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Canadian Adverse Reaction Newsletter

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In This Issue

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk-benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada toll free

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Form available at:

www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf

Marketed Health Products Directorate

A new directorate within Health Canada is being created in April 2002 to ensure a consistent risk-management approach for the post-approval surveillance and assessment of health products on the Canadian market. The *Canadian Adverse Reaction Newsletter* is now produced by this directorate and plays an important role in the communication of health product-related risks to health professionals and the public. As of April 2002 the newsletter will be distributed to physicians as a separate document mailed with the *Canadian Medical Association Journal*. Pharmacists, other health professionals and interested parties will continue to receive the newsletter by mail or the Internet.

Selective COX-2 inhibitors: suspected cardiovascular/cerebrovascular adverse reactions

Nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to exert their pharmacological effects through inhibition of the enzyme cyclo-oxygenase (COX). Two COX isoforms have been identified: COX-1 and COX-2. The prostaglandins produced by COX-1 play a key role in platelet aggregation and are among the factors that maintain the gastrointestinal mucosa barrier. Although COX-2 is responsible for the synthesis of mediators of pain, inflammation and fever, it plays a physiological role in a number of tissues including the female reproductive tract, the kidney and vascular endothelium. All NSAIDs inhibit both COX isoforms, but to varying degrees. At therapeutic doses used in arthritis, selective COX-2 inhibitors do not inhibit COX-1. Rofecoxib (Vioxx) and celecoxib (Celebrex) are believed to be selective COX-2 inhibitors.[1,2] Meloxicam (Mobicox) has been shown to inhibit COX-2 in several in-vitro and ex-vivo systems, while COX-1 inhibition is dose dependent and incomplete at anti-inflammatory

Table 1: Reports submitted to Health Canada of suspected cardiovascular/cerebrovascular ARs associated with selective COX-2 inhibitors from date marketed to Oct. 12, 2001*

Variable	Celecoxib	Rofecoxib	Meloxicam
Date marketed in Canada	Apr. 19, 1999	Nov. 8, 1999	Sept. 26, 2000
Total no. of AR reports	528	348	28
No. of reports with suspected cardiovascular/cerebrovascular reactions†	70‡	68§	2¶
History of cardiovascular disease	42	36	–
No history of cardiovascular disease	21	22	1
History unknown	7	10	1

Note: COX = cyclo-oxygenase.
*These data cannot be used to determine the incidence of ARs because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
†Reports of chest pain were not included owing to unspecified diagnosis.
‡Age range 4–96 years, median 66 years (age unknown in 3 cases); 38 females, 31 males (sex unknown in 1 case).
§Age range 36–90 years, median 68.5 years (age unknown in 10 cases); 39 females, 25 males (sex unknown in 4 cases).
¶Age 53 and 55 years; 2 females.

doses.[3] No significant inhibition of platelet aggregation has been observed at therapeutic doses of meloxicam.[3]

A recent meta-analysis suggested that the use of selective COX-2 inhibitors may lead to increased cardiovascular events.[4] Unlike the platelet inhibition afforded by COX-1 inhibitors, COX-2 inhibitors do not share this antithrombotic property.[4] It was postulated that selective COX-2 inhibitors decrease vasodilatory and anti-aggregatory prostacyclin production and may affect the hemostatic balance in favour of a prothrombotic state, which would lead to increased cardiovascular thrombotic events.[5] However, it is unclear whether cardiovascular effects are common to all selective COX-2 inhibitors. There have been many divergent opinions with regard to the methodology and the interpretation of the above meta-analysis.[6]

Analyses of postmarketing data based on spontaneous adverse reaction (AR) reports from the World Health Organization database suggested that the risk of renal and cardiovascular adverse events (cardiac failure, hypertension) associated with the use of rofecoxib may be significantly greater than those associated with celecoxib and other NSAIDs (diclofenac and ibuprofen).[7] Interpretation of the analysis of data from spontaneous AR reports has many limitations that must be taken into consideration.

Suspected cardiovascular/cerebrovascular ARs associated with rofecoxib (Vioxx), celecoxib (Celebrex) and meloxicam (Mobicox) reported to Health Canada from their date marketed to Oct. 12, 2001, are summarized in Table 1. Of the reports with suspected cardiovascular/cerebrovascular events, 7 (celecoxib) and 9 (rofecoxib) reports were of a fatal outcome. Most of these patients presented with multiple ARs, pre-existing medical conditions or the use of concomitant medications. The types of suspected cardiovascular/cerebrovascular reactions reported are presented in Table 2. The ARs in Table 2 represent spontaneous postmarketing reports, which are generally presumed to underestimate the risks associated with drug treatments.

When interpretating whether these cardiovascular effects are related to COX-2 inhibitors, several factors must be considered such as pre-existing medical conditions, the prevalence of cardiovascular disease in the population for whom the drugs are indicated and concomitant use of drugs that can cause cardiovascular reactions or drug interactions. Because some patients with cardiovascular conditions use anticoagulant therapy (warfarin), caution should be exercised to prevent hemorrhagic complications such as cerebrovascular hemorrhagic events with the concomitant use of COX-2 inhibitors.

