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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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Botulinum toxin type A (Botox) and distant toxin spread

Botulinum toxin health products have recently been the subject of safety notices because of their suspected association with the potential spread of the toxin to sites in the body distant from the sites of administration (distant or systemic toxin spread).[1,2] In Canada, botulinum toxin type A is marketed as Botox and Botox Cosmetic. Botox is indicated for the treatment of cervical dystonia, blepharospasm associated with dystonia, strabismus, dynamic equinus due to spasticity in pediatric cerebral palsy patients, hyperhidrosis of the axilla and focal spasticity.[3] Botox Cosmetic is indicated for the treatment of facial wrinkling.[4]

Toxin spread may occur locally, when botulinum toxin disperses to surrounding tissues, as in the case of dysphagia reported with the use of botulinum toxin type A in patients with cervical dystonia.[3] In addition, adverse reactions (ARs) suggestive of botulism were also reported and may occur as the result of systemic toxin spread beyond the site of injection.[2] Symptoms of botulism can include muscle weakness or paralysis, dysarthria, dysphagia and dysphonia.[5] Serious complications of botulism include respiratory depression and dysphagia, which may lead to aspiration pneumonia. These manifestations may be fatal if untreated.[5,6]

As of Mar. 28, 2008, Health Canada received 13 reports describing ARs suggestive of distant toxin spread suspected of being associated with Botox and Botox Cosmetic (Table 1). None was medically confirmed as distant toxin spread. Ten of the 13 cases were deemed to be serious owing to life-threatening reaction (1 case), hospitalization (3 cases), ongoing disability (1 case) or fatal outcome (5 cases). Reports involved 7 adults and 4 children (age not provided in 2 cases). All but 1 patient received Botox for a therapeutic rather than a cosmetic indication; 4 patients received Botox for an off-label indication.

Health care professionals and consumers are reminded that botulinum toxin health products should be administered only at the recommended doses and for authorized indications. Patients should contact their physician or pharmacist if they have questions about Botox or Botox Cosmetic, or if they experience an adverse reaction. Health professionals are also encouraged to report to Health Canada any adverse reactions suspected of being associated with Botox or Botox Cosmetic.

Mélanie Derry, PhD; Kelly Robinson, MSc; Elaine Taylor, MD, FCFP, Health Canada

References

1. *Health Canada reviewing issue of distant toxin spread potentially associated with Botox and*

Botox Cosmetic. Ottawa: Health Canada; 2008 Feb 20. Available: www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2008/2008_32-eng.php (accessed 2008 June 9).
2. *Early communication about an ongoing safety review — Botox and Botox Cosmetic (botulinum toxin type A) and Myobloc (botulinum toxin type B)*. Rockville (MD): US Food and Drug Administration; 2008 Feb 8. Available: www.fda.gov/cder/drug/early_comm/botulinium_toxins.htm (accessed 2008 Apr 15).
3. *Botox (botulinum toxin type A for injection)* [product monograph]. Markham (ON): Allergan Inc.; 2007.
4. *Botox Cosmetic (botulinum toxin type A for injection)* [product monograph]. Markham (ON): Allergan Inc.; 2007.
5. Brook I. Botulism: the challenge of diagnosis and treatment. *Rev Neurol Dis* 2006;3(4):182-9.
6. Palmer JL, Metheny NA. Preventing aspiration pneumonia in older adults with dysphagia. *Am J Nurs* 2008;108(2):40-8.

Table 1: Summary of reports of adverse reactions suggestive of distant toxin spread suspected of being associated with botulinum toxin type A submitted to Health Canada as of Mar. 28, 2008*

