Health Canada Santé Canada

Canada

Canadian Adverse Reaction Newsletter

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www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_adverse_newsletter_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 Centre free of charge

Phone: 866 234-2345
Fax: 866 678-6789
Email: cadrmp@hc-sc.gc.ca

Form available at:

www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf

Gatifloxacin (Tequin™): hypoglycemia and hyperglycemia

Gatifloxacin (Tequin™) is a broad-spectrum antibacterial fluoroquinolone with activity against gram-negative and gram-positive aerobic and anaerobic microorganisms and is also effective against clinically important atypical microorganisms.[1] Health Canada's database of spontaneous reports of adverse reactions indicates that hypoglycemia and hyperglycemia have been reported more frequently with gatifloxacin than with other quinolone antibiotics. Case reports of hypoglycemia associated with gatifloxacin have also been published.[2–5] The Canadian product monograph for Tequin™ was recently updated in response to reported cases of serious, and in some cases life-threatening, disturbances of glucose homeostasis.[1]

Health Canada received 28 reports of abnormal glucose metabolism associated with gatifloxacin (44% of total reports received for the drug) from Feb. 21, 2001 (the date marketed in Canada), to Feb. 28, 2003: 19 were of hypoglycemia, 7 were of hyperglycemia, and 2 were of both hypoglycemia and hyperglycemia (Table 1). Twenty-five of the cases involved patients with type 2 diabetes (determined from the patient's history or use of concomitant medications), 2 involved nondiabetic patients, and in 1 case the diabetic status was unknown. The 28 cases were serious, and 19 of the patients were admitted to hospital or had a prolonged hospital stay because of the reaction. The 2 patients who died (86 and 102 years of age) had hyperglycemia, no prior history of diabetes and decreased renal function at the time of the reaction.

Concomitant use of hypoglycemic agents was noted in 18 of the 19 cases in which a hypoglycemic reaction was reported. The exact mechanism of hypoglycemia is unknown, but some hypotheses include a possible increase in the serum insulin level following the administration of gatifloxacin or the existence of a possible interaction between glyburide and gatifloxacin.[2–5]

A postmarketing study of gatifloxacin involving more than 15 000 patients reported an incidence of hypoglycemic events of 0.3 per 1000 among nondiabetic patients and 6.4 per 1000 among diabetic patients.[1] The corresponding rates for hyperglycemia were 0.07 per 1000 and 13 per 1000. All of these cases were reversible with appropriate treatment, which included the discontinuation of gatifloxacin.[1]

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Newsletter and Advisories by email

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References

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Key points[1]

- Hypoglycemia and hyperglycemia have been reported following the use of gatifloxacin, usually but not always in diabetic patients.
- Hypoglycemic reactions frequently occurred within the first day of therapy and usually within 3 days. These reactions were reported in diabetic patients receiving either sulfonylurea or non-sulfonylurea oral hypoglycemic medications.
- Most hyperglycemic reactions occurred 4 to 10 days after the start of therapy; very elderly patients (> 75 years of age) who may have unrecognized diabetes, age-related decrease in renal function or underlying medical problems or are taking concomitant medications associated with hyperglycemia may be at particular risk.
- Blood glucose levels should be monitored carefully when gatifloxacin is used in diabetic patients.
- Gatifloxacin therapy should be stopped and appropriate treatment started immediately if any signs or symptoms of hypoglycemia or hyperglycemia appear.
- Gatifloxacin is mainly eliminated by the kidneys; therefore, a reduced dosage is recommended in patients with a creatinine clearance of less than 0.67 mL/s (40 mL/min).
- Patients should be educated about these possible adverse reactions with gatifloxacin.

