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Canadian Adverse Reaction Newsletter

1991 – 2011 20th anniversary

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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 stimulate adverse reaction reporting as well as 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

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Proton pump inhibitors: hypomagnesemia accompanied by hypocalcemia and hypokalemia

Key points

- Prolonged treatment (≥ 1 year) with proton pump inhibitors (PPIs) is suspected of being associated with hypomagnesemia.
- In published cases, some patients presented with symptoms of potentially life-threatening cardiac arrhythmias and neurologic manifestations.
- The effects of PPIs on magnesium serum levels seem to be reversible.

Proton pump inhibitors (PPIs) are widely used for the treatment of conditions related to gastric acid secretion (e.g., duodenal and gastric ulcers, reflux esophagitis and gastroesophageal reflux disease). In Canada, 6 marketed PPIs are available as prescription medications: omeprazole (first marketed in 1989), lansoprazole (1995), pantoprazole (1997), esomeprazole (2001), rabeprazole (2002) and dexlansoprazole (2010).

The potential association between PPI treatment and hypomagnesemia has been suggested in the literature and communicated by other regulatory authorities.[1–8] Recent studies have suggested that hypomagnesemia can be induced by several if not all PPIs.[1,2,4,6]

The mechanism by which PPIs induce hypomagnesemia is unclear. It may involve defects in magnesium absorption in the small intestine by affecting the function of the transient receptor potential melastin 6 (TRPM6) channel.[1,2,6] Effects on magnesium absorption have not been reported with short-term use of PPIs. Published case reports suggest that PPI-induced hypomagnesemia occurs after prolonged use (≥ 1 year).[1–6] Magnesium is involved in bone metabolism. Its deficiency may induce parathyroid dysfunction and hypoparathyroidism, thereby affecting the regulation of calcium levels.[9–11] Hypomagnesemia may also trigger hypokalemia via activation of the potassium channel of the thick ascending limb of the loop of Henle, resulting in urinary potassium wasting.[4,12]

The effects of PPIs on serum magnesium levels seem to be reversible.[1–6] In all published cases, electrolyte levels returned to normal following cessation of PPI treatment (positive dechallenge*). Recurrence of hypomagnesemia following reintroduction of the PPI (positive rechallenge†) was documented in

*Response to withdrawal of the drug. Abatement of reaction after the drug is stopped or the dose is reduced is considered a positive dechallenge.

†Response to reintroduction of the drug. Reappearance of the AR after reintroduction of the drug is considered a positive rechallenge.

3 cases.[1,3,6] In most cases, secondary hypokalemia or hypocalcemia, or both, accompanied the hypomagnesemia, with some patients presenting with symptoms of potentially life-threatening cardiac arrhythmias and neurologic manifestations (e.g., seizures, loss of consciousness and tetany).

As of Jan. 31, 2011, Health Canada received 5 reports of hypomagnesemia suspected of being associated with the following PPIs: omeprazole ($n = 2$), lansoprazole ($n = 1$), pantoprazole ($n = 1$) and esomeprazole ($n = 1$). One case was life threatening, and 4 patients required hospital care. Secondary hypokalemia was reported in 3 of the cases. One report described a positive dechallenge* and a positive rechallenge.†

Health professionals are reminded that, in some patients, hypomagnesemia may occur after prolonged treatment with PPIs, and it may be accompanied by hypocalcemia and hypokalemia. This adverse reaction may be underdiagnosed and underreported because of the low frequency of magnesium measurement in routine clinical practice.[1,6] Health care professionals are encouraged to report any cases of hypomagnesemia suspected of being associated with the use of PPIs.

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Adverse reaction and incident reporting — 2010

Canada Vigilance Program

The Canada Vigilance Program collects reports of suspected adverse reactions (ARs) to health products (pharmaceuticals, biotechnology products, blood products and biologics, natural health products, radiopharmaceuticals, and cells, tissues and organs). Further information about the program and its database can be found at www.health.gc.ca/medeffect.

