potentiating effects of unfractionated heparin, two different LMWH products, and danaparoid in both normal volunteers and patients treated in intensive care units. Although all four anticoagulants potentiated platelet aggregation in normal volunteers and ICU patients, danaparoid had the least effect.

Adverse Effects: The most common adverse effect reported with danaparoid is pain at the injection site (13.7%), commonly described as mild tingling. Unlike unfractionated heparin and the LMWH, delayed onset thrombocytopenia has rarely occurred in patients receiving danaparoid. Other adverse effects reported include generalized pain (8.7%), fever (7.3%), nausea (4.1%), urinary tract infection (4%), constipation (3.5%), and rash (2.1%). The risk of bleeding is a concern with all antithrombotic therapies. When danaparoid was compared to placebo and other active treatments, no increased risk of bleeding was found either during operative procedures or post-operatively. Due to its lack of efficacy, protamine is not recommended as an antidote for bleeding complications associated with danaparoid.

Drug Interactions: Danaparoid may interfere with laboratory monitoring of prothrombin time for up to five hours after administration. Oral anticoagulant therapy during this time should be monitored closely. No clinically significant drug interactions have been identified with danaparoid.

Contraindications and Precautions: Danaparoid is contraindicated in any patient with active bleeding or who is at high risk for bleeding. Patients with known hypersensitivity to the drug or other pork products should avoid danaparoid. Danaparoid contains sodium sulfite, a product which may cause allergic-type reactions in sensitive patients.

Dosage and Administration: For prophylaxis of DVT and PE following hip surgery, the recommended dose of danaparoid is 750 anti-Xa units (0.6 mL) subcutaneously every 12 hours. Therapy should be initiated one to four hours

pre-operatively and no sooner than two hours post-operatively. Duration of treatment may range from seven to fourteen days. It is important to emphasize that the anti-Xa unit activity of danaparoid is not interchangeable (unit for unit) with doses of either heparin or LMWH.

Conclusion: Danaparoid is an expensive alternative to unfractionated heparin. This agent, however, has minimal potential for cross reacting with unfractionated heparin and LMWH and appears to be safe in patients with HITTS.

References available upon request

Clonidine Hydrochloride Injection (Duraclon®): A Brief Review

Clonidine hydrochloride injection (Duraclon®) is a centrally-acting analgesic for use in continuous epidural infusion devices. The FDA approved Duraclon® in October 1996 for use in conjunction with opioid analgesics for the treatment of severe pain uncontrolled with opioid analgesics alone.

Pharmacology: Epidurally administered clonidine produces a dose-dependent analgesia that is not antagonized by opioid antagonists. Clonidine is thought to produce pain relief at spinal presynaptic and postjunctional α_2 -adrenoceptors in the spinal cord by preventing pain signal transmission in the brain. Pain relief occurs only for the body regions innervated by the spinal segments where analgesic concentrations of clonidine exist.

Pharmacokinetics: Epidurally administered clonidine readily distributes into plasma via the epidural veins and achieves systemic concentrations (0.5 - 2 ng/mL) that are associated with a centrally-mediated hypotensive effect. Clonidine is metabolized in the liver, and four metabolites have been detected. Only one metabolite, the inactive *p*-hydroxylated derivative, has been identified. The excretion of epidurally administered clonidine has not been fully

Table 1. Cost Comparison of Danaparoid and Various Anticoagulants¹

Drug	Usual Dosage Regimen (for Prevention of DVT)	Cost of 14 Days of Therapy (\$)²	Cost of 14 Days of Therapy (\$)³
Unfractionated heparin	5000 units q 8 h	\$20.49	\$58.38
Enoxaparin (Lovenox®)	3000 anti-Xa units q 12 h 4000 anti-Xa units/d	\$257.43 \$343.22	\$470.40 \$313.60
Dalteparin (Fragmin®)	2500 anti-Xa units/d (5000 anti-Xa units in high-risk patients)	\$117.81 (\$168.15)	\$195.30 (\$390.60)
Ardeparin (Normiflo®)	50 anti-Xa units/kg q 12 h	\$246.79	\$432.60
Danaparoid (Orgaran®)	750 anti-Xa units q 12 h	\$317.52³	\$3,024.00

¹ Adapted from *The Medical Letter* 1997;39(1011):94-5.