Case	Patient age/sex	Adverse reaction† (time to onset‡)	Indication	Dose	Additional information	Outcome§
1	69/F	Dysphagia (day 2); asthenia (day 2); respiratory disorder (day 3)	Cervical dystonia	100 U	Parkinsonism with possible striatonigral degeneration; concomitant medications: levodopa-carbidopa, pergolide, temazepam	Death
2	NA/M	Gastrointestinal disorder; paresthesia; peripheral vascular disorder; asthenia (same day)	Not specified	Not specified	Previous Botox exposure with no adverse reactions	Not recovered
3	54/F	Respiratory arrest; aphonia; hoarseness (NA)	Migraine and occipital cephalalgia (off-label)	100 U	Bupivacaine use (co-suspect for respiratory arrest); aphonia and hoarseness possibly attributable to intubation	Recovered without sequelae
4¶	31/F	Dysphagia; throat swelling nonspecific; headache; allergic reaction; facial palsy; fatigue (same day)	Facial wrinkling	20 U	Possible allergic reaction to Botox Cosmetic; patient was taking sleep aids, which suggested fatigue was pre-existing	Not recovered (fatigue)
5	55/M	Slurred speech; dysarthria; muscle weakness (same day)	Torticollis	300 U	Symptoms also suggestive of stroke	Not specified
6	36–37/F	Asthenia legs; dizziness; bladder control disorder (same day)	Muscle spasms	Not specified	Muscle spasms in left leg due to multiple sclerosis	Not recovered
7	60/F	Aspiration pneumonia; dysphagia (1 month)	Muscle spasms	500 U	Muscle spasticity due to cerebral palsy; progressive choking disorder (6 months)	Death
8	1/M	Transverse myelitis (9 days)	Talipes (off-label)	94 U	Possible misdiagnosis of toxin spread as transverse myelitis	Not recovered
9	9/M	Respiratory disorder (11 days)	Drooling (off-label)	90 U	Cerebral palsy; clonazepam use; history of seizures	Death
10	11/F	Respiratory infection (3 days)	Drooling (off-label)	100 U	Severe cerebral palsy; general anesthetic used; 3 episodes of respiratory infections occurred after Botox exposures on 3 different dates	Recovered without sequelae
11	13/M	Aspiration pneumonia (14 days)	Muscle spasms	400 U	Cerebral palsy; severe seizure disorder; recurrent respiratory infections, including aspiration pneumonia; severe reflux	Death
12	67/F	Aspiration pneumonia; apnea; asthenia; blepharoptosis; dyspnea; chest pain; muscular weakness (3 weeks)	Cervical dystonia	220 U	Myotonic dystrophy; atrial fibrillation; hypothyroidism; osteoarthritis	Death
13	NA/M	Migraine; weakness; fever; blurred vision (a few days)	Hyperhidrosis	300 U	Lorazepam	Not recovered (weakness at injection site)

Note: NA = not available.
***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.**
†Terms are listed according to the *World Health Organization Adverse Reaction Terminology* (WHOART).
‡Estimated from the beginning of the treatment.
§At the time of reporting.
¶Patient received Botox Cosmetic.

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.

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.

Intravenous immune globulin: suspected association with transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is a clinical syndrome that presents as acute hypoxemia and noncardiogenic pulmonary edema during or within 6 hours after blood transfusion.[1,2] TRALI is an important cause of transfusion-associated death, even though it is probably still underdiagnosed and underreported.[2] There have been few literature reports of TRALI in patients administered intravenous immune globulin (IVIG).[3] The Canadian product monograph for Gamunex (human IVIG 10%) recommends that IVIG recipients be monitored for pulmonary adverse reactions.[4]

Health Canada received a report of a 38-year-old man who had received Gamunex for the treatment of streptococcal thoracic cellulitis, which had also required débridement. Two hours and 50 minutes into the infusion, after receiving 57.5 g of Gamunex, the patient experienced hypotension and dyspnea. The infusion was stopped. The results of a chest radiograph were compatible with a diagnosis of TRALI. The patient was transferred to the intensive care unit, where he required intubation. The result of an anti-human leukocyte antigen test was pending at the time of reporting.

References

1. Kleinman S, Caulfield T, Chan P et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. *Transfusion* 2004;44(12):1774-89.
2. Toy P, Popovsky MA, Abraham E et al. Transfusion-related acute lung injury: definition and review. *Crit Care Med* 2005;33(4):721-6.
3. Rizk A, Gorson KC, Kenney L, et al. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001;41(2):264-8.
4. *Gamunex (immune globulin intravenous human 10%)* [product monograph]. Toronto: Bayer Inc; 2005.

Cesium chloride and ventricular arrhythmias

Nonradioactive cesium chloride (CsCl) is used orally as a natural health product. Although not authorized for therapeutic use in Canada, unauthorized cesium products are accessible for purchase (e.g., on the Internet) and are used for the self-treatment of cancer. As of May 28, 2008, Health Canada received 3 reports of prolonged QT interval and ventricular tachyarrhythmia suspected of being associated with the oral use of CsCl.

One case involved an 84-year-old woman who took CsCl (reagent-grade powder, 1 g orally 3 times daily) to self-treat renal cell carcinoma. One month later, she was admitted to hospital with decreased level of consciousness and ventricular tachycardia with prolonged QT interval. She received Prussian blue and isoproterenol to maintain her heart rhythm. The patient had not yet recovered at the time of reporting.

