

ARTICLE

Analysis of Spontaneous Reports of Hypoglycemia and Hyperglycemia Associated with Marketed Systemic Fluoroquinolones Made to the Canadian Adverse Drug Reaction Monitoring Program

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ABSTRACT

Hypoglycemia, an adverse effect that may develop rapidly and progress to cause potentially serious consequences over a short period of time, is difficult to monitor in both outpatients and inpatients, and may be associated with serious central nervous system sequelae. Four recently published cases of severe acute hypoglycemia with gatifloxacin stimulated a review of the published literature and spontaneous adverse drug reaction reports made in Canada on fluoroquinolone-induced hypoglycemia or hyperglycemia. A search of the English literature for published reports of hypoglycemia associated with ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin revealed 2 published case reports of hypoglycemia attributed to the potential drug–drug interaction of an oral hypoglycemic agent with ciprofloxacin; 4 such reports with gatifloxacin; and no reports with either levofloxacin or moxifloxacin. All spontaneously reported adverse drug reactions made to the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) listed under the Metabolic and Nutritional Disorders category for the 3 marketed respiratory fluoroquinolones (gatifloxacin, levofloxacin, and moxifloxacin) were then obtained. Altogether, 25 (93%) of 27 reports in this category were due to either hypoglycemia or hyperglycemia with gatifloxacin; 4 (11%) of 35 reports, with levofloxacin; and 1 (10%) of 10 reports, with moxifloxacin. The number of case reports for hypoglycemia ($\chi^2 = 24$; $p < 0.001$), hyperglycemia ($\chi^2 = 8$; $p < 0.05$), and total (hypoglycemia, hyperglycemia, and both hypoglycemia and hyperglycemia) ($\chi^2 = 46$; $p < 0.001$) was significantly higher for gatifloxacin than for either levofloxacin or moxifloxacin. The CADRMP reports for hypoglycemia or hyperglycemia with the respiratory fluoroquinolones may have identified a safety signal for

RÉSUMÉ

L'hypoglycémie, effet indésirable qui peut survenir rapidement et dont l'évolution peut entraîner des conséquences graves en peu de temps, est difficile à surveiller tant chez les patients hospitalisés qu'externes, et peut être associée à de graves séquelles sur le système nerveux central. Quatre cas d'hypoglycémie aiguë grave secondaire à l'administration de gatifloxacine publiés récemment ont motivé une revue de la littérature et des notifications volontaires des effets indésirables des médicaments au Canada relatives à l'hypoglycémie et à l'hyperglycémie attribuables aux fluoroquinolones. Une recherche bibliographique de rapports publiés en anglais sur l'hypoglycémie associée à l'administration de ciprofloxacin, de gatifloxacine, de lévofloxacine et de moxifloxacine ont mis au jour deux rapports de cas d'hypoglycémie attribuable à l'interaction médicamenteuse potentielle entre un hypoglycémiant oral et la ciprofloxacin, quatre en relation avec la gatifloxacine et aucun en relation avec la lévofloxacine ou la moxifloxacine. Toutes les notifications volontaires d'effets indésirables des médicaments effectuées dans le cadre du Programme canadien de surveillance des effets indésirables des médicaments (PCSEIM), dans la catégorie troubles du métabolisme et de la nutrition, relativement aux trois fluoroquinolones respiratoires commercialisées (gatifloxacine, lévofloxacine et moxifloxacine) ont par la suite été obtenues. Dans l'ensemble, 25 rapports sur 27 (93 %) dans cette catégorie étaient attribuables à des cas d'hypoglycémie ou d'hyperglycémie causées par la gatifloxacine; 4 sur 35 (11 %) à des cas causés par la lévofloxacine, et 1 sur 10 (10 %) à un cas causé par la moxifloxacine. Le nombre de rapports de cas d'hypoglycémie ($\chi^2 = 24$; $p < 0,001$), d'hyperglycémie ($\chi^2 = 8$; $p < 0,05$), et de cas totaux (hypoglycémie, hyperglycémie et les deux à la fois)



gatifloxacin. A systematic analysis to determine causality, risk factors, and incidence of hypoglycemia or hyperglycemia may be warranted.

Key words: fluoroquinolones, gatifloxacin, hypoglycemia, hyperglycemia

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($\chi^2 = 46$; $p < 0,001$) était considérablement plus élevé pour la gatifloxacin que pour la lévofloxacin ou la moxifloxacin. Les rapports de cas d'hypoglycémie ou d'hyperglycémie aux fluoroquinolones respiratoires déclarés au PCSEIM pourraient bien avoir dégagé un signal d'alerte quant à l'utilisation de la gatifloxacin. Une analyse systématique permettant de déterminer la cause, les facteurs de risque et l'incidence des cas d'hypoglycémie ou d'hyperglycémie semble justifiée.

