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Direction des produits therapeutiques

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Canadian Adverse Drug Reaction Newsletter

In this issue:

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Statins: rhabdomyolysis and myopathy

Statins belong to a class of cholesterol-lowering agents that inhibit the liver enzyme 3-hydroxy-3-methylglutaryl–coenzyme A (HMG–CoA) reductase. The use of HMG–CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis.[1-6]

The statins approved for sale in Canada include atorvastatin (Lipitor), cerivastatin (Baycol), fluvastatin (Lescol), lovastatin (Mevacor, Apo-Lovastatin, Gen-Lovastatin), pravastatin (Pravachol, Apo-Pravastatin, Bio Pravastatin, Lin-Pravastatin) and simvastatin (Zocor). On Aug. 8, 2001, Bayer Inc. voluntarily suspended the marketing and distribution of Baycol in Canada.[7,8] The continued scrutiny of postmarketing reports of rhabdomyolysis, including related deaths, has revealed an increased reporting rate of rhabdomyolysis with Baycol than with the other statins, especially when gemfibrozil is prescribed concurrently.[7]

The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has received reports of rhabdomyolysis or myopathy with all statins approved for sale in Canada (Table 1). In severe cases, rhabdomyolysis can result in kidney failure.[8] The statin cases of rhabdomyolysis outlined in Table 1 with which acute renal failure was also reported were: atorvastatin (2 cases), cerivastatin (15), lovastatin (5), pravastatin (1) and simvastatin (2). The reports of rhabdomyolysis with a fatal outcome were: atorvastatin (1), cerivastatin (2) and lovastatin (1).

Table 1: Rhabdomyolysis, myopathy and increased CPK reactions associated with statins as reported to the CADRMP from date marketed in Canada to Aug. 24, 2001*

	Drug and year marketed in Canada; no. of reports					
Reaction†	Atorvastatin 1997	Cerivastatin 1998	Fluvastatin 1994	Lovastatin 1988	Pravastatin 1990	Simvastatin 1990
Rhabdomyolysis	10	54	–	12	3	7
Myopathy‡	32	8	5	24	17	34
CPK increased with myopathy‡	16	11	1	6	4	6
CPK increased without myopathy‡	5	6	–	4	6	5
Total no. of reports received	231	121	43	182	123	170

Note: CPK = creatine phosphokinase, CADRMP = Canadian Adverse Drug Reaction Monitoring Program.
*** These data cannot be used to determine the incidence of adverse drug reactions because neither patient exposure nor the amount of time the drug was on the market has been taken into consideration. See caveat at the end of the newsletter.**
^ Each report may contain more than 1 of these reactions; however, reports were only included in the most significant category.
‡ Myopathy may include muscle symptoms such as myositis, myalgia, muscle ache, muscle weakness, muscle cramp, muscle discomfort.

Various factors may increase the risk of myopathy and rhabdomyolysis with statins. Rhabdomyolysis can occur with all statins when used alone and particularly when combined with other drugs or chemicals that are themselves myotoxic or that elevate the concentrations of the statin to the toxic range.[9] Evidence suggests that myopathy is dose-dependent,[9] and it is usually recommended that statin therapy be initiated at lower therapeutic doses.[1-6] Combined use with niacin in lipid-lowering doses, with fibric acid derivatives such as bezafibrate, fenofibrate and gemfibrozil,[1-6] or with drugs or foods that inhibit the cytochrome P450 (CYP450) system, particularly CYP3A4, (including but not limited to cyclosporins, macrolide antibiotics, antidepressants such as nefazodone, azole antifungals and grapefruit juice) can potentially increase the toxicity of statins.[1,3,5,6,9] Atorvastatin, cerivastatin, lovastatin and simvastatin are metabolized mainly by CYP3A4.[10] Lovastatin and simvastatin may particularly be affected by the inhibition of first-pass metabolism, which could result in 10- to 20-fold elevations (oral availability increasing from 5% to 100%) in steady-state concentrations with a marked potential for drug toxicity.[9] Pravastatin is not metabolized by CYP3A4 to a clinically significant extent.[2] Fluvastatin is metabolized mainly by CYP2C9[4,10] and would have a different spectrum of interactions than would statins metabolized by CYP3A4.[9] Further information concerning drug interactions may be obtained from the product monograph of each statin.[1-6] In addition, caution should be exercised when using statins in patients with impaired renal function.[1-6]

