Health Canada Santé Canada

Canada

Canadian Adverse Reaction Newsletter

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www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index_e.html

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 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

Contact Health Canada or a Regional AR Monitoring Office free of charge

Phone: 866 234-2345
Fax: 866 678-6789

Online form available at:

www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/index_e.html

BioGlue Surgical Adhesive: reported incidents of chronic inflammation and foreign-body reactions

BioGlue is the commercial name of a surgical adhesive composed of bovine serum albumin (BSA) and glutaraldehyde.[1] The glutaraldehyde molecules covalently bond the BSA molecules to each other and, upon application, to tissue proteins at the repair site.[2] BioGlue was originally licensed for sale in Canada in 2000 for use in the repair of acute aortic dissections and pulmonary tissues. In 2003, its indication was expanded to include the repair of most other soft tissues. BioGlue is indicated for use as an adjunct to standard methods of surgical repair (e.g., sutures, staples, electrocautery and patches) to bond, seal or reinforce soft tissue.[1] It may also be applied alone to seal or reinforce damaged parenchyma when other procedures are ineffective or impractical.[1]

From Jan. 1, 2000, to June 1, 2006, Health Canada received 13 domestic reports of adverse incidents suspected of being associated with BioGlue. All reports were received in 2004 and 2005. Seven of the reports described events consistent with ongoing inflammatory processes upon reoperation at sites where BioGlue had been used months earlier. In 4 of these 7 cases, BioGlue was suspected of contributing to a sterile discharge or persistent infection. In the other 3 cases, foreign-body reactions were reported that required the removal of BioGlue-containing masses at the surgical site. A short description of these 3 cases follows:

Case 1: A patient who received BioGlue to help seal dural tissue during a spinal procedure experienced recurring clear drainage over a period of months postoperatively. Upon reoperation, a cyst-like mass alleged to contain BioGlue was removed, and the patient recovered without further complication. The surgeon described the patient's experience as a foreign-body reaction to BioGlue.

Case 2: A patient received BioGlue to help repair dural leaks. During reoperation 5 months later for removal of spinal hardware, the wound area was explored, and the surgeon found and removed a firm, green inflammatory mass. The pathologist indicated that the mass was a matrix of BioGlue containing fragments of Gelfoam and that it appeared to be the result of a histologic foreign-body reaction.

Case 3: A patient who had received BioGlue during a spinal procedure to help repair a dural defect subsequently experienced pain at the site. Upon reoperation more than 4 months later, the BioGlue was found in place and attached to the dura, but a dural leak was evident and a dark green mass was removed. The pathologist stated that the mass contained BioGlue, displayed evidence of a florid foreign-body granulomatous reaction and may have caused a mechanical pain-stimulus effect on the adjacent nerve root.

Severe, active inflammation surrounding a BioGlue remnant with multiple granulocytes and histiocytes

and a massive foreign-body reaction with numerous multinucleated giant cells has been reported at 3 months after BioGlue application.[3] Intense, focal acute and chronic nongranulomatous inflammation has also been observed at a site where persistent concretions of BioGlue were identified 2 years after application.[4]

Although "inflammatory and immune response" is listed among the possible complications in the device labelling, resorption times are not discussed[1] and additional long-term studies would help to evaluate these effects.[2] The medical literature suggests that, even when BioGlue appears to yield a clear benefit, it should be used sparingly and its toxic potential should be considered.[2,4]

Andrew Gaffen, BSc, DDS; Hui Zheng, MSc; Gina Coleman, MD, Health Canada

References

1. *BioGlue Surgical Adhesive* [Canadian instructions for use]. Kennesaw (GA): Cryolife, Inc.; 2004.
2. Furst W, Banerjee A. Release of glutaraldehyde from an albumin-glutaraldehyde tissue adhesive causes significant in vitro and in vivo toxicity. *Ann Thorac Surg* 2005;79(5):1522-9.
3. Erasmi AW, Sievers HH, Wolschlager C. Inflammatory response after BioGlue application. *Ann Thorac Surg* 2002;73(3):1025-6.
4. Ngaage DL, Edwards WD, Bell MR, et al. A cautionary note regarding long-term sequelae of biologic glue. *J Thorac Cardiovasc Surg* 2005;129(4): 937-8.

New tool for reporting adverse reactions to health products

Health Canada's ***MedEffect*** Web site (www.healthcanada.gc.ca/medeffect) has been updated to accept online transmittable reports of suspected adverse reactions (ARs) to health products marketed in Canada. Now, in addition to the previous reporting methods, including mailing reports or using the toll free fax or telephone numbers, health care professionals and consumers can submit reports of ARs online. Upon the online submission of a report, the system will generate a file that can be printed and stored electronically by the reporter. Information related to the identity of the patient and the reporter of the AR will be protected as per the Access to Information Act and the Privacy Act.