Table 1: Reports submitted to Health Canada of suspected adverse reactions (ARs) of hypoglycemia and hyperglycemia associated with gatifloxacin (Tequin™) from Feb. 21, 2001, to Feb. 28, 2003*

Variable	Hypoglycemia *n = 19*	Hyperglycemia *n = 7*	Hypoglycemia and hyperglycemia *n = 2*
Mean age (and range) of patients, yr	74 (49–87)	75 (52–102)	70 (61–79)
Female:male ratio	1:1	4:3	1:1
Blood glucose values reported, mmol/L†	1.4–3.8	15–58	3.0–14
Onset of reaction after start of gatifloxacin therapy (no. of reports)	< 24 h (16) 24–72 h (2) > 72 h (1)	< 4 d (3) 4–10 d (4)	< 24 h (2)
Reaction terms reported‡ (no. of reactions)	Hypoglycemia (18), tremor (2), hypoglycemic coma (1), NPN (serum creatinine) increased (1), confusion (1), paresthesia (1), dyspnea (1), nausea (1), convulsions (1), ataxia (1)	Hyperglycemia (7), dehydration (2), plasma osmolality increased (2), NPN (serum creatinine) increased (2), renal function abnormal (2), diabetic coma (1), malaise (1), electrolyte abnormality (1), respiratory insufficiency (1), tachycardia (1), atelectasis (1), bundle branch block (1), cardiac failure (1), confusion (1), polydipsia (1), polyuria (1), nausea (1)	Hypoglycemia (2), hyperglycemia (2)
Outcome reported, no. of reports	Recovered: 17 Unknown: 2	Recovered: 5 Death: 2	Recovered : 1 Not yet recovered: 1
History of diabetes, no. of reports	Type 2: 18 Unknown: 1	Type 2: 5 None: 2	Type 2: 2
Concomitant use of hypoglycemic agent, no. of reports§	18	2	2
Creatinine clearance < 0.67 mL/s (40 mL/min), no. of reports¶	8	3	–

***These data cannot be used to determine the incidence of ARs because ARs remain underreported and total patient exposure is unknown.**

†Normal range for fasting or before-meal glucose level is 3.8–6.1 mmol/L in nondiabetic patients; target range in diabetic patients is 4–7 mmol/L.[6]

‡Several reaction terms may be listed per AR report. Reaction terms are based on the "preferred term" of the World Health Organization (WHO) *Adverse Reaction Dictionary* (WHOART).

§Hypoglycemic agents: glyburide, glicazide, tolbutamide or insulin.

¶Renal function was reported in 13 of the 28 cases: decreased renal function (11), renal function in normal range (2) and unknown (15).

Serotonin syndrome

Serotonin syndrome is a potentially life-threatening disorder of excessive serotonergic activity. It usually occurs when 2 or more serotonin-modifying agents are used in combination, but it has also been reported with the use of a single agent.[1] For example, the concomitant use of meperidine, certain migraine medications (e.g., triptans), dextromethorphan (DM) and sibutramine can potentially precipitate symptoms of serotonin excess in patients being treated with selective serotonin reuptake inhibitors (SSRIs).[2,3] Table 1 lists some of the products that enhance serotonergic activity.

From Jan. 1, 1998, to Dec. 30, 2002, Health Canada received 53 reports of suspected serotonin syndrome. Serotonin syndrome was most often reported with the use of SSRIs (33), monoamine oxidase inhibitors (MAOIs) (10) and venlafaxine (9). Some of these reports involved combinations of these drugs. Four of the 53 cases were fatal.

Serotonin syndrome often presents soon after initiation of, or changes in, serotonergic therapy, with an onset of < 24 hours in about 75% of patients.[1,2,4] The syndrome is diagnosed on a clinical basis where there is known exposure to serotonergic agents, demonstration of specific signs and symptoms and exclusion of other medical and psychiatric conditions.[1,5] The clinical presentation is usually marked by the triad of cognitive or behavioural changes (confusion, agitation, lethargy, coma), autonomic instability (hyperthermia, tachycardia, diaphoresis, nausea, vomiting, diarrhea, dilated pupils) and neuromuscular changes (myoclonus, hyperreflexia, tremor).[1,4,5] There is a broad range in both the severity and constellation of symptoms.[2] Similarities between serotonin syndrome and neuroleptic malignant syndrome can present the clinician with a diagnostic challenge when serotonergic and neuroleptic drugs are used concurrently.[2] Serotonin syndrome is often self-limited with a good outcome, particularly if it is recognized early, therapy with the suspected serotonergic agent(s) is discontinued and supportive care is provided.[1,4]

