VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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In This Issue...

Changes to Formulary

Additions

1. **Morphine Extended Release capsules 10,15,30,60,100,200mg (M-Eslon®)**
- to replace MS Contin® tablets
- capsules may be opened and the sprinklets added to foods or liquids
- cost $0.30/30mg BID (comparison: MS Contin® $0.60/30mg BID)

2. **Desflurane 240mL (Suprane®)**
- inhalational anesthetic for maintenance of general anesthesia

3. **Clodronate 300mg ampoule (Bonefos®, Ostac®)**
- bisphosphonate indicated in the management of hypercalcemia of malignancy, osteolytic bone metastases and Paget's disease
- Cost: $99.00/1500mg IV (comparison pamidronate $307-512/60-90mg IV)

4. **Aerosol Cloud Enhancer (ACE®) Spacer Device**
- spacer device to be used with a metered dose inhaler to improve inhalation of medication
- cost: $7.65/device (comparison Aerochamber® $10.95/device)

Deletions

1. **Morphine Sustained Release tablets (MS Contin®)**
- alternative: M-Eslon® capsules

Updated Policies/Procedures

1. Ranitidine-Cimetidine Interchange

Currently, cimetidine is the reference-based H-2 receptor antagonist in B.C. for outpatients. As there are an average of 15 cimetidine prescriptions per month for patients admitted to VHHSC, the Drugs and Therapeutics Committee has chosen to implement an automatic substitution from cimetidine to raniditine. Ran-

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itidine remains the sole H-2 receptor antagonist on the hospital formulary due to equal efficacy, fewer side effects and drug interactions, and lower cost than cimetidine.

Commencing October 14,1997, all prescriptions for oral cimetidine will be automatically substituted with oral ranitidine at the dosage equivalence as listed in the following table. Should a physician prescribe cimetidine and write "do not substitute", cimetidine supplies will be procurred for the duration of patient stay.

Table 1. Dosage Equivalence for Cimetidine and Ranitidine

Cimetidine Daily Dose	Ranitidine Daily Dose
< 800mg	150mg
≥ 800mg	300mg[1]
2400mg	600mg[1]

[1] if cimetidine is prescribed at an interval > once daily, ranitidine is converted to twice daily dosing

2. TPN Signing

All initial TPN orders written by ICU, GI or surgical residents must be co-signed by a staff physician prior to dispensing. Subsequent orders are to be reviewed with a staff physician at least once weekly.

3. Prevention of Chemotherapy Administration Errors

In order to prevent intrathecal administration of a chemotherapy agent intended for the parenteral route (intravenous, subcutaneous), a red auxiliary label stating :
"CAUTION - NOT FOR INTRATHECAL USE"
will be attached onto the barrel and plunger tip of all syringes for vinblastine, vincristine, bleomycin and cytarabine arabinoside.

4. Revised Drug Administration Policies

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

- **Diltiazem injection** may be administered **on any nursing unit.** On general nursing units, the direct IV route must be administered by a physician. Diltiazem infusions are still restricted to critical care areas.

- The **maximum peripheral concentration** for **potassium phosphate** injection is **15mMol phosphate/250mL** IV solution. More concentrated solutions must be given centrally.

5. New Spacer Device to replace Aerochamber®

We have switched the spacer device to be used with a metered dose inhaler (MDI) from Aerochamber® to ACE® (Aerosol Cloud Enhancer). There are several advantages to this product: 1) it can be used in ventilated patients and those receiving high flow oxygen (a mask can be attached; 2) there is a greater amount of medication in the respirable range; 3) the ACE® is less costly compared to the Aerochamber®; and 4) the device can be cleaned and recycled.

The main difference with this spacer device is that the MDI canister is removed from the outer shell and then placed in the device. Pharmacy will include an instruction sheet illustrating appropriate use of the ACE® device with each prescription. After the patient is discharged, the device should be placed in the soiled respiratory equipment bin for cleaning. The devices should not be sent home with the patient.

6. VHHSC Formulary - 1997

All hospital drug formularies have been upa-

Olanzapine and Bone Marrow Suppression - An Update

Dr. Karen Shalansky, Pharmacotherapeutic Specialist
Reviewed by Dr. S. Flynn, Psychiatry, Dr. P. Loewen, Dr. P. Jewesson, Pharmacy

Olanzapine, clozapine and risperidone are currently available antipsychotic agents that purport to have "atypical" side effect and efficacy profiles. Olanzapine has recently been added to formulary and is pharmacologically and structurally related to clozapine.

