Health Canada Santé Canada

Your health and safety…our priority. *Votre santé et votre sécurité… notre priorité.*

Canadian Adverse Reaction Newsletter

Volume 19 • Issue 1 • January 2009

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
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

Did you know?

To receive the **Newsletter** and health product **advisories** free by email, **subscribe** to the **MedEffect™ e-Notice** at **www.healthcanada.gc.ca/medeffect**

Local anesthetic infusion with postoperative pain pumps and articular chondrolysis

Postoperative pain pumps are infusion devices designed to continuously deliver controlled amounts of medication.[1,2] They can be used to infuse local anesthetic solutions directly into operative sites, for pain management following surgical procedures. The device consists of a reservoir containing the local anesthetic solution, which is delivered by gravity or by electric pump through a catheter implanted directly into the surgical wound. Bupivacaine is an anesthetic commonly used with postoperative pain pumps.[3] A combination of bupivacaine and epinephrine is also used, with the epinephrine inducing vasoconstriction and slowing down the absorption of bupivacaine.

As of July 2008, Health Canada received 8 incident reports of articular chondrolysis following shoulder surgery that were suspected of being associated with the use of postoperative pain pumps. The pain pumps were used for about 48 hours after surgery. All of the patients received bupivacaine with epinephrine. Chondrolysis was diagnosed between 1 month and 1 year after the surgeries and the use of the pain pumps.

Chondrolysis is a progressive degeneration of the cartilage for which the cause is not fully understood.[4,5] Chondrolysis of the shoulder results in narrowing of the joint space, leading to pain and loss of motion; it is a debilitating condition that requires medical attention and possibly surgery.[3,4] Chondrolysis is listed among the possible adverse incidents in the device labelling of pain pumps.[1,2] The device labelling states that the continuous intra-articular infusion of anesthetics, particularly when epinephrine is also used, is not recommended.

The association between postoperative pain pumps and the development of chondrolysis is difficult to identify. Indeed, chondrolysis may appear many months after the use of a pain pump.[3–5] In addition, confounders such as the concomitant use of health products (e.g., gentian violet, chlorhexidine, bone cement) and radiofrequency devices may be responsible for causing chondrolysis after shoulder surgery.[5–10]

Health care professionals are encouraged to follow the instructions for use and refrain from using postoperative pain pumps for continuous intra-articular infusion of local anesthetics, particularly with epinephrine, after shoulder surgery.[1,2]

They should report adverse incidents following the use of pain pumps or other medical devices to the Health Products and Food Branch Inspectorate through the Inspectorate Hotline (800 267-9675).

Fannie St-Gelais, PhD, Health Canada

References

1. *On-Q PainBuster* [Canadian instructions for use]. Lake Forest (CA): I-Flow Corporation; 2008.
2. *Donjoy Pain Control Device* [Canadian instructions for use]. Huntington Beach (CA): Curlin Medical Inc; 2007.
3. Hansen BP, Beck CL, Beck EP, et al. Postarthroscopic glenohumeral chondrolysis. *Am J Sports Med* 2007;35(10):1628-34.
4. Yarbrough R, Gross R. Chondrolysis: an update. *J Pediatr Orthop* 2005;25(5):702-4.
5. Petty DH, Jazrawi LM, Estrada LS, et al. Glenohumeral chondrolysis after shoulder arthroscopy: case reports and review of the literature. *Am J Sports Med* 2004;32(2):509-15.
6. Shibata Y, Midorikawa K, Koga T, et al. Chondrolysis of the glenohumeral joint following a color test using gentian violet. *Int Orthop* 2001;25(6):401-3.
7. van Huyssteen AL, Bracey DJ. Chlorhexidine and chondrolysis in the knee. *J Bone Joint Surg Br* 1999;81(6):995-6.
8. Leclair A, Gangi A, Lacaze F, et al. Rapid chondrolysis after an intra-articular leak of bone cement in treatment of a benign acetabular subchondral cyst: an unusual complication of percutaneous injection of acrylic cement. *Skeletal Radiol* 2000;29(5):275-8.
9. Jerosch J, Aldawoudy AM. Chondrolysis of the glenohumeral joint following arthroscopic capsular release for adhesive capsulitis: a case report. *Knee Surg Sports Traumatol Arthrosc* 2007;15(3):292-4.
10. Ciccone WJ II, Weinstein DM, Elias JJ. Glenohumeral chondrolysis following thermal capsulorrhaphy. *Orthopedics* 2007;30(2):158-60.