Underreporting of ARs is a well-known global issue. International studies have estimated that only 1%–10% of all ARs are reported. Health professionals have identified barriers to reporting that relate to the inconvenience and lack of user-friendliness of reporting. The new user-friendly online AR reporting form will make the process more convenient and should contribute to increased AR reporting.

Visit the ***MedEffect*** Web site at www.healthcanada.gc.ca/medeffect to submit an AR report online and to view the latest advisories, AR information and other reporting initiatives.

Physician reporting of adverse reactions: continuing medical education

Health Canada, in collaboration with the Canadian Medical Association (CMA), developed a continuing medical education (CME) course entitled "Physician Reporting of Adverse (Drug) Reactions" to improve physicians' knowledge of the program and processes for reporting adverse reactions in Canada (see Box). This CME course was posted on CMA's physician Web portal as a 1-year pilot between May 27, 2005, and May 27, 2006.

Learning objectives of the course "Physician Reporting of Adverse (Drug) Reactions"

- To describe an adverse reaction (AR)
- To associate AR reporting with current work practice
- To describe the reporting process
- To report an AR

A number of reference resources were made available via hyperlinks to Health Canada's ***MedEffect*** Web site. During the pilot period, extensive marketing of the course helped to raise physicians' collective awareness of reporting ARs to Health Canada.

Because of the quality of the program and the success of the working relationship, the CMA has decided to continue to make the course available on their Web portal until Health Canada requests its removal. Future steps for the online course include posting it on Health Canada's ***MedEffect*** Web site and pilot testing the course in the medical undergraduate curriculum. The latter initiative is being achieved with CMA's help by facilitating contact between Health Canada and the National Undergraduate eLearning Committee. If successful, this initiative will result in the course being made available to all undergraduate medical programs in the country.

Outside the medical community, the development of the online AR course has generated interest and requests for similar education initiatives from other health professions and consumers. An online module for naturopathic doctors has been posted on ***MedEffect*** (with a link from the Canadian Association of

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Naturopathic Doctors Web site to the learning centre section of ***MedEffect***) and will be integrated into the Canadian College of Naturopathic Medicine's curriculum this fall. Another online module and corresponding guidebook to assist consumers and patients on how to report ARs to their health care professional or Health Canada will be made available on the ***MedEffect*** Web site.

Anyone wishing to provide comments or feedback on these education initiatives may contact Health Canada's Marketed Health Products Directorate by email (mhpd_dpsc@hc-sc.gc.ca) or phone (613 954-6522).

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.

Atomoxetine (Strattera): suspected association with tics

Health Canada has received 1 domestic report of tics and 1 domestic report of exacerbation of tics suspected of being associated with atomoxetine. In the first case, a 7-year-old girl was prescribed atomoxetine 25 mg/d for attention deficit hyperactivity disorder (ADHD). Subsequently, the dose was increased to 40 mg/d, and 7 to 10 days later the patient experienced new-onset motor tics. After a few days the dose was decreased to 25 mg/d by the parents. The tics persisted but were decreased in severity. The atomoxetine was continued, risperidone was added to the regimen, and the tics disappeared.

The second case described exacerbation of tics in an 11-year-old boy who had been prescribed atomoxetine for ADHD: the dose was 18 mg/d for 1 week initially and then was increased to 25 mg/d for 1 week, 40 mg/d for 3 weeks and then 60 mg/d. His medical history included bipolar disorder, Gilles de la Tourette's syndrome and insomnia. Concomitant medications included risperidone and clonidine. He had previously been taking extended-release methylphenidate 36 mg/d that was reduced to 18 mg/d before being discontinued; the 60-mg dose of atomoxetine overlapped with the 18-mg dose of extended-release methylphenidate for 1–2 days. While receiving atomoxetine 60 mg/d, the patient experienced dramatic worsening of vocal tics, which lasted 10–12 hours per day, and his ADHD was not well controlled. His physician decreased the dose of atomoxetine to 40 mg/d. The patient continued to experience tics and had not yet recovered at the time of reporting.

There has been a previous report of tics with the use of atomoxetine.[1] Data submitted in the development of the Canadian product monograph for atomoxetine state that "Strattera does not worsen tics, and may be used in patients with ADHD and comorbid motor tics or diagnosis of Tourette's Disorder."[2] Health Canada will continue to monitor reports of adverse reactions associated with the use of atomoxetine.

