Health Canada Santé Canada

Canada

Canadian Adverse Reaction Newsletter

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www.healthcanada.gc.ca/carn

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 or a Regional AR Monitoring Office free of charge

Phone: 866 234-2345
Fax: 866 678-6789

Online form available at:

www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/index_e.html

Quetiapine: pancreatitis and thrombocytopenia

Quetiapine (Seroquel) is an atypical antipsychotic drug indicated for the management of the symptoms of schizophrenia and the acute management of manic episodes associated with bipolar disorder.[1] In Canada, quetiapine has been marketed since December 1997.

From Dec. 1, 1997, to Oct. 31, 2006, Health Canada received 615 domestic reports of adverse reactions (ARs) suspected of being associated with the use of quetiapine. Nine reports involved cases of pancreatitis and 11 involved cases of thrombocytopenia. Neither of these ARs is mentioned in the Canadian product monograph.[1]

Pancreatitis

The 9 reported cases of pancreatitis involved patients aged 24–71 years (median 32 years). One patient experienced severe hemorrhagic pancreatitis, and another had necrotizing pancreatitis. In one case, the patient experienced pancreatitis on 2 occasions while taking quetiapine. In 5 cases, quetiapine was the only suspect drug; in the other 4 cases, reported co-suspect drugs included medications that, like quetiapine, have been associated with pancreatitis: clozapine, divalproex sodium, fenofibrate and minocycline.[2,3]

Acute pancreatitis typically presents as an acute inflammation of the pancreas that may or may not involve the surrounding tissues.[2] Gallstones and heavy alcohol use are the most common causes.[2] Drug-induced pancreatitis is less common, with an incidence of 2%–5% of reported cases of acute pancreatitis in the general population.[2] Of the 9 cases reported to Health Canada, concomitant alcohol use was reported in 1 case. The severity of drug-induced pancreatitis is variable; the majority of patients recover without any long-term morbidity, but 5%–15% of patients experience life-threatening complications.[4] People at risk of drug-induced pancreatitis include elderly patients taking multiple medications, patients who are HIV positive, patients who have cancer and patients receiving immunomodulatory agents.[5]

Thrombocytopenia

The 11 reported cases of thrombocytopenia involved patients aged 28–84 years (median 63.5 years). In 6 cases, quetiapine was the only suspect drug. In 1 of these 6 cases, the patient was rechallenged 1 month after the drug was stopped; the thrombocytopenia recurred 3 months after the quetiapine was reintroduced. In 5 cases, reported co-suspect drugs included medications that, like quetiapine, have been associated with thrombocytopenia: citalopram, clozapine, olanzapine, pantoprazole, rofecoxib and zuclopenthixol.[6–12]

Thrombocytopenia is usually defined as a platelet count of less than 150×10^9/L or a 50% decrease in the platelet count from baseline.[6] Some reports define drug-induced thrombocytopenia as a platelet count of less than 100×10^9/L.[6] Although

relatively rare, drug-induced thrombocytopenia may be associated with risks of morbidity and mortality.[6] Perhaps because of its low incidence and idiosyncratic nature, drug-induced thrombocytopenia has often gone unrecognized during early clinical trials of drugs and was first reported after marketing.[6]

Health Canada continues to monitor ARs suspected of being associated with quetiapine. Health professionals are encouraged to report any cases of pancreatitis or thrombocytopenia in patients receiving quetiapine.