Natural health products and adverse reactions: update

Many Canadians use natural health products (NHPs) on a regular basis,[1] either alone or in combination with other health products. However, NHPs may be associated with potential health risks, including adverse reactions (ARs) and interactions with drugs, other NHPs or food. The January 2004 issue of the *Canadian Adverse Reaction Newsletter* discussed safety concerns suspected of being associated with the use of echinacea, ginkgo and St. John's wort. The concerns were based on reports of ARs received by Health Canada from Jan. 1, 1998, to June 30, 2003.[2] Table 1 provides an update on ARs reported for these NHPs since that publication.

Table 1: Summary of reports of adverse reactions (ARs) suspected of being associated with echinacea, ginkgo and St. John's wort received by Health Canada from July 1, 2003, to May 31, 2008*

Product	No. of reports of ARs	Previously reported safety concerns†	Other reported ARs‡
Echinacea	21	Allergic reactions§ (3 reports)	• Agitation • Diarrhea • Discoloured faeces • Dyspnea • Fecal incontinence • Insomnia • Proctalgia • Pyrexia • Vertigo • Vomiting
Ginkgo	24	Bleeding¶ (1 report)	• Dizziness • Increased blood pressure • Palpitations • Syncope
St. John's wort	11	Drug interactions** (2 reports)	• Hepatitis • Increased hepatic enzyme levels • Pain • Photosensitivity†† • Rash

***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 health product was on the market has been taken into consideration.**
†Reported in the January 2004 issue of the *Canadian Adverse Reaction Newsletter*.
‡This is not an exhaustive list of reported ARs. Several reaction terms may be listed per AR report. Reaction terms are listed according to the *World Health Organization Adverse Reaction Terminology* (WHOART) or the *Medical Dictionary for Regulatory Activities* (MedDRA).
§Allergic reactions are mentioned in the *Echinacea purpurea* monograph.[3]
¶This report described nose bleeds. The ginkgo biloba monograph warns against using ginkgo in combination with other health products that affect blood coagulation (e.g., blood thinners, clotting factor replacements, acetylsalicylic acid, ibuprofen, fish oils, vitamin E), because such use may increase the risk of spontaneous bleeding.[4]
**Drug interactions involved levonorgestrel-ethinyl estradiol (oral contraceptive) in one case, and ibuprofen in the second case.
††The St. John's wort monograph contains a warning to avoid prolonged exposure to sunlight, ultraviolet light or ultraviolet therapy.[5]

In addition, safety concerns suspected of being associated with valerian have been reported. Valerian may be used as a sleep aid or sedative.[6] From Jan. 1, 1990, to May 31, 2008, Health Canada received 31 reports of ARs suspected of being associated with valerian-containing products; 15 of the reports described psychiatric ARs, such as visual hallucination, nightmares and abnormal thinking. There have also been reports in the literature of visual hallucinations,[7] delirium[8] and cardiac complications[8] following cessation of valerian use. Other reports received by Health Canada describing ARs suspected of being associated with valerian-containing products include gastrointestinal disturbances (e.g., vomiting, diarrhea, nausea), allergic reactions, increased

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.

Key points for health care practitioners

- Ask patients about their use of natural health products (NHPs) as part of their medical record
- Report adverse reactions to NHPs to Health Canada's Canada Vigilance Program at: www.hc-sc.gc.ca/dhp-mps/medeff/vigilance-eng.php
- Product monographs for NHPs are available on the Health Canada website at: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/index-eng.php
- NHPs that have been issued a product licence by Health Canada can be found in the Licensed Natural Health Products Database at: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/lnhpd-bdpsnh-eng.php

hepatic enzyme levels and cardiac complications (e.g., bradycardia, arrhythmia).