Domestic and foreign AR reports

In 2010, Health Canada received 32 921 domestic AR reports,* of which 77% were considered to be serious.† Domestic AR reports received by product type are provided in Table 1. The 32 921 reports represent 22 241 AR cases. A case consists of all information describing the AR(s) experienced by one patient at one time and suspected of being related to the use of one or more health products; thus, an AR case will include an initial AR report as well as any subsequent additional information received as follow-up report(s).

In Canada, Market Authorization Holders (MAHs) are required to

Table 1: Number of domestic reports* of adverse reactions by product type in 2010

Product type	No. (%) of reports
Pharmaceuticals	22 104 (67.1)
Biotechnology products	8 860 (26.9)
Blood products and biologics	903 (2.7)
Natural health products	677 (2.1)
Radiopharmaceuticals	348 (1.1)
Cells, tissues and organs	29 (0.1)
Total	32 921 (100.0)

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.

*This excludes 1035 AR reports received for product types that do not fall under the review of the Canada Vigilance Program, as outlined above. These reports were redirected to the appropriate AR reporting program.

†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."

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.

submit AR reports received in accordance with the requirements of the *Food and Drugs Act* and Regulations. MAHs are required to send, within 15 days, all reports of serious ARs that have occurred in Canada (domestic) and all reports of serious unexpected ARs[‡] that have occurred outside Canada (foreign) to the Canada Vigilance Program. In 2010, MAHs submitted 78.9% of all the domestic reports received. The remaining reports were received directly from the community and hospitals (Table 2).

The number of domestic AR reports was 19.7% higher in 2010 than in 2009 (Fig. 1). Most of the domestic reports received by both MAHs and Health Canada originated from health care professionals (Table 3).

In 2010, the number of foreign AR reports received from MAHs was 363 961 (Fig. 2). At this time, foreign reports are not included in the Canada Vigilance database.

Sex and age

The distribution for the 22 241 cases by sex was 57% female, 38% male and 5% sex unknown. The distribution by age group is 7% pediatric (< 19 years), 47% adult (19–64 years), 25% elderly (≥ 65 years) and 21% age unknown.

Suspect products

The top 10 groups of suspect products most commonly identified in AR reports are listed in Table 4. Anatomical Therapeutic Chemical (ATC) groups are classified according to the World Health Organization's ATC classification system (www.whocc.no/atc_ddd_index). Several factors may influence the number of ARs reported for a specific health product or product type, such as length of time a product is on the market, volume of use, publicity of an AR, regulatory actions, method of data collection (reports submitted voluntarily v. organized data-collection systems). For example, ARs may be reported more frequently in organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) and may affect the pattern of reporting. It is not possible to compare the risk of health products based solely on numbers of AR reports. In addition, rare and serious reactions may not necessarily represent a large number of reported ARs.

Adverse reactions

Table 5 displays the top 10 ARs reported to the Canada Vigilance Program, based on System Organ Class.[§] The most commonly reported ARs were general disorders and administration site conditions, which include disorders that affect several body systems or sites (e.g., drug ineffective, fatigue, fever, edema, pain, reactions at the administration site).

Table 2: Number of domestic reports* of adverse reactions by source in 2010

Source	No. (%) of reports	
MAH	25 967	(78.9)
Community†	5 727	(17.4)
Hospital	1 120	(3.4)
Other	107	(0.3)
Total:	32 921	(100.0)

Note: MAH = Market Authorization Holder.
*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.
†Consumer, patient and non-hospital–based health care professionals.

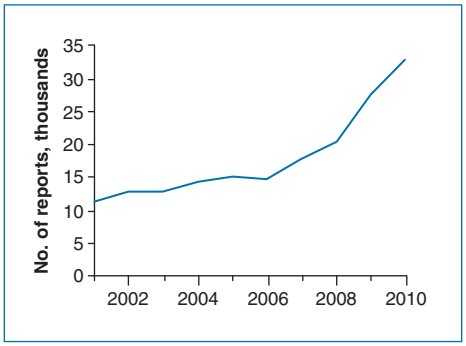

Fig. 1: Number of domestic reports of adverse reactions received by Health Canada from 2001 to 2010.

