VANCOUVER HOSPITAL & Health Sciences Centre

DRUG AND THERAPEUTICS NEWSLETTER

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In This Issue...

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

1. Isosulfan Blue (Lymphazurin®)

- Used for lymphatic mapping in sentinel node biopsy procedures for breast cancer and melanomas

Updated Policies/Procedures

1. Ceiling Dose for Simvastatin in Renal Failure

A revision to the statin Therapeutic Interchange Policy places a ceiling dose for simvastatin of 40mg daily for patients with creatinine clearances less than 30mL/minute. For example, atorvastatin 40mg would normally convert to 80mg simvastatin. However, in patients with creatinine clearances less than 30mL/minute, the maximum dose for simvastatin conversion would be 40mg. This ceiling dose is due to an increased risk of myopathy in renal failure.

2. Health Care Team's Obligations In Carrying Out Medication Orders

No member of the healthcare team is obliged to participate in the preparation, dispensing, or administration of any medication that is unsafe or contrary to hospital policy (e.g. Parenteral Drug Therapy Manual Policy). Refusal to carry out a medication order must be discussed with the supervisor and prescribing physician.

3. Critical Care Compatibility Chart

A yellow Critical Care Y-site injection drug compatibility chart has been posted in all critical care areas This chart is in addition to the white Y-site compatibility chart (general drugs) already on the nursing units. Please contact Dr. Karen Shalansky at 604-875-4839 if you require further copies of this chart.

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4. Verbal/telephone Orders

The following revised policy will appear in the green pages of the next formulary update (May/2003):

Safety is the overriding principle in accepting verbal or telephone orders. Verbal and telephone orders have a higher potential for errors as these orders can be misheard, misinterpreted and /or mistranscribed.

POLICY

- Verbal and telephone orders may be accepted by a registered nurse, licensed practical nurse, respiratory therapist, or a pharmacist when it is impossible or impractical for the physician to write them.
- Licensed practical nurses (LPNs) (see criteria in Formulary policy 5.1, green pages) may accept medication orders for assigned stable patients (i.e. adult populations whose outcomes are predictable) in designated patient care units for medications administered by the enteral, percutaneous, intramuscular and subcutaneous routes (excluding intravenous and intrathecal routes).
- Respiratory therapists may accept orders for medications which they are approved to administer as per Formulary policy 5.1 and their professional practice guidelines.
- Verbal and telephone orders for chemotherapy drugs may not be taken by anyone except a pharmacist.
- Generic drug names should be used when drug orders are given.
- Abbreviations should be avoided when an order is given or received.

PROCEDURE

1. The physician identifies self, specifies the patient's name, and communicates the order.
2. The receiver:
   - documents the order immediately on the physician's order form including the date, time, physician's name and pager number/ service, receiver's name, status, and signature
   - repeats the order back to the physician including the:
     - patient name
     - drug name and spelling of the drug to avoid an error due to sound alike drugs
     - dosage, pronouncing it in single digits (e.g. 15 mg should be read as one five)
     - route
     - frequency (e.g. three times daily, not TID)
   - requests the indication for the medication to assist in avoiding errors.
   - questions the physician if there is any uncertainty regarding the order.
3. The physician must countersign the order within 24 hours (or as soon as possible) after communicating the order.

5. Modification to Heparin/Warfarin Standardized Protocol

The VGH Laboratory recently switched to using new equipment and reagent for measuring aPTT. As a result, the **therapeutic aPTT range** (based on anti-Xa heparin levels) **has increased to 60-85 seconds** from 51-75 seconds. This new range corresponds to anti-Xa heparin levels of 0.4-0.6 U/ mL. This range is in keeping with the current American College of Chest Physicians guidelines which recommend a target aPTT range equivalent to heparin levels of 0.3-0.7 U/mL for DVT and PE.[1]

Note that the CCU Heparin Protocol will remain unchanged with a therapeutic aPTT range of 51-75 seconds. This range corresponds to anti-Xa heparin levels of 0.3-0.5 U/mL. This range is to correspond with the American Heart Association Guidelines that recommend lower heparin dosing relative to treatment of venous thrombosis.[2] Patients in the CCU frequently receive additional potent anti-thrombotic agents (e.g. glycoprotein inhibitors, aspirin, clopidogrel, fibrinolytics) which can increase the risk of bleeding with heparin

References

1. Hirsh J et al. Heparin and low-molecular-weight-heparin. Chest 2001;119:69S.
2. Braunwald E et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction. 2002 (www.acc.org/ clincal/guidelines/unstable/unstable.pdf)

6. Revised Drug Administration Policies

- There is now only **one standard concentration of ketamine for intravenous infusions: 0.5mg/mL**. The standard concentration for subcutaneous infusions remains at 5mg/mL.

