

February 2002

Volume 9, Number 1

In This Issue...

Changes to Formulary	1
New Bowel Protocol Policy	2
Revised Drug Administration Policies	2
Pyxis Implementation	2
Iron Sucrose Injection (Venofer®)	3
Dalteparin	4
Pharmacy Awards	5
Adverse Drug Reactions 2001	6

All formulary changes and policy/procedure updates have been approved by the Drugs and Therapeutics (D&T) Committee and Medical Advisory Council (MAC).

This and other Drug and Therapeutic Newsletters are on the Web at www.vhpharmsci.com

Changes to Formulary

Additions

- Iron Sucrose injection (Venofer®)**
 - Intravenous iron product to be used in patients intolerant to iron dextran
 - See page 3 for drug review
- Dalteparin injection (Fragmin®)**
 - Low-molecular-weight heparin for the prophylaxis and management of deep vein thrombosis (DVT)
 - Alternative to adjusted dose warfarin for the prophylaxis of DVT following hip surgery
 - See page 4 for drug review
- Mycophenolate injection (Cellcept®)**
 - Immunosuppressive agent used in the prevention of rejection in solid organ transplant patients

4. Pantoprazole 40mg tablets (Pantoloc®)

- Proton pump inhibitor for the management of various gastrointestinal disorders including reflux esophagitis, peptic ulcer disease and *Helicobacter pylori* infection
- Omeprazole MUPS 20mg will still be retained on formulary for nasogastric or other tube administration

Drug	VH Acquisition Cost
Pantoprazole 40mg tablet 40mg injection	\$0.45/tablet \$13.70/vial
Omeprazole MUPS 20mg tablet	\$1.10/tablet
MUPS = Multiple Unit Pellet System	

Deletions

1. Apraclonidine 0.5% eye drops (Iopidine®)

- Alternative: Brimonidine 0.2% eye drops
- Both brimonidine and apraclonidine are alpha-2 agonists used to lower intraocular pressure in patients with ocular hypertension and open-angle glaucoma
- Brimonidine is as efficacious as apraclonidine, but better tolerated (lower incidence of local allergic reactions and tachyphylaxis), and less expensive

EDITORIAL STAFF:

Karen Shalansky, Pharm.D., FCSHP

Peter Loewen, Pharm.D.

Rubina Sunderji, Pharm.D., FCSHP

Peter Jewesson, Ph.D., FCSHP

Any comments, questions or concerns with the content of the newsletter should be directed to the editors. Write to CSU Pharmaceutical Sciences Vancouver General Hospital, 855 W12th Ave, Vancouver BC V5Z 1M9, send a FAX to 604-875-5267 or email kshalans@vanhosp.bc.ca
Find us on the Web at www.vhpharmsci.com

Updated Policies/Procedures

1. New Hospital Bowel Protocol Policy

Phase 1: VGH Acute Care Units

Over the years, many patient care areas have developed their own bowel protocols which resulted in having over 30 different protocols in use at VGH. Much effort has been expended in consolidating these into 17 pre-printed orders (PPO).

Effective April 1, 2002, if a prescription is simply written for "Bowel Protocol" it will be interchanged with the appropriate protocol using a PPO in accordance with the patient location. The pharmacy will enter the order into PCIS and send a copy to the unit for the physician to sign. If this bowel protocol is unsuitable or there is no existing PPO for a specific location, the physician may choose an alternative PPO or write specific medication orders for the patient (including dose, form & frequency).

The following is a list of the current hospital pre-printed Bowel Protocols available, along with the page number required to order a supply from the Printing department. Having the orders available on the units will enable the physicians to select the desired protocol at the time of prescribing.

Bowel Protocol	PPO Page Number
Burns	2
Burns Pediatric	1
Cardiovascular	70
ENT	285
Liver Transplant	40
Medicine/Geriatrics	19
Nephrology	22
Neurosciences	38
Orthopedics & Trauma	39
Orthopedics-Spinal	264
Palliative Care	71
Respirology	142
Renal Transplant	41
TB Respirology	124
Thoracic surgery	86
Urology	500
Vascular surgery	51

2. Revised Drug Administration Policies

- **Vancomycin desired trough (pre-dose) serum levels** have been increased to **5-15mg/L (up to 20mg/L for aggressive therapy)**. Desired **peak serum levels (immediate post-dose)** are **20-40mg/L (3 hour post-dose level 15-30mg/L)**.
- **Glycoprotein IIb/IIIa inhibitors** administration has been **extended** to the **Day Bed Area**.
- After a **bolus test injection of intrathecal baclofen, temperature, pulse, respiratory rate, oxygen saturation and blood pressure must be monitored** q30minutes x 2 post injection, then q1h until patient is discharged.

