Intrathecal baclofen (Lioresal): suspected adverse incidents associated with implantable drug pump system

Baclofen (Lioresal) is a muscle relaxant and antispastic agent. Intrathecal baclofen (ITB) is indicated for the management of severe spasticity in patients with spinal cord injury or multiple sclerosis unresponsive to oral baclofen therapy or who experience unacceptable adverse reactions at effective oral doses. It is also used in patients with spasticity of cerebral origin. ITB injection, which delivers the drug directly to its site of action, can achieve cerebrospinal fluid levels up to 30 times higher than those achieved using oral baclofen therapy, with minimal serum concentrations.

Patients receive baclofen as a continuous intrathecal infusion from a surgically implanted pump system. During chronic therapy, most patients require gradual dose increases because of decreased responsiveness or disease progression.

From Jan. 1, 1992, to June 30, 2005, Health Canada received 21 reports of adverse reactions suspected of being associated with ITB. Ten reports implicated the implantable drug pump system (IDPS). Of these 10 reports, 5 involved problems specific to the catheter system and 5 involved coma following implantation surgery (suspected improper pump preparation leading to inadvertent bolus). Device-related adverse events are mentioned in the Lioresal Intrathecal product monograph and in the Medtronic pump systems information.

One of these reports has already been published in the medical literature and describes a case with confusing symptomatology. A 6-year-old boy with cerebral palsy underwent implantation of an intrathecal baclofen pump to manage his spasticity. Two years later, he was admitted to hospital twice in a 3-day span with symptoms of apparent baclofen overdose. His parents described a 2-month history consistent with intermittent symptoms of baclofen overdose in the morning (reduced consciousness, hypotonia) followed by symptoms of baclofen tolerance or withdrawal later in the day (increased rigidity). Routine investigation of the IDPS did not yield any significant findings, but a microfracture of the catheter was visible on electron microscopy. The catheter was replaced, the patient recovered, and a lower maintenance dose was established. In this case, the intermittent symptomatology was thought to have been due to posture-
related effects on the catheter microfracture. It was postulated that the microfracture was closed when the patient was supine at night and forced open when he was positioned upright during the day, leading to leakage of the medication.4

The exact nature of catheter-related complications associated with the use of IDPS may not always be identified using the various procedural checks in an established protocol.5 In some cases, surgery fails to identify the cause of the catheter malfunction; however, replacement of the catheter may restore the clinical response to ITB.5

Health care professionals should be aware of potential IDPS-related adverse events, which may present with confusing signs and symptoms. Device-related issues should be considered when evaluating the need for dose adjustments.

Andrew Gaffen, BSc, DDS; Momir Nestic, MD, PhD; Gina Coleman, MD, Health Canada

Statins and memory loss

The role of HMG–CoA reductase inhibitors, or statins, in cardiovascular protection is well established. However, evidence in the current literature is conflicting as to the effect of statins on cognitive function.1 It has been postulated that statins may prevent dementia of the Alzheimer’s type through inhibition of β-amyloid production and thus decreased production of neurofibrillary tangles and plaques.2 Other studies have suggested that statins can contribute to memory loss.1–4 The proposed mechanism relates to cholesterol’s essential role in myelin production. Statins, especially the more lipophilic ones (e.g., atorvastatin and simvastatin), may cross the blood–brain barrier and decrease the amount of central nervous system (CNS) cholesterol necessary for the formation of myelin.23 Inadequate myelin production may result in demyelination of nerve fibres in the CNS and thus lead to memory loss.2 Memory impairment is listed in the product monograph for Pravachol.3

From the date of marketing of statins in Canada to May 31, 2005, Health Canada received 19 reports of amnesia suspected of being associated with these drugs (Table 1). The onset was reported to occur within 1 month after starting statin therapy in 5 cases, within 1 year in 7 cases and after 1 year in 3 cases. Four cases did not report an onset date. Eleven reports described that the amnesia resolved or improved when the drug was discontinued or the dose reduced, and one of them also described a positive rechallenge. Other reports did not provide this information.

