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Canadian Adverse Reaction Newsletter

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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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Pico-Salax (sodium picosulfate/ magnesium citrate) and convulsions

Key points

- Pico-Salax (sodium picosulfate/ magnesium citrate) is an oral purgative indicated for the clearance of the bowel prior to x-ray examination, endoscopy or surgery.
- Health Canada received 11 reports of convulsions suspected of being associated with Pico-Salax.
- Health care professionals are encouraged to inform patients of the importance of drinking a variety of clear fluids containing electrolytes, and not just water alone, while using this medication.

Pico-Salax contains sodium picosulfate and magnesium citrate (also referred to as citric acid and magnesium oxide) and is available as a nonprescription oral purgative indicated for the clearance of the bowel prior to x-ray examination, endoscopy or surgery.[1] In addition to Pico-Salax, there are 4 other marketed medications containing sodium picosulfate/magnesium citrate in Canada: Picodan, Purg-Odan, Picoflo and Oral Purgative.

Pico-Salax acts as an osmotic laxative, stimulates peristalsis and has a powerful "washing out" effect within 3 to 6 hours or less of administration.[1] The diarrhea produced by the medication can lead to dehydration and loss of electrolytes, particularly sodium which may result in hyponatremia and convulsions.[1–3] Elderly and debilitated individuals are particularly at risk. Pico-Salax may also decrease the absorption of oral medications due to an increase in gastrointestinal transit rate, and may be associated with convulsions in patients taking anticonvulsants.[1]

As of June 30, 2012, Health Canada received 11 reports of convulsions suspected of being associated with Pico-Salax. In 5 cases, patients developed hyponatremia, of which 4 drank mainly water as a means of rehydration. In another 3 cases, patients with a history of seizures had their convulsions controlled by anticonvulsants prior to taking Pico-Salax. No deaths were reported in any of the cases, however 6 patients required hospital care. In one case, the patient had a history of alcohol consumption and withdrawal. Another case was unassessable due to limited information. Patient age ranged from 36 to 74 years. Age was not reported in 2 cases.

Several articles in the literature reported incidents of seizures and hyponatremia or emphasized the risk of electrolyte disturbances when using sodium picosulfate/magnesium

citrate.[4–7] It is important to replace electrolytes as well as fluids when rehydrating.[8] Both the risk of hyponatremia and decreased drug absorption are well described in the prescribing and consumer information for Pico-Salax.[1] The prescribing and consumer information for Pico-Salax have also been updated to emphasize the need to drink a variety of clear fluids containing electrolytes, and not just water alone. Health Canada is currently working to align the prescribing information for all other sodium picosulfate/magnesium citrate products.

Health care professionals are encouraged to inform patients of the importance of replacing fluid and electrolyte losses with the intake of a balanced electrolyte solution and are reminded of the risk of convulsions suspected of being associated with the use of Pico-Salax or any product containing sodium picosulfate/magnesium citrate.

Anne Cornet, MD, FRCP(C), Health Canada

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Risperidone and rhabdomyolysis independent of neuroleptic malignant syndrome

Key points

- Health Canada received 5 reports of rhabdomyolysis without the presence of neuroleptic malignant syndrome suspected of being associated with the use of risperidone.
- Four of the 5 cases included a positive dechallenge.
- Health Canada is currently working with the manufacturer with the aim of updating the product label for risperidone.

Risperidone is an atypical antipsychotic agent indicated for the treatment or management of schizophrenia, inappropriate behaviour associated with severe dementia and manic episodes associated with Bipolar I disorder.[1] All atypical antipsychotics marketed in Canada, including risperidone, can trigger neuroleptic malignant syndrome (NMS), and rhabdomyolysis can be part of this syndrome.

Rhabdomyolysis refers to the disintegration of striated muscle and the consequent release of muscular cell contents such as myoglobin into extracellular fluid and circulation. Myoglobin is normally bound to plasma globulins, of which a small amount may be excreted in the urine. When a massive amount of myoglobin is released, and the binding capacity of plasma proteins is surpassed, myoglobin is filtered by the glomeruli and eventually reaches the tubules, where it can cause obstruction and may lead to renal failure.[2] Clinical signs and symptoms of rhabdomyolysis include muscle pain, weakness, and dark red-coloured urine. Serum creatine phosphokinase (CPK) levels are also typically markedly elevated and can be used to assess the presence and intensity of muscle damage.[2,3]

Other atypical antipsychotics including clozapine, olanzapine, quetiapine, aripiprazole and one paliperidone product are currently labelled for the risk of rhabdomyolysis independent of NMS, as well as part

Table 1: Summary of 5 reports of rhabdomyolysis independent of neuroleptic malignant syndrome suspected of being associated with the use of risperidone submitted to Health Canada as of June 30, 2012*

Case	Age/sex	Daily dose, mg†	Onset of reaction‡	Peak serum creatine phosphokinase, IU/L	Dechallenge§
1¶	31/M	4.5	17 days	14 000	Positive
2	16/M	0.5	19 months	1 023	Positive
3	54/F	Unknown	< 2 months	39 000	Positive
4	44/F	6	5 years	8 974	Negative
5**	42/M	1.5	10 years	6 000	Positive

*** 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.**

† Total daily dose at the time of reaction onset.