3. Pyxis Implementation at UBC Hospital

Cathy Figura, Pyxis Co-Project Manager, Information Systems
Luciana Frighetto Pyxis Co-Project Manager, Pharm. Sci. CSU

The implementation of an automated dispensing system (ADS) is a major undertaking for a hospital and primarily affects nursing, pharmacy and information systems personnel. The goal of an ADS is improved patient care through an improved medication distribution system. The benefits of such a system in the acute care setting include:

- increased nurse and pharmacist time for direct patient-care activities
- potential for reduced medication errors and
- improved drug inventory management including narcotic system management.

The ADS selected for implementation at the UBC Hospital is Pyxis. Pyxis Medstation dispensing cabinets that resemble "ATMs" have been installed on select patient care areas to offer easy, secure, computer-controlled access to medications. Each dispensing cabinet is connected to a central (host) computer in the pharmacy department that, in turn, is interfaced with the existing hospital computer system.

The first phase of the Pyxis ADS implementation at UBC Hospital was the introduction of the Pyxis Medstations as a night cupboard, ward stock, and narcotic medication distribution system. The system went live over the two-week period of January 21, 2002 to February 01, 2002. On behalf of Clinical Information Systems and Pharmaceutical Sciences CSU, we would like to thank all the nurses at UBC Hospital for their patience and support during the project's development and implementation. Your

participation was instrumental in achieving its successful activation!

In the future, there are plans to implement an ADS at VGH. In addition, the ADS at both sites should be expanded to access all patient medication from the Pyxis Medstations in order to achieve all the benefits of this system.

New Drug/Drug Products

1. Iron Sucrose Injection (Venofer®)

Karen Shalansky, Pharm.D., FCSHP

Parenteral iron products are indicated in patients with iron deficiency anemia when the oral route is not feasible due to intolerance or malabsorption, or severe iron deficiency where a rapid therapeutic response is desired. The administration of erythropoietin to patients with end-stage renal disease has also increased the demand for parenteral iron administration. A new product, iron sucrose, has been added to formulary at VHHSC.

Comparison to Iron Dextran

Until recently, iron dextran has been the only form of intravenous iron available in Canada. Iron dextran is, however, associated with a variety of adverse reactions, including pruritis, rash, abdominal pain, flank pain, arthralgias, myalgias, fever, hypotension, pulmonary edema, wheezing, stridor, and angioedema.¹ In a review of 573 uremic patients, the overall incidence of adverse reactions to iron dextran was 4.7% over a 2 year period.² Of these, 0.7% were considered serious anaphylactoid reactions. An initial intravenous test dose of iron dextran 25mg is required to determine tolerability even though less than 20% of all adverse reactions occur with the test dose. Intolerance to iron dextran is thought to be due to the dextran portion of the complex and not to the iron itself.³

Iron sucrose offers improved tolerability compared to iron dextran. Reported adverse effects appear to be infrequent and non-life threatening (metallic taste, headache, nausea/vomiting, muscular pain, pruritis, pyrexia). In a trial of 23 hemodialysis patients with documented allergy to iron dextran, all patients were successfully switched to iron sucrose.¹ Iron dextran allergies were classified as a) mild reactions (n=16): urticaria, pruritis, back pain or b) severe anaphylactoid reactions (n=7): dyspnea, wheezing, hypotension, angioedema. All patients were switched to iron sucrose (no test

dose) given as either 100mg IV push over 5 minutes (n=184 doses) or IV infusion over 1 hour (n=39 doses). Only 2 mild reactions were reported: metallic taste and rate-related pruritis.

Iron sucrose has been studied in several populations with iron deficiency, although primarily in patients with renal disease. Three trials assessing a total of 183 pre-dialysis and hemodialysis patients found no immediate or delayed reactions with 1000mg given in divided doses over several weeks.⁴⁻⁶ Test doses were not employed in any of these studies.

