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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

Gadolinium-containing contrast agents and nephrogenic systemic fibrosis: update

Gadolinium (Gd)-containing media are used to enhance the contrast of magnetic resonance images. Those authorized for sale in Canada include Magnevist, Omniscan, OptiMARK, Gadovist, ProHance, MultiHance and Vasovist.

Nephrogenic systemic fibrosis (NSF), also known as nephrogenic fibrosing dermopathy (NFD), is a systemic disorder whose most prominent and visible effects are on the skin.[1] It is associated with significant morbidity.[2,3] The fibrosis can extend beyond the dermis and involve subcutaneous tissues, muscles and internal organs.[2,3] The disease was first described in the medical literature in 2000,[4] but the first case was reported in 1997.[2,4] To date, NSF has been observed only in patients with kidney disease.[1]

Internationally, cases of NSF have been observed with 5 different Gd-containing contrast agents,[5] and a causal association has recently been suggested.[6] In March 2007, Health Canada communicated this safety concern to the public and health professionals.[2,3] As of June 27, 2007, 5 cases of NSF suspected of being associated with Gd-containing contrast agents have been reported in Canada. This recently discovered disease is currently not described in the Canadian product monographs for these agents.

The association between NSF and the use of Gd-containing contrast media needs to be characterized further. In particular, are other patient populations at risk for NSF (e.g., neonates)? Does the risk vary according to the nature of underlying renal disorder? What is the role of dialysis in the prevention and treatment of NSF?

Valuable information could be obtained from adverse reaction (AR) reports. Spontaneous reporting can be useful to identify the clinical spectrum of the drug–AR pair, the patient subtypes and medical circumstances associated with a suspected AR.[7] It can also provide clues to the mechanism of action whereby a product can lead to an AR.[7] The addition of clinical information in reports, such as the duration of kidney disease and its underlying cause, laboratory values (e.g., glomerular filtration rate), the type and dose of the contrast agents, and concomitant conditions and medications, is important to help characterize the risk factors of NSF. In summary, voluntary reporting to Health Canada remains an important postmarketing surveillance tool to further elucidate this disorder.

Newsletter and Advisories by email

To receive the Newsletter and health product Advisories ***free*** by email, join Health Canada's ***MedEffect*** mailing list. ***Go to www.healthcanada.gc.ca/medeffect***

Tanja Kalajdzic, MSc, Health Canada

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Contraindicated use of sibutramine and cardiovascular adverse reactions

Sibutramine (Meridia), a serotonin and norepinephrine reuptake inhibitor, is an antiobesity agent marketed in Canada since February 2001. Sibutramine is indicated as adjunctive therapy within a weight management program for obese patients with an initial body mass index (BMI) of 30 kg/m^2 or higher, and for obese patients with an initial BMI of 27 kg/m^2 or higher in the presence of other risk factors (e.g., controlled hypertension, type 2 diabetes, dyslipidemia, visceral fat).[1]

The Canadian product monograph of sibutramine includes several contraindications (Table 1). Noncompliance with contraindications could result in serious adverse reactions (ARs).*

Health Canada continues to receive reports of ARs in patients using sibutramine who have contra-indications. From Jan. 1, 2001, to May 31, 2007, Health Canada received 65 reports of cardiovascular ARs suspected of being associated with sibutramine. Thirteen of these reports involved patients with at least 1 contraindicated condition. A brief description of these 13 cases follows.

A patient with a history of myocardial infarction (MI) who was taking fluoxetine experienced fatal ventricular fibrillation 2 days after starting sibutramine therapy.

A patient with a history of MI experienced a non ST-segment elevation MI 21 days after starting sibutramine therapy. Three patients experienced serotonin syndrome, with cardiovascular ARs (e.g., hypertension, palpitation and tachycardia), from the concomitant use of a selective serotonin reuptake inhibitor (SSRI) and sibutramine.

Five patients with a previous history of arrhythmia had arrhythmia while taking sibutramine. One patient took 10 capsules in 3 days and experienced tachycardia and confusion during concomitant use of sibutramine with other weight-reducing agents not currently authorized for sale in Canada. One patient, who experienced unstable hypertension after surgery, resumed her preoperative regimen of sibutramine 2 days after surgery and experienced worsening hypertension, headache and cerebral edema. In this case, meperidine was reported as a co-suspect drug. One patient experienced a vitreous hemorrhage approximately 10 days after starting sibutramine therapy. In this case, paroxetine and bupropion were stopped 1 day before sibutramine was started.

