REVIEW ARTICLE

Drug Safety 2008; 31 (4): 283-292
0114-5916/08/0004-0283/$48.00/0

Dysglycaemias and Fluoroquinolones

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Contents

Abstract

The fluoroquinolones are an extremely popular class of antibacterials, owing to their broad spectrum of activity and the convenience of their intravenous and oral dosage formulations. Overall, the currently available fluoroquinolones have a good safety profile; however, certain fluoroquinolones within the class have been associated with severe and life-threatening adverse drug reactions. Dysglycaemic episodes (hyperglycaemia and hypoglycaemia) have been observed in patients taking multiple antibacterials, including the fluoroquinolones. Although gatifloxacin has been associated with dysglycaemias more frequently than other fluoroquinolones, dysglycaemic events have been reported with some of the other currently available fluoroquinolones as well. Hypoglycaemia appears to be related to insulin release and is an early-onset event. However, hyperglycaemia tends to present several days into therapy and the exact mechanism by which it is caused is still unclear. Recent studies point towards the important role of the adenosine triphosphate (ATP)-sensitive K^+ channels in the pancreatic β cell and the importance of anti-insulin hormones. Several retrospective studies have elucidated risk factors associated with fluoroquinolone exposure and subsequent dysglycaemic events. These studies suggest that dysglycaemia is a dose-related adverse effect involving the fluoroquinolone class; however, some drugs within the class appear to have a greater association. This may be related to the affinity of fluoroquinolones to the ATP-sensitive K^+ channel or higher concentrations of drugs achieved in certain patients who are already at risk for hyperglycaemia and hypoglycaemia.

Understanding these risk factors will allow the fluoroquinolones to be utilized in a way that minimizes the probability of associated dysglycaemic events.

Nalidixic acid was the first quinolone antibacterial and was introduced in the US in 1963 for the treatment of urinary tract infections.[1] Since then, fluorinated derivatives have been developed that have provided a broader antimicrobial activity, lending them to treatment options for a variety of infectious diseases such as respiratory tract infections, skin and soft tissue infections, intra-abdominal wound infections, sexually transmitted diseases, urinary tract infections and some are used as second-line agents to treat tuberculosis.[2] In addition to their broad antimicrobial activity, and a high volume of distribution in the human body, fluoroquinolones, when administered orally, achieve similar concentration-time profiles as when administered intravenously.

The increase in the use of fluoroquinolones has resulted in the recognition of rare adverse events in certain patients. Temafloxacin was voluntarily recalled 5 months after US FDA approval as a result of a high number of reported adverse reactions including haemolytic anaemia, hepatic toxicity and hypoglycaemia. In addition, grepafloxacin and sparfloxacin have been removed from the US market due to increases in corrected QT interval, which can increase the risk of fatal cardiac arrhythmias. Trovafloxacin was associated with hepatic toxicity early in the post-marketing phase and is not recommended for routine use. Most recently, gatifloxacin was removed from the US market because of an increased risk of hyper- and hypoglycaemia seen in patients treated with this agent.

Gatifloxacin is a broad-spectrum fluoroquinolone that was first marketed in the US in 1999. It is an 8-methoxy fluoroquinolone with good activity against many Gram-positive, Gram-negative and atypical organisms, and anaerobes. It has excellent oral bioavailability and a prolonged plasma half-life, allowing for once daily administration.[3] Starting in 2002, increasing numbers of reports of hypo- and hyperglycaemia in diabetic and non-diabetic patients began to emerge and the drug was ultimately removed from the US market in May 2006.[4-11]

This article will explore the putative mechanisms for hyper- and hypoglycaemia and the risk factors for dysglycaemia that have been attributed to gatifloxacin, with an expanded discussion of the entire class of fluoroquinolones. Peer-reviewed articles familiar to the authors through an exchange of information amongst international research colleagues as well as a MEDLINE search (1996–2007) were used to prepare this review. For the MEDLINE search, combinations of key terms including 'dysglycaemia', 'hypoglycaemia' and 'hyperglycaemia' with 'fluoroquinolones', 'gatifloxacin', 'ciprofloxacin', 'levofloxacin' and 'moxifloxacin' were used.

