

HEALTH AND DRUG ALERTS

People with diabetes should avoid antibiotic gatifloxacin

Reason for posting: Gatifloxacin (Tequin) is commonly used to treat respiratory infections, including community-acquired pneumonia, acute exacerbations of chronic bronchitis, sinusitis and urinary tract infections. Health Canada has previously warned health care providers about cases of clinically significant hypoglycemia and hyperglycemia in patients taking the drug, usually those with diabetes.¹ A recent case-control study confirmed the dysglycemic effects of the drug in patients with and without diabetes, and quantified its risks compared with other antibiotics.² Health Canada has advised that the drug not be prescribed to patients with diabetes.³

The drug: Gatifloxacin is a third-generation, broad-spectrum fluoroquinolone with activity against gram-negative and gram-positive aerobic, anaerobic and atypical microorganisms. It undergoes minimal biotransformation and is excreted renally.

The recent case-control database study identified Ontario patients over 65 years of age seen in hospitals after they experienced either hypo- or hyperglycemia who had received an outpatient prescription for an oral fluoroquinolone, a second-generation cephalosporin or a macrolide during the preceding month.² Because dysglycemia can result from infections or be caused by a hospital stay in itself, patients who had been taking macrolides (which are used for similar indications but which do not affect glycemic control) were chosen to form the control group. Each case of dysglycemia was matched (by the patient's age, sex, presence or absence of diabetes, and timing of the adverse event with respect to the initiation of the antibiotics) with up to 5 controls.

Patients who experienced hypoglycemia were in excess of 4 times as likely to have been treated with gatifloxacin rather than a macrolide, when compared with their matched controls

Table 1: Association between dysglycemia and recent antibiotic use

Drug in use	Adjusted odds ratio* (95% confidence interval) for a dysglycemia-related hospital visit	
	Hypoglycemia	Hyperglycemia
Patients with diabetes		
Gatifloxacin†	4.2 (2.8-6.3)	23.6 (12.4-44.6)
Levofloxacin†	1.5 (1.2-2.0)	1.6 (1.0-2.5)
Moxifloxacin†	0.8 (0.5-1.3)	1.7 (0.8-3.9)
Ciprofloxacin†	0.9 (0.7-1.1)	1.3 (0.9-1.8)
Cephalosporins	0.8 (0.6-1.1)	1.0 (0.6-1.7)
Macrolides (reference group)	1.0	1.0
Patients without diabetes		
Gatifloxacin†	9.0 (1.3-63.4)	12.8 (5.9-27.8)
Levofloxacin†	2.1 (0.7-6.0)	1.0 (0.5-1.8)
Moxifloxacin†	1.7 (0.2-11.8)	1.6 (0.7-3.9)
Ciprofloxacin†	1.2 (0.5-2.9)	0.9 (0.6-1.6)
Cephalosporins	2.3 (0.8-6.7)	1.5 (0.8-2.7)
Macrolides (reference group)	1.0	1.0

Adapted from Park-Wyllie LY et al.² *N Engl J Med* 2006;354. Available at www.nejm.org (10.1056/NEJMoa055191).

*Adjusted for the presence of liver and renal disease; alcohol abuse; hospital admissions during the preceding 2 years that involved dysglycemia, and total admissions during the preceding year; days during the previous year that included visits to an endocrinologist, internist or family physician; prescriptions within the preceding 180 days for insulin, oral hypoglycemic agents, other drugs that could influence glycemic control, and common inducers or inhibitors of cytochrome P450 isoenzyme 2C9; socioeconomic status; and (as an index of comorbidity) number of drugs taken or received during the previous year.

†Fluoroquinolones.

(Table 1). The risks of both diabetic and nondiabetic patients were increased by use of gatifloxacin. Of the 788 patients treated for hypoglycemia, fewer than half (366) were admitted to hospital. Of these, 30 patients (8.1%) died before discharge. The median time from initiation of gatifloxacin therapy to hospital presentation was 6 days.

