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Canadian Adverse Reaction Newsletter

1991 – 2011 20th anniversary

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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 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

Canada Vigilance Program
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Did you know?

Starting in 2011, annual statistics on adverse reaction and incident reporting will now appear in the July issue of the **Newsletter**.

Fluticasone propionate and osteonecrosis

Key points

- Health Canada received 5 reports of osteonecrosis suspected of being associated with fluticasone propionate.
- The potential for osteonecrosis with high doses of inhaled corticosteroids has been suggested in the literature.
- Because corticosteroid-induced osteonecrosis tends to occur in younger patients and treatment options for advanced disease are limited, early identification is important.

Fluticasone propionate is a highly potent glucocorticoid anti-inflammatory steroid. In Canada, it is available as an aqueous nasal spray, an inhalation aerosol, a powder for inhalation and a topical cream (Table 1).[1–3]

Steroid-induced osteonecrosis, or avascular necrosis, is characterized by bone cell death resulting from compromised blood supply. Corticosteroids, administered orally or parenterally, have been associated with osteonecrosis.[4] Osteonecrosis related to inhaled or topical use of steroids has also been reported, but the oral or parenteral use of steroids was a confounding factor.[4] The potential for osteonecrosis with high doses of inhaled corticosteroids, such as in the treatment of severe persistent asthma or eosinophilic esophagitis, has been suggested.[4]

As of Oct. 31, 2010, Health Canada received 5 reports of osteonecrosis suspected of being associated with fluticasone propionate. In one report, a 33-year-old man had avascular necrosis of both hips requiring surgery after using inhaled fluticasone 3 times a day for several years. A history of previous steroid therapy (type not specified) was the only identified risk factor reported. Another report of osteonecrosis involved a 46-year-old man who had been using Advair Diskus for 4 months, Flovent and another inhaled corticosteroid (beclomethasone) for about 8 years, and Flonase Nasal Spray occasionally for about 3 years. The report did not state any previous use of systemic corticosteroids. The other 3 reports contained limited information.

Systemic adverse reactions may occur with intranasal and inhaled use of corticosteroids.[1,2] The long-term effects of fluticasone propionate are still unknown. The relative determinants of systemic adverse reactions to inhaled and intranasal corticosteroids have been assessed, and fluticasone propionate was determined to have a high systemic potency.[5] Because corticosteroid-induced osteonecrosis tends to occur in younger patients (the average age at onset is 33) and treatment options for advanced disease are limited, early identification is important.[4] Health care professionals, patients and caregivers should be aware of the potential for osteonecrosis with inhaled or intranasal corticosteroids and

Table 1: Products containing fluticasone propionate available on the Canadian market*

Product (year of marketing)	Route of administration	Indication
Flonase (1993)	Intranasal	Allergic rhinitis[2]
Flovent Diskus (1998)	Inhalation	Prophylactic management of asthma in children and adults[1]
Flovent HFA (2001)	Inhalation	Prophylactic management of asthma in children and adults[1]
Advair Diskus† (1999) and Advair HFA† (2001)	Inhalation	Maintenance treatment of asthma and chronic obstructive pulmonary disease in patients when the use of a combination product is considered appropriate[3]
Cutivate (2004)	Topical cream	Relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses

*Generic products are also available for intranasal spray.
†Fluticasone propionate/salmeterol xinafoate combination products.

are encouraged to report any suspected cases to Health Canada.

Nadiya Jirova, MSc, Health Canada

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Rosiglitazone–fenofibrate interaction: severe paradoxical decreased high-density lipoprotein cholesterol levels

Key points

- Health Canada received 8 reports of decreased high-density lipoprotein (HDL) cholesterol levels in patients using rosiglitazone and fenofibrate concomitantly.
- Observational studies and case reports support the possible occurrence of severe paradoxical lowering of HDL cholesterol with the use of various fibrates (e.g., fenofibrate, bezafibrate).
- Some studies and case reports suggest that, in some patients, such decreases involve the interaction of rosiglitazone with fenofibrate or bezafibrate.

Rosiglitazone is indicated in Canada to improve glycemic control in patients with type 2 diabetes mellitus when all other oral antidiabetic agents are inadequate, contraindicated or cannot be tolerated.[1] It was marketed for the first time in Canada in 2000 under the brand name Avandia. Fenofibrate is indicated for the treatment of several forms of dyslipidemia.[2] It was marketed for the first time in Canada in 1990 under the brand name Lipidil.