1. Early Observations of Hypoglycaemia

Initial recognition of hypoglycaemia associated with quinolones was seen in patients with falciparum malaria who were being treated with quinine, a drug with structural similarities to the quinolones.[12-14] In a retrospective cohort of 151 patients with falciparum malaria from eastern Thailand, 17 (11%) developed severe hypoglycaemia.[15] Of the patients that developed hypoglycaemia, 16/17 (94%) of them had received quinine, which has the same 4-quinolone nucleus as the fluoroquinolones. In a subsequent evaluation of healthy volunteers, plasma insulin levels increased and glucose concentrations decreased in conjunction with infusions of intravenous quinine. It has been shown that quinine inhibits activity of the adenosine triphosphate (ATP)-sensitive K^+ channels in the pancreatic β

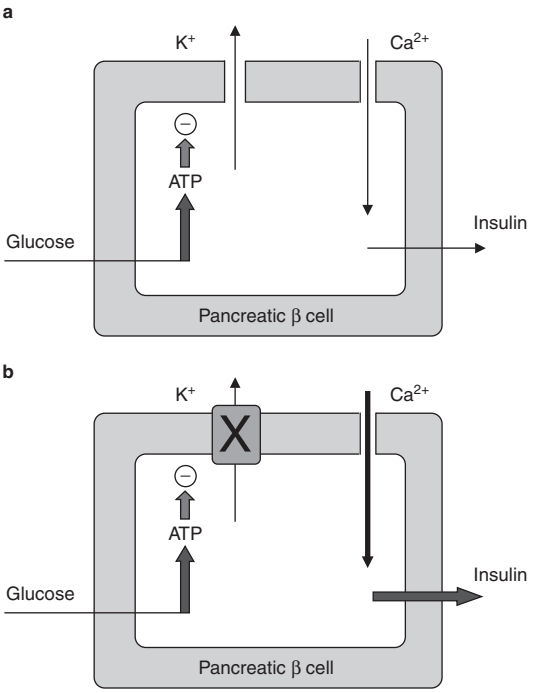

Fig. 1. Mechanism of fluroquinolone-associated insulin surge and potential hypoglycaemia. **ATP** = adenosine triphosphate; **X** = inhibition.

cells, thereby stimulating insulin secretion.[16,17] While it is recognized that *Plasmodium falciparum* consumes large amounts of glucose *in vivo*, in retrospect, the early and unrecognized structure-activity relationship that we now know exists might have provided some of initial evidence that compounds with the 4-quinolone nucleus may be associated with hyperinsulinaemia and hypoglycaemia.

2. Physiology of Glucose Metabolism

Glucose homeostasis is a complex physiological process that requires the tight regulation of insulin production and secretion (see figure 1a).[18] In the pancreatic β cell, the ATP-sensitive K^+ channels regulate glucose-dependent insulin secretion. An increase in plasma glucose leads to an increase in the glucose uptake and metabolism by the β cell, which in turn leads to elevation in the level of intracellular ATP resulting in the closure of ATP-sensitive K^+ channels. Membrane depolarization then leads to the opening of the voltage-dependent calcium channels causing an influx of Ca^{2+}, raising the intracellular calcium concentration and resulting in exocytosis of insulin granules. Sulfonylurea drugs act by inhibiting the ATP-sensitive K^+ channels and thus cause an increase in insulin secretion.[19,20] In addition, fluoroquinolones can also inhibit these K^+ channels (figure 1b) leading to hyperinsulinaemia and a resulting lowering of serum glucose concentrations.[21] This can occur independently of the serum glucose concentration. Normally, compensatory mechanisms keep blood sugar within a tight range.[22] Even in patients in whom a drug effect increases insulin release, this is quickly compensated for with other anti-insulin hormones, such as glucagon and catecholamines. However, in patients where there is some alteration in glucose/insulin homeostasis pathway present (e.g. in patients with non-insulin-dependent type 2 diabetes mellitus), symptomatic hypoglycaemia may develop as a result of the inability to compensate for this drug response.

