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Canadian Adverse Drug Reaction Newsletter

Therapeutic Products Programme

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Adverse drug reaction reporting - 1999

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 5688 reports of suspected ADRs in 1999. The ADRs were reported for the most part by health professionals (pharmacists, physicians, nurses, dentists, coroners and others), either directly to the CADRMP or indirectly through another source (Table 1).

The increase in the number of reports received through regional ADR centres may be related to increased awareness by physicians and pharmacists of these centres and the opening of the Ontario Regional ADR Centre in September 1998. A further analysis of the total number of reports by reporter type (originator) is outlined in Table 2.

Of the ADR reports received, 2999 were classified as serious. A serious ADR 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."

The CADRMP would like to thank all who have reported ADRs for their contribution to the program.

Table 1:	Source of reports of adverse drug reactions (ADRs) received by the CADRMP in 1998 and 1999			
	No. (and %) of reports received			
Source	1998		1999	
Manufacturer	2200	(47.2)	2750	(48.3)
Regional centre	1464	(31.4)	2506	(44.0)
Other*	999	(21.4)	432	(7.7)
Total	4663	(100.0)	5688	(100.0)

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program.
*Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2:	Number of ADR reports by type of reporter (originator)	
Reporter	No. (and %) of reports	
Pharmacist	2103	(37.0)
Physician	1446	(25.4)
Health professional*	1051	(18.5)
Consumer/patient	516	(9.1)
Nurse	447	(7.9)
Other	125	(2.2)
Total	5688	(100.0)

*Type not specified in report.

Written by: Heather Sutcliffe, BScPharm, Bureau of Drug Surveillance.

Celecoxib (Celebrex™): 1 year later

Celecoxib (Celebrex™), a nonsteroidal anti-inflammatory drug (NSAID), was first approved for sale in Canada in April 1999 and is used to relieve the signs and symptoms of acute and chronic osteoarthritis and rheumatoid arthritis in adults.[1] It is a diaryl-substituted pyrazole derivative containing a sulfonamide substituent and is the first of 2 selective cyclooxygenase (COX)-2 inhibitors marketed in Canada. Unlike previously available NSAIDs, which inhibit both COX-1 and COX-2, celecoxib selectively inhibits COX-2. Inhibition of COX-1 is responsible for some of the major adverse effects of older NSAIDs, such as upper gastrointestinal ulcers and inhibition of platelet aggregation.[2] The newer agents are designed to limit the side effects of gastric erosion, ulceration and bleeding by sparing COX-1.[3]

Between Apr. 14 and Dec. 23, 1999, the CADRMP received 220 reports of suspected adverse drug reactions (ADRs) associated with the use of celecoxib in which 562 adverse reactions were described (several reaction terms may be listed for one ADR report); 101 reports

were of a serious nature (59 women, 41 men, 1 sex unknown; age range 21-92 years). Of the serious spontaneous reports 48% occurred in patients 70 years of age or older.

Six deaths associated with the use of celecoxib were reported. The causes of death and the direct relation to drug therapy are unclear in most cases because insufficient data are available. All of the patients used recommended celecoxib doses. Three cases involved concomitant use of warfarin. The 6 cases are described as follows:

Case 1: A 37-year-old man complained of mild chest pain after starting celecoxib for the treatment of arthritis. The pain gradually increased in intensity during therapy; however, the patient delayed seeking medical advice. He died at home after 12 days of celecoxib therapy. The cause of death was not specified.

Case 2: A 43-year-old man with cardiac valve replacement who was taking concomitant celecoxib and warfarin therapy for 3 months had a diffuse subarachnoid hemorrhage and subsequently died. On admission to hospital his International Normalized Ratio (INR) was 4.6 (normal range 0.9–1.1; recommended therapeutic range for valve replacement 2.5–3.5[4]).

Case 3: A 74-year-old woman with various underlying medical conditions and receiving numerous concomitant medications had been treated with warfarin for 3 weeks for bilateral deep vein thromboses. Sixteen days after starting concomitant celecoxib she experienced a fatal intra cranial hemorrhage. The INR was 2.1 on the day of event.

Case 4: A 61-year-old woman died from cardiorespiratory failure 11 days after starting celecoxib. She had a history of asthma, cardiovascular disease and penicillin allergy. Concomitant medications included salbutamol and beclomethasone.

Case 5: An 82-year-old man was admitted to hospital and found to have a gastrointestinal hemorrhage. He had a history of chronic renal failure, coronary artery disease and ASA allergy and used several concomitant medications including prednisone. He had been receiving concomitant warfarin and celecoxib therapy for 2 weeks. Two days following admission and discontinuation of celecoxib and warfarin therapy, the patient's INR was 6.0. He died 6 days after admission. The cause of death was not specified.

