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## Changes to Formulary

### Additions

- Dolasetron 50mg, 100mg tabs, 20mg/mL - 5mL vial (Anzemet®)**
  - 5-HT<sub>3</sub> receptor antagonist added on formulary to replace ondansetron
  - Limited Access Drug (LAD) used in standardized antiemetic protocols
  - refer to dolasetron article, page 3
- Danaparoid 750 units/0.6mL ampoule (Orgaran®)**
  - low molecular weight heparinoid
  - restricted to prescription by a hematologist for use in patients with heparin-induced thrombocytopenia (HIT)
  - refer to danaparoid monograph, page 4
- Remifentanil injection (Ultiva®)**
  - narcotic analgesic derivative of fentanyl with ultra-short duration of action
  - restricted for use for lithotripsy procedures
  - refer to remifentanil monograph, page 5
- Cisatracurium 20mg/10 mL (Nimbex®)**
  - non-depolarizing neuromuscular blocker

- stereoisomer of atracurium carrying no risk of histamine-mediated cardiovascular events
- cost \$7.00-14.00/hour for 70kg patient

### Deletions

- Atracurium 10mg/mL inj. (Tracrium®)**
  - alternative: cisatracurium injection
- Ondansetron 4mg, 8mg tabs, 2mg/mL injection (Zofran®)**
  - alternative: dolasetron tablets and injection
- Doxycycline 100mg inj. (Vibramycin®)**
  - available as emergency release only
  - alternative for pleurodesis: talc
- Chlorpheniramine 10mg/mL injection (Chlortripolon®)**
  - discontinued by manufacturer
  - alternative: diphenhydramine, hydroxyzine
- Phosphate Sandoz 500mg tablets**
  - discontinued by manufacturer
  - alternative: phosphate solution 500mg/4mL
  - all orders for phosphate 500mg will be dispensed with phosphate solution 4mL

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## *Updated Policies/Procedures*

### **1. Revised Drug Administration Policies**

The following changes will be added to the next Parenteral Drug Therapy Manual (PDTM) update:

- **Methylprednisolone for acute spinal cord injury** is administered for a **total of 24 hours if given within 3 hours of injury or 48 hours if given 3-8 hours after injury**
- **Furosemide** may be administered **subcutaneously (SC) in any nursing unit**

### **2. Pharmaceutical Industry Representative (PIR) Activities at VHHSC**

To monitor and control PIR drug-related promotional activities at VHHSC, the following regulations were implemented April 1, 1991:

- 1 All PIR are required to register at the CSU Pharmaceutical Sciences administration office upon arrival and departure from hospital, including any building on the VHHSC site. Registration includes written documentation of date/time, name, affiliation, contact person or persons at hospital and intent (including drug(s) to be detailed).
- 2 Upon registration, an identification tag will be provided which the representative must wear during the visit. This tag must be returned to the pharmacy prior to leaving the hospital site.
- 3 Activities of the PIR are restricted to office and meeting room areas of the hospital only. Under no circumstances are representatives permitted to carry on any detailing activities in patient care areas.
- 4 Only medical, pharmacy and purchasing staff may be detailed about drug products.
- 5 Appointments with physicians, pharmacists and purchasing staff must be arranged with these individuals directly and take place in an office area. Where the office is located inside a clinical area of the hospital, the visit must not intrude on the clinical activity of the area.
- 6 Educational or promotional material must not be posted or displayed in the hospital.
- 7 Any discussions regarding drugs which are not listed in the VHHSC Drug Formulary must include notification of that fact. Requests for addition of a drug to the VHHSC Formulary must be made by physicians by contacting the CSU Pharmaceutical Sciences.
- 8 Copies of all promotional or other drug literature which is intended for distribution to physicians must be provided to the CSU Pharmaceutical Sciences prior to dissemination in the hospital.
- 9 Samples must not be distributed to hospital personnel for patient use. Under no circumstances are samples to be left in patient care areas of the hospital.
- 10 Pharmaceutical displays are not permitted in any area of the hospital.
- 11 Copies of medical staff lists are intended for the use of hospital staff only, and will not be made available to PIR.
- 12 Hospital communication systems (i.e. paging systems) must not be used by PIR to locate hospital personnel.