- **Erythropoietin** (EPO) should **not be left out** of the fridge for **greater than 1 hour**. The **multidose vial should not be shaken** and will be sent to the wards via the dumbwaiter or special messenger only.

Cardiovascular Effects of COX-2 Inhibitors

Roxane Carr, Pharm.D., Karen Shalansky, Pharm.D., FCSHP, Rubina Sunderji, Pharm.D., FCSHP

The cyclooxygenase-2 (COX-2) inhibitors, rofecoxib (Vioxx®), celecoxib (Celebrex®) and meloxicam (Mobicox®), were developed with the goal of providing similar efficacy and greater safety with respect to adverse gastrointestinal (GI) effects compared to traditional non-steroidal anti-inflammatory drugs (NSAIDs).

There have been two large randomized, comparative trials of COX-2 inhibitors with NSAIDs. The Vioxx Gastrointestinal Outcomes Research (VIGOR)[1] trial compared rofecoxib 50mg daily with naproxen 500mg twice daily in 8076 patients with rheumatoid arthritis for a median of 9 months. Both drugs displayed similar efficacy but there was a significantly lower incidence of complicated GI events (perforation, obstruction, severe upper GI bleeding) in the rofecoxib group (rofecoxib 0.40% vs naproxen 0.92%, p=0.005). The Celecoxib Long-Term Arthritis Safety Study (CLASS)[2] consisted of two separate trials: celecoxib 400mg twice daily compared to diclofenac 75mg twice daily or ibuprofen 800mg 3 times daily. Six month interim analysis of 4573 patients revealed no significant differences in the primary end point of ulcer perforation, gastric-outlet obstruction, or upper GI bleeding (celecoxib 0.8% vs NSAID group 1.5%, p=0.09).

Recently, information suggesting a potential risk of cardiovascular (CV) events in patients taking COX-2 inhibitors has emerged from a subgroup analysis of the VIGOR trial[1] and numerous case reports to Health Canada.

Data Assessing CV Events with COX-2 Inhibitors

Health Canada

Table 1 demonstrates all adverse events from COX-2 inhibitors from date of marketing to Oct 2001.[3] The primary adverse CV events were increased blood pressure, heart rate/rhythm disturbances, and CHF.

Randomized Controlled Trials

Although not a primary endpoint, CV events were assessed in the VIGOR[1] trial because it was known that rofecoxib does not inhibit platelet aggregation and the possibility existed that the incidence of thrombotic events may be lower among patients treated with traditional NSAIDs. The rofecoxib arm had an higher rate of the composite endpoint of nonfatal myocardial infarction (MI), nonfatal stroke, and death from any vascular event (0.8% rofecoxib vs 0.4% naproxen, p<0.05). The rates for myocardial infarction (MI) alone were 0.4% in the rofecoxib arm and 0.1% in the naproxen arm (p< 0.01). The use of aspirin, ticlopidine or anticoagulants was an exclusion criterion for this study. Of note, 4% of the patients studied met FDA criteria for secondary prophylaxis with ASA for CV events; this group accounted for 38% of the patients who had a MI.

Table 1. Health Canada Adverse Reaction Report (from date of marketing to October 2001)[3]

Drug	Celecoxib	Rofecoxib	Meloxicam
Date Marketed in Canada	April 1999	November 1999	September 2000
Suspected Reports of CV Events	70	68	2
History of CV Disease	42	36	-
Fatal Outcome	7	9	-
Types of CV Events¶			
High Blood Pressure	20	21	1
Heart Rate/Rhythm Disorders	24	20	-
Myocardial Infarction	8	9	1
Angina	-	2	-
CHF	7	17	-
Cerebrovascular Event	10	9	-
Thromboembolism	8	-	-

CV = cardiovascular; CHF = congestive heart failure
¶more than 1 event may be contained in a given report

The CLASS[2] trial did not show any difference in cardiovascular events (stroke, MI, angina) between the two groups (celecoxib 0.9% vs NSAID groups 1.0%). Patients were allowed to take up to 325mg ASA per day. Approximately 21% of patients in both treatment arms took ASA and 1% of patients in each group were taking anticoagulants.

Whelton *et al* published a 6-week trial comparing celecoxib 200mg and rofecoxib 25mg with respect to their effects on cardio-renal function in 810 older (> 65 years) hypertensive patients with osteoarthritis.[4] Significant differences in blood pressure (rofecoxib 17% vs celecoxib 11%, p=0.032) and edema (rofecoxib 9.5% vs celecoxib 4.9%, p=0.014) were found. Four patients, all in the rofecoxib group, developed congestive heart failure (CHF). Of note, more patients in the celecoxib arm were treated with angiotensin-converting enzyme inhibitors (40.3% vs 29.1% rofecoxib) which could account for the higher event rate of CHF and elevated blood pressure with rofecoxib.