Table 3: Number of domestic reports* of adverse reactions by type of originating reporter in 2010

Reporter type	No. (%) of reports	
Consumer/patient	8 733	(26.5)
Physician	8 102	(24.6)
Health professional†	5 782	(17.6)
Nurse	5 100	(15.5)
Pharmacist	4 615	(14.0)
Dentist	12	(0.04)
Naturopath	5	(0.02)
Other	572	(1.7)
Total	32 921	(100.0)

*Canada Vigilance receives reports for both initial and follow-up information concerning suspected adverse reactions.
†Type not specified in report.

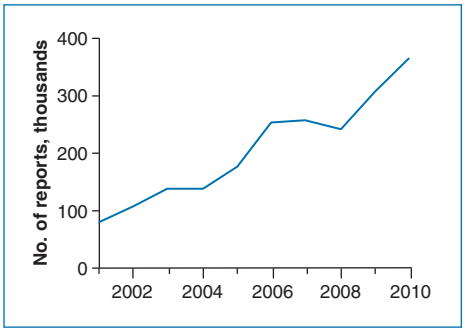

Fig. 2: Number of foreign reports of adverse reactions received by Health Canada from Market Authorization Holders from 2001 to 2010.

[‡]In the *Food and Drugs Act* and Regulations, 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."

[§]Adverse reactions are coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) Terminology. The terminology is organized in a hierarchical structure where the System Organ Class is the highest level of the hierarchy and represents the broadest concept of groupings. Further information about the MedDRA Terminology can be found at www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/meddra-eng.php.

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.

The next most common ARs were gastrointestinal disorders.

Conclusion

Health Canada would like to thank all who have contributed to the Canada Vigilance Program and encourages the continued support of postmarketing surveillance through AR reporting. The purpose of postmarket spontaneous reporting systems is the identification and analysis of new safety information for health products. Any ARs suspected of being associated with the use of health products can be reported to the Canada Vigilance Program (www.health.gc.ca/medeffect).

Medical device incidents

Medical device incidents are collected by the Health Products and Food Branch Inspectorate and are entered into the Medical Device System database. The Inspectorate is responsible for compliance monitoring activities for a broad spectrum of regulated health products, including medical devices which range from adhesive bandages to pacemakers. It is also responsible for the delivery of a national compliance and enforcement program in an effort to minimize health risks to Canadians while maximizing the safety of health products. A major component of this program involves the collection, review and follow-up of incidents related to medical devices, which are reported to the Inspectorate via the submission of mandatory and voluntary problem reports. Manufacturers and importers are required to submit mandatory reports as per sections 59 to 61 in the Medical Devices Regulations. Voluntary reports are submitted mostly by health care professionals and patients/users.

In 2010, a total of 7588 reports were entered into the Medical Device System database. Of these reports, 5828 (76.8%) were domestic mandatory reports, 1354 (17.8%) were foreign mandatory reports, and 406 (5.4%) were domestic voluntary reports.

Information on mandatory and voluntary reporting of medical device incidents can be found on the Health Canada Web site (www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/md-im/index-eng.php).

Completed Medical Devices Problem Report forms can be submitted by email as attachments to: mdpr@hc-sc.gc.ca. Please include the acronym MDPR in the subject line of the email in order to generate an automated confirmation of receipt by the Inspectorate.

Table 4: Top 10 groups of suspect health products most commonly reported in 2010, by Anatomical Therapeutic Chemical (ATC) group*

Health product (ATC group)	No. (%) of times reported†
Immunosuppressants (L04)	5 208 (20.4)
Psychoanaleptics‡ (N06)	1 563 (6.1)
Psycholeptics‡ (N05)	1 459 (5.7)
Drugs for treatment of bone diseases (M05)	1 340 (5.2)
Antineoplastic agents (L01)	1 295 (5.1)
Analgesics (N02)	1 110 (4.3)
Antibacterials for systemic use (J01)	907 (3.6)
Lipid-modifying agents (C10)	799 (3.1)
Agents acting on the renin–angiotensin system (C09)	653 (2.6)
Drugs for acid-related disorders (A02)	569 (2.2)

*Solicited reports or organized data-collection systems (e.g., patient registries, surveys, patient support and disease management programs) may affect the total number of ARs reported for specific products or product types.
†One case may contain one or more suspect product(s). The total number of suspect health products reported was 25 551 in a total of 22 241 cases.
‡N05 psycholeptics: antipsychotics, anxiolytics, hypnotics and sedatives; N06 psychoanaleptics: antidepressants, psychostimulants, psycholeptics and psychoanaleptics in combination, anti-dementia drugs.