Case 6: Following 2 doses of celecoxib, an 88-year-old man with a history of hypertension was admitted to hospital because of chest pain. He had a cardiac arrest and died.

A number of ADR reports included the use of other drugs such as ASA, warfarin, glucocorticoids and other NSAIDs. Of the 220 reports, ADRs occurred most frequently in the following system organ classes (some reports appear in more than one category):

- **Gastrointestinal** (75 reports [34%]): e.g., gastrointestinal hemorrhage, melena, abdominal pain, hematemesis, vomiting, nausea, pancreatitis, gastric ulcer, diarrhea, duodenal ulcer.
- **Dermatological** (74 reports [34%]): e.g., pruritus, rash, erythematous rash, maculopapular rash, urticaria, angioedema, bullous eruption.
- **Body** (66 reports [30%]): e.g., asthenia, chest pain, fatigue, fever, rigors, anaphylactoid reaction, allergic reaction.

- **Central and peripheral nervous system** (41 reports [19%]): e.g., dizziness, headache, hypertonia, stupor.
- **Respiratory** (27 reports [12%]): e.g., dyspnea, bronchospasm, pulmonary edema.
- **Psychiatric** (26 reports [12%]): e.g., confusion, depression, insomnia, somnolence, hallucination.
- **Metabolic and nutritional** (19 reports [9%]): e.g., increased alkaline phosphatase level, weight decrease.
- **Cardiovascular** (18 reports [8%]): e.g., cardiac failure, hypotension, bradycardia, myocardial infarction, hypertension.
- **Urinary system** (17 reports [8%]): e.g., acute renal failure, facial edema, micturition frequency.
- **Hematological** (15 reports [7%]): e.g., prothrombin time increased, bleeding time increased, cerebrovascular disorder, cerebral hemorrhage, intra cranial hemorrhage, pulmonary embolism, thrombocytopenia.

Of the 220 reports 12 involved the concomitant use of warfarin; 11 of these were serious (as defined in the Food and Drugs Act and Regulations). The celecoxib product monograph states that caution should be used when administering the drug with warfarin because patients taking warfarin are at increased risk of bleeding complications.[1] This precaution is supported by the seriousness of reports received, some of which documented elevated INR values when celecoxib and warfarin were used concomitantly.

Forty-nine of the 75 reports involving gastrointestinal disorders were serious (29 women and 20 men; age range 21–92 years). Even though celecoxib is designed to limit gastric side effects, gastrointestinal disorders do occur in some patients. Certain patient populations are at increased risk for gastrointestinal complications from NSAIDs (Table 1).

Table 1: Risk factors for gastrointestinal complications from NSAIDs

- Elderly patients
- High doses or multiple NSAIDs (including low-dose ASA therapy)
- Anticoagulant therapy
- Comorbid medical conditions, including rheumatoid arthritis
- History of peptic ulcer disease
- Cardiovascular disease (especially in patients taking ASA)[3]

The CADRMP received 74 reports of suspected allergic-type reactions, 2 of which were anaphylactoid reactions. Sixteen reports indicated that the patient had a previous adverse reaction to sulfa. Since celecoxib contains a sulfonamide substituent, health care professionals are reminded that the use of celecoxib in people with a known sulfa hypersensitivity is contraindicated.

Use caution when prescribing celecoxib in patients

- demonstrating allergic-type reactions to sulfonamides because use of the drug is contraindicated
- using warfarin, because of increased risk of bleeding complications
- receiving concomitant drugs known to inhibit cytochrome P450 2C9 [5], because celecoxib is predominantly metabolized by this enzyme
- who are elderly and debilitated, to minimize the risk of an adverse gastrointestinal event; the lowest effective dose should be used for the shortest possible duration[1]

Prospective, long-term studies are required to compare the incidence of serious, clinically significant gastrointestinal adverse events of celecoxib with those of other NSAIDs; therefore, general warnings for NSAIDs should be borne in mind.[1] The safety profile of new drugs evolves over time depending on different population groups, drug interactions, concomitant medical conditions and previously undetected adverse drug reactions that may emerge once the drug has been marketed. Therefore, health professionals are requested to continue reporting any suspected reactions associated with the use of celecoxib.

Written by: Marielle McMorran, BSc (Pharm), and Iza Morawiecka, BSc Phm, Bureau of Drug Surveillance.