Mots clés : fluoroquinolones, gatifloxacin, hypoglycémie, hyperglycémie

INTRODUCTION

Currently, 6 known class-related adverse reactions are associated with fluoroquinolones: phototoxicity, QTc prolongation, central nervous system toxicity, tendonitis or tendon rupture, hepatotoxicity, and alterations in blood glucose (either hypoglycemia or hyperglycemia). Postmarketing experience has indicated that the propensity for causing class-related adverse reactions is not uniform amongst the fluoroquinolones.¹ For example, temafloxacin was withdrawn from the market as a result of reports of patients having severe hypoglycemia, hepatic and renal dysfunction, hemolytic anemia, and anaphylaxis after taking the drug²; similarly, grepafloxacin was withdrawn by the manufacturer because of reports of cardiovascular death and QTc prolongation³; and trovafloxacin became a limited-use drug as a result of reports of serious liver toxicity, including death.¹ The systemically active fluoroquinolones that are currently available in Canada are ciprofloxacin (IV or PO), gatifloxacin (IV or PO), levofloxacin (IV or PO), moxifloxacin (IV or PO), and ofloxacin (PO).

Hypoglycemia is an adverse effect that may develop rapidly and progress to cause potentially serious consequences over a short period of time. Patients with type 2 diabetes taking oral hypoglycemic agents have a relatively low incidence of hypoglycemic episodes, and those that do occur tend not to be severe enough to result in reduced consciousness, causing the patient to require assistance (e.g., an injection of glucagon). Unlike patients with type 1 diabetes who take insulin injections and frequently monitor their own blood glucose levels, those with type 2 diabetes are less likely to be aware that they are developing hypoglycemia and are less prepared to take appropriate action to prevent its progression to severe hypoglycemia. Although serious hypoglycemia during fluoroquinolone therapy

seems to be rare, the potential for serious central nervous system sequelae, including convulsions and coma, with possible permanent neurological deficit, is of concern.

Menzies and others⁴ reported 3 cases of severe, persistent hypoglycemia attributed to gatifloxacin in hospitalized older adults (> 70 years old) with diabetes mellitus who were taking oral hypoglycemic agents. Each of the 3 patients experienced a rapid decline in blood glucose to very low levels (< 2 mmol/L) at 1 to 15 h after the first dose of gatifloxacin. Administration of oral hypoglycemic agents was temporarily interrupted, and administration of multiple bolus doses of IV dextrose 50% or an IV infusion of hypertonic dextrose, or both, were required to restore and maintain normoglycemia. Hypoglycemia seemed to resolve upon discontinuation of gatifloxacin and did not recur, despite resumption of oral hypoglycemic drug administration.

Baker and Hangii⁵ published a fourth case report of hypoglycemia caused by gatifloxacin. A 73-year-old man with type 2 diabetes mellitus came to the emergency department with a blood glucose value of 1.2 mmol/L on the fourth day of gatifloxacin treatment. He had never before experienced symptomatic hypoglycemia while taking his antidiabetic medications. Despite discontinuation of glyburide and metformin, and IV administration of 3 doses of 50% dextrose, he required a continuous infusion of hypertonic dextrose and 3 further bolus doses of 50% dextrose over a 24-h period to maintain normoglycemia. Assessing the reaction for causality using the Naranjo probability scale⁶ for adverse drug reactions, Baker and Hangii⁵ categorized the reaction as possibly caused by gatifloxacin.

These recently published case reports^{4,5} of severe acute hypoglycemia with gatifloxacin stimulated this group from Sunnybrook and Women's College Health



Sciences Centre, Toronto, Ontario, to review the published literature and the spontaneous adverse drug reaction (ADR) reports completed in Canada on fluoroquinolone-induced hypoglycemia or hyperglycemia as part of our institutional formulary review of available respiratory fluoroquinolones. The results of this review are presented here.

REVIEW OF THE EVIDENCE

Review of the Literature

A literature search for published reports of hypoglycemia associated with ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin was completed with SUMSearch (<http://sumsearch.uthscsa.edu>) to retrieve English medical evidence up to June 10, 2003. SUMSearch is a tool that combines searches of textbooks (emedicine, PubMed), practice guidelines (National Guideline Clearinghouse, PubMed), systematic reviews (DARE, which includes Cochrane abstracts; PubMed), and original research (PubMed). In addition, reference lists of relevant publications on fluoroquinolones were reviewed to identify publications that might not have been retrieved with the search tool.