Table 5: Top 10 adverse reactions reported in 2010, by System Organ Class*

System Organ Class	No. (%) of times reported†
General disorders and administration-site conditions	15 540 (21.4)
Gastrointestinal disorders	8 395 (11.6)
Nervous system disorders	6 915 (9.5)
Investigations	6 080 (8.4)
Psychiatric disorders	4 758 (6.6)
Skin and subcutaneous tissue disorders	4 392 (6.0)
Musculoskeletal and connective tissue disorders	4 095 (5.6)
Respiratory, thoracic and mediastinal disorders	3 807 (5.2)
Infections and infestations	2 859 (3.9)
Injury, poisoning and procedural complications	2 521 (3.5)

**Medical Dictionary for Regulatory Activities* (MedDRA) Terminology, version 13.1; reactions at preferred term level. Further information about the MedDRA terminology can be found at www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/meddra-eng.php.
†One case may contain one or more reaction(s). The total number of ARs reported was 72 683 in a total of 22 241 cases.

Marielle McMorran, BSc, BSc(Pharm); Melanie Adams, PhD, Health Canada

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.

Floseal hemostatic matrix: suspected association with misinterpretation as recurrent malignant disease

Floseal is a granular hemostatic agent that consists of a bovine-derived gelatin matrix component and a human-derived thrombin component. Before application, these two components are combined to allow the mixing and reconstitution of the thrombin into the gelatin matrix. Floseal is indicated in surgical procedures (other than ophthalmic) as an adjunct to hemostasis when control of bleeding by ligature or conventional methods is ineffective or impractical. Floseal is expected to resorb in the tissues within 6 to 8 weeks.[1] In Canada, the product is regulated as a class IV medical device (highest risk class).

In 2010, Health Canada received 2 reports of adverse incidents in which Floseal was suspected of persisting at surgical sites following partial nephrectomy for cancer. In both cases, follow-up radiographic imaging several months after surgery (6 and 9 months, respectively) revealed an asymptomatic mass (1 cm × 1.5 cm, and 3 cm × 4 cm, respectively) that was initially interpreted as recurrent malignant disease. The physician later reinterpreted the mass as a possible persistence of Floseal. In both cases, the report suggested that the mass could have been related to excess use of Floseal without adequate irrigation. Other cases have been reported in the medical literature in which Floseal persisted in the tissues after tumour resection and was misinterpreted as recurrent malignant disease during follow-up.[2,3]

Health Canada encourages the reporting of similar adverse incidents suspected of being associated with Floseal to the Health Products and Food Branch Inspectorate through the toll-free hotline (1-800-267-9675).