A review of eight double-blind, placebo controlled phase IIb/III osteoarthritis trials (n=5435) failed to show a difference in the risk of CV events between rofecoxib 12.5-25mg (i.e. lower than VIGOR trial dose of 50mg), traditional NSAIDs (diclofenac, ibuprofen or nabumetone) and placebo.[5] The median exposure to study drugs was 8 months.

Retrospective Observations

A retrospective cohort study evaluated the risk of coronary heart disease (CHD) in 251,046 users of COX-2 inhibitors and NSAIDS (primarily ibuprofen and naproxen) and 202,916 non-users.[6] Those on high-dose rofecoxib (> 25mg daily) had a 70% higher rate of serious CHD compared to celecoxib and non-users. This rate was only significant in new users of high-dose rofecoxib with a cardiac event rate of 1.93 (95% CI 1.09-3.42, p=0.024) compared to the latter 2 groups. In contrast, the risk of CHD did not increase amongst users of lower dose rofecoxib (≤ 25mg daily), or usual and high doses of celecoxib, naproxen and ibuprofen.

Two short-term, large, retrospective studies provide evidence against CV risks with COX-2 inhibitors. Newly diagnosed MI or hypertension occurring within 90 days of receiving either meloxicam (n=4359) or NSAIDS (n=10,000 for diclofenac, naproxen and piroxicam) was compared.[7] In no instance was meloxicam associated with an increased CV risk. A second study involving over 70,000 new users of NSAIDs or COX-2 inhibitors found no significant difference in short-term (within 30 days) MI risk between celecoxib, rofecoxib or other NSAIDs compared to 100,000 non-NSAID users.[8] Specific information on doses was not given in either of these trials.

In summary, several suspected adverse CV events from COX-2 inhibitors have been reported to Health Canada. Two large studies, one randomized and one retrospective, demonstrated that high dose rofecoxib (> 25mg daily) was associated with increased CV events.

Prothrombotic Mechanism

COX-1 enhances the conversion of arachidonic acid to thromboxane A2. Thromboxane A2 is a prothrombotic agent synthesized in platelets, and causes platelet aggregation, vasoconstriction and smooth muscle proliferation.[9] COX-1 is also responsible for producing prostaglandins that mediate protection of the GI mucosa. Inhibition of COX-1 is considered to result in both the antiplatelet effects and undesirable toxic GI effects (GI perforation, ulcer, bleeding) of NSAIDs.[9-11]

COX-2 catalyzes the conversion of arachidonic acid to prostacyclin, an antithrombotic agent synthesized in vascular endothelium.[9] Prostacyclin causes vasodilation and inhibits platelet aggregation. COX-2 is also responsible for production of inflammatory prostaglandins. Inhibition of COX-2 is considered responsible for the anti-inflammatory and analgesic effects of NSAIDs.[9,11]

At therapeutic doses, COX-2 inhibitors selectively inhibit COX-2, whereas NSAIDs inhibit both COX-1 and COX-2 to varying degrees[3,9] (Table 2). Unlike rofecoxib and celecoxib, meloxicam has dose

Table 2. COX Inhibition and Thrombotic Risk[9]

	COX-1	COX-2	Thrombotic Risk
Low-Dose ASA	↓	-	↓
Traditional NSAIDs	↓	↓	Unclear
COX-2 Inhibitors	-	↓	?↑

dependent COX-1 inhibition which is incomplete at anti-inflammatory doses.[3]

The selective inhibition of the prothrombotic thromboxane A2 synthesis by low dose ASA is thought to be the mechanism by which ASA reduces the incidence of CV death, MI and stroke.[9,10] Conversely, when COX-2 inhibitors are used, a selective reduction in prostacyclin may tip the balance in favour of the prothrombotic effects of thromboxane A2, potentially leading to CV adverse events.[11]

Conclusion

Until more prospective, randomized trials specifically investigating the association between COX-2 inhibitors and CV risk are done, a causal relationship cannot be determined. In the interim, caution should be used in prescribing these agents to patients at risk of CV disease, particularly rofecoxib doses greater than 25mg daily. Importantly, patients should continue on ASA for primary or secondary CV prophylaxis while taking COX-2 inhibitors. Patients should also be instructed to monitor for signs of chest pain or congestive heart failure (ie. shortness of breath, swelling of lower extremities , fatigue).[3]