² Federal Supply Schedule

³ Average Wholesale Price (AWP), *Drug Topics Red Book*, 1997.

characterized. However, following intravenous administration of ^{14}C -clonidine, 72% of the administered dose was excreted in the urine in 96 hours, 40-50% of which was unchanged clonidine. Renal clearance of clonidine was determined to be 133 ± 66 mL/min. A study, in which ^{14}C -clonidine was given to subjects with various degrees of renal function, found that the elimination half-lives varied as a function of creatinine clearance. The half-lives ranged from 17.5 to 41 hours.

Selected Clinical Studies: In a double-blind, multicenter study conducted by Eisenach and colleagues, 85 patients with severe cancer pain unresponsive to maximally tolerated doses of oral or epidural opioids were randomized to receive epidural clonidine 30 $\mu\text{g}/\text{h}$ (38 patients) or placebo (47 patients). All patients received epidural morphine via patient-controlled analgesia (PCA) as needed for breakthrough pain control. Therapeutic success, defined as a reduction in either epidural morphine use or visual analog scale (VAS) pain score, was more common in patients receiving clonidine (45%) than placebo (21%). Improved pain control with clonidine was especially evident in a subgroup of patients with neuropathic pain (56% success with clonidine vs. 5% with placebo). Glynn evaluated the effects of epidural clonidine, epidural lidocaine, and the combination of epidural clonidine and lidocaine in a double-blind cross-over study in 20 patients with chronic low-back pain and nine patients with neuropathic pain. Twelve of the 17 patients who completed all three arms of the study reported superior pain control with the combination of epidural clonidine and lidocaine.

Epidural administration of clonidine has also been shown to prolong and intensify anesthesia from epidural local anesthetics. Anzai and Nishikawa conducted a study in 20 patients (status-post radical gastrectomy) to evaluate the ability of epidurally administered clonidine to potentiate the post-operative analgesia produced by epidural morphine. Patients were randomized to receive an epidural bolus injection of morphine 0.05 mg/kg plus clonidine 3 $\mu\text{g}/\text{kg}$ (10 patients) or morphine 0.05 mg/kg alone (10 patients) immediately prior to completion of surgery. All patients received intravenous morphine via PCA for 24 hours post-operatively. The primary variable of efficacy was morphine PCA utilization. The number of morphine PCA doses used per hour for 24 hours post-operatively was significantly lower in the group that received the clonidine and morphine bolus intraoperatively.

Adverse Effects: Adverse reactions seen during continuous epidural clonidine infusions are dose-dependent. The adverse effects most frequently reported in clinical trials were hypotension, postural hypotension, bradycardia, rebound hypertension, dry mouth, nausea, confusion, dizziness, and somnolence. Hypotension is the adverse event most frequently requiring treatment and is usually responsive to intravenous fluids. If necessary, parenterally administered ephedrine can be given. Hypotension occurred more frequently in women and in lower-weight patients.

Drug Interactions: Duraclon[®] may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating

drugs. Narcotic analgesics may increase the hypotensive effects of clonidine, tricyclic antidepressants may antagonize the hypotensive effects of clonidine, and beta-blockers may increase the rebound hypertension of clonidine withdrawal. Concurrent use of clonidine and agents known to affect sinus node function or AV nodal conduction (e.g., digoxin, calcium channel blockers, and beta-blockers) may result in an increased incidence of bradycardia and AV block. However, the clinical significance of this interaction with epidurally administered clonidine has not been well characterized. Epidural clonidine may also prolong the duration of the pharmacologic effects of epidurally administered local anesthetics.

Precautions and Contraindications: Duraclon[®] is contraindicated in patients with a history of sensitization or allergic reactions to clonidine. Epidural administration is contraindicated in the presence of an injection-site infection, in patients on anticoagulant therapy, and in those with a bleeding diathesis. Administration of Duraclon[®] above the C4 dermatome is contraindicated since there are no adequate safety data to support such use. The manufacturer does not recommend Duraclon[®] for obstetrical, post-partum, or perioperative pain management since the risk of hemodynamic instability, especially hypotension and bradycardia, from epidural clonidine may be unacceptably high. Vital signs should be monitored frequently, especially during the first few days of epidural clonidine therapy. Duraclon[®] should be avoided in most patients with severe cardiovascular disease or in those who are otherwise hemodynamically unstable.