The product monograph of each statin has no clear recommendation for biochemical monitoring of muscle effect (creatine phosphokinase [CPK] measurement). In the absence of symptoms, there is no evidence to suggest that routine monitoring of plasma CPK activity is of benefit.[10] However, further

investigation is required to provide more definitive monitoring guidelines. It was suggested in a recent review article[10] that it is important to measure the baseline CPK level at least once before starting statin therapy.

Patients taking a statin or a fibrate should be made aware of rhabdomyolysis as a potential side effect. They should be advised to report promptly any signs of muscle problems (i.e., unexplained muscle weakness, tenderness or pain, either occurring at rest or exacerbated by exercise) and dark urine, particularly if these symptoms are accompanied by malaise or fever.

Written by: Duc Vu, MSc, PhD, Mano Murty, MD, CCFP, FCFP, and Marielle McMorran, BScPharm, Bureau of Licensed Product Assessment.

References

1. *Mevacor, lovastatin tablets* [product monograph]. Kirkland (QC): Merck Sharp & Dohme Canada; 1998 Sept 10.
2. *Pravachol, pravastatin sodium tablets* [product monograph]. Montréal (QC): Bristol-Myers Squibb Canada; 2000 Feb 22.
3. *Zocor, simvastatin tablets* [product monograph]. Kirkland (QC): Merck Frosst Canada; 1999 Aug 23.
4. *Lescol, fluvastatin sodium capsules* [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada; 2001 Feb 14.
5. *Lipitor, atorvastatin calcium tablets* [product monograph]. Kirkland (QC): Pfizer Canada; 2001 May 31.
6. *Baycol, cerivastatin sodium tablets* [product monograph]. Etobicoke (ON): Bayer; 2000 Dec 27.
7. *Market withdrawal of Baycol (cerivastatin)* [Dear Healthcare Professional letter]. Toronto (ON): Bayer; 2001 Aug 8. Available: http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/baycol_cerivastatin_e.html (accessed 2001 Dec 5).
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Alendronate: suspected pancreatitis

Alendronate (Fosamax) is a bisphosphonate inhibitor of bone resorption indicated in Canada for the treatment of Paget's disease of bone and osteoporosis, including glucocorticoid-induced osteoporosis in men and women. It is also used to prevent osteoporosis in postmenopausal women and in patients receiving glucocorticoids.[1]

Between December 1995, when alendronate was marketed in Canada, and Aug. 31, 2001, the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) received 6 reports of suspected pancreatitis associated with alendronate (Table 1). Pancreatitis can be a serious and life-threatening condition.[2] The current product monograph for Fosamax does not mention pancreatitis as a possible side effect.[1]

The causal relation between alendronate and pancreatitis is difficult to establish because of the limited information in the reports received. Onset ranged from 13 days to several years after starting alendronate therapy. Furthermore, it is unknown whether a rechallenge was done in any of the cases. Case 3 may emphasize a causal relation (Table 1). The acute pancreatitis resolved after the alendronate therapy was stopped. The patient lacked the most common causes of pancreatitis (alcohol abuse and gallstones)[2] and was not reported to have taken concomitant medications. Numerous drugs have been implicated as the cause of acute pancreatitis[2,3] and their use may be a source of confounding factors in some of the other cases (Table 1).

Since there is underreporting of adverse drug reactions (ADRs) and patient exposure is unknown, the incidence of alendronate-associated pancreatitis cannot be derived from the reported cases. The mechanism involved and associated risk factors are unknown.