#### Enforcement:

These guidelines are distributed to all PIR. To maximize compliance with the guidelines, PIR activities are monitored by medical and pharmacy personnel. Where PIR have been identified as having violated hospital visitation privileges, the individual will be contacted by the Director of CSU Pharmaceutical Sciences (or delegate) to reinforce the guidelines. A second violation of the guidelines will result in written communication between the Director and the company. In this correspondence, the company will be notified that the PIR is on probation. A third violation will result in loss of hospital privileges for a minimum of six months.

#### Reporting:

The Drugs and Therapeutics Committee will receive reports of the extent and nature of PIR activities on an annual basis. Problem PIR will be reported to the Committee when identified.

### 3. DOLASETRON (ANZEMET®)

Dolasetron is one of the newest 5-HT<sub>3</sub> receptor antagonists on the Canadian market and has been added to the VHHSC formulary to replace ondansetron as a limited access drug (LAD). Currently, dolasetron is indicated in Canada for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy. Its efficacy and safety profile is comparable to that of ondansetron; however, dolasetron is administered once daily compared to twice or three times per day for ondansetron and it offers potential cost-savings (Table 1).

**Table 1. Comparison of Ondansetron and**

Drug	Ondansetron	Dolasetron
<b>Dosage Form (Cost)</b>	4mg tab (\$13.14) 8mg tab (\$17.40) 2mg/mL x 20mL vial (\$172.00)	50mg tab (\$13.00) 100mg tab (\$26.00) 20mg/mL x 5mL vial (\$10.50)
<b>Dose</b>	8mg po/iv pre-chemo, then q8-12h on days of select chemotherapy	150mg <sup>1</sup> po or 100mg <sup>1</sup> iv pre-chemo, then q24h on days of select chemotherapy
<b>Daily Cost<sup>2</sup></b>	\$56.34 po \$117.63 iv	\$40.38 po \$15.31 iv

<sup>1</sup> for patients > 90kg, can increase to 200mg po or 150mg iv

<sup>2</sup> based on acquisition, preparation and delivery costs of ondansetron 8mg po/iv pre-chemo and 2 doses post-chemo versus dolasetron 150mg po/100mg iv q24h

Similar to ondansetron use at VHHSC, dolasetron is approved for prescription on a preprinted LAD form or antiemetic protocol order form. The LAD form has been revised and categorizes chemotherapeutic agents according to their emetogenic potential. Dolasetron is indicated for single agents or combination regimens with high emetogenic potential (>60% incidence of vomiting). For non-approved indications, please contact a pharmacist.

## ABSTRACT

(Pharmacotherapy 1997;17(6):1233-1237)

### Is Oral Sotalol Effective in Converting Atrial Fibrillation to Sinus Rhythm?

Erna Ferreira, M.Sc. (Pharm.), Rubina Sunderji, Pharm.D., and Kenneth Gin, MD, FRCP(C)

d,l-sotalol is a noncardioselective beta-blocker that exhibits class III antiarrhythmic activity. It is often used to convert atrial fibrillation (AF) to normal sinus rhythm. Since class III agents increase action potential duration and refractoriness in atrial tissue without affecting conduction, they are theoretically considered ideal agents for the treatment of re-entrant arrhythmias such as AF. We reviewed the literature evaluating the efficacy of sotalol for restoring sinus rhythm in patients with acute or chronic AF. Articles indexed on MEDLINE (1966 to 1996) and referenced articles not identified by MEDLINE that compared sotalol to placebo or another antiarrhythmic agent were included. Sotalol was significantly inferior to quinidine in converting AF of recent onset (< 48 hours) to sinus rhythm. In patients with duration of AF of more than 48 hours, sotalol was significantly less effective than quinidine and comparable with placebo. Conversion rates for sotalol in all studies combined ranged from 8-49%. Published studies do not support the drug for conversion of AF to sinus rhythm. Larger well-designed studies are required to evaluate its efficacy and optimum dosage for this indication. Until further data are available, pharmacologic cardioversion with traditional class I antiarrhythmic agents may be preferable as they are effective particularly for recent-onset AF.

## NEW DRUGS/DRUG PRODUCTS

### DANAPAROID (Orgaran®)

Karen Shalansky, Pharm.D.

Danaparoid sodium is an alternative anticoagulant in patients who develop heparin-induced thrombocytopenia (HIT) from heparin therapy. This drug is restricted to prescription by a hematologist.