The literature search revealed 2 published reports^{7,8} of hypoglycemia attributed to a potential drug–drug interaction of an oral hypoglycemic agent with ciprofloxacin, and no reports with either levofloxacin or moxifloxacin.

The observed drug interaction with glyburide and ciprofloxacin observed in the 2 case reports^{7,8} is postulated to be the result of the inhibition of the component of the metabolism of glyburide involving the P-450 CYP3A4 enzyme.⁷ Ciprofloxacin is known to competitively inhibit the CYP3A4 isoform, although the clinical relevance of this has not been established.⁹ The widespread postmarketing use of both ciprofloxacin and levofloxacin and the scarcity of published reports of drug-induced hypoglycemia by either a drug–drug interaction or a direct effect suggests that symptomatic hypoglycemia would be an extremely rare risk with these agents.

In addition to the 4 published case reports of hypoglycemia with gatifloxacin,^{4,5} 3 studies^{10–12} evaluating the effect of gatifloxacin on glucose homeostasis have been published. Each of these published papers was completed by investigators employed by Bristol-Myers Squibb. The first study,¹⁰ published only as an abstract, evaluated the effect of multiple-dose gatifloxacin on glucose tolerance, glucose and insulin homeostasis, and glyburide pharmacokinetics in patients with type 2 diabetes mellitus. This study concluded that gatifloxacin

was well tolerated in the 34 study patients on oral glyburide; had no effect on the oral glucose tolerance test, or on glucose or insulin homeostasis; and had no pharmacokinetic or pharmacodynamic interaction with glyburide. However, neither the parameters used to define significant changes in the oral glucose tolerance test or in glucose and insulin homeostasis, nor the values observed for these parameters were presented in the abstract, making interpretation of the findings difficult.

The second study¹¹ was a dose-escalation study of the safety, tolerability, and pharmacokinetics of IV gatifloxacin in healthy adult men. This study concluded that there were no significant differences in fasting blood glucose, insulin, or C-peptide concentrations between those given a placebo and those given gatifloxacin in doses from 200 to 800 mg IV as a 1-h infusion for 14 days. The investigators described mild-to-moderate transient decreases in fasting blood glucose in healthy adult men at the end of the infusions, but did not provide any specific quantification.

The final published study¹² evaluated the effect of multiple-dose gatifloxacin or ciprofloxacin on glucose homeostasis and insulin production in patients with type 2 diabetes mellitus whose condition was controlled with diet and exercise. This randomized, double-blind, placebo-controlled, multiple-dose study concluded that gatifloxacin was well tolerated and had no significant effect on glucose homeostasis, β -cell function, or long-term fasting blood-glucose levels.

Lack of effect in this study¹² was defined as 90% confidence intervals of 0.67 to 1.5 for the ratio of the means of treatment (either gatifloxacin or ciprofloxacin) to those of the placebo. Therefore, a statistically significant event would require a reduction in the area under the curve for either glucose or insulin of at least 43%, or an increase of at least 50%. The assignment of this ratio for significance was not explained or referenced. The investigators observed mean values for the area under the curve for fasting glucose levels that were 27% and 15% lower for gatifloxacin than for the placebo on days 1 and 10, respectively. Based on their definition of statistical significance, these results were not considered significant.

However, these drops may be clinically important. For example, a patient with a fasting glucose level of 4 mmol/L who experiences a 25% reduction in fasting glucose level with gatifloxacin, resulting in a low fasting glucose level of 3 mmol/L, may experience symptomatic hypoglycemia. In addition, the investigators¹² observed a