Risk factors for hyperglycaemia and hypoglycaemia are multifactorial (see table I), and include sepsis, decreased albumin levels, malignancy, insulin treatment, increased alkaline phosphatase levels, age, female sex and increased serum creatinine making assessments of effects independently associated with a drug difficult.[23,24] In addition, several antimicrobials, including fluoroquinolones, have been

Table I. Risk factors for fluoroquinolone-associated dysglycaemia

Hypoglycaemia
Diabetes mellitus
Concomitant hypoglycaemic therapy
Elderly
Sepsis
Hyperglycaemia
Diabetes mellitus
Excessive dose for decreased renal function
Concomitant corticosteroid use
Elderly

associated with disturbances in glucose metabolism.[25-31] Therefore, differentiating between a specific drug-effect and altered pathophysiology from a disease state that may be exacerbated by a drug requires additional examination.

3. *In Vitro* Effects of Fluoroquinolones on Insulin Secretion

Fluoroquinolones can interact with the ATP-sensitive K^+ channel in rat pancreatic β cells, resulting in a dose-related effect on insulin release.[21] However, in a clonal insulinoma cell line model, lomefloxacin inhibited ATP-sensitive K^+ channel currents in a concentration-dependent manner with high concentrations completely blocking ATP-sensitive K^+ channel current while norfloxacin had only minor effects.[32] These two studies together provide initial evidence that there may be differences in the inhibitory capabilities of different fluoroquinolones on ATP-sensitive K^+ channels. In addition, there may be a dose-related effect resulting in different degrees of insulin secretion relative to the drug concentrations achieved. The amino group at the C5 position of sparfloxacin provides for the greatest blockade of pancreatic β-cell ATP-sensitive K^+ channels and further structure-activity relationships can be differentiated.[33]

In an *in vitro* cell culture model of mouse pancreatic islets, levofloxacin, at a concentration of 300 μmol/L (a concentration that can not be achieved in humans with typical doses of levofloxacin), reduced K^+ channel currents slightly, while gatifloxacin and temafloxacin inhibited K^+ currents to a greater extent.[34] Gatifloxacin and temafloxacin caused a dose-dependent increase in insulin secretion with little effect on insulin release at low concentrations; however, at 300 μmol/L, both gatifloxacin and temafloxacin increased insulin secretion, while levofloxacin did not. The augmented insulin secretion was determined to be secondary to the inhibition of a specific subunit of the ATP-sensitive K^+ channel of the mouse pancreatic β cell ($K_{ir}6.2$ subunit).

In a cultured mouse pancreatic cell model, gatifloxacin was found to acutely stimulate insulin secretion, while long-term gatifloxacin treatment inhibited insulin biosynthesis.[35] Gatifloxacin at 100 μmol/L in a 3-day culture of pancreatic β cells demonstrated a decrease in intracellular insulin levels, similar to the effect demonstrated by levofloxacin, ofloxacin, fleroxacin and norfloxacin. However, only gatifloxacin produced this effect at a lower concentration of 20 μmol/L. When low-dose glibenclamide was added to fresh mouse pancreatic islet cells, gatifloxacin augmented the insulin release by 1.3- to 1.7-fold. The effect of gatifloxacin on the pancreatic islet cells was transient with the complete recovery of insulin secretion following discontinuation of gatifloxacin. Acute hypoglycaemia may occur because of the release of insulin from the pancreatic β cell mediated by the blockage of the ATP-sensitive K^+ channels; however, the explanation for hyperglycaemia is more complex and probably involves both the direct inhibition of insulin release that occurs over days and other yet-to-be elucidated mechanisms for insulin suppression.