Serotonin (5-hydroxytryptamine, 5-HT) levels are increased by various mechanisms (e.g., increased 5-HT synthesis, increased 5-HT release, inhibition of 5-HT reuptake, inhibition of 5-HT metabolism, postsynaptic receptor stimulation).[2] Interactions in which drugs, herbal products or foods inhibit the metabolism and excretion of serotonergic agents may also precipitate serotonin syndrome by increasing the concentration of these serotonergic drugs (e.g., serotonin syndrome was reported after concomitant use of citalopram and clarithromycin[6]). Symptoms of serotonin syndrome have also been reported with the concomitant use of 5-HT_3 receptor antagonists (e.g., dolasetron, granisetron, ondansetron) with serotonergic agents (e.g., fentanyl, mirtazapine, paroxetine, sertraline).[7,8] In addition, possible serotonin toxicity after withdrawal of clozapine, a 5-HT_{2A} receptor antagonist, in a patient taking a serotonergic agent (clomipramine) has been reported.[9]

Case example: sibutramine and serotonin syndrome

Sibutramine (Meridia®), a serotonin and norepinephrine reuptake inhibitor, is an antiobesity agent.[3] Health Canada received 87 reports of suspected adverse reactions associated with the use of sibutramine from February 2001, when it was marketed in Canada, to Dec. 31, 2002. Three of the 87 cases reported serotonin syndrome. In one case, sibutramine was taken concomitantly with fluoxetine. In the second case, sibutramine was taken with sertraline but the sertraline was stopped 2 days before the symptoms appeared. In the third case, no concomitant drugs were reported. There were no reports of a fatal outcome.

Table 1: Products that enhance serotonergic activity*

Analgesics

Codeine, fentanyl, meperidine, pentazocine

Antidepressants

MAOIs

Moclobemide, phenelzine, tranylcypromine

SSRIs

Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline

Tricyclic antidepressants

Amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline

Other

Bupropion, mirtazapine, nefazodone, trazodone, venlafaxine

Antiparkinsonians

Amantadine, bromocriptine, levodopa, selegiline

Illicit drugs

Cocaine, hallucinogenic amphetamines such as, but not limited to, MDMA ("ectasy"), LSD, mescaline

Migraine therapy

Dihydroergotamine, naratriptan, rizatriptan, sumatriptan, zolmitriptan

Miscellaneous

Brompheniramine, buspirone, carbamazepine, dextramphetamine, dextromethorphan, L-tryptophan, lithium, phentermine, reserpine, sibutramine, St. John's wort, tetrabenazine

Note: Serotonin syndrome has also been reported with dextropropoxyphene, droperidol and metoclopramide,[11] linezolid,[4] and 5-HT_3 antagonists (dolasetron, granisetron, ondansetron).[7,8] There are reports of atypical antipsychotics (clozapine, olanzapine, risperidone) associated with serotonin syndrome when used in combination with serotonergic agents.[1,9,12]

Note: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, MDMA = methylenedioxymethamphetamine, LSD = lysergic acid diethylamide.
*This list is not inclusive; some products not marketed in Canada (e.g., dexfenfluramine, fenfluramine, isocarboxazide, tramadol) are not included. This list was developed from information in references 1, 2, 10 and 11.

Concomitant use of sibutramine and other agents with serotonergic activity such as MAOIs, centrally acting drugs for the treatment of psychiatric disorders (e.g., antidepressants, antipsychotics) or herbal remedies (e.g., St. John's wort) is contraindicated in the Canadian product monograph for Meridia®.[3] At least 14 days should elapse between discontinuation of these drugs and initiation of treatment with sibutramine.[3] A 5-week discontinuation period is required for fluoxetine.[3] Despite these contraindications, 8 of the 87 cases involving sibutramine reported the concomitant use of SSRIs (citalopram [1], fluoxetine [1], fluvoxamine [1], sertraline [3]) and other serotonergic drugs (amitriptyline [1], lithium [1]).

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References

1. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome presentation of 2 cases and review of the literature. *Medicine* 2000;79:201-9.
2. Ener RA, Meglathery SB, VanDecker WA, Gallagher RM. Serotonin syndrome and other serotonergic disorders. *Pain Med* 2003;4(1):63-74.
3. *Meridia®, sibutramine hydrochloride monohydrate capsules* [product monograph]. Saint-Laurent (QC): Abbott Laboratories Ltd; 2002 Sept 6.
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12. Duggal HS, Fetchko J. Serotonin syndrome and atypical antipsychotics [letter]. *Am J Psychiatry* 2002;159(4):672-3.