If drug-induced pancreatitis is suspected in a patient with abdominal pain and increased levels of pancreatic enzymes without a medical cause, it may resolve once the suspected drug is withdrawn.[2] Continued reporting to the CADRMP of the full details of suspected cases will aid in further assessing this suspected adverse reaction.

Table 1: Summary of reports of suspected pancreatitis associated with alendronate submitted to the CADRMP between December 1995 and Aug. 31, 2001

Case	Reported reaction*	Age/ sex	Daily dose, mg	Time to onset	Findings†	Medical history	Concomitant drugs	Outcomes‡
1	Pancreatitis	68/F	10	7 mo	Epigastric pain, vomiting, dehydration. Serum amylase level 372 U/L, WBC count 18 x 10^9/L	Osteoporosis	MS Contin§	Hospital admission, discontinuation of alendronate; recovered
2	Pancreatitis, acute	76/F	10	48 d	Serum amylase level 3490 U/L, serum lipase level 7110 U/L	Osteoporosis, type 2 diabetes, stroke, cardiac insufficiency, hypertension	Diabeta, Entrophen,§ Glucophage, K-Dur, Lasix,§ Vasotec§	Hospital admission, discontinuation of all drugs; not recovered
3	Pancreatitis, acute	77/F	10	13 d	Acute epigastric pain. Serum amylase level 4339 U/L, WBC count 12.1 x 10^9/L	Osteoporosis, previously well, nondrinker, no gallstones	None	Discontinuation of alendronate; recovered
4	Pancreatitis	NA/F	NA	NA	NA	NA	NA	Death (may be drug related)
5	Pancreatitis	NA	NA	NA	NA	NA	NA	NA
6	Pancreatitis, acute	NA/F	NA	"Several years"	NA	Osteoporosis, ulcer history	Prinivil,§ Thyroxine	Hospital admission, discontinuation of alendronate

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program, NA = not available, WBC = white blood cells.
* Based on the "preferred term" of the World Health Organization Adverse Reaction Dictionary (WHOART).
† Normal ranges vary among laboratories; typical reference values are: serum amylase 0–130 U/L, serum lipase 0–160 U/L, WBC count 3.2–9.8 x 10^9/L.
‡ At the time of reporting, as indicated by the reporter.
§ Drugs for which an association with pancreatitis has been suggested.[2,3]

Written by: Written by: Barbara Cadario, BSc, BScPhm, MSc, BC Regional Adverse Drug Reaction Centre and BC Drug and Poison Information Centre, Vancouver, BC.

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1. *Fosamax, alendronate sodium* [product monograph]. Kirkland (QC): Merck Frosst Canada; 2001 Apr 2.
2. Underwood TW, Frye CB. Drug-induced pancreatitis. *Clin Pharm* 1993;12:440-8.
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HIV-associated lipodystrophy syndrome: overview and summary of case reports

HIV-associated lipodystrophy syndrome (LDS) is a disorder in HIV-infected patients receiving highly active antiretroviral therapy.[1-3] It presents as a range of *clinical* (morphologic) and *metabolic* changes. The following clinical changes have been described: body fat redistribution such as visceral adiposity (fat gain within the abdomen, breasts, over the dorsocervical spine and other lipomata) and peripheral lipoatrophy (fat loss in the face, limbs, buttocks). The metabolic changes have included hypertriglyceridemia, hypercholesterolemia, insulin resistance, type 2 diabetes mellitus, impaired glucose tolerance and lactic acidemia.[1,2,4] The term "lipodystrophy" has been used to describe fat loss, fat redistribution and, on a broader level, both clinical and metabolic features of HIV-associated LDS.[2]

The pathogenesis of LDS is unknown.[1] However, it has been associated with combination antiretroviral therapy including protease inhibitors and nucleoside reverse transcriptase inhibitors, the latter having been linked to mitochondrial toxicity.[1-3] As well, it has been suggested that LDS features are the result of chronic HIV infection, chronic immunodeficiency or recovery from immune dysfunction.[5]