4. Effects of Fluoroquinolones on Glucose Homeostasis in Animal Models

While *in vitro* cell culture experiments can provide some information on the relative effects of the different fluoroquinolones on the inhibition of ATP-sensitive K^+ channels that can result in insulin secretion, the counter effects of anti-insulin hormones are not able to be assessed.

The effect of gatifloxacin on insulin and serum glucose concentrations differs between diabetic and non-diabetic rats, is dose-dependent and is associated with the secretion of adrenaline.[36] The administration of a single injection of 100 mg/kg of levofloxacin in non-diabetic rats resulted in a de-

crease in serum glucose concentrations, which was similar to the effect in rats receiving gatifloxacin 50 mg/kg.[37] When higher doses of the drugs were used (i.e. levofloxacin 300 mg/kg and gatifloxacin 100 mg/kg) in the non-diabetic rats, hyperglycaemia was observed, which coincided with a sharp surge in the serum adrenaline levels, even though there was an incremental increase in insulin release. The increase in serum glucose levels was also associated with an increase in histamine concentrations and the hyperglycaemic effect seen with levofloxacin could be antagonized by pre-treatment with diphenhydramine, an antihistamine drug.[37]

In addition, in fasting mice, enoxacin, lomefloxacin and gatifloxacin reduced plasma glucose levels in a dose-dependent manner, whereas ciprofloxacin and levofloxacin did not demonstrate reductions in plasma glucose concentrations even with doses up to 50 mg/kg.[38]

To summarize the animal data, the effect of fluoroquinolones on serum glucose in animals is consistent with *in vitro* cell culture models. Hyper- and hypoglycaemia can be induced with multiple fluoroquinolones depending on the concentrations of drug tested in the models, and can be exaggerated with concentrations that are many-fold higher than those that can be achieved in patients. In addition, in one study,[37] the mechanism of hyperglycaemia appeared to be associated with the release of histamine that can cause an increase in the serum adrenaline concentration and can be blunted with drugs that block the histamine H_1 receptor.

5. Evaluation of Fluoroquinolone-Associated Dysglycaemias in Humans

One of the difficulties in analysing dysglycaemia data on the use of fluoroquinolones in human subjects is the absence of a well accepted value for defining both hypoglycaemia and hyperglycaemia. In the registration trials for the newer generation fluoroquinolones, the definition of hypoglycaemia was not consistent across all the different clinical trials for the various products (table II). The result of this is a perceived lower incidence of hypoglycaemia with moxifloxcacin compared with the incidence reported with gatifloxaxcin and levofloxacin. Further complicating the assessment is the clinically relevant difference in evaluating an abnormal laboratory value versus evaluating a symptomatic event due to the abnormal laboratory value. In addition, an evaluation of dysglycaemia in the absence of an adequately powered, prospective, randomized, controlled trial comparing the various quinolones with other antimicrobials for this primary outcome makes drawing overall conclusions quite difficult. Finally, most of these patients in these analyses have multiple risk factors for dysglycaemias, which makes it difficult to attribute the dysglycaemic episodes entirely to the drug.

A 5-year analysis of outpatient and discharge prescriptions for fluoroquinolones at a Veteran's Affairs Center, comprising >31 000 diabetic and non-diabetic patients, found that gatifloxacin was less likely than ciprofloxacin or levofloxacin to cause dysglycaemia.[39] Fluoroquinolone-associated hyperglycaemia was ten times more common than fluoroquinolone-associated hypoglycaemia and pa-

Table II. Influence of definitions of hypoglycaemia on rates of patients reported as having 'hypoglycaemia'

Fluoroquinolone	Definition of hypoglycaemia mg/dL (mmol/L)	Number of events/number of patients evaluated	Patients meeting criteria (%)
Gatifloxacin	<60 (3.3)	51/3000	1.7
Levofloxacin	<70 (3.8)	45/2386	1.9
Moxifloxacin	<50 (2.7)	17/2613	0.65

tients with diabetes had a higher frequency of hyperglycaemia than patients without diabetes. However, the definition of hypoglycaemia was plasma glucose levels ≤70 mg/dL and hyperglycaemia was defined as plasma glucose levels ≥140 mg/dL, which arguably are clinically insignificant values that would be unlikely to be associated with symptoms.