Angela Tonary, PhD; Stephanie Jack, MSc; David Cunningham, MD, FRCP; Karen Pilon, RN, Health Canada

References

1. *Baseline NHP survey among consumers.* Ottawa (ON): Health Canada; 2005. Available: www.hc-sc.gc.ca/dhp-mps/pubs/natur/eng_cons_survey-eng.php (accessed 2008 Oct 28).
2. Griffiths J, Jordan S, Pilon K. Natural health products and adverse reactions. *Can Advers Reaction Newsl* 2004;14(1):2-3.
3. *Echinacea purpurea* [monograph]. Ottawa (ON): Health Canada; 2008. Available: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_echinacea_purpurea-eng.php (accessed 2008 Oct 28).
4. *Ginkgo biloba* [monograph]. Ottawa (ON): Health Canada; 2008. Available: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_ginko_biloba-eng.php (accessed 2008 Oct 28).
5. *St. John's wort* [monograph]. Ottawa (ON): Health Canada; 2004. Available: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_stjohnswort-millepertuis-eng.php (accessed 2008 Oct 28).
6. *Valerian* [monograph]. Ottawa (ON): Health Canada; 2007. Available: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_valerian-eng.php (accessed 2008 Oct 28).
7. Weiner SW, Hoffman RS, Nelson LS. Withdrawal symptoms after valerian cessation [abstract]. In: Abstracts of the 2003 North American Congress of Clinical Toxicology Annual Meeting. *Clin Toxicol* 2003;41(5):641-752.
8. Garges HP, Varia I, Murali Doraiswamy P. Cardiac complications and delirium associated with valerian root withdrawal. *JAMA* 1998;280(18):1566-7.

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.

Propolis: suspected association with renal failure

Propolis is a natural resinous product collected by bees that is used in the construction of hives.[1] It is available in Canada as a single ingredient or in combination in many natural health products (NHPs). Propolis is used for the relief of various conditions, including bacterial, fungal and viral infections, inflammation and, topically, for skin and mouth lesions.[1,2] In the April 2005 issue of the *Canadian Adverse Reaction Newsletter*, an article described adverse reactions (ARs) such as allergic reactions and skin or mucous membrane irritation suspected of being associated with bee products.[3]

Health Canada received a report of a 3-year-old boy with a known history of gluten enteropathy in whom acute renal failure developed while he was taking propolis. The gluten enteropathy was stable with dietary restriction. The child received the homeopathic product containing propolis 2–3 times per week as needed as prophylaxis for infection. The exact form and dose of propolis used was not reported. The child was also taking other NHPs in a sporadic fashion; however, information on the dosage and frequency of exposure to these other products is unknown. After approximately 4 months of use of propolis, the boy's serum creatinine level increased to 84 µmol/L (normal < 53 µmol/L for children < 5 years old). Propolis was stopped, and his creatinine level returned to normal. No information was provided on the child's clinical status or need for hospital care. The cessation of propolis was the only reported form of treatment.

A case of acute renal failure requiring hemodialysis following the use of propolis was previously reported in the literature.[1] This case involved 2 exposure periods resulting in positive dechallenge and rechallenge in a 59-year-old man with a history of cholangiocarcinoma who had self-medicated with a Brazilian variety of propolis.

References

1. Li YJ, Lin JL, Yang CW, et al. Acute renal failure induced by a Brazilian variety of propolis. *Am J Kidney Dis* 2005;46(6):e125-9.
2. *Propolis.* Stockton (CA): Natural Medicines Comprehensive Database; 2008. Available: www.naturaldatabase.com (accessed 2008 July 11).
3. Sheehy C, Hall T, Pilon K. Products derived from bees: serious adverse reactions. *Can Advers Reaction Newsl* 2005;15(2):2-3.

