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Canadian Adverse Reaction Newsletter

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www.healthcanada.gc.ca/carn

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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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Clozapine and life-threatening gastrointestinal hypomotility

Key points

- Health care professionals are reminded of life-threatening gastrointestinal hypomotility suspected of being associated with the use of clozapine.
- Patients taking clozapine should be advised to notify their health care professional if constipation occurs or worsens.
- Gastrointestinal hypomotility may be aggravated by combining clozapine with other potentially constipating medications.

Clozapine is an atypical antipsychotic agent indicated in the management of treatment-resistant schizophrenia.¹ It has been marketed in Canada since 1991 under the brand name Clozaril and is now also available as generic products. Clozapine use is limited to patients who have not responded to, or are intolerant of, conventional antipsychotic medications. Constipation is a common adverse reaction (AR) to the drug. The Canadian product monograph for Clozaril indicates that constipation occurred in 14% of patients in clinical trials, and higher rates have been reported in case series.^{1,2} The Canadian product monograph also lists paralytic ileus as a contraindication to clozapine use.¹ The drug has potent anticholinergic effects that have been associated with varying degrees of

impairment of intestinal peristalsis, from constipation to intestinal obstruction, fecal impaction and paralytic ileus.¹ On rare occasions, these cases have been fatal.

Clozapine's anticholinergic and antiserotonergic effects may contribute to gastrointestinal hypomotility and colonic distension.²⁻⁴ Intraluminal distension in turn can compromise capillary circulation and lead to colonic mucosal ischemia. In addition, severe fecal retention resulting from hypomotility may promote colonic distension, accumulation of gas and fluids, and bacterial proliferation in the affected bowel segment.^{3,4} Bacteria may then invade the underlying ischemic mucosa, resulting in necrosis and systemic sepsis.

The potential for complications and death from severe gastrointestinal hypomotility is considerable.^{2,5} For instance, the rate of death from acute colonic pseudo-obstruction (acute colonic dilatation without mechanical obstruction) is 15% in the absence of complications such as ischemia and perforation.⁵ If spontaneous perforation occurs (3%–15% of cases), mortality rises to 50% or higher.⁵ Late presentation and diagnosis of bowel obstruction may contribute to fatal outcomes in patients using clozapine.² This may be related to diminished pain sensitivity in patients with schizophrenia or to difficulty in expressing their pain.^{2,6} In addition, concomitant medications may have sedative and analgesic effects, which may mask or attenuate early symptoms

and contribute to delayed diagnosis.

As of July 15, 2010, Health Canada received 704 reports of gastrointestinal ARs suspected of being associated with the use of clozapine. Of these, 28 deaths involving people with ARs related to intestinal obstruction were identified. Reports came from health care professionals and the medical literature.^{4,7} For these 28 cases, the quality of reporting varied. Many reports did not exclude other possible causes of bowel obstruction. Six cases were considered difficult to assess because the reports contained limited or conflicting clinical information. Of the remaining 22 cases, 13 involved men and 9 involved women. The median age of patients was 61 years. A prior history of constipation was noted in 6 reports. Thirteen reports involved the use of other medications with the potential to cause or aggravate constipation.

Examples included other antipsychotic agents (e.g., methotrimeprazine, loxapine and olanzapine), medications used to manage drug-induced extrapyramidal symptoms (e.g., benzotropine and procyclidine) and medications indicated for the treatment of urinary tract disorders (e.g., oxybutynin and tolterodine). Use of a laxative before the intestinal obstruction developed was reported in 4 cases. The total daily dose of clozapine, reported in 17 cases, varied from less than 300 mg (5 cases) to more than 600 mg (2 cases). The median daily dose in the remaining 10 cases was 550 mg. Time to onset of ARs ranged from about 2 weeks to many years. In 3 cases, death was related to aspiration pneumonia associated with ileus.