References

1. Ledbetter M. Atomoxetine use associated with onset of a motor tic. *J Child Adolesc Psychopharmacol.* 2005;15(2):331-3.
2. *Strattera (atomoxetine hydrochloride capsules)* [product monograph]. Toronto: Eli Lilly Canada Inc.; 2006.

How to report an adverse reaction?

There are multiple ways to report an adverse reaction (AR) to Health Canada. To report an AR, go to: www.healthcanada.gc.ca/medeffect

- complete and submit your report **online** or
- download and print a paper copy of the reporting form* and submit it:
  - by **toll-free fax**: 866 678-6789 (faxes are automatically directed to the appropriate Regional AR Monitoring Office)
  - by **mail**: to one of the Regional AR Monitoring Offices (addresses can be found on the back of the AR reporting form or at www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/centres/index_e.html)

You can also report an AR by **toll-free phone**: 866 234-2345 (calls are automatically directed to the appropriate Regional AR Monitoring Office).

Manufacturers, please report ARs to the National AR Monitoring Office at:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
Health Canada
Address Locator 0701C
Ottawa ON K1A 0K9
Tel: 613 957-0337
Fax: 613 957-0335

By submitting a suspected AR report, you are contributing to the ongoing collection of safety and effectiveness information that occurs once health products are marketed.

*The Adverse Reaction Reporting Form is also available in the *CPS* (*Canadian Compendium of Pharmaceuticals and Specialties*).

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Summary of health professional and consumer advisories posted from May 13 to Aug. 17, 2006
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject
Aug 17	Glucose monitors	Risk of misinterpreting test results on blood glucose monitors
Aug 14	Miracle II products	Reminder not to use Miracle II products from Tedco, Inc.
Aug 4	Neophase Formula for Men	Warning not to use Neophase Formula for Men
Aug 2	Lipitor	Counterfeit found again in the United Kingdom
Aug 1	Lamictal	Increased risk of non-syndromic oral clefts — GlaxoSmithKline Inc.
July 27 & 24	Remicade	Possible association with hepatosplenic T-cell lymphoma — Schering Canada Inc.
July 18	Baike Wan	Foreign product alert
July 18	Safi	Foreign product alert
July 18	Fufang LuHui Jiaonang	Foreign product alert
July 18	Zhuifeng Tougu Wan	Foreign product alert
July 13	D-TRONplus	Recall of Insulin Pump Power Packs — Disetronic Medical Systems Inc.
July 12	Omniscan	Nephrogenic systemic fibrosis / Nephrogenic fibrosing dermopathy — GE Healthcare Canada Inc.
July 7 & June 28	Comfort Shield	Safety information on specific lots of Incontinence Care Washcloths — Source Medical Corporation
July 6	Fat Rapid Loss Capsules	Foreign product alert
July 6 & June 29	Aptivus	Intracranial hemorrhage — Boehringer Ingelheim (Canada) Ltd
June 29	ACE inhibitors	Advisory not to use ACE inhibitors during pregnancy
June 26	Pacemakers and defibrillators	Safety information on certain Guidant/Boston Scientific pacemakers and defibrillators — Guidant Canada Corporation
June 23	Anzemet	New contraindications
June 19	Cialis, Levitra and Viagra	Visual problems — Eli Lilly Canada Inc., Bayer Inc. and Pfizer Canada Inc.
June 14	Ayurvedic products	High levels of heavy metals
June 5	Iressa	Safety and efficacy information — AstraZeneca Canada Inc.
May 30	Triaminic Vapour Patch	Warning not to use Triaminic Vapour Patch
May 29	Ocean Plasma products	Warning not to use Ocean Plasma Isotonic and Hypertonic Living Water
May 26	Oral laxative mineral oil	United Pharmacists brand oral laxative mineral oil added to list of recalled products
May 26	ADHD drugs	Updating of product monographs
May 23	Weight loss products	Advisory not to use products containing ephedrine and caffeine
May 18	Evista	Important safety information — Eli Lilly Canada Inc.
May 16	L-arginine	Advisory: heart patients not to use products containing L-arginine
May 12	Tequin	Serious hypoglycemia and hyperglycemia — Bristol-Myers Squibb Canada
Apr 18, 13 & 10	Glucose meters	Recall of certain SureStep blood glucose meters — LifeScan Canada Ltd.
Mar 31	Infusion sets	Recall of Accu-Chek Ultraflex infusion sets — Disetronic Medical Systems, Inc.

To receive the Newsletter and health product Advisories free by email, join Health Canada's ***MedEffect*** mailing list. ***Go to*** **www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index_e.html**

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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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