‡ 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.

¶ Concomitant use of irbesartan was reported.

** Concomitant use of valsartan was reported.

of NMS, in their respective Canadian product monographs.[4–8] Risperidone and ziprasidone are not labelled for the risk of rhabdomyolysis independent of NMS.[1,9]

As of June 30, 2012, Health Canada received 5 reports of rhabdomyolysis independent of NMS suspected of being associated with risperidone (Table 1). All but one patient had recovered at the time of reporting. No deaths were reported.

Reports of significant and transient elevation of CPK in stable patients without the presence of NMS involving risperidone and other antipsychotics have been described in the literature.[3,10,11] However, the exact pathophysiological mechanism that mediates this association remains unclear. There are individual vulnerability factors involved in the development of rhabdomyolysis in the presence of antipsychotics.[12] It has also been proposed, based on animal studies, that the accumulation of serotonin in skeletal muscle can play a role in the development of muscle injury.[11]

Health Canada is currently working with the manufacturer with the aim of updating the product label for risperidone. Health professionals should be aware of the risk of rhabdomyolysis without the presence of NMS suspected of being associated with the use of risperidone. Health Canada encourages the reporting of adverse reactions through the Canada Vigilance Program at **www.health.gc.ca/medeffect**.

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Docetaxel and serious respiratory-related adverse reactions

Key points

- Health Canada received 31 reports of pneumonitis, interstitial lung disease, lung infiltration or respiratory failure suspected of being associated with docetaxel.
- The Canadian product monograph for docetaxel (Taxotere) has recently been strengthened to further emphasize the potential for pulmonary toxicity.
- Early recognition of respiratory-related adverse reactions associated with docetaxel may lead to earlier treatment and improved patient outcomes.

In Canada, docetaxel (Taxotere) is an injectable chemotherapy drug that was first marketed on December 31, 1995. It is currently indicated for the treatment of breast, non-small cell lung, ovarian and prostate cancer, as well as squamous cell carcinoma of the head and neck.[1] Currently, there is one generic product marketed in Canada under the name of Docetaxel for Injection.

Docetaxel belongs to a group of antineoplastic medicines known as taxanes. It acts by disrupting the microtubular network essential for cell division.[1] Specifically, it promotes the assembly and stabilization of microtubules and leads to the production of microtubule bundles without normal function, resulting in the inhibition of mitosis in cells.

Several antineoplastic drugs, including docetaxel, have been known to induce pulmonary toxicity, which may result in a variety of pathological syndromes ranging from unspecified dyspnea to pulmonary pneumonitis that may lead to permanent pulmonary fibrosis and possible death.[2,3] This type of drug-associated lung injury typically occurs as a result of cellular dysfunction which can trigger apoptosis or by impairing the cell and tissue repair sequence.[4]

As of July 31, 2012, Health Canada received 31 reports of respiratory-related adverse reactions (ARs) suspected of being associated with docetaxel involving pneumonitis, interstitial lung disease (ILD), lung infiltration or respiratory failure. Among these cases, 23 patients required hospitalization. A fatal outcome was reported in 9 cases. Patient age ranged from 34 to 69 years. Age was not reported in 4 cases. Time to onset of the ARs varied from several days after one dose to several weeks after multiple doses.

Several cases of serious respiratory-related ARs in patients using docetaxel, either alone or in combination with other antineoplastic agents, have been reported in the literature*. Reported ARs included pneumonitis or interstitial pneumonitis, pulmonary infiltrates, acute respiratory distress syndrome, respiratory failure, ILD, interstitial infiltrates and pneumocystis pneumonia. Some of these cases resulted in fatal outcomes. For example, one article describes 4 patients who developed severe interstitial pneumonitis that could not be explained by any other cause other than docetaxel-associated toxicity.[5] None had metastatic disease to the lung, and all had normal liver function before receiving chemotherapy. The patients presented with symptoms of acute dyspnea and fever within 1 to 2 weeks of receiving docetaxel. All 4 patients eventually developed progressive interstitial infiltrates and respiratory failure. Two of the patients died of related complications.