Both drugs are known to increase serum concentrations of high-density lipoprotein (HDL) cholesterol.[1,2] Severe paradoxical decreases of HDL cholesterol (defined as < 0.52 mmol/L) associated with the concomitant use of rosiglitazone and fenofibrate have been reported in the literature.[3] Serum concentrations of HDL cholesterol below 1.03 mmol/L are considered to be a risk factor for cardiovascular disease.[4,5]

As of Sept. 30, 2010, Health Canada received 8 reports of decreased HDL cholesterol levels in patients using rosiglitazone and fenofibrate concomitantly. In these patients, the lowest reported levels ranged from 0.02 to 0.43 mmol/L. One of the reports was described in the *Canadian Adverse Reaction Newsletter* in 2005.[6] Another was published in the literature.[7] In 3 of the 8 patients, the HDL cholesterol levels improved after discontinuation of rosiglitazone while fenofibrate was continued. In another patient, the HDL cholesterol level improved after discontinuation of both drugs. One of these cases was discovered during the clinical investigation for an acute stroke. None of the patients died.

Observational studies and case reports have reported the possible occurrence of a severe decrease in HDL cholesterol levels with the use of various fibrates (fenofibrate, bezafibrate or ciprofibrate) without concurrent exposure to rosiglitazone.[3,8–10] However, additional study data and recently published case reports suggest that, in some patients, such decreases involve the interaction of rosiglitazone with fenofibrate or bezafibrate.[3,7–18]

Rosiglitazone is a peroxisome proliferator-activated receptor (PPAR)-γ agonist,[1] and fenofibrate is a PPAR-α agonist.[2] It has been suggested that genetic polymorphisms in the response to PPAR agonists could influence the

metabolism of apolipoprotein AI, the major lipoprotein of HDL cholesterol.[12–14] The mechanism of action for the potential interaction between rosiglitazone and fenofibrate remains unknown.

Health professionals are encouraged to report any cases of decreased HDL cholesterol levels suspected of being associated with fenofibrate and rosiglitazone used alone or in combination.

Patrice Tremblay, MD, Health Canada

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Varenicline and hyperglycemia in patients with diabetes

Key points

- Health Canada received 18 reports of hyperglycemia suspected of being associated with varenicline in patients with type 1 and type 2 diabetes.
- Of these 18 reports, 7 described a positive dechallenge.

Varenicline (Champix) is indicated for smoking-cessation treatment in adults in conjunction with smoking-cessation counselling.[1] The current Canadian product monograph lists diabetes mellitus and hypoglycemia under "less common clinical trial adverse drug reactions" and describes these adverse reactions (ARs) as infrequent and rare, respectively.[1]

From the date of marketing in April 2007 to Sept. 30, 2010, Health Canada received 18 reports of hyperglycemia suspected of being associated with varenicline in patients with type 1 and type 2 diabetes (Table 1). Of these 18 reports, 2 indicated that the patient required hospital admission. Seven of the reports described a positive dechallenge (abatement of AR upon stopping or reducing the dosage of varenicline), and one described a negative dechallenge (the AR did not subside after discontinuation of varenicline). In one patient, blood glucose levels were reported to increase after each dose of varenicline. Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycemia and consequently is a confounder in all of the cases. Other confounders identified in some of the reports included infection, medications (e.g., insulin, oral antidiabetic agents, diuretics), alcohol consumption and smoking cessation. In some instances, the patient was still smoking while taking varenicline.

No reports of hyperglycemia suspected of being associated with varenicline in patients with diabetes were found in the medical literature. In one published report describing multiple episodes of hypoglycemia in a diabetic patient after starting varenicline, recommendations were made to intensify home-monitoring

of plasma glucose levels.[2]

Voluntary reporting to Health Canada is an important postmarketing surveillance tool to obtain valuable information about ARs to health products. Health care professionals and patients are encouraged to report ARs suspected of being associated with varenicline.