Patients who had experienced hyperglycemia, on the other hand, were almost 17 times as likely to have been treated with gatifloxacin rather than a macrolide (Table 1). Of the 470 patients with hyperglycemia identified, about half (237) were admitted and 39 (16.5% of those admitted) died in hospital. The median time from initiation of therapy to arrival at hospital was 5 days.

Levofloxacin was also associated with a slightly increased risk of hypoglycemia (Table 1) but not hyperglycemia. In supplementary analyses, the frequency of dysglycemia occurring within 30 days after antibiotic prescription was found to be highest for gatifloxacin (1.1%), followed by ciprofloxacin (0.3%), levofloxacin (0.3%), moxifloxacin and second-generation cephalosporins (both 0.2%), and least for macrolides (0.1%).² These frequencies are probably underestimates, since visits to a hospital or emergency department were included in the database only when hypoglycemia or hyperglycemia was established.

Although the mechanism of these opposing adverse effects is unclear, gatifloxacin may cause hypoglycemia by promoting insulin release, and hyperglycemia by causing vacuolation of pancreatic beta cells, which would reduce insulin levels.²

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What to do: Until now, risk factors for gatifloxacin's life-threatening dysglycemic effects were felt to include a patient's advanced age (> 75 yr), having diabetes or decreased renal function, and taking hypoglycemic medications (i.e., drugs to lower blood sugar) concurrently. The study's findings clearly indicate that even people without diabetes are at risk. People with diabetes

should not be prescribed gatifloxacin; alternative antibiotics are preferable (levofloxacin should be used with caution). When gatifloxacin is prescribed, remember to warn the patient of the

signs and symptoms of hypo- and hyperglycemia, and consider having the patient's blood glucose monitored during at least the first week of treatment with the drug.

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All Health and Drug Alerts are posted online ahead of print and are available at www.cmaj.ca. This article was posted on Mar. 22, 2006.

IN THE LITERATURE

Does pioglitazone prevent macrovascular events in patients with type 2 diabetes?

Dormandy JA, Charbonnel B, Eckland DJ, et al; the PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-89.

Background: Most patients with type 2 diabetes have, in addition to their hyperglycemia, a myriad of other metabolic and vascular abnormalities associated with insulin resistance. These metabolic disturbances increase the risk of macrovascular disease. Patients who have type 2 diabetes are at increased risk of myocardial infarction and stroke, whether fatal or nonfatal. Pioglitazone is a member of the thiazolidinedione class of oral glucose-lowering agents that are peroxisome proliferator-activated receptor gamma (PPAR γ) agonists. Laboratory research has shown that insulin resistance is reduced by means of this action, which results in improved glucose control.

Moreover, several studies suggest that pioglitazone confers additional clinical benefits, such as improved dyslipidemia and reduced vascular inflammation.¹ Given these benefits, pioglitazone has the potential to prevent cardiovascular events as well as to improve glycemic control.

Design: A large, double-blind, multi-centre, randomized controlled trial, the PROactive study was conducted between 2001 and 2005 in 321 centres in 19 European countries. The investigators enrolled 5238 people 35-75 years of age with type 2 diabetes that was managed with diet or oral glucose-lowering drugs (combinations of oral

Table 1: Incidences and hazard ratios of primary and secondary outcomes in patients with type 2 diabetes managed with diet or oral glucose-lowering drugs, who were treated with pioglitazone versus placebo

Outcome	Group; no. (%) of patients			
	Pioglitazone n = 2605	Placebo n = 2633	Hazard ratio (95% CI)	p value
Primary: a composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndromes, endovascular or surgical intervention in the coronary or leg arteries, or amputation above the ankle	514 (19.7)	572 (21.7)	0.90 (0.80-1.02)	0.095
Secondary: a composite of all-cause mortality, nonfatal myocardial infarction and stroke	301 (11.6)	358 (13.6)	0.84 (0.72-0.98)	0.027

Note: CI = confidence interval.