The product monograph for olanzapine states that there are no data to suggest olanzapine adversely affects bone marrow function, even in patients with a history of clozapine-associated neutropenia or leukopenia.[1] However, the monograph also reports an incidence of blood dyscrasias as listed in the following table (refer to definitions):

Table 2. Incidence of leukopenia and neutropenia from antipsychotics

Drug	Leukopenia (%)	Neutropenia (%)
Olanzapine[1] Haloperidol[1] Placebo[1]	1.0%[a] 1.3%[a] 0.0%[a]	2.1%[b] 2.6%[b] 1.3%[b]
Risperidone[2]	rare	not reported
Clozapine[3]	not reported	3.0%[c] 0.7% agranulocytosis
Phenothiazines (e.g. chlorpromazine)[4]	~ 1 in every 3 patients	0.01% agranulocytosis

[a] reported as WBC $\leq$ 3.0 x 10^9/L
[b] reported as neutrophil count $\leq$ 1.5x 10^9/L
[c] reported as granulocytopenia

In a previous edition of this newsletter (June 1997), we described some preliminary local reports of olanzapine-associated bone marrow suppression. Further information is available and we are now able to describe 4 cases (3 original and 1 additional case) in greater detail.

Three cases involved the early replacement of clozapine with olanzapine in patients who had developed acute clozapine-related decrease in granulocytes.[5] Two patients were granulocytopenic and one had a granulocyte count of 1.8 x 10^9/L at the time olanzapine was initiated. All 3 patients developed worsening granulocytopenia with one developing agranulocytosis requiring granulocyte-macrophage colony-stimulating factor (GM-CSF). Granlocyte count recovery to greater than 1.5 x 10^9/L took a mean of 24.3 days following olanzapine discontinuation. Mean recovery time for clozapine-induced granulocytopenia when olanzapine was not initiated was 3.4 days (range 1-9).[5] Olanzapine was subsequently reinstituted in one patient following count recovery with no further sequelae. These cases suggest that olanzapine, as with most antipsychotics and many other medications, should be avoided when possible in patients with acute clozapine-induced depression of granulocytes until count recovery has occurred.

The fourth case involved a mild neutropenia (not agranulocytosis as previously reported) in a patient receiving olanzapine and paroxetine. Granulocytes decreased from a baseline of 4.0 x 10^9/L to 1.8x 10^9/L within 7 weeks of initiation of olanzapine. The patient had complaints of a sore throat. Olanzapine was discontinued and the granulocyte count recovered to greater than 2.0 x 10^9/L within 9 days.

These cases suggest that olanzapine, in common with most antipsychotics, may be associated with bone marrow dysfunction. While too rare to warrant hematological monitoring, clinicians should be aware of this side effect.

References

DEFINITIONS[6]:
Leukopenia: WBC < 4 x 10^9/L
Neutropenia: mild - neutrophil count 1.0-2.0 x 10^9/L
mod - neutrophil count 0.5-1.0x 10^9/L
severe - neutrophil count < 0.5x 10^9/L
Granulocytopenia: granulocyte count < 1.5x 10^9/L
Agranulocytosis - granulocyte count < 0.5x 10^9/L

Granulocytes = neutrophils, basophils, eosinophils

1. Zyprexa® product monograph, Apr 29, 1997.
2. Risperdal® product monograph, Mar 14, 1997.
3. Clozaril® product monograph, CPS 1997.
4. Phenothiazine-induced agranulocytosis and leukopenia. Micromedex Consults, Dec 1995.
5. Flynn SW et al. Prolongation of clozapine-induced granulocytopenia associated with olanzapine. (In Press)
6. Berkow R, ed. The Merck Manual of Diagnosis and Therapy, 16th ed. Merck Research Laboratories:NJ;1992.

New Drugs/Drug Products

CLODRONATE (BONEFOS®, OSTAC®)

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Parenteral clodronate, a bisphosphonate, has been added to formulary as a replacement for pamidronate in the management of hypercalcemia of malignancy, osteolytic bone metastases and paget's disease. Pamidronate will still remain on formulary as part of the BC Cancer Agency multiple myeloma protocol.