No validated case definition of LDS has yet been formulated. However, a working case definition has been described as having at least one *clinical* feature and at least one *metabolic* abnormality, and no AIDS-defining event or other severe clinical illness or use of anabolic steroids, glucocorticoids or immune modulators within 3 months of assessment.[4]

The CADRMP database was searched for LDS-related ADRs up to Aug. 31, 2001. The search focused on metabolic and nutritional disorders and endocrine disorders associated with antiretroviral drugs containing abacavir, amprenavir, delavirdine, didanosine, efavirenz, indinavir, lamivudine, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir (base and mesylate), stavudine or zalcitabine. A total of 119 ADR reports were found, of which only 4 met the LDS working case definition (Table 1).

In addition to the cases described in Table 1, other reports found in the database denoted potential LDS: lipodystrophy (3 cases) and fat disorder (13 cases). These additional cases did not clearly report the presence of combined clinical and metabolic features, possibly because of the available scientific knowledge at that time.

Retrospective studies have reported a prevalence of LDS of 17%–84% among HIV-infected cohorts receiving highly active antiretroviral therapy.[6] It is clear that LDS is highly underreported to Health Canada. Reports of ADRs are an important source of potential new and undocumented signals. To this end, a pilot project underway within the Therapeutic Products Directorate is promoting increased reporting to Health Canada of ADRs in HIV-infected patients.[7] Its purpose is to develop alternative methods and formats for clinicians and patients to report ADRs. One such method proposed for testing in the pilot project is the electronic entry of ADR data as part of the everyday practice of clinicians.

Table 1: Cases of potential lipodystrophy syndrome* associated with antiretroviral drugs reported to the CADRMP up to Aug. 31, 2001

Case	Age/ sex	Reported clinical reactions†	Reported metabolic reactions†	Concomitant drugs	Duration of treatment	Suspect drug reported	
						PI	NRTI
1	56/F	Lipodystrophy	Diabetes mellitus	Lamivudine, nadolol, Prevacid, Zoloft	NA	-	Stavudine
2	33/M	Fat disorder	Hyperglycemia	Lamivudine, stavudine	26 wk	Indinavir	-
3	44/M	Fat disorder	Hyperglycemia, hypertriglyceridemia	Nelfinavir	NA	Saquinavir	-
4	49/M	Lipodystrophy, enlarged abdomen	Hypertriglyceridemia	Azithromycin, lamivudine, saquinavir, stavudine	Continuing	Ritonavir	-

Note: CADRMP = Canadian Adverse Drug Reaction Monitoring Program, PI = protease inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NA = not available.
* Met working case definition: at least one clinical feature and at least one metabolic abnormality, and no AIDS-defining event or other severe clinical illness or use of anabolic steroids, glucocorticoids or immune modulators within 3 months of assessment.
† Based on the "preferred term" of the World Health Organization Adverse Reaction Dictionary (WHOART).

Written by: Susanne Reid, BSc, RT, Bureau of Licensed Product Assessment.

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Summary of health professional and consumer advisories issued since Aug. 18, 2001

Date	Product	Subject and Web address
Nov 29	Glitazones (Actos and Avandia)	Patient safety information - congestive heart failure www.hc-sc.gc.ca/english/protection/warnings/2001/2001_132e.htm
Nov 26	Eprex (epoetin alfa)	Pure red blood cell aplasia http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/eprex_e.html
Nov 13	Avandia (rosiglitazone)	Congestive heart failure http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/avandia_e.html
Nov 6	Actos (pioglitazone)	Congestive heart failure http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/actos_e.html
Oct 23	Remicade (infliximab)	Congestive heart failure http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/remicade_e.html
Oct 5	Aristolochic acid	Additional products containing aristolochic acid and toxicity http://www.hc-sc.gc.ca/english/protection/warnings/2001/2001_105e.htm
Sept 24	Zyban (bupropion)	Seizures, allergic reactions, drug interactions http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/zyban2_e.html
Sept 17	Aristolochic acid	Recall of products containing aristolochic acid http://www.hc-sc.gc.ca/english/protection/warnings/2001/2001_100e.htm
Sept 13	Topamax (topiramate)	Acute myopia and secondary angle closure glaucoma http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/topamax_e.html
Sept 10	Carnitor (levocarnitine)	Precautions related to use in end-stage renal disease http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/carnitor_e.html
September	Gleevec (imatinib)	Notice of Compliance with Conditions (NOC/C) http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/industry/gleevec_e.html
Aug 27	Zirconia	Recall of ceramic femoral heads for use in hip replacement http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/advisory/tpd/zirconia_e.html