Sibutramine used at therapeutic doses has been reported to substantially increase blood pressure and heart rate in some patients.[1,2] Such increases were observed within the first 4 months of therapy.[1] Regular monitoring of blood pressure and heart rate is required when prescribing sibutramine.[1] In the first 3 months of treatment, these parameters should be checked at least every 2 weeks and regularly every 1–3 months thereafter.[1]

In 2002 and 2003, international regulatory actions were taken, including safety notices, concerning cardiovascular ARs associated with sibutramine.[2–4] Health Canada and other foreign regulatory agencies reviewed the safety of sibutramine and concluded that the benefit–risk profile of sibutramine remained favourable.[4] Contraindications to the use of sibutramine are well detailed in

Table 1: Contraindications for sibutramine therapy include:[1]

- History of coronary artery disease, congestive heart failure, arrhythmias or cerebrovascular disease (stroke or transient ischemic attack)
- Inadequately controlled (> 145/90 mm Hg) or unstable hypertension
- Psychiatric illness
- Concomitant use of centrally acting drugs (e.g., antidepressants and antipsychotics) or herbal remedies (e.g., St John's Wort) for the treatment of psychiatric disorders; monoamine oxidase inhibitors; or other centrally acting weight-reducing agents
- History of, or presence of, a major eating disorder such as anorexia nervosa or bulimia nervosa
- Hypersensitivity to sibutramine or to any ingredient in the formulation or component of the container

*A serious adverse reaction is one 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 that require significant medical intervention to prevent one of these outcomes are also considered to be serious.

the Canadian product monograph. Health Canada continues to monitor ARs suspected of being associated with sibutramine.

Before starting treatment with sibutramine, health professionals are encouraged to review its labelled contraindications in the product monograph. Consumers are encouraged to consult the consumer information leaflet provided in the original packaging, particularly the section "When it should not be used".

Patrice Tremblay, MD, Health Canada

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Expert Advisory Committee on the Vigilance of Health Products

Health Canada's Marketed Health Products Directorate, Health Products and Food Branch, is establishing the Expert Advisory Committee on the Vigilance of Health Products. To obtain more information on this committee, visit the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

Swedish Adjustable Gastric Band: erosion and other reported incidents leading to explantation

The Swedish Adjustable Gastric Band (SAGB) is an implantable, adjustable gastric band indicated for use in the treatment of morbid obesity in adults.[1] It consists of a reinforced silicone gastric band fitted around the stomach and an injection port placed under the skin and connected to the band by tubing. The SAGB is designed to reduce food intake and can be inflated or deflated as needed after implantation to meet weight-loss requirements without the need for further surgery. The SAGB was originally licensed for sale in Canada in November 2002. A modified version of the device, the SAGB Quick Close (SAGB-QC), was added to the licence as part of a device licence amendment in August 2004.[2]

Although band erosion is listed among the possible adverse events in the device labelling for physicians,[2] the device labelling for patients states that the overall rate of reoperation following placement of the SAGB is low and that extensive use of the SAGB has led to a method where failure is uncommon.[3] By definition, band erosion is "a situation where a part of the band has eroded through the full-thickness gastric wall and migrated into the lumen."[4] This represents a total failure of the gastric banding procedure.[5]

From Nov. 1, 2002, to June 15, 2007, Health Canada received 19 reports of incidents suspected of being associated with the SAGB and 17 with the SAGB-QC. Thirteen of the 36 reports described cases of band erosion necessitating removal of the band. Other reports described incidents such as band slippage, band leakage, abscess, dysphagia and regurgitation. In 35 of the 36 reports, band explantation was reported as an outcome.