Nadia Aziz, BScPharm; Gilbert Roy, BPharm, Health Canada

References

1. *Seroquel (quetiapine fumarate tablets)* [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2006.
2. Eltookhy A, Pearson NL. Drug-induced pancreatitis. *Can Pharmacists J* 2006;139(6):58-60.
3. Gropper D, Jackson CW. Pancreatitis associated with quetiapine use. *J Clin Psychopharmacol* 2004;24(3):343-5.
4. Kale-Pradhan PB, Conroy JL. Pancreatitis. In: Tisdale JE, Miller DA, editors. *Drug-induced diseases: prevention, detection, and management*. Bethesda (MD): American Society of Health-System Pharmacists, Inc.; 2005. p. 537-47.
5. Adverse Drug Reactions Advisory Committee (ADRAC). Drug induced pancreatitis. *Aust Adv Drug Reactions Bull* 2006;25(6):22.
6. Skirvin JA. Thrombocytopenia. In: Tisdale JE, Miller DA, editors. *Drug-induced diseases: prevention, detection, and management*. Bethesda (MD): American Society of Health-System Pharmacists, Inc.; 2005. p. 649-59.
7. Kentos A, Robin V, Lambermont M, et al. Probable rofecoxib-induced thrombocytopenia. *Rheumatology (Oxford)* 2003;42(5):699-700.
8. Hirshberg B, Gural A, Caraco Y. Zuclopenthixol-associated neutropenia and thrombocytopenia. *Ann Pharmacother* 2000;34(6):740-2.
9. Huynh M, Chee K, Lau DH. Thrombotic thrombocytopenic purpura associated with quetiapine. *Ann Pharmacother* 2005;39(7-8):1346-8.
10. Watson TD, Stark JE, Vesta KS. Pantoprazole-induced thrombocytopenia. *Ann Pharmacother* 2006;40(4):758-61.
11. *Celexa (citalopram hydrobromide tablets)* [product monograph]. Montreal: Lundbeck Canada Inc.; 2006.
12. *Clozaril (clozapine tablets)* [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2006.

Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Telithromycin (Ketek): suspected association with toxic epidermal necrolysis

A 26-year-old woman with a history of rash to penicillin and sulfonamides and gastrointestinal intolerance to erythromycin was prescribed a 12-day course of telithromycin (800 mg/d), a ketolide antimicrobial, for sinusitis. Two days after this course of therapy, she presented at her doctor's office with sinusitis, pharyngitis and fever (39°C). She was prescribed a second course of telithromycin at the same dose along with topical treatment with ophthalmic fusidic acid. Later the same day, after taking the first dose of telithromycin, the patient saw her doctor again because of a rash and tingling. The telithromycin therapy was stopped, and she was prescribed diphenhydramine and cefprozil. That night, she was admitted to hospital after being found semiconscious with red eyes and skin as well as swollen face and lips. The following day her fever (40.9°C) and rash persisted, and she was admitted to the intensive care unit, where clindamycin and vancomycin therapy were started. Water blisters developed on her thorax, back and face. Her arms were red, and her skin was peeling from head to thigh; more than 50% of her body was involved. Acute respiratory distress syndrome developed and necessitated intubation. A skin biopsy confirmed a diagnosis of toxic epidermal necrolysis. The patient was transferred to a burn unit. Four weeks after admission to hospital, she was discharged and recovered with sequelae. She has scars over her body and face, has lost her eyelashes and has been affected psychologically. A detailed description of this case has been published in the literature.[1]

Reference

1. Hamel C. Une nécrolyse épidermique toxique associée à la télithromycine. *Québec Pharmacie* 2007;54(1):27-30.

Bitter orange or synephrine: update on cardiovascular adverse reactions

Synephrine is an α_1-adrenergic agonist found in bitter orange (*Citrus aurantium*). It is used in a variety of natural health products promoted for weight loss as an alternative to ephedrine. Such products are not authorized for sale in Canada. Safety issues identified with synephrine include effects on heart rate and blood pressure, which are significantly potentiated by caffeine.[1,2] Health Canada has previously notified consumers and health professionals of these potential cardiovascular adverse reactions (ARs).[3,4]

In the October 2004 issue of the *Canadian Adverse Reaction Newsletter*, it was reported that, from Jan. 1, 1998, to Feb. 28, 2004, Health Canada received 16 domestic reports of cardiovascular ARs suspected of being associated with bitter orange or synephrine.[4] Health Canada continues to receive reports of ARs suspected of being associated with synephrine-containing natural health products. From Mar. 1, 2004, to Oct. 31, 2006,

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.

21 additional domestic reports were received; 15 of these were of cardiovascular ARs, of which 10 were serious, including 1 case of myocardial infarction. Certain people may have an increased risk of ARs associated with the use of synephrine-containing products:

- People with heart conditions, diabetes, thyroid disease, central nervous system disorders, glaucoma, pheochromocytoma, hypertension, known risk factors for cardiovascular disease, or enlarged prostate.[3]
- Underweight people.[5]
- People taking thyroid hormones, monoamine oxidase inhibitors, medications to control heart rate or blood pressure, or caffeine-containing products.[1,4,6,7]

Consumers should be aware of the potential serious ARs when using products containing bitter orange or synephrine and may wish to consult a health professional with regard to their use. Health professionals are encouraged to ask their patients about the natural health products they are taking and to report to Health Canada any suspected ARs associated with the use of these products. More information on the safe use of weight-loss products will be published in an *It's Your Health* article on this topic at www.hc-sc.gc.ca/iyh-vsv/index_e.html.