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COMMUNIQUÉ

The CADRMP wishes to provide feedback and increase awareness of recently reported ADRs. The following cases have been selected on the basis of their seriousness, or the fact that the reactions do not appear in the official Canadian product monograph. (Reactions are expressed based on the "preferred term" in the World Health Organization *Adverse Reaction Dictionary*.)

Ibuprofen pediatric oral liquid: gastrointestinal bleeding
Two reports have been received involving children aged 14 months and 2½ years who vomited “large blood clots” (1 case) and passed “black, tarry, foul-smelling stool” followed by “nonspecific abdominal pain, irritability and lethargy” (1 case) after receipt of ibuprofen as a pediatric oral liquid. Symptoms were reported to have occurred after only a few doses (as early as after the first dose in 1 case).

If you have observed any suspected ADRs with the drug in the Communiqué, *please report them* to the :

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Adverse Reaction Information Unit
Bureau of Licensed Product Assessment
AL: 0201C2, Ottawa, ON K1A 1B9
Tel: (613) 957-0337 Fax: 613 957-0335
Consumers and Health Professionals may contact us Toll free at:
Tel: 866 234-2345, Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Please Note: A voluntary reporting system thrives on intuition, lateral thinking and open mindedness. Most adverse drug reactions (ADRs) can only be considered to be suspicions, for which a proven causal association has not been established. Because ADRs are under reported and because a definite causal association cannot be determined, spontaneous ADR reports cannot be used to estimate the incidence of adverse reactions. ADRs are nevertheless valuable as a source of potential new and undocumented signals. Health Canada does not assume liability for the accuracy or authenticity of the ADR information contained in the newsletter articles. Furthermore, the Therapeutic Products Directorate monitors and assesses suspected ADRs as a means of continuously evaluating drug safety profiles. Regulatory decisions are not made within the context of this newsletter.

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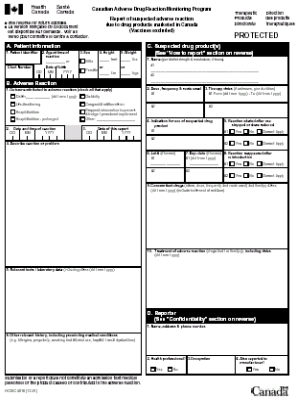
Reporting Adverse Drug Reactions:

To report a suspected adverse drug reaction (ADR) for drug products marketed in Canada, please complete a copy of the ADR Reporting Form, included in the *Compendium of Pharmaceuticals and Specialties (CPS)*, which is also available on the Health Canada Website at:
http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
Complete the reporting form and send it to the CADRMP or to one of the participating Regional Centres mentionned below.



List of Regional Adverse Drug Reaction Reporting Centres

British Columbia
BC Regional ADR Centre
c/o BC Drug and Poison
Information Centre
1081 Burrard Street
Vancouver BC V6Z 1Y6
Tel: 604 806-8625
Fax 604 806-8262
adr@dpic.bc.ca

Ontario
Ontario Regional ADR Centre
LonDIS Drug Information Centre
London Health Sciences Centre
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London ON N6A 5A5
Tel: 519 663-8801
Fax: 519 663-2968
adr@lhsc.on.ca

New Brunswick, Nova Scotia, Prince Edward Island and Newfoundland
Atlantic Regional ADR Centre
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Sciences Centre
Drug Information Centre
1796 Summer Street, Rm. 2421
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Other provinces and territories
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