Dosage and Administration

The dosage of iron sucrose is 1000mg total dose divided into thrice weekly to monthly increments of 100-500mg. Compared to iron dextran, the drug can be administered over a shorter period of time. Doses of 100mg or less can be given over 15-30 minutes, 200-250mg over 1-2 hours and doses up to 500mg over 3-4 hours. In comparison, iron dextran 100mg should be administered over at least 1 hour and higher doses (to a maximum of 1000mg) over a more prolonged period of 3-8 hours. A test dose of iron sucrose is not required, which alleviates both nursing and physician time.

Cost Comparison

Table 1. Comparison of IV Iron Preparations

Drug	Strength	Cost
Iron Dextran (Infufer®)	100mg/2mL	\$15.50/100mg
Iron Sucrose (Venofer®)	100mg/2mL	\$37.00/100mg

Conclusion

Iron sucrose should be used as an alternative to intravenous iron dextran in those patients who are intolerant to the dextran molecule. Although more costly, the sucrose formulation offers improved tolerability, no test dose requirement, and faster rate of infusion.

References

1. Van Wyck DB et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran. *Am J Kid Dis* 2000;36:88-97.
2. Fishbane S et al. The safety of intravenous iron dextran in hemodialysis patients. *Am J Kid Dis* 1996;28:529-34.
3. Hanstra RD et al. Intravenous iron dextran in clinical medicine. *JAMA* 1980;243:1726-31.
4. Silverberg DS et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. *Am J Kid Dis* 1996;27:234-8.
5. Silverberg DS et al. Intravenous ferric saccharate as an iron supplement in dialysis patients. *Nephron* 1996;72:413-7.

2. Dalteparin (Fragmin®)

Rubina Sunderji, Pharm.D., FCSHP

Dalteparin is indicated for prevention of deep vein thrombosis (DVT) in general and hip surgery, treatment of DVT and acute coronary syndromes (ACS), and prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in conjunction with renal failure.¹

Pharmacology

Dalteparin, like other low molecular weight heparins (LMWH), exerts its anticoagulant effect by activating antithrombin III. Unlike unfractionated heparin (UFH), LMWH have greater activity against factor Xa than against thrombin (factor IIa). For dalteparin, the ratio of anti-Xa to anti-IIa activity is 2.7:1. The importance of factor Xa relative to thrombin inhibition in mediating antithrombotic effects of LMWH is unclear but there is evidence that both are necessary.²

Compared to UFH, LMWH produce a more predictable anticoagulant response reflecting their better bioavailability, longer half-life and dose-independent clearance.^{2,3} As a result, LMWH are more convenient to use because of the ease of once or twice daily subcutaneous administration and the lack of need for laboratory monitoring of anticoagulant effect.³

The onset of action of LMWH following subcutaneous administration is immediate.⁴ The peak inhibitory effect of dalteparin on plasma anti-Xa levels occurs within 4 hours.¹ The primary route of dalteparin elimination is renal and the drug has a serum elimination half-life of 119 to 139 minutes.^{2,3} Guidelines for dosage adjustment in renal failure are not available and, therefore, monitoring of anti-Xa levels is recommended in severe renal failure.

Clinical Trials of DVT Prophylaxis in Orthopedics

Total hip replacement (THR): Current guidelines for pharmacotherapy of DVT prophylaxis in THR include LMWH or low intensity warfarin (target INR range 2-3).⁵ Adjusted dose heparin is also acceptable but is not preferred as it is a cumbersome and complex method.

Previous studies comparing warfarin and various LMWH started 12-24h post-operatively have shown similar efficacy.⁵ While pre-operative initiation of LMWH has shown to be superior to warfarin, there is concern for increased bleeding risk.⁶ The recent

North American Fragmin trial (NAFT) is the first randomized, double-blind trial showing superiority of a LMWH, dalteparin, over warfarin when started early post-op.⁷ The initial dose was 2500IU 4-6 hours post-op, followed by 5000IU daily. The use of an initial lower dose post-op was associated with equivalent bleeding risk to warfarin (6.5% vs 4.5% with warfarin).