#### Pharmacology

Danaparoid is a low molecular weight heparinoid derived from porcine gut mucosa. Its active components consist of heparan sulfate, dermatan sulfate and chondroitin sulfate. The major difference between danaparoid and other low molecular weight heparins (LMWH) is that danaparoid is devoid of heparin or heparin fragments. However, similar to LMWHs, it exerts its antithrombotic effect principally through anti-thrombin III-mediated inhibition of factor Xa and, to a much lesser extent, thrombin.<sup>1,2</sup>

Danaparoid is primarily eliminated via the kidneys. The elimination half-life based on anti-Xa activity ranges from 17-28 hours (mean 25 hours).

#### Comparison to Other Formulary Agents for Management of HIT

The incidence of HIT is approximately 1-3% with unfractionated heparin.<sup>1</sup> Typical LMWHs (e.g. tinzaparin) exhibit a significant cross-reactivity with heparin-induced antibodies (incidence 79-100%) and thus have a high likelihood of causing platelet aggregation in patients with HIT.<sup>1-3</sup> The cross-reactivity of danaparoid with heparin-induced antibodies is reported as less than 10% (range 0-20%).<sup>2,3</sup>

Ancrod represents a distinct anticoagulant that is derived from snake venom. Ancrod will not cross-react with heparin-induced antibodies, but neutralizing anti-ancrod antibodies can develop

in patients who receive this agent for several weeks.<sup>4</sup> Ancrod acts to reduce fibrinogen levels, thereby decreasing plasma viscosity. It does not inhibit thrombin, which may limit its use in some HIT patients, particularly those who have disseminated intravascular coagulation (DIC) or septicemia.<sup>4</sup> As well, ancrod may not be useful in patients who are already hypofibrinogenemic.

Warfarin represents a third distinct anticoagulant. However, its onset of action is slow, taking up to 5 days for full anticoagulant effect.

**Table 2. Comparison of Danaparoid and Ancrod**

Drug	Danaparoid	Ancrod
Cross-reactivity with heparin-induced antibody ( <i>In vitro</i> )	< 10% (range 0-20%)	0%
Mechanism of action	Anti-Xa:Anti-IIa activity = 28:1 <sup>5</sup>	reduces fibrinogen levels and blood viscosity
Other considerations		limited use if coexisting DIC or septicemia
Clotting Test Assessment	none (does not affect global clotting tests e.g. aPTT, INR, thrombin time)	fibrinogen levels
Cost/day (excludes loading doses)	\$115.00/day	\$243.00/day plus cost of fibrinogen levels

#### Monitoring

As with all anticoagulants, the major side effect of danaparoid is bleeding; thrombocytopenia can rarely occur. Patients being treated for HIT should have daily CBC (with platelet counts) while receiving this drug.

Cross-reactivity of danaparoid with heparin-induced antibodies is less than 10%. However, if after 48 hours following cessation of heparin and the initiation of danaparoid the platelets do not increase, the possibility of cross-reactivity should be considered and therapy switched to ancrod.

(Continued from page 4)

**Dosing**

Table 3. Danaparoid Dosing	
<b>Therapeutic Anticoagulation</b>	
<b>Loading Dose:</b>	
< 60 kg	1500 units IV
60-75 kg	2250 units IV
76-90 kg	3000 units IV
> 90 kg	3750 units IV
<b>Maintenance Dose:</b>	400 units/hr x 4 hrs, then 300 units/hr x 4 hrs, followed by 200 units/hr
<b>DVT Prophylaxis</b>	
<= 90 kg	750 units SC q12h
> 90 kg	750 units SC q8h or 1250 units SC q12h

**Conclusions**

Danaparoid offers a less expensive, more convenient alternative to ancrod for anticoagulation in patients who develop HIT. Unlike ancrod, administration of danaparoid does not require routine laboratory test assessment for anticoagulation. It is important to continue to monitor daily platelet levels following cessation of heparin and initiation of danaparoid to ensure there is no cross-reactivity with heparin-induced antibodies.

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**REMIFENTANIL (Ultiva®)**

Byron O'Malley, B.Sc. (Pharm) and Karen Shalansky, Pharm.D.

