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Canadian Adverse Reaction Newsletter

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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 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

Levofloxacin: dysglycemia and liver disorders

Levofloxacin, marketed in Canada since 1997, is a broad-spectrum fluoroquinolone antibiotic that is indicated for the treatment of certain respiratory tract, skin and urinary tract bacterial infections in adults.[1] Dysglycemia[2–4] and liver disorders[5,6] in association with levofloxacin have been reported in the literature.

From Jan. 1, 1997, to June 30, 2006, Health Canada received 22 domestic reports of dysglycemia suspected of being associated with levofloxacin. Described dysglycemic adverse reactions (ARs) included 1 report of diabetes mellitus, 2 reports of hyperglycemia alone, 16 of hypoglycemia alone and 3 of hyperglycemia and hypoglycemia combined. The majority of reported cases of dysglycemia involved patients with diabetes (15/22 [68%]), and the median age (for all cases that reported an age) was 71 years (range 26–92 years).

It is postulated that one of the mechanisms behind the development of hypoglycemia with levofloxacin may involve the inhibition of pancreatic β-cell potassium channels. This inhibition results in the release of insulin, which in turn could result in hypoglycemia.[7] Disturbances of blood glucose levels are labelled in the product monograph.[1]

With regards to liver disorders, from Jan. 1, 1997, to June 30, 2006, Health Canada received 44 domestic reports of liver and biliary disorders suspected of being associated with levofloxacin. Of these 44 cases, there were 5 cases of hepatic failure, 9 of hepatitis and 1 of hepatorenal syndrome. Five of these 15 cases of liver disorders were fatal. The remaining 29 reports included ARs of increased liver enzyme levels, cholestatic hepatitis and jaundice. The median time to onset of the 44 ARs was 5 days (range 1–39 days), which can be considered a short to intermediate time to onset. The median age (for all cases that reported an age) was 48.5 years (range 19–84 years). Liver and biliary disorders are labelled in the product monograph.[1]

The mechanisms leading to the development of liver disorders with levofloxacin are not well defined. Although drug-induced liver diseases can mimic all forms of acute and chronic hepatobiliary diseases, a particular drug generally has a characteristic clinical and pathological signature and latency period when liver injury occurs. Most drug-induced liver disorders are similar to acute hepatitis, cholestasis, or mixed presentation.[8] In the 44 cases reported to Health Canada, where sufficient information was provided, cases of hepatocellular, cholestatic and mixed liver injuries were observed. Drug-induced toxic effects are a common cause of liver injury. The early identification of an AR can prevent the occurrence of irreversible liver damage.[8]

Health Canada will continue to monitor ARs suspected of being associated with levofloxacin. Health care professionals are encouraged to report any cases of dysglycemia or liver disorder in patients receiving levofloxacin.

Melissa Hunt, BScH, MSc, Health Canada

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Domperidone: heart rate and rhythm disorders

Domperidone is a peripheral dopamine antagonist structurally related to the butyrophenones with antiemetic and gastroprokinetic properties.[1] In Canada, Motilium (domperidone) was marketed in 1985 but has not been available since 2002. However, many generic brands are currently available.

Domperidone is indicated for the symptomatic management of upper gastrointestinal motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis. It may also be used to prevent gastrointestinal symptoms associated with the use of dopamine agonist antiparkinsonian agents.[1] In addition, the off-label clinical use of antidopaminergic drugs to induce and maintain adequate lactation in breast-feeding women has been suggested.[2,3]

From Jan. 1, 1985, to Aug. 15, 2006, Health Canada received 9 domestic reports of heart rate and rhythm disorders suspected of being associated with the use of domperidone. Reports involved patients aged 2 months to 74 years (median age 45 years). Two reports described prolongation of the QT interval, and 4 described Torsade de Pointes; 4 of these 6 reports indicated corrected QT intervals (QTc). The 3 remaining reports included adverse reactions (ARs) of arrhythmia, atrial fibrillation, ventricular tachycardia, bradycardia and palpitation. In 8 of the cases, domperidone was used for gastrointestinal motility disorders and diabetic gastroparesis; the indication for use was not reported for 1 case. At the time of reporting, 5 patients had recovered, and the outcome was unknown in 4 cases. Most reports revealed the use of multiple concomitant medications and complex medical histories; therefore, causality in these cases is difficult to establish.

Arrhythmia is labelled in the product monograph of Motilium, but QT prolongation and Torsade de Pointes are not.[1]

Domperidone has been reported in the medical literature to induce QTc prolongation and Torsade de Pointes.[4,5] Some non-drug-related factors that may be associated with QT prolongation include female sex, advanced age, bradycardia, cardiac disease and electrolyte disturbance.[6]

The main metabolic pathway of domperidone is via cytochrome P450 3A4 (CYP3A4). Studies of interactions have shown marked CYP3A4 inhibition by ketoconazole, which results in an increased plasma concentration of domperidone and a slightly prolonged QT interval.[7] Other examples of CYP3A4 inhibitors include macrolide antibiotics, HIV protease inhibitors, selective serotonin reuptake inhibitors (SSRIs) and grapefruit juice.[1,6,8] The combined use of multiple drugs that prolong the QTc interval can also increase the risk for Torsade de Pointes.[9]

Attention should be paid to any drug interactions and clinical risk factors that could result in an exaggerated prolongation of the QT interval. Health Canada continues to monitor ARs suspected of being associated with the use of domperidone and is working with the manufacturers of generic domperidone to update their product monographs.

