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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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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 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 intransal 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.3 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...
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.1 It has been suggested that genetic polymorphisms in the response to PPAR agonists could influence the...

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.

Nadiya Jirova, MSc, Health Canada

References

metabolism of apolipoprotein AI, the major lipoprotein of HDL cholesterol.\textsuperscript{1-14} 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

References


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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

Maria Longo, RPh, BScPharm, Health Canada

References


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

Note: ASA = acetylsalicylic acid, NA = not available.

*Two of the 18 reports are not included in the table because they contained limited information.

\textsuperscript{\dagger}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.

\textsuperscript{\$}Estimated from the beginning of treatment.

\textsuperscript{\¶}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.

\textsuperscript{\¶}Patient reported to have brittle diabetes.

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†
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. The recommended dose for adults is 600 mg (equivalent to 500 mg of quinine base) orally, 3 times a day for 3–7 days. 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 Specialities (CPS) was updated in 2010 to emphasize this. However, quinine sulfate is used for the prevention and treatment of leg cramps, at a dose of 200 to 300 mg at bedtime. 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. 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.

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. 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.

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.

References


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.

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 suspicious, 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.