Given these findings, changes in cognitive status temporally associated with statin therapy should be monitored.5

Michel Trottier, BScPhm, RPEBC, RPh, Health Canada

Table 1: Reports submitted to Health Canada of amnesia* suspected of being associated with statins from date marketed in Canada to May 31, 2005†

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin</th>
<th>Cerivastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of AR reports with amnesia</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Positive dechallenge§</td>
<td>4</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Median age (and range) of patients, yr</td>
<td>70 (50–78¶)</td>
<td>NR</td>
<td>–</td>
<td>61 (41–81)</td>
<td>–</td>
<td>57 (51–69)</td>
<td>67 (65–81¶)</td>
</tr>
</tbody>
</table>

Note: AR = adverse reaction, NR = not reported.
*Includes forgetfulness, memory disturbance, memory impairment and memory loss according to the World Health Organization Adverse Reaction Terminology (WHOART).
†These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.
‡Cerivastatin withdrawn from the market in 2001.
§Response to withdrawal of the drug.
¶Age unknown in 1 case.

References

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.

In 2004, Health Canada received a report of an adverse reaction involving a medication incident related to look-alike product labelling and packaging. An 80-year-old man was prescribed potassium chloride. When the prescription was refilled, pms-Chloral Hydrate 100 mg/mL syrup was dispensed in place of pms-Potassium Chloride 20 mmol/15 mL oral solution. The stock bottles of these products, similar both in packaging and labelling (Fig. 1, left), were stored side-by-side on the pharmacy shelf. The patient received a total of 300 mL (30 g) of chloral hydrate over approximately 40 hours and died shortly thereafter. Postmortem screening indicated highly toxic blood levels of trichloroethanol, the major active metabolite of chloral hydrate.\(^1,2\) The patient was taking multiple concomitant medications, but there was no suggestion of any interactions with the chloral hydrate.

The Institute for Safe Medication Practices Canada (ISMP Canada) has indicated that it also received a report of the event and will be issuing an information bulletin with detailed preventive strategies. Since the occurrence of the fatal incident, Pharmascience, the manufacturer of both products, has modified the labels to improve their differentiation (Fig. 1, right).

Look-alike packaging and labelling of health products can increase the risk of errors when dispensing or administering medications. Such errors can result in serious patient harm, and sometimes in death.\(^3,4\) The processes and designs of medication systems should be examined to help prevent human error. Creating safe medication systems requires a culture that supports identifying errors and leadership.\(^5\) Information on where and how errors occur can be acquired through voluntary medication incident reporting systems.

Health Canada, ISMP Canada and the Canadian Institute for Health Information are currently developing the Canadian Medication Incident Reporting and Prevention System, a program that will strengthen the Canadian health care system's capacity to report, analyse and prevent medication incidents. Until the program is fully operational, medication incidents and near misses (defined by ISMP Canada at www.ismp-canada.org/definitions.htm) should be reported to ISMP Canada (www.ismp-canada.org; email info@ismp-canada.org; tel 866 544-7672). If you suspect an adverse reaction, please submit the case to Health Canada (www.healthcanada.gc.ca/medeffect; tel 866 234-2345; fax 866 678-6789).\(^6\)

Lili Loorand-Stiver, BScPhm, Health Canada

References

Fig. 1: Chloral hydrate and potassium chloride bottles before (left) and after (right) labelling changes made by the manufacturer.
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.

Ayurvedic medicines: lead contamination

A 53-year-old woman with rheumatoid arthritis was admitted to hospital because of fatigue, weakness, nausea and abdominal pain. Laboratory data showed anemia not associated with hemolysis or blood loss. Abnormal hematologic results were hemoglobin 77 (normally 115–155) g/L, hematocrit 0.24 (normally 0.35–0.45), red blood cell (RBC) count 2.8 (normally 3.8–5.1) × 1012/L and reticulocyte count 148 (normally 25–100) × 109/L. Irregularly contracted RBCs and polychromasia were present. Packed RBCs and ferrous gluconate were administered; 6 days later the hematological parameters were improved, and the patient was discharged. Medications on admission were Pantoloc, Dicetel, Plaquenil and Eltroxin.

Two months after discharge, the patient admitted to having taken, for about 3 months, 2 Ayurvedic products purchased in India. Both products had been discontinued after the patient was in hospital. Laboratory analysis revealed that the 2 products contained lead, mercury and arsenic. At this time, the patient’s blood lead level was 2.54 µmol/L. Three months after discharge, the patient’s hematologic parameters were within normal ranges and her blood lead level had decreased.