Health care professionals are reminded of the potential for life-threatening gastrointestinal hypomotility

suspected of being associated with the use of clozapine. It has been recommended that patients taking clozapine should be monitored for the development of constipation and that appropriate therapy be instituted in a timely manner to prevent complications.² Symptoms of serious gastrointestinal complications may be nonspecific and may include abdominal pain or distension, vomiting, constipation, change in bowel habit and fever.² Whenever possible, concomitant use of other medications with the potential to cause or aggravate constipation, particularly those with anticholinergic properties, should be avoided.^{2,7}

Erin Smith, MD, Danielle Brûlé-Brown, MD,
Health Canada

References are available in the online version (www.healthcanada.gc.ca/carn) and upon request.

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.

Bio-Alcamid soft-tissue endoprosthesis: suspected association with late infection

Bio-Alcamid is a colourless, gelatinous injectable filler consisting of 4% synthetic amide-imide alkyl-type polymer and 96% nonpyrogenic water.¹ In Canada, this product is regulated as a medical device and is indicated for the treatment of facial lipoatrophy resulting from the use of antiretroviral medications. When injected subcutaneously, Bio-Alcamid can restore lost volume in facial areas that have been depleted, typically in the regions of the temples and cheeks.¹ Its use may help restore natural facial structure and contours.

In April 2009, Health Canada received a report of a patient with massive left-sided facial swelling. A buccal space infection was diagnosed. The infection was suspected of being associated with Bio-Alcamid material that had been implanted in 2006. The affected area was incised and drained; the implanted material had become infected and was removed. Similar late complications, including reports of infection and migration occurring one year or more after Bio-Alcamid injection, have been described in the literature.²⁻⁴ Cases of late infection associated with Bio-Alcamid have been described involving patients with and without a recent history of possible triggering events such as local trauma or medical and dental interventions.^{2,3} The medical literature also suggests that the resultant abscesses may be challenging to treat and may recur or persist after medical or surgical intervention.^{3,4}

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

References are available in the online version (www.healthcanada.gc.ca/carn) and upon request.

Natural health product identification in adverse reaction reports

Health product identifiers: more than just a name!

It is important to include as many health product identifiers as possible in the adverse reaction reporting form.

Information needed:

- Exact product brand name (including modifying prefix or suffix)
- Natural Product Number (NPN), Exemption Number (EN)* or Homeopathic Medicine Number (DIN-HM)
- List of ingredients (or a copy or picture of the label or container) and their amount per serving
- Lot number
- Expiration date
- Company name
- Where the product was purchased (e.g., Internet, pharmacy, ethnic store)

Under the *Natural Health Products Regulations* (www.hc-sc.gc.ca/dhp-mpps/prodnatur/legislation/acts-lois/prodnatur/index-eng.php), which came into effect on Jan. 1, 2004, natural health products (NHPs) are defined as vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines such as traditional Chinese medicines, probiotics, and other products such as amino acids and essential fatty acids. Thousands of NHPs are available directly to Canadian consumers off store shelves (e.g., at supermarkets, health food stores, pharmacies and ethnic stores) or through other means (e.g., the Internet and personal importation). To properly evaluate safety issues associated with NHPs, Health Canada needs your help in providing quality reports of adverse reactions (ARs).

According to international guidelines, the minimum data elements needed for an AR report are patient information, description of the reaction,

information about the suspected health product and the reporter's contact information.¹ However, more comprehensive information, such as details about the suspected NHP(s) or concomitant health product(s) (see examples of health product identifiers in the box above), is needed to ensure the quality and usefulness of the report. For instance, provision of the NHP's ingredient list allows for identification of an ingredient known for its association with an AR, or its potential for interaction, or for overdose if several products with the same ingredient are used concomitantly. The lot number and company name allow for more efficient regulatory actions when cases of adulteration or contamination are suspected.

Several factors may confound the identity of an NHP in reports of ARs submitted to Health Canada, which may limit the ability to assess the data.

*Information on Exempted Products under the *Natural Health Products (Unprocessed Product Licence Applications) Regulations* is available at www.hc-sc.gc.ca/dhp-mpps/prodnatur/legislation/acts-lois/exemption/index-eng.php (accessed 2010 Oct. 7).