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Table 1: Summary of 16* reports of hyperglycemia suspected of being associated with varenicline in patients with diabetes submitted to Health Canada as of Sept. 30, 2010†

Case	Age/ sex	Onset of reaction‡	Dechallenge§	Increase in blood glucose level, mmol/L	Concomitant health products
1¶	63/F	10 days	Positive	To 12; (to 70 the following day)	Insulin lispro and NPH, ramipril, furosemide
2	52/F	4 days	Positive	From 5.7 to 16	Metformin, enteric-coated ASA, atorvastatin, metoclopramide, nifedipine, pantoprazole, perindopril, triamterene, hydrochlorothiazide
3	NA/M	3 days	Positive	To 22	Insulin, unspecified hypocholesterolemic agent, levothyroxine sodium
4	50/M	Unknown	Positive	To 30	Rosiglitazone, cilazapril, lansoprazole, oxycodone, topiramate
5	49/F	Unknown	Positive	To 16–19	Glyburide, metformin, ASA, rosuvastatin
6	42/F	Unknown	Positive	To 35	Metformin, cetirizine, pantoprazole, pravastatin, salbutamol, venlafaxine, verapamil
7	43/F	2 days	Unclear	From 5–13 to 31–33	Insulin NPH and R, pancrelipase, budesonide / formoterol inhaler, clonazepam, rabeprazole, spironolactone
8	NA/NA	2 days	Unknown	From 7 to 18–20	Multiple antidiabetic medications (detail not provided in report)
9	57/M	3 days	Negative	To 15	Glyburide, metformin, diltiazem, doxazosin, hydrochlorothiazide, losartan, omeprazole, simvastatin
10	40/F	Unknown	Not applicable	To 20	Insulin
11	NA/F	Unknown	Unknown	From 6–13 to 24–30	Insulin
12	50/F	Unknown	Unknown	From 7 to 17–18	Insulin glargine (reported as co-suspect), insulin lispro, enteric-coated ASA, calcium and vitamin D, mesalazine
13	65/M	Unknown	Unknown	From 5.5 to 19	Insulin, atorvastatin, doxazosin, ezetimibe, pantoprazole, ramipril
14	59/M	Unknown	Not applicable	To 33	Glyburide; report stated patient was taking about 10 concomitant medications for hypertension, cholesterol and gout
15	60/M	Unknown	Unknown	To 16–17	Insulin, naproxen, lorazepam
16	66/F	Unknown	Positive	To above 33	Metformin, glyburide, enteric-coated ASA

Note: ASA = acetylsalicylic acid, NA = not available.
*Two of the 18 reports are not included in the table because they contained limited information.
†**These data cannot be used to determine the incidence of adverse reactions (ARs) because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**
‡Estimated from the beginning of treatment.
§Response to withdrawal of the drug. Abatement of the reaction after the drug is stopped or the dose is reduced is considered a positive dechallenge.
¶Patient reported to have brittle diabetes.

Quinine sulfate and serious adverse reactions

Key points

- Quinine sulfate is not indicated in Canada for the prevention or treatment of nocturnal leg cramps.
- Health Canada received 71 reports of serious adverse reactions suspected of being associated with the use of quinine sulfate, including 41 that were life-threatening or required hospital admission.
- Among the reports that specified the indication for use, 43 listed cramps (leg, muscle or nocturnal leg). Twenty of these reports listed thrombocytopenia, often severe, as the adverse reaction.

Quinine sulfate, in combination with a second antimalarial drug, is recommended in Canada for the treatment of uncomplicated *Plasmodium falciparum* malaria.[1] The recommended dose for adults is 600 mg (equivalent to 500 mg of quinine base) orally, 3 times a day for 3–7 days.[1] Quinine sulfate has been marketed in Canada since 1951.