Key points

- Successful management of serotonin syndrome relies on prevention, early recognition, prompt treatment by the discontinuation of the suspected serotonergic agent(s) and institution of supportive care.[1,5]
- The concomitant use of agents that inhibit the metabolism of a serotonergic drug, thus causing its accumulation, should be considered as a potential precipitating factor for serotonin syndrome.
- Health care professionals are encouraged to consult the product monographs of serotonergic agents for contraindications and for recommendations for washout periods when switching serotonergic agents.

Summary of health professional and consumer advisories posted since Feb. 18, 2003
(advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

Date	Product/topic	Subject and type
May 27	Hua Fo Vigor-Max	Health Canada warns public not to use Hua Fo Vigor-Max — consumer information
May 23	Servo 300/300A ventilators	Important advisory to users of Siemens Servo 300 / 300A ventilators — Siemens Canada Ltd. — health professional advisory
May 8	Seavite	Health Canada advises against use of Seavite products containing iodine — consumer information
Apr 29	SARS	Health Canada is advising Canadians to be wary of products with claims concerning the prevention or treatment of SARS — consumer information
Apr 28 & 2	Diathermy therapy	Health Canada is advising Canadians of a dangerous interaction between diathermy therapy and implanted metallic leads — notice to hospitals and consumer information
Apr 17 & 14	Permax®	Important safety information regarding Permax® (pergolide mesylate) and cardiac valvulopathy — Eli Lilly Canada Inc. and Draxis Health Inc. — health professional advisory and consumer information
Apr 10	Diane®-35	Important safety information about Diane®-35 and the risk of venous thromboembolism — Berlex Canada Inc. — health professional advisory and consumer information
Apr 1	Fragmin®	Clarification of dosing recommendations for Fragmin® (dalteparin sodium injection) — Pharmacia Canada Inc. — health professional advisory
Mar 18	Diethylstilbestrol (DES)	Advisory on diethylstilbestrol (DES) and the risk of genital and obstetrical complications — health professional advisory
Mar 12	Ethyol®	Important safety information regarding Ethyol® (amifostine) and severe cutaneous reactions — health professional advisory
Mar 5 & Feb 28	Zoloft™	New safety information associated with the use of Zoloft™ in patients taking pimozide — Pfizer Canada Inc. — health professional advisory and consumer information
Feb 28	Meridia®	Health Canada reports back to public on safety profile of Meridia® (sibutramine) — consumer information
Feb 19	Rapamune®	New warning regarding Rapamune® (sirolimus) and bronchial anastomotic dehiscence including fatal cases —Wyeth Pharmaceuticals — health professional advisory

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Go to **www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/subscribe_e.html**.

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.

How to report adverse reactions

To report a suspected adverse reaction (AR) to therapeutic products marketed in Canada, health professionals should complete a copy of the AR Reporting Form (see page 6) and forward it to the appropriate Regional AR Centre by mail (see addresses below) or by toll free fax (866 678-6789). Copies of the form are also available from your Regional AR Centre or the National AR Centre, the *Canadian Compendium of Pharmaceuticals and Specialties* (*CPS*) and the Health Canada Web site (www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf).

British Columbia
BC Regional AR Centre
c/o BC Drug and Poison Information Centre
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Saskatchewan
Saskatchewan Regional AR Centre
c/o Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
Tel: 306 966-6329
Fax: 306 966-2286
vogt@duke.usask.ca

Ontario
Ontario Regional AR Centre
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London Health Sciences Centre
339 Windermere Rd.
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Tel: 519 663-8801; Fax: 519 663-2968
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Québec
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Tel: 902 473-7171; Fax: 902 473-8612
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All other provinces and territories
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
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Tel: 613 957-0337; Fax: 613 957-0335
Toll free: Tel 866 234-2345; Fax 866 678-6789

Case Presentation

Recent cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Please report similar reactions.