The Canadian product monograph for Taxotere has been updated to include the potential for respiratory-related ARs in the Warnings and Precautions section, as well as the addition of pneumonitis, ILD, lung infiltration and respiratory failure in the Post-Market Adverse Drug Reactions section. Strengthening the product label is intended to alert health care professionals about the potential for an increased risk of serious respiratory-related ARs associated with docetaxel, as well as to promote earlier risk detection and possible intervention.

Health Canada is continuing to monitor ARs suspected of being associated with docetaxel and encourages health care professionals to report similar cases through the Canada Vigilance Program.

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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.

Ear drops containing peanut oil and suspected association with anaphylaxis

Health Canada received a report of a 7-year-old girl who experienced an anaphylactic reaction after being administered Cerumol ear drops by a parent. According to the report, she received 4 drops of Cerumol ear drops in each ear to loosen earwax. Within 4 minutes, she required her "blue inhaler" normally used for her asthma problems (product not specified), stating that it was too hard to breathe. She then collapsed, went into anaphylactic shock and was taken to the emergency room but was not hospitalized. The treatment she received while in the emergency room was not specified; however, after discharge she was administered diphenhydramine (Benadryl) at home for a couple of days. The report indicated that she had recovered. It was also reported that she had a known peanut allergy and that she was a regular user of ciclesonide (Alvesco) and montelukast (Singulair) for the treatment of her asthma.

Cerumol ear drops include a warning on the box and in the patient information leaflet indicating that the product contains peanut oil and instructs patients allergic to peanuts and soya not to use it. The label on the box and the bottle lists peanut oil as a non-medicinal ingredient. Despite this, the parent reported that she was unaware that Cerumol contained peanut oil.

Health professionals are encouraged to remind patients with food allergies to always check the list of medicinal and non-medicinal ingredients of health products, including topical preparations, such as creams, ointments and ear drops, and to consistently check for allergen warnings prior to using any product. Manufacturers sometimes change the ingredients used in familiar products. Different varieties and sizes of the same brand may contain different ingredients. Patients with peanut allergies should also be aware that licensed Canadian natural health products and pharmaceuticals may be labelled as containing arachis oil, which is another term for peanut oil.

Health Canada encourages the reporting of adverse reactions suspected of being associated with allergen-containing natural health products and pharmaceuticals to the Canada Vigilance Program.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: August 20, 2012 – November 18, 2012)

Date*	Product	Subject
Nov 16	Prolia (denosumab)	New safety information on the risk of atypical femoral fractures
Nov 7 and 13	Zocor (simvastatin)	New safety recommendations on dosage
Oct 31 and Nov 5	Riata and Riata ST Silicone Endocardial Defibrillation Leads	Updated safety information and recommendations
Oct 30 and Nov 2	Infanrix Hexa vaccine	Recall: potential microbial contamination of one lot
Oct 30	Products from the New England Compounding Center	Update on U.S. meningitis outbreak linked to contaminated health products
Oct 29	Carboplatin Injection, 600mg/60mL	Recall: visible particles in one lot
Oct 26 and 31, Nov 5 and 6	Agriflu and Fluad vaccines	Suspension of distribution and related updates
Oct 25	Pollen Allergy or Tongqiao Biyan Pian	Recall: arsenic levels exceed safety limit
Oct 19	Proton pump inhibitors and methotrexate	New safety information: possible interaction
Oct 15 and 18, Nov 6	Antimicrobial Foaming Hand Soap and X3 Clean Alcohol-Free Foaming Hand Sanitizer	Recall: microbial contamination
Oct 15 and 17	Epicardial pacemaker leads	Risk of cardiac strangulation in pediatric patients with implants
Oct 9	Insulin pumps	It's Your Health: Insulin pumps
Oct 3 and 9	Zofran (ondansetron)	Dosage restriction for intravenous use
Oct 1 and 4	Typhim Vi vaccine	Recall: potentially lower than expected antigen content
Sept 18	Zhuifeng Tougu Wan	Recall: unauthorized health product
Sept 17	Propofol Injectable Emulsion 1%, 10mg/mL	Recall: presence of particulate matter in one lot
Sept 14	ImmuCyst (BCG vaccine)	Update on supply status
Sept 10	HIV and STD home test kits	Web site selling unauthorized home-use test kits
Sept 4	BiCNU (carmustine for injection, USP),100mg/vial	Recall: overfilled vials
Aug 21 and 23	Gilenya (fingolimod)	Stronger recommendations regarding first-dose cardiovascular monitoring

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**

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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.