In a randomized, placebo-controlled trial of 48 patients with diet and exercise-controlled type 2 diabetes who were not receiving oral hypoglycaemics, the effects of gatifloxacin and ciprofloxacin on glucose homeostasis were compared.[40] A transient increase in serum insulin concentrations 1 hour after administration of gatifloxacin was observed; however, this effect was not seen with ciprofloxacin. While a slight increase in insulin was seen with gatifloxacin, overall, neither gatifloxacin nor ciprofloxacin had any significant effects on glucose tolerance, serum insulin or C peptide levels.

A nested case-control study[41] of patients >66 years of age who received broad spectrum antibacterials was conducted using the Ontario Drug Benefit Database, the Canadian Institute for Health Information Discharge Abstract Database and the National Ambulatory Care Reporting System to evaluate the relationship between outpatient antibacterial therapy and hospitalizations for hyper- and hypoglycaemia. Both gatifloxacin and levofloxacin were associated with an increased risk of hospitalization due to hypoglycaemia relative to patients treated with a macrolide, with adjusted odds ratios (ORs) of 4.3 (95% CI 2.9, 6.3) and 1.5 (95% CI 1.2, 2.0), respectively. Ciprofloxacin, moxifloxacin and cephalosporins were not associated with an increased risk of hospitalization due to hypoglycaemia. In patients who were admitted to the hospital with hyperglycaemia, only gatifloxacin was associated with an increased risk (adjusted OR = 16.7; 95% CI 10.4, 26.8) compared with patients who received macrolides. The risk for hyperglycaemia was higher in fluoroquinolone-treated patients with diabetes compared with patients without diabetes.

The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction) trial was a multinational, double-blind, placebo-controlled trial that involved >4000 patients who received gatifloxacin orally on an 'on/off' basis for approximately 2 years to evaluate the effect of antibacterial treatment for *Chlamydia pneumoniae* after an acute coronary syndrome.[42] Although the primary endpoint of the trial was overall mortality from cardiovascular events, dysglycaemic episodes in the gatifloxacin-treated group compared with placebo were evaluated. The average age of the patients enrolled was 58 years and 18% had diabetes at baseline. Among the non-diabetic patients, new-onset diabetes (defined as the presence of one or more nonfasting serum glucose values of ≥200 mg/dL, two or more nonfasting serum glucose values of ≥140 mg/dL or two or more fasting serum glucose values of ≥126 mg/dL) was more common in the gatifloxacin group compared with placebo, although this difference was not statistically significant (4.6% vs 3.4%, p = 0.08). In addition, among patients with diabetes, hyperglycaemia and hypoglycaemia were more common in the gatifloxacin group compared with placebo (30.7% vs 25.4%, p = 0.11 and 2.6% vs 1.5%, p = 0.32 respectively), although these differences were not statistically significant. Even though a concomitant risk factor appraisal was not provided, this trial nevertheless raised a pertinent concern on the safety of long-term use of gatifloxacin with regards to glucose homeostasis.

In a prospective evaluation of dysglycaemic episodes in 216 elderly, hospitalized patients who had an initial normal blood glucose level, the incidence of early morning hypo- and hyperglycaemia in patients treated with gatifloxacin or piperacillin/tazobactam were compared.[43] A higher rate of hypoglycaemia was observed at day 1 in patients treated

with gatifloxacin compared with piperacillin/tazobactam (5.3% vs 0%, p = 0.04) when a blood glucose level of <65 mg/dL was used as the definition for hypoglycaemia. However, there was no difference in the incidence of hypoglycaemia between gatifloxacin and piperacillin/tazobactam when the definition of hypoglycaemia was reduced to <50 mg/dL (1% vs 0%, p = 0.4). When a blood glucose level of >140 mg/dL was used to define hyperglycaemia, piperacillin/tazobactam accounted for a significantly higher incidence compared with gatifloxacin (33.3% vs 15%, p = 0.03). However, when the threshold for hyperglycaemia was raised to a blood glucose level >160 mg/dL, this difference, once again, disappeared (21.3% vs 11.5%, p = 0.07). The results of this study illustrate the importance of categorical assignments based on objective data and the influence this has on the interpretation of the data.