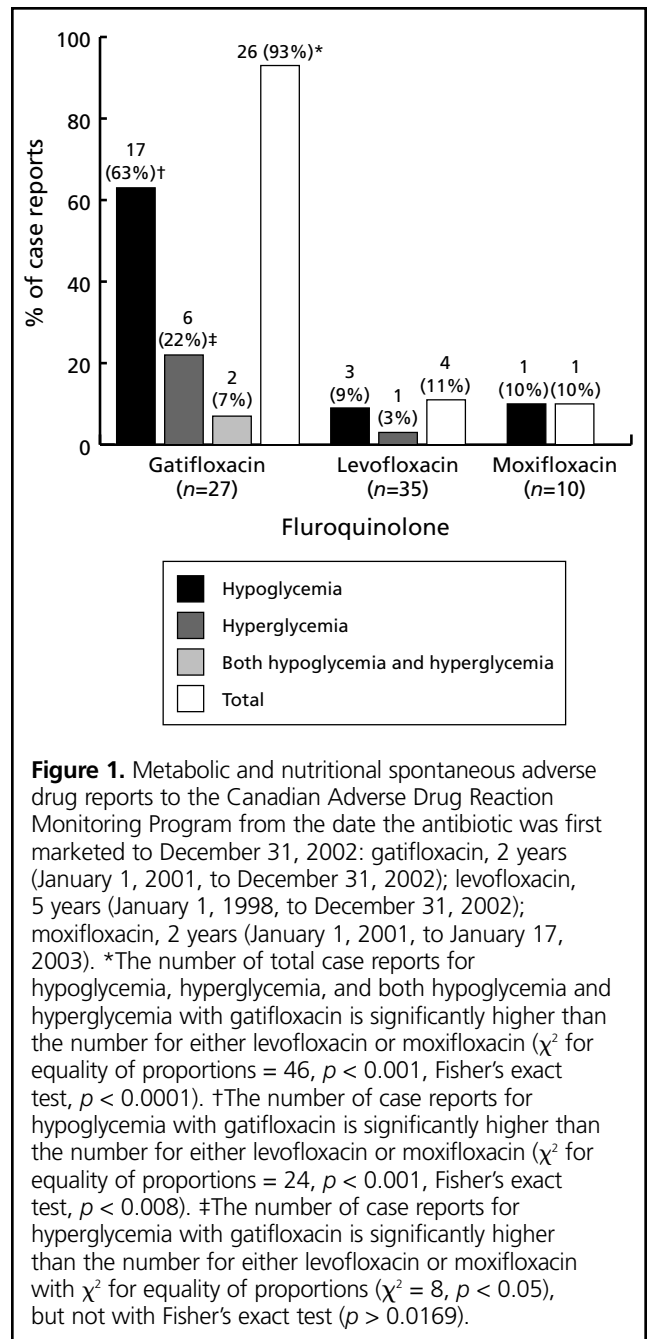
mean area under the curve for fasting insulin levels that was significantly higher (43%) for gatifloxacin than for the placebo on day 1 ($p < 0.05$).

The respiratory fluoroquinolones (levofloxacin, gatifloxacin, and moxifloxacin) do not affect the P-450 isoenzyme system.¹³ The mechanism by which these fluoroquinolones may affect blood glucose levels is not clear. However, it has been hypothesized that fluoroquinolones may directly stimulate pancreatic β -cell function to cause an increased release of insulin, resulting in a decrease in blood glucose concentrations.¹²

Review of Spontaneously Reported Adverse Drug Reactions Made to the Canadian Adverse Drug Reaction Monitoring Program

After a review of the published literature, all spontaneously reported ADRs of either hypoglycemia or hyperglycemia submitted to Health Canada's Adverse Drug Reaction Monitoring Program (CADRMP) were obtained. The CADRMP coordinates national spontaneous ADR reporting in Canada. Spontaneous or voluntary ADR reporting in Canada may be done by patients, health care professionals, or manufacturers. However, manufacturers and market authorization holders in Canada are mandated to report adverse reactions to Health Canada, according to section C.01.016 of the Food and Drug Regulations.¹⁴ The CADRMP tracks reports of hypoglycemia or hyperglycemia in a category called Metabolic and Nutritional Disorders. All the Metabolic and Nutritional Disorder case reports for each respiratory fluoroquinolone from the CADRMP that were entered into the CADRMP database were obtained from the date that each respiratory fluoroquinolone was marketed to December 31, 2002, inclusive. Based on the date of marketing, the reporting periods were 2 years for gatifloxacin, 5 years for levofloxacin, and 2 years for moxifloxacin.

Of a total of 27 different reports made in the Metabolic and Nutritional Disorders category for gatifloxacin, 25 (93%) were due to either hypoglycemia or hyperglycemia (Figure 1), whereas 11% (4/35) of reports for levofloxacin and 10% (1/10) of reports for moxifloxacin were due to either hypoglycemia or hyperglycemia. The number of case reports in the Metabolic and Nutritional Disorders category for hypoglycemia ($\chi^2 = 24$; $p < 0.001$), hyperglycemia ($\chi^2 = 8$; $p < 0.05$), and total (i.e., hypoglycemia, hyperglycemia, and both hypoglycemia and hyperglycemia) ($\chi^2 = 46$; $p < 0.001$) were significantly higher for gatifloxacin than either levofloxacin or moxifloxacin (Figure 1).



