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Safety Profile of the Fluoroquinolones
Focus on Levofloxacin

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Abstract

The fluoroquinolone class of antibacterial agents are among the most frequently prescribed drugs, with utility in a broad range of bacterial infections. Although very useful agents, the fluoroquinolones as a class are associated with a number of adverse events, some with considerable clinical significance. In the past 15–20 years, tolerability concerns have led to restrictions on the use of the fluoroquinolones and, in some instances, the withdrawal of agents from the market.

This review focuses on the safety and tolerability of levofloxacin, a third-generation fluoroquinolone, relative to other fluoroquinolones. A literature search was performed of the MEDLINE database encompassing the dates 1980–2009, using as keywords the drug names levofloxacin and concurrently marketed fluoroquinolones combined with the words 'safety', 'adverse effect' or 'adverse drug reaction', or the name of the specific adverse effect.

Adverse events commonly associated with the fluoroquinolones include gastrointestinal and CNS toxicity (most frequently headache and dizziness), as well as other adverse events including ECG abnormalities (for example QT interval prolongation), disrupted glucose metabolism, phototoxicity, tendon and joint disorders, hypersensitivity and skin disorders, and hepatic toxicity.

Package inserts for the fluoroquinolones in Europe and the US contain warnings regarding these risks. US package inserts also carry 'black-box' warnings regarding the risk of tendon rupture and joint disorders with these agents; however, there is a substantial body of evidence to indicate that there are marked differences in the tolerability profiles of the individual agents within the fluoroquinolone class. These differences may be explained, at least in part, by structural differences: all fluoroquinolones share a basic quinolone core, with differences in specific side chains underlying the adverse event relationships. Furthermore, many of the fluoroquinolone-associated adverse effects and toxicities occur more frequently in patients with pre-existing risk factors, or in certain subpopulations. Notably, package inserts for the fluoroquinolones carry warnings regarding use in the elderly, paediatric patients and patients with pre-existing, or factors predisposing to, seizure disorders. Because of this, many adverse reactions with these agents could be prevented by improving patient screening and education. The recent withdrawal of gatifloxacin due to dysglycaemia makes it timely to review the safety and tolerability of the individual agents in this class. Overall, it appears that levofloxacin is relatively well tolerated, with low rates of clinically important adverse events such as CNS toxicity, cardiovascular toxicity and dysglycaemia.

The fluoroquinolones are an important antibacterial drug class and were the most commonly prescribed drugs in the US between 1995 and 2002.[1] They have utility in the treatment of a broad range of bacterial infections, including those of the respiratory and urinary tracts, skin and soft tissue infections, and bone and joint infections. Earlier fluoroquinolones are still the drugs of choice for Gram-negative infections, but newer fluoroquinolones are preferred for lower respiratory tract infections.[2] Gastrointestinal infections also respond well to fluoroquinolone therapy, as do some sexually transmitted diseases.[3]

As a class, the fluoroquinolones are associated with several well recognized adverse events, some of which are considered class effects; however, there are distinct differences in the safety and tolerability profiles of the individual fluoroquinolones. In the past 15–20 years, tolerability concerns have led to restrictions on use of the fluoroquinolones and, in some instances, the withdrawal of agents from the market, including sparfloxacin and grepafloxacin, both of which were withdrawn due to prolongation of the QT interval. Most recently, in 2006, gatifloxacin was withdrawn due to dysglycaemias; both hypo- and hyperglycaemic effects. We therefore felt it was timely to review the safety of the fluoroquinolones, with particular focus on one of the more established agents, levofloxacin. To locate relevant studies, a literature search was performed of the MEDLINE database encompassing the dates 1980–2009, using as keywords the drug names levofloxacin and concurrently marketed fluoroquinolones combined with the words 'safety', 'adverse effect' or 'adverse drug reaction'. From these references, a list of significant (either frequently encountered or associated with high morbidity or mortality) adverse drug reactions was compiled. A literature search of these terms was then performed. Finally, the package insert for each of the fluoroquinolones was also used as a data source as this frequently captured unpublished data. Additional references were sourced from the bibliographies of relevant articles. This review focuses on the safety profile of levofloxacin relative to other fluoroquinolones. The use of these agents in specific patient populations, such as the elderly, the paediatric population and pregnant women, will also be discussed.