In an inpatient, nested case-control study involving >7000 patients, the incidence of hypoglycaemia requiring treatment with glucagon or 50% dextrose after levofloxacin or gatifloxacin administration was 11/1000 patients and 21/1000 patients, respectively.[44] The median time to onset of hypoglycaemia after starting fluoroquinolones was 1 day and concomitant hypoglycaemic drug therapy, renal failure and sepsis syndrome were identified as independent risk factors for hypoglycaemia among hospitalized patients. However, there was a higher incidence of hypoglycaemic events after gatifloxacin use with an adjusted OR of 2.81 (95% CI 1.02, 7.70; p = 0.045) after accounting for confounders of hypoglycaemia.

A review of the US FDA Adverse Events Reporting System database in 2003 revealed 568 dysglycaemic events with the four most commonly prescribed quinolones (ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin).[8] Gatifloxacin accounted for 80% of the reported adverse events, with dysglycaemia occurring more frequently in elderly patients and in those receiving concomitant treatment for diabetes. Of the 25 patients who had a fatal outcome, gatifloxacin was prescribed in 17 of them. The majority of all adverse events associated with gatifloxacin use occurred in women; however, sex was not an overall risk factor for dysglycaemia. Overall, gatifloxacin was associated with a substantially higher rate of adverse drug event reports involving glucose homeostasis abnormalities compared with other fluoroquinolones. However, the use of spontaneous adverse event reports provide reporting rates which are not synonymous with incidence rates.[45]

A 2-year retrospective cohort study by Lodise et al.[46] was conducted to evaluate rates of hypo- and hyperglycaemia amongst elderly, hospitalized patients with normal baseline blood glucose levels after receiving levofloxacin or gatifloxacin. Of the total of 937 patients, 532 received gatifloxacin and 405 received levofloxacin. The two groups were similar at baseline for all characteristics examined except prior healthcare history. In the logistic regression analysis, gatifloxacin was independently associated with both hypoglycaemia (adjusted OR, 2.5; 95% CI 1.2, 5.7; p = 0.04) and hyperglycaemia (OR 2.4; 95% CI 1.5, 3.6; p < 0.001) compared with levofloxacin-treated patients. Hypo- and hyperglycaemia in both treatment groups were most notable among patients with diabetes. Differences in hypoglycaemia between agents were primarily noted early during the course of therapy and differences in hyperglycaemia were observed later in treatment. Of the 532 patients receiving gatifloxacin, 465 patients received the appropriate dose (87.4%), yet gatifloxacin was associated with higher rates of hypo- and hyperglycaemia compared with patients receiving levofloxacin.

In a retrospective cohort study of >17 000 hospitalized patients who received gatifloxacin, levofloxacin, ciprofloxacin or ceftriaxone during an 18-month period, dysglycaemia was more likely to occur in patients who received fluoroquinolones

than in those receiving ceftriaxone (relative risk 3.32, $p < 0.05$).[47] Overall, the rate of dysglycaemia did not differ between gatifloxacin and levofloxacin with 1.01% and 0.93%, respectively ($p = 0.8$). A majority of the patients with a blood glucose abnormality were hyperglycaemic (blood glucose level >200 mg/dL). Hypoglycaemia (blood glucose level <50 mg/dL) occurred in only nine patients, all of whom had type 2 diabetes. A multivariate analysis of the patients who received fluoroquinolones revealed that only concomitant sulfonylurea therapy was an independent risk factor for the development of hypoglycaemia compared with patients who experienced hyperglycaemia.