Although reported rates of band erosion vary across published studies, evidence in the medical literature suggests that the frequency of band erosion is approximately linear over time following surgery, with erosions still being diagnosed 5 or more years after implantation.[4,5] Since band erosion is often asymptomatic or only mildly symptomatic initially and since the condition is best diagnosed by gastroscopy, which may not be included in the follow-up of asymptomatic patients, the true incidence of band erosion is underestimated in the literature and its diagnosis can be markedly delayed.[4,5] Moreover, band erosion is associated with dense scarring and distortion of tissues, which can complicate revision procedures.[5]

The complication rates and outcomes associated with SAGB and reported in the literature are variable. Although the authors of some studies have concluded that use of the SAGB demonstrates acceptable levels of safety and effectiveness,[6,7] others have reported high long-term complication and failure rates and poor long-term outcomes.[4,5] The medical literature suggests that, until reliable selection criteria for patients at low risk for long-term complications are determined, alternative treatment options should be considered and gastric banding should be performed only in carefully selected and fully informed patients.[5]

Andrew Gaffen, BSc, DDS; Gina Coleman, MD, Health Canada

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Summary of health professional and consumer advisories posted by Health Canada from May 15 to Aug. 16, 2007
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject
Aug 16	Prexige	New safety information on liver events
Aug 16 & 10	Permax	Cease sale of Permax in Canada as of Aug. 30, 2007 — Eli Lilly Canada Inc.
Aug 15	Drugs online	Reminder about the risks of buying drugs online
Aug 9	Losec & Nexium	Safety information on cardiac events
Aug 8	Rituxan	Safety information — Hoffmann–La Roche Ltd.
Aug 1	Lancing devices	Reminder to use lancing devices as directed
July 27	Resolve	Unauthorized product Resolve may pose health risk
July 26, 6 & 5, June 29 & 21	Toothpastes	Public warnings on counterfeit toothpastes, toothpastes containing harmful bacteria and toothpastes containing diethylene glycol
July 23	Liviro3	Advisory not to use Liviro3 dietary supplement
July 20	Xylocaine Jelly 2%	Safety information on single-use syringe — AstraZeneca Canada Inc.
July 20	Zencore Tabs	Warning not to use Zencore Tabs
July 18 & June 14	Sleep supplement	Sleep supplements found to contain habit-forming drug
July 16, May 30 & 16	Unauthorized foreign products	Foreign product alerts: Kui Hua Chut Lee San Bird's Nest & Pearl; Dai Dai Hua Jiao Nang, Darling Capsules, Dali Capsules, Spanish Fly Capsules, an unnamed product; Jie Jie Pills and Chuan Xiong Cha Tiao Wan; Power 58 Extra, Platinum Power 58 Extra, Enhanix New Extra Men's Formula, Valentino, King Power Oral Solution, and Stretch Up Capsules; HS Joy of Love; Xiaokeshuping Jiangtangning Jiaonang
July 9	MdMt	Warning not to use the dietary supplement MdMt
June 25	Encore Tabs for Men	Warning not to use Encore Tabs for Men
June 21	Fluotic	Voluntary recall and product discontinuation — Sanofi-Aventis Canada Inc.
June 19	Sensipar	Product update: new information — Amgen Canada Inc.
June 18	CADD Medication Cassette Reservoirs	Product safety and recall notification — Smiths Medical Canada Ltd.
June 15	Vitamin D	Vitamin D and health
June 13 & 5	Fraxiparine	Voluntary recall of graduated syringes — GlaxoSmithKline Inc.
June 12	Ventolin	For pregnant women & labour and delivery — GlaxoSmithKline Inc.
June 6	Colleague Pumps	Product information — Baxter Corporation
June	Avastin	Association with tracheo-esophageal fistula — Hoffmann–La Roche Ltd.
June 1 & May 30	Avandia	Cardiac safety — GlaxoSmithKline Inc.
May 30	Complete All-In-One	Recall
May 30	Bone cements	Complications in vertebroplasty and kyphoplasty
May 17	S8 flow generator devices	Recall of certain models — ResMed Corp
May 14 & 11	Depakene	Voluntary recall of 500-mg enteric-coated capsules — Abbott Laboratories Ltd.
May 11	Insulin Pump	Safety information on MiniMed Paradigm — Medtronic of Canada Ltd.
May 11	Ratio-Valproic	Voluntary recall of 500-mg enteric-coated capsules — ratiopharm inc.
May 3	Myozyme	Recent reports of black particles after reconstitution — Genzyme Canada Inc.
May & Apr 30	OneTouch Ultra Test Strips	Safety information — LifeScan Canada Ltd.

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Canada Vigilance

Health Canada is pleased to announce Canada Vigilance as the new name for the Canadian Adverse Drug Reaction Monitoring Program. The Canada Vigilance Program is also implementing a new information system that will provide an enhanced capacity for the postmarketing surveillance of adverse reactions. For more information visit the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

Canadian Adverse Reaction Newsletter

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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.