1. Levofloxacin: An Overview

According to a four-generation fluoroquinolone classification system proposed by King

Table I. Quinolone classification[4]

Agent	Notable adverse drug reactions	Implications
First-generation		
Nalidixic acid	Nausea, dizziness	No longer in common use
Cinoxacin		
Second-generation		
Norfloxacin	Tendinitis and tendon rupture	Black-box warning July 2008
Lomefloxacin		
Enoxacin		
Ofloxacin	Tendinitis and tendon rupture	Black-box warning July 2008
Ciprofloxacin	Tendinitis and tendon rupture	Black-box warning July 2008
Third-generation		
Levofloxacin	Tendinitis and tendon rupture	Black-box warning July 2008
Sparfloxacin	Phototoxicity, QTc interval prolongation	Product package insert warnings added 1996
Gatifloxacin	Dysglycaemia	Withdrawn from the market in 2006
Moxifloxacin	QTc interval prolongation	Product package insert warnings added 1999
	Tendinitis and tendon rupture	Black-box warning July 2008
Fourth-generation		
Trovafloxacin	Serious hepatic events	Withdrawn or limited use 1999

et al.,[4] and based on antimicrobial spectrum, levofloxacin is classified as a third-generation fluoroquinolone (table I). The third-generation fluoroquinolones have expanded activity against Gram-positive bacteria and atypical pathogens.[4] More specifically, compared with older generation fluoroquinolones, levofloxacin has improved activity against both *Streptococcus pneumoniae* and *Enterococcus* species, and also has activity against *Mycoplasma* and *Chlamydia* species.[4] There is only one fourth-generation agent, trovafloxacin, which was withdrawn, or had severe restrictions placed on its use, in 1999 due to serious hepatic events.[5,6]

Levofloxacin was first launched in 1993 and has since been used in the treatment of over 647 million patients worldwide. It is approved for a range of indications, including acute exacerbations of chronic bronchitis, acute sinusitis, inhalational anthrax (post-exposure), nosocomial and community-acquired pneumonia, prostatitis, pyelonephritis, skin and soft tissue infections and urinary tract infections.[7]

Most adverse events associated with levofloxacin are mild and rarely result in treatment discontinuation. As with all fluoroquinolones, the most common events are gastrointestinal related (e.g. nausea, diarrhoea) or CNS events (e.g. headache, insomnia).

Pooled safety data from 29 phase III clinical trials of levofloxacin (n = 7537) revealed that discontinuation of levofloxacin due to adverse drug reactions occurred in 4.3% of patients. The most common adverse drug reactions leading to discontinuation with the 250 and 500 mg doses of levofloxacin were gastrointestinal (1.4%), primarily nausea (0.6%), vomiting (0.4%), dizziness (0.3%) and headache (0.2%). With the 750 mg dose, the most common ADRs leading to discontinuation were gastrointestinal (1.2%), primarily nausea (0.6%), vomiting (0.5%), dizziness (0.3%) and headache (0.3%).[7]

These safety data have been supported by postmarketing surveillance data, which have reported an overall rate of adverse drug reactions of between 3 and 9.9% with levofloxacin.[8-10]

There are distinct differences among the fluoroquinolones with regard to their safety and tolerability profiles. Clinical evidence suggests that some of the fluoroquinolone-associated tolerability concerns can be predicted by the different structures of the agents. All fluoroquinolones share a basic quinolone core, and it is differences in specific side chains that appear to underlie the

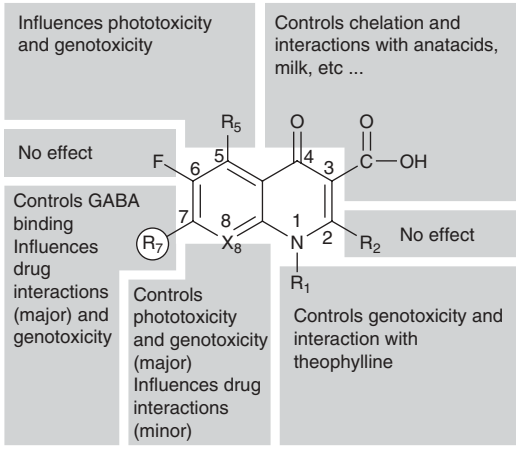

Fig. 1. Chemical structure of fluoroquinolones with structural side effect relationships (this information was originally published in Mandell and Tillotson.[11] Reproduced with permission from the *Canadian Journal of Infectious Diseases and Medical Microbiology*).

adverse effect relationship (see figure 1). The purported mechanism of these differences in adverse effect profiles will be discussed in the relevant sections of this review.

2. Levofloxacin Tolerability in the Context of Other Fluoroquinolones

A significant body of evidence exists regarding the safety and tolerability of the fluoroquinolones, particularly those that have been widely used for a number of years. In addition to the clinical data collected for individual agents during clinical development, sources of tolerability information for approved drugs include phase IV postmarketing studies as well as individual cases submitted to regulatory authorities such as the US FDA and the European Medicines Agency in Europe.[12] The most clinically important adverse drug reactions associated with fluoroquinolones (in no particular order) are as follows: QT interval prolongation; tendinitis and tendon rupture; headache; dizziness; seizures; dysglycaemia; anaphylaxis; liver injury; and liver failure.

Overall, the total body of evidence for the fluoroquinolones has indicated that adverse effects commonly associated with the fluoroquinolones as a class include gastrointestinal and CNS toxicity, with less frequent adverse events, including ECG abnormalities and disrupted glucose metabolism.