The other 2 cases described similar symptoms and were published in the literature. In one case, a 52-year-old woman took CsCl (3 g orally daily) to treat colon cancer with liver metastasis;[1] in the second case, a 62-year-old man took CsCl (1 g orally 3 times daily) for prostate cancer.[2] The latter patient had also received prior naturopathic treatment with 2 g of intravenous CsCl 4 times a day for 2 weeks. In these 2 cases, other reported adverse reactions included ventricular extrasystoles, syncope and hypokalemia. In the second case, torsades de pointes was also reported, and the tachyarrhythmia with prolonged QT interval persisted after the serum potassium level returned to normal. Both patients recovered after they stopped taking CsCl.

CsCl's effects on cardiac rhythm have been demonstrated in animal studies, where it has been used to experimentally induce ventricular arrhythmias.[3] Although the mechanism is not fully understood, CsCl is known to block a variety of potassium channels, including many of those involved in the cardiac action potential.[4,5]

Health care professionals should be aware that cancer patients may use unauthorized alternative therapies. They are encouraged to discuss such use with their patients. Adverse reactions involving CsCl should

be reported to Health Canada's Canada Vigilance Program (www.healthcanada.gc.ca/medeffect).

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References

1. Lyon AW, Mayhew WJ. Cesium toxicity: a case of self-treatment by alternative therapy gone awry. *Ther Drug Monit* 2003;25(1):114-6.
2. Pinter A, Dorian P, Newman D. Cesium-induced torsades de pointes. *N Engl J Med* 2002;346(5):383-4.
3. Jones DL, Petrie JP, Li HG. Spontaneous, electrically, and cesium chloride induced arrhythmia and afterdepolarizations in the rapidly paced dog heart. *Pacing Clin Electrophysiol* 2001;24(4 pt 1):474-85.
4. Vyas H, Johnson K, Houlihan R, et al. Acquired long QT syndrome secondary to cesium chloride supplement. *J Altern Complement Med* 2006;12(10):1011-4.
5. Zhang S. Isolation and characterization of I_{Kr} in cardiac myocytes by Cs^+ permeation. *Am J Physiol Heart Circ Physiol* 2006;290(3): H1038-49.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: May 16 – Aug. 1, 2008)

Date	Product	Subject
July 31	Ceftriaxone	Fatal interactions ceftriaxone-calcium
July 24	Foreign products	Foreign product alerts
July 22	Jin Bu Huan	Warning not to use anodyne tablets
July 22	Wild Vineyard	Unauthorized products pose a risk to health
July 18	Ratio-Metformin	Safety information on lot 638812
July 18	Toothbrushes	Advisory concerning a potential choking risk
July 18 & 17	Sandoz Timolol	Recall of 0.25% and 0.5% ophthalmic solutions
July 15	DDAVP	Nasal solutions and increased risk of hyponatremia
July 11	Twinject	Reported malfunctions pose potential health risks
July 11	Avastin	Microangiopathic anemia with the combined use of Avastin and sunitinib
July 10	Purepillz	Advisory not to use unauthorized products
July 9 & 8	Ratio-Morphine	Recall due to risk of accidental overdose
July 7	Foreign products	Foreign product alert
July 3	Acid concentrates	Recall of Hemodialysis acid concentrates
June 30	Foreign products	Foreign product alerts
June 25	Heat Patches	Product recall: Tensor Heat Therapy
June 24	Foreign products	Foreign product alerts
June 23 & 18	Abacavir	Potential increased risk of myocardial infarction
June 18	6-OXO and 1-AD	Warning not to use these supplements
June 13	Champix	New safety information
June 11	Heparin	Contaminated heparin-coated medical devices
June 5	Desire	Lots found to contain an unlabelled ingredient
June 2	Somavert	Increased risk of hepatic enzyme elevations
June 2	Tysabri	Liver injury and hypersensitivity
May 30	Foreign products	Foreign product alert
May 28	Foreign toothpaste	Update on toothpaste containing diethylene glycol
May 23	Definity	Serious adverse cardiopulmonary reactions
May 22	Desire	Warning not to use unauthorized products
May 7	Trillium Coating	Information concerning bypass devices manufactured with contaminated heparin
May 7	Carmeda Coating	Information concerning bypass devices manufactured with contaminated heparin

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