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References

1. Haller CA, Benowitz NL, Jacob P. Hemodynamic effects of ephedra-free weight-loss supplements in humans. *Am J Med* 2005;118(9):998-1003.
2. Bui LT, Nguyen DT, Ambrose PJ. Blood pressure and heart rate effects following a single dose of bitter orange. *Ann Pharmacother* 2006;40(1):53-7.
3. *Health Canada warns consumers not to use "Thermonex"*. Ottawa: Health Canada; 2004 May 28. Available: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2004/2004_30_e.html (accessed 2007 Jan 12).
4. Jordan S, Murty M, Pilon K. Products containing bitter orange or synephrine: suspected cardiovascular adverse reactions. *Can Adverse Reaction Newsl* 2004;14(4):3.
5. Gray S, Woolf AD. *Citrus aurantium* used for weight loss by an adolescent with anorexia nervosa. *J Adolesc Health* 2005;37(5):415-6.
6. Firenzuoli F, Gori L, Galapai C. Adverse reaction to an adrenergic herbal extract (*Citrus aurantium*). *Phytomedicine* 2005;12(3):247-8.
7. *Gen-levothyroxine (levothyroxine)* [product monograph]. Toronto: Genpharm Inc.; 2005.

Adverse reaction reporting — 2006

In 2006, Health Canada received reports of 10 518 new domestic cases of suspected adverse reactions (ARs) to health products (pharmaceuticals, biologics [e.g., fractionated blood products, and therapeutic and diagnostic vaccines], natural health products and radiopharmaceuticals), which were derived from 14 549 reports. The initial report and all subsequent information received as follow-up reports are combined and considered to be one case. Domestic cases were reported for the most part by health professionals, either directly to Health Canada or indirectly through another source (Table 1). A further analysis of the total number of cases by reporter type (originator) is outlined in Table 2. In Canada, Market Authorization Holders (MAHs) of health products are required to submit to Health Canada all reports of serious domestic ARs within 15 days of receipt. In addition, MAHs are required to send within 15 days all reports of serious unexpected ARs that have occurred outside Canada (foreign ARs) for the products they sell in other countries as well as in Canada. Of the domestic cases received, 7000 (67 %) were classified as serious.*

The reporting of domestic ARs in Canada has increased steadily over the last several years, with 108 more cases in 2006 than in 2005 (Fig. 1).

Health Canada also received 252 493 reports of foreign ARs in 2006, a 43% increase since 2005 (Fig. 2). Because of this volume and the capacity of the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database, foreign reports are not included in the domestic AR database.

Health Canada would like to thank all who have contributed to the program and encourages the continued support of postmarketing surveillance through AR reporting. To report an AR, go to www.healthcanada.gc.ca /medeffect and:

- complete and submit a report online, or
- download and print a paper copy of the reporting form and submit

*In the Food and Drugs Act and Regulations, a serious AR is defined as "a noxious and unintended response to a drug that occurs at any dose and that requires in-patient 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 serious unexpected AR is defined as "a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out on the label of the drug."

Table 1: Source of domestic cases* of adverse reactions (ARs) received by Health Canada in 2005 and 2006

Source	No. (%) of cases received 2005		2006	
Manufacturer	6 482	(62.3)	6 937	(66.0)
Regional AR Monitoring Office	3 470	(33.3)	3 370	(32.0)
Other†	458	(4.4)	211	(2.0)
Total	10 410	(100.0)	10 518	(100.0)

*Cases result from the merge of initial, follow-up and duplicate reports.
†Includes, but not limited to, professional associations, nursing homes, hospitals, physicians, pharmacists, Health Canada regional inspectors, coroners, dentists and patients.