Ilhemme Djelouah, BScPhm, DIS, AFSA, Medical Biology (University of Paris V); Christianne Scott, BPharm, MBA, Health Canada

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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*).

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.

Green tea extract (Green Lite): suspected association with hepatotoxicity

A previously healthy 42-year-old woman was admitted to hospital for investigation of stomach discomfort and jaundice. Upon admission, results of the patient's liver function tests were abnormal, her international normalized ratio (INR) was 5 (normal 1), her ammonia levels were elevated, and her CT scan was normal. Results of hepatitis B and C screens were negative. The patient's condition deteriorated; she became confused and encephalopathic and was comatose 9 days after admission. Fourteen days after admission the following abnormal laboratory findings were reported: direct bilirubin 234 µmol/L (normal < 4), total bilirubin 423 µmol/L (normal < 16), alanine aminotransferase 432 IU (normal 1–20), aspartate aminotransferase 217 IU (normal 10–42), INR 3.4. The hepatic biopsy result was reported as "toxic hepatitis." A liver transplant was performed 17 days after presentation. For about 6 months before admission, the patient had been taking 6 capsules of Green Lite Polyphenon per day. This product contains a decaffeinated extract of green tea, providing 100 mg of catechins per capsule. The product has been used for weight loss and is not authorized for sale in Canada. The reporter indicated that an unidentified flea spray was used at the patient's home, and the only concomitant medication was Depo-Provera injections, 150 mg every 3 months, over the previous few years.

Hydroalcoholic extracts of green tea have been associated with hepatotoxicity in humans.[1]

Reference

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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.

Summary of health professional and consumer advisories posted from Aug. 18 to Nov. 14, 2006
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject
Nov 11	Acetaminophen	Recall in the United States
Nov 10	Rituxan	Bowel obstruction and gastrointestinal perforation — Hoffmann–La Roche Limited
Nov 2	Natural health products	Advisory not to use 4 unauthorized natural health products
Nov 2	Natural health products	Advisory not to use unauthorized products for sexual enhancement
Oct 25	Syringe pumps	Risk of delay in detection of occlusion
Oct 25	Neutragel	Advisory not to use a specific lot of Neutragel
Oct 24	Avastin	Hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome — Hoffmann–La Roche Limited
Oct 19	Lifescan test strips	Warning about counterfeit Lifescan blood glucose test strips
Oct 13	CellCept	Acute rejection among cardiac transplant patients — Hoffmann–La Roche Limited
Oct 13	Intravenous health products	Warning not to use unauthorized intravenous health products
Oct 12	Natural health products	Advisory not to use 2 unauthorized natural health products
Oct 3 & Sept 29	Ketek	Hepatic events, aggravation of myasthenia gravis and syncope — Sanofi–aventis Canada Inc.
Sept 28	Insulin products	*It's Your Health* update: Insulin products
Sept 27	Xylocaine 2% Jelly	Advisory to stop using AstraZeneca Xylocaine 2% Jelly single-use plastic syringes
Sept 21	Gleevec	Left ventricular ejection fraction reduction and congestive heart failure — Novartis Pharmaceuticals Canada Inc.
Sept 21	ADHD drugs	Uncommon psychiatric adverse events
Sept 19	Libidus	Warning not to use Libidus
Sept 14	Jambrulin	Advisory against use of Jambrulin because of lead content
Aug 31	Chao Nongsu Qingzhi Jiaonang	Foreign product alert
Aug 31	Conting Qianweisu Slimming Herbs	Foreign product alert
Aug 30	Dietary supplement	Advisory not to use Salt Spring Herbals Sleep Well
Aug 28	Alaris SE Pump	Important safety information — Cardinal Health
Aug 24	Lipitor	Another batch of counterfeit Lipitor found in the United Kingdom
Aug 23	VG	Foreign product alert
Aug 23	Meng Rong	Foreign product alert
Aug 23	Yixinjiaonang	Foreign product alert
Aug 23	Reduce Weight	Foreign product alert
Aug 22 & 18	Rapamune	High rate of acute rejection among *de novo* renal transplant patients — Wyeth Pharmaceuticals
Aug 21	Hydrogen peroxide	Warning against drinking hydrogen peroxide
Aug 18	Black cohosh	Possible link with liver damage
Aug 17	Medical devices	*It's Your Health* article: Buying medical devices over the Internet
July 18	Intubating stylet	Recall of Mallinckrodt Satin-Slip Intubating Stylet – 6 FR — Tyco Healthcare Canada

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

Health professionals/consumers report toll free:

Tel 866 234-2345
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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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