Since the application of the χ^2 statistic may be inaccurate for small sample sizes or when a given cell value is less than 5, the analysis was confirmed by means of the Fisher's exact test with Bonferroni's correction of the p value to ensure that the risk of a type I error did not exceed 5%, even with multiple comparisons (i.e., gatifloxacin versus levofloxacin, gatifloxacin versus moxifloxacin, and levofloxacin versus moxifloxacin) per analysis (i.e., hypoglycemia, hyperglycemia, and total). From the Bonferroni's error rate correction, it was determined that a statistically



significant two-tailed p value of < 0.0169 was needed for the Fisher's exact test to maintain a type I error rate of $< 5\%$. With the Fisher's exact test, the number of case reports in the Metabolic and Nutritional Disorders category for hypoglycemia ($p < 0.008$) and total (hypoglycemia, hyperglycemia, and both hypoglycemia and hyperglycemia) ($p < 0.0001$) remained statistically higher with gatifloxacin than with levofloxacin and moxifloxacin. However, the Fisher's exact test comparing respiratory fluoroquinolones for the number of cases of hyperglycemia did not reach statistical significance (gatifloxacin versus levofloxacin, $p = 0.04$, and gatifloxacin versus moxifloxacin, $p = 0.16$).

DISCUSSION

The *Canadian Adverse Reaction Newsletter* published a review¹⁵ of the CADRMP reports for hypoglycemia and hyperglycemia with gatifloxacin in July 2003. The mandate of the CADRMP newsletter is to alert health care professionals to potential signals detected from a review of case reports submitted to Health Canada. This report indicated that 44% of all ADR reports made for gatifloxacin from February 21, 2001, to February 28, 2003, were due to abnormal glucose metabolism and that a total of 28 reports of abnormal glucose metabolism were made during this period.¹⁵

Analysis of abnormal glucose metabolism with gatifloxacin in the current review included only those reports provided by CADRMP from January 1, 2001, to December 31, 2002, and consisted of 25 different reports. Letourneau and others¹⁵ indicated that hypoglycemia and hyperglycemia were reported more frequently with gatifloxacin than with other fluoroquinolones; however, they did not conduct a statistical analysis to demonstrate this. The current review's analysis of reports made with each of the respiratory fluoroquinolones approved for use in Canada provides the statistical analysis that supports the conclusion of Letourneau and others¹⁵. Since the number of cases of hyperglycemia with gatifloxacin in the current analysis was significantly higher with χ^2 analysis ($\chi^2 = 8$; $p < 0.05$), but not with the Fisher's exact test, a type II error resulting from an insufficient sample size cannot be ruled out in the statistical comparisons for hyperglycemia.

The gatifloxacin (Tequin) product monograph¹⁶ was recently revised (December 2002) by the manufacturer to provide more information about the glucose dysregulation reported during the postmarketing experience. The monograph recommends careful monitoring of blood glucose when gatifloxacin is

administered to patients with diabetes. The prescribing information warns that hypoglycemic episodes may be severe and potentially life-threatening, and tend to occur early in the therapy (in the initial 1 to 3 days). In addition, the monograph states that hyperglycemia tends to occur later in the course of treatment (from 4 to 10 days after initiation of therapy) and may be severe, manifesting as hyperglycemic hyperosmolar syndrome (or coma). Based on the postmarketing surveillance of 15 000 patients, the manufacturer estimates that the incidence of hypoglycemia and hyperglycemia for patients with diabetes is 0.64% and 1.30%, respectively. In nondiabetic patients, the corresponding incidence values quoted by the manufacturer are 0.030% and 0.007%, respectively.¹⁶

The limitations of reviewing spontaneous ADR reports include an inability to determine the incidence or causality of an ADR, since ADRs are underreported and the actual population exposure is unknown.¹⁷⁻¹⁹ Many factors may influence the reporting of ADRs, including the length of time that a product has been on the market, approved indications, prescription and drug-use practices, geographic location, publication in scientific journals, and issuance of risk advisories. However, the CADRMP reports may identify potential safety signals associated with a marketed drug. Although identification of a signal with a given drug does not imply causation to the adverse reaction, it should prompt investigation of a potential association between the drug and the occurrence of a given toxicity.

The results of this review indicate that the CADRMP reports for hypoglycemia or hyperglycemia with gatifloxacin compared with either levofloxacin or moxifloxacin may have identified a safety signal for gatifloxacin. A systematic analysis to determine causality, risk factors, and incidence of hypoglycemia or hyperglycemia may be warranted.

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