Abrupt termination of clonidine treatment has produced symptoms of withdrawal such as nervousness, agitation, headache, and tremor, accompanied or followed by a rapid increase in blood pressure. The dose should be decreased gradually over two to four days to minimize the risk of withdrawal symptoms. The Duraclon[®] dose should be adjusted for impaired renal function, and these patients should be monitored closely for hypotension and bradycardia.

Dosage and Administration: The initial dose of Duraclon[®] for continuous epidural infusion is 30 $\mu\text{g}/\text{h}$. The dosage may be titrated based on pain relief and adverse effects. Experience with dosage rates above 40 $\mu\text{g}/\text{h}$ is limited.

Cost: The cost of Duraclon[®] is \$30.38/10 mL vial.

Conclusion: Epidural clonidine offers specific advantages over the currently available agents for the treatment of acute and chronic pain syndromes. Intraoperative administration of Duraclon[®] with a local anesthetic prolongs and intensifies the anesthetic effect. Post-operatively, the combination of epidural clonidine and reduced-dose opioid provides adequate pain control and offers the advantage of decreased opioid-related adverse effects. When combined with opioids for refractory pain of malignancy, the combination regimen provides superior pain control compared to that achieved with an opioid alone.

References available upon request

Did You Know . . .

- ❖ The FDA recently approved raloxifene (Evista™, Eli Lilly and Company), a selective estrogen-receptor modulator (SERM), for the prevention of post-menopausal osteoporosis.
- ❖ As of October 1997, there have been 35 post-marketing reports of varying degrees of liver injury associated with the new thiazolidinedione derivative, troglitazone (Rezulin®), used for the treatment of Type II diabetes. The FDA recommends that serum transaminase levels be measured at baseline and monthly for the first 6 months of therapy.
- ❖ Sermorelin acetate (Geref®, Serono Laboratories), a synthetic growth hormone-releasing hormone (GHRH) was recently approved by the FDA for the treatment of idiopathic growth hormone deficiency in children.
- ❖ The prevalence of cardiac valvular disease reported from five echocardiographic surveys in 284 patients who received dexfenfluramine or fenfluramine, either alone or in combination with phenteramine (fen-phen), ranged from 30% to 38.3%. An echocardiogram should be considered for any patient who has taken these drugs, either alone or in combination with other medications, in the presence of signs or symptoms of heart or lung disease.
- ❖ Combivir®, a combination anti-retroviral product containing 300 mg of zidovudine (AZT) and 150 mg of lamivudine (3TC), was recently approved by the FDA for treatment of HIV infection. Combivir® is dosed twice daily and is now available on the NIH CC Formulary.
- ❖ Fortovase®, a new soft-gelatin formulation of saquinavir with improved bioavailability compared to the current hard-gelatin formulation (Invirase®), was approved by the FDA. Invirase® was the first FDA-approved protease inhibitor for the treatment of HIV infection. Hoffman-La Roche, Inc. will continue to produce Invirase® for the next six months.

Editor's Note

We wish to thank McDonald Horne, M.D. for reviewing the article on danaparoid and acknowledge Rebecca Slone, Pharm.D. and Judith Smith, Pharm.D. for their contributions to this issue of *Pharmacy Update*.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary actions:

Additions:

- ❖ Alprostadil urethral suppository (Muse®)
An intraurethral formulation of prostaglandin E₁ for the treatment of erectile dysfunction. The use of this agent is restricted to the NCI Urology Service.
- ❖ Clonidine injection for epidural use (Duraclon®)
The use of this agent is restricted to the Anesthesiology Department.
- ❖ Danaparoid (Orgaran®)
The use of this agent is restricted to the Clinical Hematology Service.
- ❖ Estradiol transdermal system (Alora®)
- ❖ Ketoconazole shampoo (Nizoral®)
- ❖ Methylcellulose powder (Citrucel®)

Drug Information Service

- ☞ Patient-specific medication information and pharmacotherapy consultations
- ☞ Nutritional and metabolic support consultations
- ☞ Comprehensive information about medications, biologics, nutrients, and drug therapy
- ☞ Investigational drug information (pre-clinical and clinical)
- ☞ Research support and assistance with study design, protocol development, and critical literature evaluation

496-2407

Pager #104-2619-7

Building 10, Room 1N-257



**Drug Information Service
Pharmacy Department
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland 20892-1196**