Bisphosphonates (clodronate, pamidronate, etidronate, alendronate) act to regulate bone metabolism, primarily by inhibiting osteoclast-mediated bone resorption. A double-blind study of 41 patients with hypercalcemia of malignancy (serum calcium >2.7 mmol/L) compared pamidronate 90mg IV to clodronate 1500mg IV.[1] The number of patients achieving normocalcemia was similar, although the duration of response with pamidronate was longer (Table 3). Due to the significantly lower cost of clodronate, there is an anticipated annual cost savings of $22,000-35,000.

Table 3. Clodronate and Pamidronate for Treatment of Hypercalcemia of Malignancy

Drug	Clodronate IV	Pamidronate IV
Onset of Action[1,2]	within 2 days	1-2 days
Normocalcemia[1,2]	3-5 days	3-7 days
Median Duration of Effect[1,3]	14 days (range 7-21)	14-28 days (range 10-28)
Adverse Effects from IV Administration[1]	mild-moderate serum creatinine increase	flu-like symptoms, fever >1ºC up to 48hrs
Dose	1500mg IV x 1	60-90mg IV x 1
Cost	$99.00	$307.00-512.00

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1. Purohit OP et al. Brit J Cancer 1995;72:1289-9.
2. Plosker GL, Goa KL. Drugs 1994;47:945-82.
3. Nussbaum SR et al. Amer J Med 1993;95:297-304.

Low Molecular Weight Heparins For DVT Prophylaxis In Orthopedics

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Introduction

Deep-vein thrombosis (DVT) is a major source of morbidity and mortality in high risk orthopedic patients. Approximately 50% of these patients will develop DVT and up to 20% will develop pulmonary embolism (PE) in the absence of prophylaxis.[1-3] At VHHSC, two low molecular weight heparins (LMWH), tinzaparin and enoxaparin, were recently approved for DVT prophylaxis in patients with spinal cord injury, knee arthroplasty and major trauma.

Comparative Studies

Several randomized studies assessing the efficacy of LMWHs for DVT prophylaxis in high risk orthopedic patients have been published (Table 4).[4-8] An important consideration in the evaluation of these studies is the method of DVT detection employed. The most sensitive and specific method for detection is contrast venography. Bilateral venography provides a more accurate representation than unilateral leg venography which can significantly underestimate DVT incidence. Furthermore, the comparator agent employed is dependent on the patient population studied. With knee arthroplasty, warfarin (INR 2-3) offers the most valid comparison and is recommended in this setting since low-dose heparin has shown inferior results.[9] In spinal cord injury and major trauma patients, low-dose heparin (5000 units SC BID-TID) is the comparator for DVT prevention.

In the single study available in spinal cord injury patients, tinzaparin 3500 IU SC daily was compared to heparin 5000 IU SC TID.[4] The incidence of total and proximal DVTs was significantly lower in the tinzaparin group as compared to the heparin group.

Of the 3 trials available in the knee arthroplasty population, two involved enoxaparin in a 30 mg

SC q12h regimen[6,7] while the remaining trial involved tinzaparin 75 IU/kg SC daily.[5] In all 3 studies, the incidence of total DVTs was significantly reduced in the LMWH group as compared to the warfarin group. In only one of these studies was there a significant difference in the incidence of proximal DVTs in favour of the LMWH group.[7] However, this study employed unilateral venography for DVT detection and is available only in abstract form. There were no differences in the rates of PE among treatment groups in any of these studies.

One study has been published in the major trauma population comparing enoxaparin to heparin.[8] In this study, enoxaparin 30 mg SC q12h was significantly more effective than heparin 5000 IU SC q12h in reducing the incidence of total and proximal DVTs.

All of the studies comparing LMWHs to either warfarin or heparin have shown a significant benefit in favour of the LMWHs with regards to development of total DVTs. However, the effects of LMWHs in reducing proximal DVTs, which carry a higher risk of PE, have been inconsistent.

To date, there are no head-to-head trials comparing the various LMWHs. The available evidence in knee arthroplasty patients suggest similar efficacy and bleeding rates with tinzaparin and enoxaparin.