In a study by Ambrose et al.,[48] the relationship between gatifloxacin exposures and severe hyperglycaemia was evaluated. Based on a population pharmacokinetic model of patients with community-acquired pneumonia, ten patients who were identified in the FDA's Med Watch database developed severe hyperglycaemia were further evaluated. All ten patients received 400 mg of gatifloxacin daily, and the predicted mean area under the concentration-time curve $(AUC)_{24}$ was estimated to be 74 mg • h/L (range 57–100), a 2-fold higher AUC than would be predicted if appropriate dose reductions had taken place. In patients ≥85 years old in whom the dosage had been reduced to 200 mg/day, the probability that the AUC would have exceeded 70 mg • h/L was still 5.48%. However, the probability decreased to <1% if the patient was ≤65 years of age with a 200-mg dose but exceeded 35% with a 400-mg dose. Thus, the authors concluded that the risk of severe hyperglycaemia could be reduced with a reduction of the gatifloaxcin dosage from 400 to 200 mg/day.

A case-control study[49] as a follow-up to the cohort study conducted by Mohr et al.[47] evaluated risk factors for hospitalized, adult patients who developed hyperglycaemia (blood glucose level >200 mg/dL) in patients receiving gatifloxacin and levofloxacin. The median time to the development of hyperglycaemia was 4 days. On multivariate analysis, diabetes was the most significant risk factor, followed by inappropriate dose according to renal function. After controlling for diabetes, dose inappropriately adjusted for renal function remained an independent predictor for hyperglycaemia and concomitant steroid use emerged as a significant risk factor. When the risk factors in the multivariate analysis were adjusted, the risk for the development of hyperglycaemia was not different between patients who received gatifloxacin and levofloxacin (OR = 1.12, 95% CI 0.63, 4.26). The lack of appropriate dose adjustments in patients with renal insufficiency as a risk factor for hyperglycaemia is consistent with the dose-response effects observed *in vitro* cell culture data and animal models, as well as pharmacodynamic evaluations of elderly patients receiving gatifloxacin who developed hyperglycaemia.

6. Conclusion

Fluoroquinolones have the advantage of being available in oral and parenteral dosage formulations with similar concentration-time profiles and can be used for the treatment of a wide spectrum of infections, making them a popular choice of antibacterials for physicians and patients. While it is safe to conclude that dysglycaemia has been associated with the use of certain fluoroquinolones, primarily gatifloxacin, the concern that a class effect may be responsible cannot be totally excluded, especially as higher doses of levofloxacin are being utilized and some case reports are beginning to emerge.[50-52] In addition, case reports of ciprofloxacin-associated hypoglycaemia have been reported. However, these reports have been in conjunction with the use of glibenclamide, making it difficult to ascertain the influence of ciprofloxacin on the event.[53,54] While large analyses of pooled data from patients receiving moxifloxacin fail to identify any signals of dysgly-

caemias associated with the drug, this may be a function of the lack of need for dose adjustment in elderly patients and patients with renal insufficiency because of the pharmacokinetics of the drug.[55]

However, we feel it is prudent to educate patients at the highest risk for the development of dysglycaemias (elderly patients, patients with diabetes, patients with renal insufficiency and those concomitantly using hypoglycaemic drugs) of the signs and symptoms of hypo- and hyperglycaemia when fluoroquinolones, or in fact any antibacterial, are prescribed. Finally, the importance of adherence to the recommended doses of fluoroquinolones based on the prescribing information of the drug relative to renal function in reducing the overall incidence of all dose-related adverse events, including dysglycaemia, cannot be underemphasized.

Acknowledgements

No sources of funding were used to assist in the preparation of this review article. Dr Mohr has received grants and honoraria from Bristol Myers-Squibb and honoraria from Schering-Plough. Dr Lewis has no conflicts of interest that are directly relevant to the content of the article.

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