Table 2: Number of domestic AR cases* by type of reporter (originator) in 2005 and 2006

Reporter	No. (%) of cases 2005	2006
Physician	2 970 (28.5)	3 077 (29.2)
Pharmacist	2 592 (24.9)	2 396 (22.8)
Nurse	926 (8.9)	806 (7.7)
Health professional†	1 267 (12.2)	1 281 (12.2)
Consumer/ patient	2 304 (22.1)	2 544 (24.2)
Other	351 (3.4)	414 (3.9)
Total	10 410 (100.0)	10 518 (100.0)

*Cases result from the merge of initial, follow-up and duplicate reports.
†Type not specified in report.

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it by toll-free fax (866 678-6789) or by mail to one of the Regional AR Monitoring Offices (addresses are on page 2 of the form).

You can also report an AR by toll-free phone (866 234-2345); calls will automatically be directed to the appropriate Regional AR Monitoring Office. Incidents involving medical devices are not collected in the CADRMP database and should be reported toll free through the Inspectorate Hot Line (800 267-9675).

Jennifer Lo, BSc, BA, Health Canada

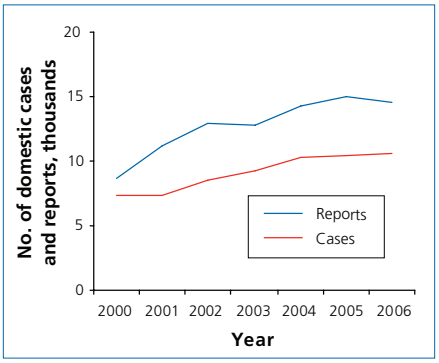

Fig. 1: Number of domestic reports and cases of adverse reactions (ARs) received by Health Canada from 2000 to 2006. (Reports include follow-up, duplicate and unenterable reports. Cases result from the merge of initial, follow-up and duplicate reports.)

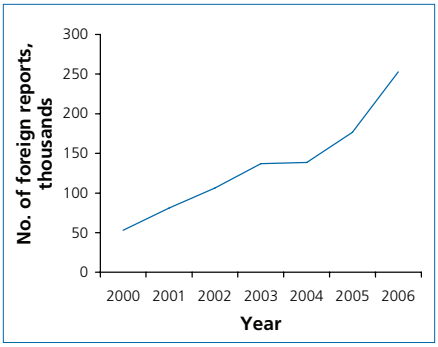

Fig. 2: Number of foreign AR reports received by Health Canada from 2000 to 2006. (Reports include follow-up, duplicate and unenterable reports.)

Summary of health professional and consumer advisories posted by Health Canada from Nov. 15, 2006 to Feb. 14, 2007
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject
Feb 9	Bone cements	Complications in vertebroplasty and kyphoplasty procedures
Feb 6	Masks and connectors	Information concerning the recall of continuous positive airway pressure (CPAP) masks and connectors — Fisher & Paykel Healthcare
Feb 1	Unauthorized products for erectile dysfunction	Foreign product alert
Jan 5	Kang Da	Foreign product alert
Jan 5	Qing Zhi	Foreign product alert
Dec 21	Xigris	Increased mortality and risk of serious adverse events — Eli Lilly Canada Inc.
Dec 13	Herbal sleep supplement	Advisory not to use a product that can be habit-forming
Dec 11	Detox Peptide	Foreign product alert
Dec 11	Slim	Foreign product alert
Dec 8	Patient lifts	Safety information on attachment handles
Dec 7	Robaxacet	Lack of a child-resistant cap on certain bottles
Dec 1	Iressa	Lack of survival benefit and increased incidence of tumour hemorrhage — AstraZeneca Canada Inc.
Nov 29	Tamiflu	International reports of hallucinations and abnormal behaviour
Nov 29	Xylocaine Jelly 2%	Restrictions and updated handling instructions on single-use plastic syringe — AstraZeneca Canada Inc.
Nov 24 & 23	Benzocaine sprays	Methemoglobinemia
Nov 22	Embrun de mer	Risk of serious bacterial infection
Nov 21	Evra	Venous thromboembolism and product monograph update — Janssen-Ortho Inc.
Nov 17	Incubator	Modification of Air-Shields Isolette C2000/C2000e controller — Draeger Medical Canada Inc.

To receive the Newsletter and health product Advisories free by email, join Health Canada's ***MedEffect*** mailing list. ***Go to*** **www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index_e.html**

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