Adverse Effects

Table 4. Summary of Controlled DVT Prophylaxis Trials in Orthopedics Involving a Valid Comparator

Ref.	Design	Drug/Dose	N	Method of DVT Diagnosis	Total DVT (%)	Prox. DVT (%)	PE (%)	Major Bleed (%)
Spinal Cord								
Green 1990[4]	P,R,NB	H 5000 SC q8h T 3500 SC daily	21 20	Symptoms & serial venous flow studies; confirmation by venography	14.2 0[1]	14.2 0[1]	9.5 0	9.5 0
Knee Replacement								
Hull 1993[5]	P,R,DB	W (INR 2-3) T 75 IU/kg SC daily	324 317	Bilateral contrast venography	54.9 45.0[1]	12.3 7.8	n/a n/a	0.9 2.8
Leclerc 1996[6]	P,R,DB	W (INR 2-3) E 30mg SC q12h	334 336	Bilateral contrast venography	51.7 36.9[1]	10.4 11.7	0.9 0.3	1.8 2.1
Spiro 1994[7]	P,R,NB	W (INR 2-3) E 30mg SC q12h	176 173	Unilateral contrast venography	45.4 25.4[1]	11.4 1.7[1]	0.6 0	2.3 5.2
Major Trauma								
Geerts 1996[8]	P,R,DB	H 5000 SC q12h E 30mg SC q12h	136 129	Bilateral contrast venography	44 31[1]	15 6[1]	n/a n/a	0.6 2.9

N=number of patients; P=prospective; R=randomized; NB=non-blinded; DB=double-blinded; H=unfractionated heparin; T=tinzaparin; W=warfarin; E=enoxaparin; n/a = not available

[1] $p<0.05$

The risk of bleeding was not statistically different between the LMWH group and the comparator agent in any of the above studies. In one trial involving knee arthroplasty patients, the risk of major bleeding with enoxaparin was more than two-fold higher than with warfarin (5.2% vs 2.3%).[7] This incidence of major bleeding with enoxaparin was similar to the 5.0% incidence reported by Knudson *et al* in major trauma patients treated with this agent.[10] LMWHs may also cause thrombocytopenia with a reported incidence of <3%. Although the optimal frequency of monitoring the complete blood count (CBC) is unknown, the current recommendation is for twice weekly CBC monitoring for all patients receiving LMWHs.

Comparative Costs

As there is no scientific evidence to support superior efficacy and safety of one LMWH over another, cost considerations in the choice of a LMWH become imperative (Table 5). The annual cost savings associated with prescribing tinzaparin versus enoxaparin averages approximately $100,000 in this high risk population.

Table 5. Cost Analysis for DVT Prophylaxis

[a]Acquisition cost quotes provided by the manufacturers to the Logistics Department at VHHSC in May 1997

Drug	Tinzaparin	Tinzaparin	Enoxaparin
Regimen	3500 IU SC daily[b]	5250 IU SC daily[c]	30mg SC BID
Cost[a] ($/day)	5.60	8.40	12.07
Cost ($/7 days)	39.20	58.80	84.49
Cost[a] ($/90 days)	504.00	756.00	1086.30

[b] Dose of 50 IU/kg for a 70kg patient
[c] Dose of 75 IU/kg for a 70kg patient

Formulary Recommendation

Tinzaparin is currently the only formulary LMWH agent at VHHSC approved for the treatment of established DVT. Based on the available scientific evidence and cost considerations, the Drugs and Therapeutics Committee recommended expansion of the current hospital-approved indication for tinzaparin to include DVT prophylaxis in spinal cord injury and knee arthroplasty patients. In recognition of the lack of published data involving tinzaparin in major trauma, this Committee recommended approval of the addition of enoxaparin to the formulary restricted to DVT prophylaxis for patients with major orthopedic trauma (non-spine).

The Medical Advisory Committee has requested that an external analysis be performed by the Pharmacoeconomic Initiative Scientific Committee (PISC) and BC Office of Health Technology Assessment (BCOHTA). This report is expected to be available by the Fall of 1997. Until then, both LMWHs will be available for DVT prophylaxis for major orthopedic sugery, spinal cord injury, and total knee arthroplasty. Preprinted order forms have been created to facilitate prescribing of the LMWHs pending the decision of the PISC/BCOHTA review.

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