Certain Ayurvedic products have been identified as being contaminated with heavy metals.1–3

References

How to report adverse reactions

To report a suspected adverse reaction (AR) to health products marketed in Canada, health professionals and consumers should telephone toll free (866 234-2345) or complete a copy of the AR Reporting Form (see page 5) and forward it to the appropriate Regional AR Centre or the National AR Centre by mail or by fax toll free (866 678-6789). Copies of the form are also available from your Regional AR Centre or the National AR Centre, and the Canadian Compendium of Pharmaceuticals and Specialties (CPS).

Regional Adverse Reaction (AR) Centres

British Columbia
British Columbia Regional AR Centre
C/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
adr@dpic.ca

Alberta
Alberta Regional AR Centre
C/o Ste. 730, 9700 Jasper Ave.
Edmonton AB T5J 4C3
Alberta_AR@hc-sc.gc.ca

Saskatchewan
Saskatchewan Regional AR Centre
C/o Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place

Atlantic
Atlantic Regional AR Centre
For New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador
C/o Queen Elizabeth II Health Sciences Centre
Drug Information Centre
2421–1796 Summer St.
Halifax NS B3H 3A7
adr@cdha.nshealth.ca

Québec
Québec Regional AR Centre
C/o Drug Information Centre
Hôpital du Sacré-Coeur de Montréal
5400, boul. Gouin ouest
Montréal QC H4J 1C5
Quebec_AR@hc-sc.gc.ca

Ontario
Ontario Regional AR Centre
C/o LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
London ON N6A 5A5
adr@lhsc.on.ca

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.
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La version française de ce document est disponible à:

Canadian Adverse Drug Reaction Monitoring Program

Report of suspected adverse reaction due to health products* marketed in Canada

PROTECTED B**
(when completed)

A. Patient Information
(See “Confidentiality” section below)

| 1. Identifier |
| 2. Age at time of reaction |
| 3. Sex | 4. Height | 5. Weight |
| Male | feet | or | lbs |
| Female | or | cm | or | kgs |

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)
   - Death (dd/mm/yyyy)
   - Life-threatening
   - Congenital malformation
   - Hospitalization
   - Hospitalization - prolonged
   - Other: ________________

2. Date of reaction
3. Date of this report

4. Describe reaction or problem

C. Suspected Health Product(s)
(See “How to report” section below)

| 1. Name (give labeled strength & manufacturer, if known) |
| 2. Dose, frequency & route used |
| 3. Therapy dates (if unknown, give duration) |
| 4. Indication for use of suspected health product |
| 5. Reaction abated after use stopped or dose reduced |
| 6. Lot # (if known) |
| 7. Exp. date (if known) |
| 8. Reaction reappeared after reintroduction |
| 9. Concomitant health products (name, dose, frequency and route used), and therapy dates (dd/mm/yyyy) (exclude treatment of reaction) |

D. Reporter Information
(See “Confidentiality” section below)

| 1. Name, address & phone number |
| 2. Health professional? | 3. Occupation | 4. Also reported to manufacturer? |
| Yes | No |

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.

* Use this form to report suspected adverse reactions to pharmaceuticals, biologics (including fractionated blood products, as well as therapeutic and diagnostic vaccines), natural health products or radiopharmaceuticals.

** As per the Treasury Board of Canada Secretariat Government Security Policy.

HC/SC 4016 (02/05)
### Summary of health professional and consumer advisories posted from May 19 to Aug. 18, 2005
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

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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

### New MedEffect Web site

MedEffect is a new Health Canada Web site dedicated to adverse reaction (AR) information. It provides health professionals and consumers access to new health product safety information, guidelines and forms for reporting suspected ARs. A searchable AR database can also be accessed through MedEffect. You can visit MedEffect at: www.healthcanada.gc.ca/medeffect

### Canadian Adverse Reaction Newsletter

marketed Health Products Directorate
AL 0701B
Ottawa ON K1A 0K9
Tel 613 954-6522
Fax 613 952-7738

Health professionals/consumers report toll free:
Tel 866 234-2345
Fax 866 678-6789

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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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