Quinine sulfate is not indicated in Canada for the prevention or treatment of nocturnal leg cramps. The Canadian Pharmacists Association monograph available in the *Compendium of Pharmaceuticals and Specialties* (*CPS*) was updated in 2010 to emphasize this.[2] However, quinine sulfate is used for the prevention and treatment of leg cramps, at a dose of 200 to 300 mg at bedtime.[2] The use of quinine sulfate to prevent leg cramps has been a subject of recent concern. Several international regulators have taken actions to either withdraw this indication for use or have added conditions for its use for leg cramps.[3–6] In addition, the US Food and Drug Administration has recently approved a risk management plan to warn against the use of quinine for leg cramps.[7]

As of Sept. 30, 2010, Health Canada received 71 reports of serious* adverse reactions (ARs) suspected of being associated with the use of quinine sulfate. Forty-one of the reports mentioned ARs that were either life-threatening or required hospital admission. Only 4 of the 71 reports listed malaria as the indication for use of the drug. Of the remaining 67 reports, 43 listed cramps, leg cramps, muscle cramps or nocturnal leg cramps as the indication for use; 17 of them were received after 2000. For the remaining 24 reports, the indication for use could not be determined or other uses were listed (e.g., neuropathic pain). Twenty of the 43 reports listed thrombocytopenia, often severe, as the AR. Other ARs included Stevens–Johnson syndrome, vasculitis and arrhythmia.

ARs to quinine sulfate include life-threatening blood-related reactions, such as sudden, severe thrombocytopenia.[8] Reports of potentially fatal hypersensitivity reactions, particularly quinine-induced thrombocytopenia, are of particular concern, because these reactions are not dose-related and their occurrence is unpredictable. Profound thrombocytopenia can occur rapidly within days or occur after months or years of use.[9]

Health care professionals are reminded of the serious ARs suspected of being associated with the use of quinine sulfate and that quinine sulfate is not indicated for the prevention or treatment of nocturnal leg cramps.

*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."

Catherine Younger-Lewis, MD, Health Canada

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CARN turns 20

Since 1991, the *Canadian Adverse Reaction Newsletter* (*CARN*) has strived to provide feedback on adverse reaction (AR) reports received by Health Canada and to stimulate AR reporting. *CARN* continues to be an early-stage risk communication tool, summarizing information on suspected ARs to raise awareness of emerging safety issues with health products.

We thank our many readers and all those who have contributed to the Newsletter over the years.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Nov. 13, 2010 – Feb. 18, 2011)

Date*	Product	Subject
Feb 17	Lubricating jelly products	Additional recall of lubricating jelly products
Feb 16	Methylene blue injectable	Serotonin toxicity when used in combination with serotonin reuptake inhibitors
Feb 8	Pharmetics Inc. products	Recall of selected lots of 6 health products
Feb 4	Health products co-packaged with recalled alcohol prep pads	Recall of Triad alcohol prep pads
Feb 3	Pegetron Redipen	Recall of alcohol prep pads co-packaged with Pegetron Redipen
Feb 2	Exact Multi Greens Powder and Capsules	Recall due to allergy risk for people with milk sensitivities
Jan 28	Nutrex Research Lipo 6X	Recall of unauthorized weight loss product
Jan 26	Medication	It's Your Health: Disposal and use of medication
Jan 25	Medicines	It's Your Health: Safe use of medicines
Jan 24	Injectable cosmetic treatments	It's Your Health: Injectable cosmetic treatments
Jan 14	Triad products	Recall of alcohol swabsticks, swabs and prep pads
Jan 13	Acetaminophen	Using acetaminophen safely
Jan 12	Copaxone	Recall of alcohol prep pads co-packaged with Copaxone
Jan 11	Shandex Sales Group Alcohol Swabs	Recall due to potential contamination
Jan 7	Synerate	Recall of unauthorized weight loss product
Dec 23 & 24	Probiotic natural health products	Products may contain trace amounts of milk or soy protein
Dec 15 & 20	Thelin	Product withdrawal: concerns about hepatotoxicity
Dec 13	ResurreXX	Recall of unauthorized product
Dec 10	"Durazest" and "Once More"	Recall of certain lots of male sex enhancement products
Dec 10	Rolaid products	Recall: reports of foreign materials in products
Dec 10	Flat Stomach Concept Extra	Recall because of missing label statements
Dec 7	Semen	Information regarding semen donation
Dec 1	"Fat Burner No. 1"	Recall of unauthorized product
Nov 25 & Dec 1	Darvon-N	Recall and withdrawal: risk of serious abnormal heart rhythms
Nov 24	Children's Benadryl Allergy Meltaways	Recall because of quality control concerns
Nov 9 & 18	Avandia, Avandamet and Avandaryl	New restrictions because of information on cardiovascular-related events
Nov 13 to Feb 18	Foreign products	20 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.healthcanada.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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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.