Canadian Adverse Reaction Newsletter: distribution changes

The January 2009 issue of the *Canadian Adverse Reaction Newsletter* (*CARN*) is the last issue to be published in the *Canadian Medical Association Journal* (*CMAJ*). *CARN* will continue to be available on the MedEffect™ Canada website and by subscribing to MedEffect™ e-Notice. Print versions are available to interested individuals upon request. In addition, in October 2008, highlights of *CARN* were faxed to hospitals and medical clinics. Summaries of *CARN* can also be found in various health professional journals.

- To receive *CARN* free by email, subscribe to Health Canada's MedEffect™ e-Notice at: www.healthcanada.gc.ca/medeffect.
- To receive print versions of future issues of *CARN*, contact us at:
  CARN Editorial Team
  Marketed Health Products Directorate
  Health Canada
  Address Locator 0701C
  Ottawa ON K1A 0K9
  Fax: 613-952-7738
  Email: mhpd_dpsc@hc-sc.gc.ca
- Electronic versions of the latest issue and previously published issues of *CARN* are available at: www.healthcanada.gc.ca/carn.

The *CARN* editorial team would like to take this opportunity to thank *CMAJ* for the services it has provided over the years.

Quarterly summary of health professional and consumer advisories

(posted on Health Canada's website: Aug. 2 – Nov. 12, 2008)

Date	Product	Subject
Nov 10	Foreign products	Foreign product alerts
Nov 7	Argatroban	Recall of 2 lots
Oct 28	Eros Fire	Warning not to use Eros Fire or any unauthorized products
Oct 28	Vitamin C supplements	Warning not to use two vitamin C supplements
Oct 23	Venlafaxine	Information regarding overdosage of Venlafaxine Extended-Release
Oct 17	Foreign products	Foreign product alerts
Oct 6 & 8	Codeine	Information on the use of codeine products, especially by nursing mothers
Sept 19	Foreign products	Foreign product alerts
Sept 3	Unauthorized products	Unauthorized health products found on the Canadian market
Sept 2	Ligating clips	Recall: Teleflex Weck Brand Ligating Clips
Aug 22	Foreign products	Foreign product alerts
Aug 21	Life Choice products	Advisory not to use Life Choice Ephedrine and Kava Kava
Aug 21	Viracept	Viracept can be used again in nonpregnant HIV-infected adults and children
Aug 18	Foreign products	Foreign product alerts
Aug 14	Acidophilus products	Additional "non-dairy" products posing milk allergy risk
Aug 11	Foreign products	Foreign product alerts
Aug 11 & 6	Torisel	Hypersensitivity/infusion reactions
Aug 8	Acidophilus products	Milk allergy risk identified in "non-dairy" products
Aug 6	Unauthorized products	Advisory not to use Rize 2 The Occasion Capsules
Aug 1	Accusol 35	Risk of precipitate formation with Accusol 35 hemodialysis solutions
July 31	Desmopressin	Nasal spray formulations: risk of hyponatremia and water intoxication
July 31	Defibrillators	Recall: LifePak CR Plus and LifePak Express defibrillators
June 23	Infusion pumps	Recall: damaged Curlin infusion pumps
June 2	Sling bars	Field correction program for Liko Universal SlingBar

Advisories are available at www.healthcanada.gc.ca/medeffect.

Canadian Adverse Reaction Newsletter

Health Canada
Marketed Health Products Directorate
AL 0701C
Ottawa ON K1A 0K9
Tel: 613 954-6522
Fax: 613 952-7738

Editorial Staff

Ann Sztuke-Fournier, BPharm (Editor-in-Chief)

Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V)

Gilbert Roy, BPharm

Jared Cousins, BSP

Christianne Scott, BPharm, MBA

Marielle McMorran, BSc, BSc(Pharm)

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

Canada Vigilance Program
Phone: 866 234-2345
Fax: 866 678-6789
Online: www.healthcanada.gc.ca/medeffect

ISSN 1499-9447, Cat no H42-4/1-19-1E

Aussi disponible en français

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.