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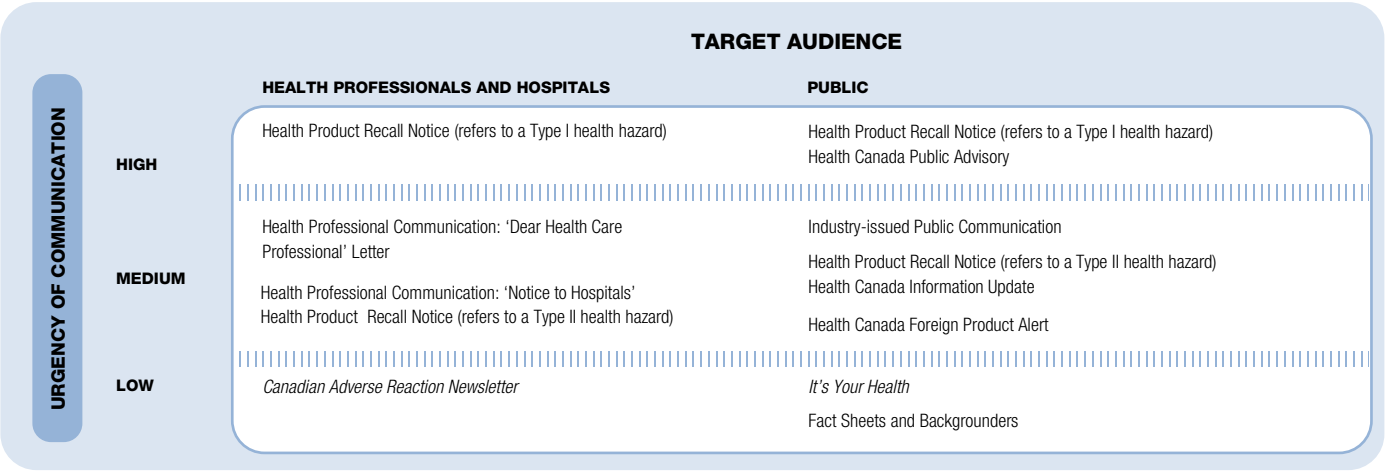
Risk communication information

Health Canada considers many factors in the evaluation of an emerging health product safety concern (e.g., availability and reliability of data, seriousness of the event) and the urgency of the communication.

The chart below outlines the urgency level of each type of communication disseminated by Health Canada and industry for public and professional audiences.

To provide health product risk information to Canadians as quickly as possible, Health Canada posts risk communications on the MedEffect™ Canada Web site at www.health.gc.ca/medeffect. This central hub of health product safety information offers the most comprehensive coverage and access to risk communications issued by both Health Canada and industry.



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Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Feb. 19, 2011 – May 20, 2011)

Date*	Product	Subject
May 6	Cytarabine injection	Potential for crystallization in vials
May 4	Omega Alpha Kidney Flush	Recall
Apr 29	Triad Group manufactured health products	Updated list of recalled products
Apr 26 & 28	Anzemet (dolasetron mesylate) intravenous injection	Product withdrawal
Apr 21	Triad Group manufactured health products	Recall: update
Apr 19	Topical benzocaine products	Reminder of health risks
Apr 18	Mary Ginseng House 100% Pure High Calibre Pow Sum Ontario Ginseng	Recall: microbial contamination
Apr 11	Vivaglobin	Risk of thrombotic events
Apr 7	U-Prosta	Recall: undeclared terazosin hydrochloride
Apr 6	RUSCH Irrigation Trays	Recall: potential contamination of co-packaged alcohol prep pads
Apr 5	Friendly Flora and Healthy Skin with Greens+	May pose serious health risks to Canadians with milk allergies
Mar 24	*Salvia divinorum*	It's Your Health: *Salvia divinorum*
Mar 21	Natural health products	It's Your Health: Adulteration of natural health products
Mar 17	Mylan-Minocycline and Mylan-Amlodipine	Recall: mislabelling of products
Mar 10 & 15	Multaq (dronedarone)	Updated safety information in regards to hepatocellular injury
Mar 9	Bertec Medical Beds	Recall of medical bed model FLH668NDCM
Mar 8	Ixiaro Japanese encephalitis vaccine	Recall of lot JEV09L37C
Feb 14 & Mar 7	Plum A+ Infusion Pumps	Recall: audible alarm failure
Feb 19 to May 20	Foreign products	8 Foreign Product Alerts (FPAs) were posted on the Health Canada Web site during this period; FPAs are available online (www.hc-sc.gc.ca/ahc-asc/media/index-eng.php) or upon request

Advisories are available at www.health.gc.ca/medeffect.
*Date of issuance. This date may differ from the posting date on Health Canada's Web site.

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Suggestions?

Your comments are important to us. Let us know what you think by reaching us at mhpd_dpsc@hc-sc.gc.ca

Reporting Adverse Reactions

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