Red yeast rice and rhabdomyolysis

A published case report of rhabdomyolysis in a stable 28-year-old female renal transplant recipient was attributed to the presence of red yeast rice (*Monascus purpureus*) in an herbal preparation.[1] Her post-transplant problems included hypertension, hyperlipidemia and obesity. The patient had a baseline serum creatinine value of 150 µmol/L (normally 60–120 µmol/L) and was taking cyclosporine, azathioprine, prednisone, enalapril, long-acting diltiazem and famotidine. She refused statin therapy when dietary intervention failed to lower her lipid levels. Without informing her health care professionals, the patient started consuming an herbal preparation containing rice fermented with red yeast, β-sitosterol, dan shen root (*Salvia miltiorrhiza*) and garlic bulb (*Allium sativum*) in an attempt to lower her cholesterol "naturally." Routine blood work demonstrated a serum creatine phosphokinase (CPK) value of 1050 U/L (normally < 130 U/L). A repeat test showed a CPK value of 2600 U/L, but the patient denied any muscular symptoms. Upon further questioning, she admitted to taking the herbal preparation for the previous 2 months and was instructed to discontinue its use. The CPK value declined to 600 U/L in 2 weeks, and she remained clinically well.

Rice fermented with red yeast contains several types of mevinic acids, including monacolin K, which is identical to lovastatin. Lovastatin is known to be associated with myopathy and increases in CPK levels. Cyclosporine is known to interfere with the metabolism of some statins through the cytochrome P450 isoform 3A4 in the liver, thus resulting in increased statin levels. The authors postulated that this interaction resulted in the adverse effect seen in this patient.[1]

Reference

1. Prasad GVR, Wong T, Meliton G, Bhaloo S. Rhabdomyolysis due to red yeast rice (*Monascus purpureus*) in a renal transplant recipient. *Transplantation* 2002;74(8):1200-1.

Canadian Adverse Reaction Newsletter

Marketed Health Products Directorate
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Ottawa ON K1A 1B9
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Fax 613 957-0335

Health professionals/consumers report toll free:
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Suggestions?
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca

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Aussi disponible en français

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Health Canada / Santé Canada

Canadian Adverse Drug Reaction Monitoring Program

Report of suspected adverse reaction
due to drug products marketed in Canada
(Vaccines excluded)

Health Products and Food Branch
Direction générale des produits de santé et des aliments

- See page 5 for return address.
- La version française de ce document est disponible sur demande. Voir page 5 pour connaître le centre à contacter.

PROTECTED

A. Patient Information

1. Patient identifier	2. Age at time of reaction	3. Sex	4. Height	5. Weight
	_____ or	☐ Male	_____ feet	_____ lbs
Chart Number	**Date of birth** DD MM YYYY	☐ Female	or _____ cm	or _____ kgs

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)

- ☐ Death _____ (dd / mm / yyyy)
- ☐ Disability
- ☐ Life-threatening
- ☐ Congenital malformation
- ☐ Hospitalization
- ☐ Required intervention to prevent damage / permanent impairment
- ☐ Hospitalization - prolonged
- ☐ Other: _____

2. Date and time of reaction DD MM YYYY

3. Date of this report DD MM YYYY

4. Describe reaction or problem

5. Relevant tests / laboratory data (including dates (dd / mm / yyyy)

6. Other relevant history, including preexisting medical conditions
(e.g. allergies, pregnancy, smoking and alcohol use, hepatic / renal dysfunction)

C. Suspected drug product(s)
(See "How to report" section on reverse)

1. Name (give labelled strength & manufacturer, if known).
#1 _____
#2 _____

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
#1	#1 From (dd / mm / yyyy) - To (dd / mm / yyyy)
#2	#2

4. Indication for use of suspected drug product	5. Reaction abated after use stopped or dose reduced
#1	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Reaction reappeared after reintroduction
#1 _____	#1 (dd / mm / yyyy) _____	#1 ☐ Yes ☐ No ☐ Doesn't apply
#2	#2	#2 ☐ Yes ☐ No ☐ Doesn't apply

9. Concomitant drugs (name, dose, frequency and route used) and therapy dates (dd / mm / yyyy) (exclude treatment of reaction)

10. Treatment of adverse reaction (drugs and / or therapy), **including dates** (dd / mm / yyyy)

D. Reporter
(See "Confidentiality" section on reverse)

1. Name, address & phone number.

2. Health professional?	3.Occupation	4. Also reported to manufacturer?
☐ Yes ☐ No		☐ Yes ☐ No

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

Canada