Of the 7 fatal cases with cardiovascular reactions associated with celecoxib, there were 2 cases of cerebral hemorrhage in patients using warfarin concomitantly.[8] Pharmacokinetic interactions between celecoxib or meloxicam and warfarin are possible, because all these drugs have the same metabolic pathway (the CYP2C9 isozyme).[2,3] Rofecoxib, which is metabolized mainly by cytosolic enzymes[3] rather than the cytochrome P450 isozymes, may have a different mechanism of interaction with warfarin. Further information concerning this interaction and others may

Table 2: Reports submitted to Health Canada on types of suspected cardiovascular/cerebrovascular ARs associated with selective COX-2 inhibitors from date marketed to Oct. 12, 2001*

	Drug; no. of reactions		
Type of reaction	Celecoxib	Rofecoxib	Meloxicam
Increased blood pressure	20	21	1
Congestive heart failure	7	17	–
Myocardial infarction†	8	9	1
Angina	–	2	–
Heart rate and rhythm disorders‡	24	20	–
Cerebrovascular events due to hemorrhage or cause nonspecified§	9	9	–
Cerebrovascular events with clot	1	–	–
Thromboembolic events¶	8	–	–
Pericardial effusion	1	–	–
Endocarditis	1	–	–
Aortic aneurysm rupture	1	–	–
Vasculitis	3	–	–

*This table reports reactions, and each report may contain more than 1 reaction. These data cannot be used to determine the incidence of ARs because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
†Includes myocardial ischemia.
‡Includes cardiac arrest, cardiac arrhythmia, atrial fibrillation, ventricular fibrillation, heart block, sick sinus syndrome, tachycardia, ventricular tachycardia, palpitation, bradycardia.
§Includes cerebrovascular accident, stroke, transient ischemic attack.
¶Includes pulmonary embolism, deep vein thrombosis, venous arm thrombosis, limb embolism, peripheral ischemia.

Summary of health professional and consumer advisories issued since Nov. 29, 2001

Date	Product	Subject and Web address
Feb 15	Hua Fo	Herbal recall — containing sildenafil www.hc-sc.gc.ca/english/protection/warnings/2002/2002_09e.htm
Feb 12	Droperidol inj	Cardiovascular toxicity www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/droperidol_e.html
Feb 8	PC SPES / SPES	Herbals with undeclared ingredients — warfarin and alprazolam www.hc-sc.gc.ca/english/protection/warnings/2002/2002_06e.htm
Jan 16	Kava	Patient safety information — liver toxicity www.hc-sc.gc.ca/english/protection/warnings/2002/2002_02e.htm
Jan 14	Clozaril (clozapine)	Cardiovascular toxicity — myocarditis www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/clozaril_e.html
Jan 9	Ephedra/ephedrine	Recall of certain products containing ephedra/ephedrine www.hc-sc.gc.ca/english/protection/warnings/2002/2002_01e.htm

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

be obtained from the Canadian product monograph of each selective COX-2 inhibitor.[1–3]

Further investigations are required to assess possible cardiovascular risks of COX-2 inhibitors. Until then, caution should be exercised in prescribing these agents to patients at risk of cardiovascular disease.[4] Patients should be advised to report promptly any symptoms of congestive heart failure (i.e., shortness of breath, swelling of lower extremities, fatigue), chest pain or hypertension to their physician.[1–3] The benefits of using selective COX-2 inhibitors in individual patients should be carefully weighed against all possible risks.

Duc Vu, MSc, PhD; Mano Murty, MD, CCFP, FCFP; Marielle McMorran, BScPharm, Health Canada

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2. *Celebrex, celecoxib capsules* [product monograph]. Mississauga (ON): Searle Canada; 2000 Mar 6.
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Oral sodium phosphates solutions: electrolyte disturbances

Oral sodium phosphates solutions (Fleet Phospho-Soda and Phosphates Solution) are over-the-counter preparations indicated for use as laxatives and as cathartics for emptying the bowel before gastrointestinal surgery or examination (e.g., colonoscopy).

In 1998 the US Food and Drug Administration (FDA) concluded that there was insufficient data to demonstrate the safety of administering more than 45 mL of sodium phosphates in a 24-hour period as part of a bowel-cleansing regimen.[1] At that time it also recommended labeling changes and required that products carry a warning to consumers not to exceed the recommended dose of 20 to 45 mL unless directed by a physician. In September 2001 the FDA issued a safety document to inform health care professionals of the risks of electrolyte disturbances associated with oral sodium phosphates solutions used for bowel preparation.[2] It reported that serious electrolyte disturbances (hypocalcemia, hyperphosphatemia, hypernatremia and hypomagnesemia), dehydration, renal failure, tetany and death have occurred in patients who were instructed to take more than the recommended 45-mL dose as a bowel preparation and in patients at risk of electrolyte disturbances because of their medical history (e.g., congestive heart failure, ascites, renal insufficiency, dehydration, gastric retention, colitis, megacolon, ileus, inability to take adequate amounts of fluids orally, use of diuretics or other medications that affect electrolytes).[2] Even people without medical contraindications who receive more than 45 mL of oral sodium phosphates may develop shifts in electrolyte levels.[3–5] The 2001 FDA document concluded by stating that physicians need to be aware of individuals at increased risk of electrolyte disturbances. It suggested that obtaining baseline electrolyte values in people instructed to take more than 45 mL of oral sodium phosphates in a 24-hour period and in those at risk of electrolyte disturbances may help physicians to avert serious electrolyte problems.