References

1. *Celebrex™ , celecoxib* [product monograph]. Mississauga (ON): Searle Canada; Kirkland (QC): Pfizer Canada; 1999 Apr 9.
2. Pray WS. Osteoarthritis and OTC therapies. *US Pharm* 1999;24(8).
3. Mandell BF. Cox 2-selective NSAIDs: biology, promises, and concerns. *Cleve Clin J Med* 1999;66(5):285-92.
4. Jacobs DS, DeMott WR, Grady HJ, Horvat RT, Huestis DW, Kasten BL. *Laboratory test handbook*. 4th ed. Cleveland: Lexy-Comp Inc; 1996. p. 262.
5. Rudy E. Using cytochrome P450 tables to predict drug interactions: caveats and cautions. *Drug Therapy Topics* [U of Washington Medical Center/Harborview Medical Center] 1998; 27(8):37-42.

Correction

In the October 1999 (vol. 9, no. 4) issue of this newsletter (Also in *CMAJ* 1999;161[7]:867) an article was published on serious hematologic reactions associated with ticlopidine. The recommendations provided in the last paragraph regarding the monitoring of the leukocyte count should have read as follows (corrected text in italics):

Hematologic monitoring of the leukocyte count along with a differential and a platelet count is recommended at baseline and every 2 weeks *to the end of the third month of therapy with ticlopidine.* If therapy has been discontinued *within the first 90 days*, an additional complete blood count with differential should be done 2 weeks after the discontinuation of therapy because of the long half-life of ticlopidine (terminal elimination half-life 4–5 days).

These recommendations are consistent with the product monograph. We apologize for any confusion this may have caused.

COMMUNIQUÉ

The CADRMP wishes to provide feedback and increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the product monograph. (Reactions are expressed based on the "preferred term" in the World Health Organization *Adverse Reaction Dictionary*.)

Orlistat (Xenical®): pancreatitis

Pancreatitis and cholecystitis associated with the use of orlistat (Xenical®), an anti-obesity agent, was reported to the CADRMP.

DRUGS OF CURRENT INTEREST

The purpose of the Drugs of Current Interest (DOCI) list is to stimulate reporting for a selected group of marketed drugs in order to identify drug safety signals. The maintenance of this list by the CADRMP facilitates regular monitoring and constitutes one element of post-approval assessment activities. The following criteria are considered for inclusion of drugs on the DOCI list:

- recently marketed drugs (< 2 years), with limited postmarketing experience and potential safety concern from premarket review;
- marketed drugs for which there are emerging safety concerns, new serious adverse drug reactions that are unlabelled in the product monograph (e.g., safety signals observed internationally);
- the first marketed drug of a new pharmacological or chemical class of medication.

abacavir (Ziagen™)
alteplase (Activase® rt-PA)
bupropion (Zyban®, Wellbutrin SR®)
celecoxib (Celebrex™)
cisapride (Prepulsid®)
clopidogrel (Plavix™)
delavirdine (Rescriptor™)
Factor VII-recombinant, activated (NiaStase™)
indinavir (Crixivan®)
mefloquine (Lariam®)
melanoma theraccine (Melacine®)
naratriptan (Amerge®)
nefazodone (Serzone®)
nevirapine (Viramune®)
pramipexole (Mirapex®)
ritonavir (Norvir®)
rofecoxib (Vioxx™)
ropinirole (Requip™)
saquinavir (Invirase™)
sildenafil (Viagra™)
terbinafine (Lamisil®)
ticlopidine (Ticlid®)
trastuzumab (Herceptin®)
trovofloxacin (Trovan™)
zanamivir (Relenza®)
zolmitriptan (Zomig®)

If you have observed any suspected ADRs with the drugs in the Communiqué or the DOCI list, *please report them* to the :

Adverse Drug Reaction Reporting Unit
Continuing Assessment Division
Bureau of Drug Surveillance
AL 0201C2, Ottawa, ON K1A 1B9
Fax: 613 957-0335;
or to a participating regional ADR centre.

The ADR form is available at:

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

British Columbia
BC Regional ADR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
tel 604 806-8625
fax 604 806-8262
adr@dpic.bc.ca

Ontario
Ontario Regional ADR Centre
LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
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adr@lhsc.on.ca

New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland
Atlantic Regional ADR Centre
Queen Elizabeth II Health Sciences Centre
Drug Information Centre
Rm. 2421, 1796 Summer St.
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Sask ADR Regional Centre
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www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/publicat.html
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Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are under reported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Programme monitors and assesses suspected ADRs as a means of continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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