Remifentanil, a derivative of fentanyl, is a new selective opioid receptor agonist that displays similar pharmacodynamic effects to other opioids in this class. It possesses an ester linkage which makes it susceptible to plasma and tissue esterases for metabolism, resulting in rapid offset of action.<sup>1</sup> Remifentanil is equipotent to fentanyl and 20-30 times more potent than alfentanil.<sup>1,2</sup>

**Table 4. Comparison of Remifentanil, Fentanyl and Alfentanil<sup>1-6</sup>**

Drug	Fentanyl	Alfentanil	Remifentanil
<b>Onset of Action</b>	immediate	immediate	immediate
<b>Metabolism</b>	Liver	Liver	Plasma & tissue esterases
<b>Terminal Half-Life</b>	3.1-3.7 hours	90 minutes	10-20 minutes
<b>Context Sensitive Half-time<sup>a</sup></b>	262 minutes	58.5 minutes	3.65 minutes
<b>Dose for Conscious Analgesia</b>	10-50 mcg, repeated q2-3 minutes up to 2 mcg/kg	5-10 mcg/kg, followed by 1-3 mcg/kg/min	1 mcg/kg, followed by 0.05-0.2 mcg/kg/min
<b>Cost<sup>b</sup></b>	(~140 mcg) \$0.75	(~2.5-4mg) \$12.50-22.00	(~300-400mcg) \$3.00-4.00

<sup>a</sup> time required for 50% reduction in blood concentration after discontinuation of a steady state infusion

<sup>b</sup> based on a 30 minute procedure for 70 kg patient

Remifentanil has a similar onset but a significantly shorter offset of action compared to alfentanil or fentanyl. Its context-sensitive half-time (related to duration of action) is constant and independent of the duration of the infusion. In contrast, alfentanil possesses the potential to accumulate due to its longer terminal half-life and hepatic clearance.

The brief duration of action of remifentanil allows for intense analgesia without residual respiratory depression post-operatively. It appears to be best suited in settings where a potent, short-acting opioid is required and there is little associated post-procedure pain. As such, remifentanil has been approved for lithotripsy use only.

(continued from page 5)

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## Adverse Drug Reaction Report 1997

There were a total of 28 suspected adverse drug reactions (ADRs) reported at VHHSC in 1997 (Table 5). Of note, 12 reactions were considered to have been the cause of hospitalization, 2 reactions resulted in extended durations of hospital stay, and one patient death was related to an ADR (amiodarone-associated pneumonitis).

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 pharmacy, or call local 62481 (VGH site) or local 27249 (UBC site). Pharmacists complete all ADR forms and forward copies to the BC Drug and Poison Information Centre (DPIC). DPIC forwards all reports to the Canadian ADR program in Ottawa for collation.

**Table 5. Adverse Drug Reactions Reported in 1997**

Allopurinol <sup>1</sup>	maculopapular rash over body (1)
Amiodarone <sup>1,3</sup>	hypersensitivity pneumonitis (2)
Carbamazepine	rash, elevated liver function tests (1)
L-Carnitine (oral)	headaches, nausea, vomiting (1)
Cotrimoxazole	leukopenia (1)
Ephedrine (in Powertrim®) <sup>1</sup>	myocardial infarction (1)
Erythromycin	partial hearing loss (1) rash with fever and pruritis (1)
Glucosamine <sup>1</sup>	rash to 50% BSA - erythematous, targetoid, papular plaques with hemorrhagic bullae (1)
Heparin <sup>2</sup>	thrombotic thrombocytopenia requiring amputation (1)
Isotretinoin <sup>1</sup>	erythema multiforme (1)
Mupirocin oint	periorbital, cheek and lip edema with rash and pruritis (1)
Nadolol	pinpoint, erythematous, itchy rash (1)
OKT3 <sup>1</sup>	loss of vision (central retinal artery occlusion) (1)
Olanzapine	alopecia (1)
Phenytoin/Phenobarb	erythema multiforme (1)
Prednisone	psychosis (1)
Quinapril <sup>1</sup>	hypoglycemia (1)
Rubella vaccine <sup>1</sup>	cellulitis and abscess at injection site (1)
Sertraline	post-withdrawal myocardial infarction (1)
Tc-99m-Sestamibi	itchy rash on hands within 10 minutes of injection (1)
Tetracaine/Dipivefrin eye drops	periorbital swelling, stinging, itchiness (1)
Thalidomide	numbness of feet and ankles with pain (1)
Ticlopidine <sup>1</sup>	elevated liver function tests with epigastric pain, fatigue, nausea and vomiting (1)
Timolol 0.5% eye drops <sup>1</sup>	bradycardia (1)
Trazodone	nightmares (1)
Vancomycin <sup>2</sup>	acute renal failure (1)
Venlafaxine <sup>1</sup>	ventricular tachycardia (1)

<sup>1</sup> hospitalized due to ADR

<sup>2</sup> ADR extended duration of hospitalization

<sup>3</sup> one patient death due to ADR