†A product line extension results when a drug is named by using the brand name of another drug with the addition of a modifying prefix or suffix that is intended to distinguish the new product from the original. In some cases, this practice has arisen as a marketing strategy to take advantage of familiarity of an original product name.²

These factors include:

- Existence of products with the same or similar brand names, such as line-extension products,[†] that contain different active ingredients.
- Identification in the AR report of a health product by a common name without further information such as dosage preparation, other medicinal ingredients or plant species.
- Presence of multiple products with different brand names under a single Natural Product Number (NPN) or Exemption Number (EN).*
- Reformulation of NHPs over time (e.g., change of medicinal ingredients or their quantity, and change of dosage form) but retention of the same brand name.
- Possibility of confusion with unauthorized NHPs, which have not been evaluated by Health Canada for quality, safety and efficacy, and which may be adulterated or counterfeit.

Health professionals are encouraged to ask patients about any NHPs they are taking, to document relevant product information and to report to Health Canada's Canada Vigilance Program (www.healthcanada.gc.ca/medeffect) any ARs suspected of being associated with their use.

Karen Kouassi, MSc, Health Canada

References are available in the online version (www.healthcanada.gc.ca/carn) and upon request.

By submitting a report of a suspected AR, you are contributing to the ongoing collection of information about the quality, safety and efficacy of marketed health products.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's Web site: Aug. 23, 2010 – Nov. 12, 2010)

Date*	Product	Subject
Nov 12	Breastlight	Recall of unauthorized breast cancer screening device
Nov 4	Medical device clocks	Reminder to switch to Standard Time
Nov 4	Unauthorized products	Removal of unauthorized health products in Vancouver Island stores
Nov 3	Prescription drugs online	Warning about buying prescription drugs online
Oct 27 & Nov 2	Invirase	Updated prescribing information
Oct 26 & 29	Emo-Cort (hydrocortisone) 2.5% Lotion	Recall of Lot 5R6
Oct 28	Glucagen Hypokit	Recall
Oct 27	Hyland's Teething Tablets	Recall
Oct 14 & 19	Innohep	Updated safety information on use in elderly patients with renal impairment
Oct 14	Bisphosphonate drugs	Possible risk of rare but serious thigh bone fractures
Oct 12 & 14	Aclasta	Association with renal dysfunction
Oct 8, 13 & 14	Sibutramine drugs	Voluntary withdrawal from the Canadian market
Oct 5	Calcium supplements	Ongoing review
Oct 4 & 5	Pegatron	Important information regarding quality, safety and supply
Oct 4	Level 1 Normothermic IV Fluid Administration Sets	Recall concerning a heat exchanger assembly manufacturing issue
Sep 20	Foreign products	Alerts: Golden aruru, Baisheng wei ge, Zhonghua niubian, Ten ka dai 1 bou, Kuai gan bei zeng chao yue zi wo (Happy felling doubly increase [sic]), Ling tou lang, SkyFruit, Chu bi ho ken, Jinbolang, Suika Koso, Lov, I ka ou (2009 nen sin hosu) and/or I ka ou (saisinsui shutsu hosu); Vialipro; Joyful Slim Herb Supplement
Sep 15	"Arth-Forth"	Unauthorized herbal product may pose serious health risks
Sep 13 & 16	Actemra	Risk of fatal anaphylaxis
Sep 13	"E.O.D. Erection on Demand"	Unauthorized health product may pose serious health risks
Sep 7	Alaris PC unit	Total bolus display error
Sep 4	Excelsior Disposable Syringe	Recall
Aug 31	Human papillomavirus (HPV)	It's Your Health update
Aug 26	Topical hemostatic agents	Delivery using spray devices — association with air/gas embolism
Aug 25	Droperidol Injection USP	Association with severe arrhythmia
Aug 25	Glucagen Hypokit	Recall
Aug 23	Stander (Tilt Standing Frame)	Addition to safety warning label
Aug 19 & 23	Avastin	Association with allergic reactions
Aug 9	Gemstar Pump Sets	Recall

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_dpssc@hc-sc.gc.ca

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