Current guidelines recommend at least 7 to 10 days of anticoagulation prophylaxis post-THR.⁵ In a concurrent study, the NAFT investigators showed dalteparin to be significantly more effective when continued beyond hospital discharge for a mean of 35 days post-THR.⁸ This result was in comparison to in-hospital warfarin prophylaxis followed by placebo post-hospital discharge. Prolonged dalteparin treatment reduced venographically detected total and proximal DVT rates by more than 50% (total DVT: placebo 10.5%, dalteparin 4.8%, p=0.03; proximal DVT: placebo 4.8%, dalteparin 1%, p=0.02). Until the economic implications are known, extended out-of-hospital LMWH is currently recommended for high-risk patients.⁵

Total knee replacement (TKR): Current guidelines for pharmacotherapy of DVT prophylaxis in TKR include LMWH or low intensity warfarin (target INR range 2-3) although pooled analyses suggest superiority of LMWH.⁵ There are no published head-to-head comparisons of dalteparin with warfarin or with other LMWH in the TKR population. Enoxaparin remains the LMWH for DVT prophylaxis in TKR.

Trauma: LMWH is the preferred method of DVT prevention in trauma patients. As studies with dalteparin are lacking in these patients, enoxaparin will continue to be used for this indication.

Clinical Trials of DVT Treatment

There are 4 studies comparing dalteparin with UFH for the treatment of DVT. Patients with known pulmonary embolism (PE) were excluded. Dalteparin was administered in doses of 200 IU/kg SC once daily in 3 studies and as 120 IU/kg SC twice daily in an earlier smaller scale study. All studies showed dalteparin to be as effective and safe as UFH in the initial management of DVT.⁹⁻¹²

Only one published study has compared dalteparin to UFH in the initial treatment of symptomatic, submassive PE.¹³ In this pilot study (n=60), UFH was administered by continuous infusion to maintain an aPTT of 2-3x control while dalteparin was given

subcutaneously at 120IU/kg twice a day, doses higher than those used in studies of DVT treatment. Oral anticoagulation was started on day 7 in both groups and continued for at least 3 months. No patient in either group experienced the primary outcome of recurrent PE within the first 10 days of therapy. There was no major bleeding in either group during the 10-day study period. Of the 48 patients who completed follow up at 3 months, none had shown clinical signs of recurrent PE or new perfusion lung scan defects.

Of note, dalteparin does not have an official indication for treatment of PE and the correct dosage for this indication is unclear since different dosages have been used in other non-comparative studies (200IU/kg/day or 120IU/kg q12h).¹⁴⁻¹⁸

Comparison with Formulary Agents

The current formulary LMWH at VH are enoxaparin and tinzaparin. Table 1 compares dosage and cost of these agents with dalteparin. Prefilled syringes are available for dalteparin in both 2500IU and 5000IU to enable administration of both the initial half-dose and full dose for DVT prophylaxis.

Table 1. Dose and Cost Comparison of LMWHs

Drug	Dose for DVT Prophylaxis (Orthopedics)	Dose for DVT Treatment	Cost*/5day
Tinzaparin	n/a	175IU/kg SC daily	P: n/a T: \$98.00
Enoxaparin	30mg SC bid	1mg/kg SC bid OR 1.5mg/kg SC daily	P: \$55.00T: T: \$105.00- 140.00
Dalteparin	2500IU SC 6 hrs post-op, then 5000IU SC qam	200 IU/kg SC daily OR 100IU/kg SC bid	P: \$33.75 T: \$105.00

*VH acquisition cost based on dose/70kg patient
n/a = not applicable; P= prophylaxis; T = treatment

Conclusion

Dalteparin was recently added to formulary for preferential use in DVT prophylaxis post-THR. This drug will also be available for other approved indications including treatment of DVT. Enoxaparin will be retained on formulary for DVT prevention post-TKR, multiple trauma and spinal cord injury, as well as management of ACS, DVT and PE. The usage of tinzaparin will be reassessed in 3-6 months for potential deletion from formulary.