References

1. Bombardier C et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis (VIGOR STUDY). NEJM 2000;343:1520-9.
2. Silverstein FE et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. (CLASS STUDY) JAMA 2000;284:1247-55.
3. Vu D et al. Selective COX-2 inhibitors: suspected cardiovascular/cerebrovascular adverse reactions. Canadian Adverse Reaction Newsletter 2002;12:1-3. (www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/publicat/adrv12n2_3.html)
4. Whelton A et al. Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Amer J Ther 2001;8:85-95.
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6. Ray WA et al. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-3.
7. Jick SS. The risk of gastrointestinal bleed, myocardial infarction, and newly diagnosed hypertension in users of meloxicam, diclofenac, naproxen, and piroxicam. Pharmacotherapy 2000;20:741-44.
8. Mamdani M et al. Effect of selective cyclooxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003;163:481-6.
9. Catella-Lawson F et al. Cyclooxygenase inhibition and thrombogenicity. Am J Med 2001;110(3A): 28S-32S.
10. Fitzgerald GA et al. The coxibs, selective inhibitors of cyclooxygenase-2. NEJM 2001;345:433-42.
11. Mukherjee D et al. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001;286:954-9.

Pharmacy Awards

Further research awards, in addition to those mentioned in our last newsletter (Dec 2002), have been given to various members of the Pharmaceutical Sciences CSU by the Canadian Society of Hospital Pharmacists (CSHP):

Vivian Leung B.Sc.(Pharm), Rubina Sunderji, Pharm.D., FCSHP, Peter Zed, Pharm.D.

- CSHP/Merck Frosst Award for their research paper co-authored with Dr. Ken Gin entitled "Switching from abciximab to eptifibatide for percutaneous coronary interventions: a local analysis (SWAP) study".

Robert Balen, Pharm.D.

- CSHP/Apotex Award for his research co-authored with Elaine Chong entitled "Education via streaming media in a large Canadian tertiary care teaching hospital".

Anne Dar Santos, B.Sc. (Pharm), Karen Shalansky, Pharm.D., FCSHP

- CSHP/Roche & Pharmacia Award for their research co-authored with Dr. J. Jastrzebski entitled "Multidisciplinary approach to erythropoietin resistance in a hemodialysis unit".

Adverse Drug Reaction Report 2002

There were a total of 30 suspected adverse drug reactions (ADRs) reported at VHHSC in 2002 (Table 1). Of note, 7 reactions were considered to have been the cause of hospitalization, 2 resulted in prolonged hospitalization and 9 required admission to the emergency department. 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 forwards them to the World Health Organization.

Table 1. Adverse Drug Reactions Reported in 2002

Drug	Suspected ADR	Drug	Suspected ADR
ASA and Ibuprofen	Acute upper GI bleed[a,c] (1)	Iron Sucrose (Venofer®)	Anaphylaxis (2); back pain, hypotension (1)
Alteplase (rtPA)	Intracerebral hemmorhage[b] (1)	Linezolid	Full body rash (1)
Atorvastatin	Proximal muscle weakness (1)	Metoclopramide	Altered mental status, abnormal eye movements (1)
Ciprofloxacin	Acute renal failure, fever, macular rash to entire body[a,c] (1); acute interstitial nephritis[b] (1); throat swelling (1)	Meloxicam and Prednisone	Upper GI bleed[a,c] (1)
Ciprofloxacin and Phenytoin	Maculopapular rash (1)	Metformin	Lactic acidosis (1)
Clarithromycin	Steven's-Johnson syndrome[a,c] (1)	Pantoprazole	Full body rash (1)
Clarithromycin and Glyburide	Hypoglycemia[c] (1)	Ramipril and Glyburide	Hypoglycemia (1)
Erythropoietin	Pure red cell aplasia[a] (1)	Quinupristin/ Dalfopristin (Synercid®)	Myalgias and arthralgias (1)
Fenofibrate	Acute cholecystitis complicated by acute myocardial infarction[a,c] (1)	Rofecoxib and Warfarin	Elevated INR (1)
Furosemide and Metoprolol	Maculopapular rash (1)	Simvastatin	Myopathy in legs (1)
Gabapentin	Anaphylaxis[c] (1)	Tacrolimus	Worsened diabetic control (1); Alopecia (1)
Haloperidol	Oculogyric crisis (1)	Warfarin	Intracerebral hemorrhage[a,c] (1)
Iron Dextran (Dexiron®)	Anaphylaxis[c] (1)		

[a]hospitalized due to ADR ; [b] prolonged hospitalization due to ADR; [c] emergency department admission