From May 27, 1997, to Oct. 31, 2001, Health Canada received 10 domestic reports of suspected ARs to oral sodium phosphates solutions. Of the 10 reports received, 9 were classified as serious. Eight involved women and one a man; their ages ranged from 24 to 77 years (age unknown in 2 cases). There were no deaths. Nine patients took oral sodium phosphates solutions as bowel preparations; 1 patient took the solution as a laxative. Five reports involved documented electrolyte disturbances, including hypocalcemia and hyperphosphatemia. Four of the 5 patients with electrolyte imbalances had a medical history of renal insufficiency, cardiovascular disease or concomitant use of medications that affect electrolytes. At least 4 of the 10 patients ingested more than 45 mL of sodium phosphates in a 24-hour period at the instruction of a physician or hospital staff.

The recommended maximum single daily dose of oral sodium phosphates solutions is 45 mL (adult dose) when used as a purgative. However, patients are sometimes instructed to take 90 mL or more in preparation for bowel examinations.[3–5] A survey of Canadian colonoscopists demonstrated that physicians who routinely prescribe oral sodium phosphates preparations may

Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

BeneFIX: allergic reaction

A 10-year-old boy with hemophilia B (Factor IX deficiency) had an allergic reaction while receiving an infusion of BeneFIX (recombinant Factor IX). The patient experienced difficulty breathing, cyanosis, gagging, increased sweating and tremor. The infusion was stopped, and the patient recovered. Symptoms occurred while the patient received the fifth treatment of BeneFIX in a 6-month period. The patient had not previously been treated with other Factor IX products, and had no previous history of antibodies against Factor IX; however, following the reaction, antibodies against BeneFIX were detected.

not be adequately informed about the risks associated with their use.[6] Health Canada is evaluating the risks associated with these medications and is taking steps to inform health care professionals of them, especially in patients predisposed to electrolyte disturbances. A letter has been sent to the manufacturers requesting labelling changes. Patients should be informed to report to their physician symptoms related to electrolyte disturbances such as tingling skin, numbness, spasms, palpitations, muscle weakness and tremors.

Maurica Maher, MD, MSc, and Lynn Macdonald, BSP, Health Canada

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Adverse reaction reporting — 2001

Health Canada received 7389 domestic reports of suspected ARs to health products in 2001. The ARs were reported for the most part by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2.

Of the AR reports received, 5376 were classified as serious. A serious AR is defined in the Food and Drugs Act and Regulations as "a noxious and unintended response to a drug which occurs at any dose and requires inpatient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death."

A steady increase in the reporting of ARs in Canada over the past 5 years has been noted, although the number of reports received in 2001 was only slightly greater than that in 2000 (Fig. 1).

Health Canada would like to thank all who have contributed to the program and encourages the continued support of postmarketing surveillance through AR reporting. Health professionals and consumers may report ARs by using the toll-free telephone (866 234-2345) and fax (866 678-6789) lines. Your call will be directed to the appropriate AR Regional Centre. Manufacturers must continue to report ARs using the established fax line 613 957-0335.

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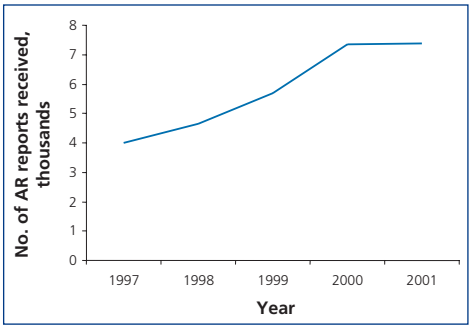

Fig. 1: Number of reports of adverse reactions received annually by Health Canada from 1997 to 2001.

Table 1: Source of reports of adverse reactions (ARs) received by Health Canada in 2000 and 2001

	No. (and %) of reports received			
Source	2000		2001	
Manufacturer	3630	(49.3)	4752	(64.3)
Regional AR centre	2595	(35.3)	2373	(32.1)
Other*	1136	(15.4)	264	(3.6)
Total	7361	(100.0)	7389	(100.0)

*Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of AR reports by type of reporter (originator) in 2000 and 2001

	No. (and %) of reports received			
Reporter	2000		2001	
Pharmacist	2420	(32.9)	2097	(28.4)
Physician	1876	(25.5)	1914	(25.9)
Health professional*	1057	(15.7)	1378	(18.6)
Consumer/ patient	1010	(13.7)	1102	(14.9)
Nurse	381	(5.2)	443	(6.0)
Other	517	(7.0)	455	(6.2)
Total	7361	(100.0)	7389	(100.0)

*Type not specified in report.

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