References

1. Dalteparin product monograph, 2001.
2. Weitz JI. Low-molecular-weight heparins. *NEJM* 1997;337:687-98.
3. Hirsh J et al. Heparin: mechanism of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1995;108:258S-75S.
4. Hyers TM et al. Antithrombotic therapy for venous thromboembolic disease. *Chest* 1995;108:335S-51S.
5. Geerts WH et al. Prevention of venous thromboembolism. *Chest* 2001;119:132S-175S.
6. Francis CW et al. Prevention of deep-vein thrombosis after total hip arthroplasty. *JBJS* 1997;79A:1365-72.
7. Hull RD et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients. *Arch Intern Med* 2000;160:2199-2207.
8. Hull RD et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients. *Arch Intern Med* 2000;160:2208-15.
9. Bratt G et al. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis. *Thromb Haemost* 1990;64:506-10.
10. Lindmarker P et al. Comparison of once-daily subcutaneous Fragmin® with continuous intravenous unfractionated heparin in the treatment of DVT. *Thromb Haemost* 1994;72:186-90.
11. Fiessinger JN et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost* 1996;76:195-9.
12. Luomanmaki K et al. A multicentre comparison of once-daily subcutaneous dalteparin and continuous intravenous heparin in the treatment of DVT. *J Intern Med* 1996;240:85-92.
13. Meyer G et al. Subcutaneous low-molecular-weight heparin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost* 1995;74:1432-6.
14. Dunn CJ et al. Dalteparin. An update of its pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2000;60:203-37.
15. Wells PS et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin. *Arch Intern Med* 1998;158:1809-12.
16. Kovacs MJ et al. Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* 2000;83:209-11.
17. Monreal M et al. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. *Thromb Haemost* 1994;71:7-11.
18. Wilson SJ et al. Outpatient treatment of deep vein thrombosis and pulmonary embolism: a hospital-based program. *Can J Hosp Pharm* 1999;52:282-8.

Pharmacy Awards

Several members of Pharmaceutical Sciences CSU were recipients of Canadian Society of Hospital Pharmacists (CSHP) 2001 national competitive research awards for excellence:

Pharmacist utilization of the DIE test to assess aminoglycoside vestibular toxicity. Denise Carr, Karen Shalansky, Fawziah Marra, Art Malinson (CSHP/Glaxo Wellcome - Pharmaceutical Care).

Patient preferences in an outpatient parenteral antibiotic therapy program. Amy Wai, Carlo Marra, Luciana Frighetto, Peter Jewesson (CSHP/Novartis - Pharmacoeconomics).

Adverse Drug Reaction Report 2001

There were a total of 24 suspected adverse drug reactions (ADRs) reported at VHHSC in 2001 (Table 1). Of note, 6 reactions were considered to have been the cause of hospitalization. The continued reporting of all suspected ADRs by nurses, physicians and pharmacists aids in an improved assessment of the magnitude and nature of adverse events. To notify Pharmacy of an ADR, either fill out a yellow ADR alert card, available on all nursing units, and send to Pharmaceutical Sciences CSU, or call local 62481 (VGH site) or local 27249 (UBC site). Pharmacists complete all ADR report forms and forward copies to the B.C. Regional ADR Centre. This Centre does preliminary analysis of the data and then forwards all reports to the Canadian ADR program in Ottawa who then forward them to the World Health Organization.

Drug	Suspected ADR
Carbamazepine	Erythema multiforme ^a (1)
Ciprofloxacin	Torsade de pointes (1)
Eptifibatide	Thrombocytopenia (1)
Heparin Infusion	Thrombocytopenia (1)
Hepatitis B Vaccine (Engerix [®])	Headache (1); fever, headache, dizziness (1)
Indomethacin	Upper GI bleed ^a (1)
Iron Dextran Infusion	Hives, urticaria (2); back pain (1); Hypotension (2)
Iron Polysaccharide (Niferex [®])	Hives, itchy rash over body including neck, face and scalp (1)
Ketorolac oral	GI bleed ^a (1)
Losartan	Cough (1)
Metronidazole	Tonic-clonic seizure (1)
Phenytoin	Macular rash (1)
Quetiapine	Diabetic ketoacidosis ^a (1)
Rofecoxib	Exacerbation of congestive heart failure ^a (1); GI bleed ^a (1)
Sotalol	Bradycardia and hypotension ^a (1)
Sulfamethoxazole-trimethoprim	Morbiliform maculopapular rash (1)
Terazosin	Acute myopathy of upper and lower extremities (1)
Warfarin	Hypovolemic shock secondary to bleeding duodenal ulcers (1)

^ahospitalized due to ADR