2.1 CNS Toxicity

The overall incidence of CNS disorders associated with fluoroquinolones is 1–3%.[10,13,14] Headache and dizziness are among the most frequently reported adverse events associated with the fluoroquinolones, including levofloxacin, for which headache is reported at a rate of at least 3%.[7] Headache is also listed among the most common side effects of ciprofloxacin,[15] but is listed as an uncommon event in the US package insert for moxifloxacin, at between 0.1% and 2%.[16]

Dizziness is reported to occur at a rate of at least 3% for levofloxacin, and patients are advised to become familiar with how they react to levofloxacin before engaging in activities that require mental alertness and coordination, such as driving.[7] Similar warnings are also included in the package inserts for ciprofloxacin, where dizziness is listed as a CNS disorder reported with a rate of <1%,[15] and for moxifloxacin, for which dizziness has been reported at a rate of 2% in clinical trials comprising data from more than 9200 patients.[16]

An elevated risk of seizures has also been reported in patients receiving fluoroquinolones.[12,17] Therefore, caution is advised when administering fluoroquinolones, including levofloxacin, ciprofloxacin and moxifloxacin, in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold.[18] Concomitant use with NSAIDs may also increase seizure risk.[19-21]

Clinical trial data indicate a seizure incidence of 0.1–1% for levofloxacin,[7] although the observed seizure rate with levofloxacin in clinical use is almost certainly closer to 0.1% than 1% as there are no post-approval spontaneous reports of seizures with levofloxacin listed in the 2008 US package insert for the agent.[7] This is comparable with reported seizure rates for other fluoroquinolones, such as ciprofloxacin (<1%),[15] with a

slightly lower rate reported in clinical trials of moxifloxacin, at <0.1%.[16]

Using structure and function relationships to predict seizure risk with the various fluoroquinolones indicates that levofloxacin should have a relatively low seizure risk.[22,23] This is because levofloxacin has a bulky alkylated side chain at the R7 position, which means that the agent is less likely to bind to GABA receptors and is therefore less likely to stimulate the CNS, compared with agents such as ciprofloxacin, enoxacin and norfloxacin, which have an unsubstituted piperazinyl ring, with high affinity for $GABA_A$ – interfering with GABA binding to its receptor.[11,22] Fluoroquinolones may also stimulate the CNS by activation of the NMDA receptor.[24,25]

Overall, the seizure risk with use of the fluoroquinolones is likely to be very low, especially if use is avoided in patients with predisposing risk factors, such as electrolyte imbalances, pre-existing seizure disorders, other conditions predisposing to seizures, including renal dysfunction, concomitant use of medications (NSAIDs, theophylline) that are also associated with an elevated seizure risk, and use in elderly patients.

2.2 Gastrointestinal Toxicity

Like other antibacterials, the fluoroquinolones appear to be associated with an elevated risk of *Clostridium difficile*-associated diarrhoea (CDAD), with increasing risk as duration of use increases.[26]

Studies suggest that moxifloxacin may be associated with higher rates of CDAD than levofloxacin; formulary changes from levofloxacin to gatifloxacin or from levofloxacin to moxifloxacin have been associated with a concurrent increase in this adverse event.[27-29] This may be due to higher stool levels of moxifloxacin compared with levofloxacin as moxifloxacin (like sparfloxacin and trovafloxacin) is excreted hepatically.[30] Lower absorption of moxifloxacin in the gastrointestinal tract may also explain this higher CDAD rate.

Further evidence of differences between the various fluoroquinolones in terms of CDAD rates comes from a prospective case-control study in which odds ratios (OR) for CDAD were 3.1 (95% CI 1.8, 5.4) for ciprofloxacin and 3.4 (95% CI 1.5, 7.7) for gatifloxacin or moxifloxacin compared with 0.6 (95% CI 0.2, 1.9) for levofloxacin compared with matched controls.[31] However, these differences may be explained, at least in part, by the small numbers of patients who received each individual agent, and the case-control design of the study not allowing for true comparisons between agents. Nevertheless, this is not the only study to indicate a lower incidence of CDAD with levofloxacin compared with other fluoroquinolone antibacterials. Notably, in one retrospective chart review, following an increase in the use of levofloxacin due to a piperacillin/tazobactam shortage, rates of CDAD decreased, suggesting that levofloxacin has less effect than piperacillin-tazobactam on gastrointestinal flora; additionally, ciprofloxacin was not found to have any relationship to CDAD incidence.[32]

2.3 Phototoxicity

Although phototoxicity is an established class effect of the fluoroquinolones, there is considerable variation in prevalence within the class due to structural differences.[22,23,33,34] The development of phototoxicity is associated with site X_8 on the fluoroquinolone molecule (figure 1).[22] Agents with a halogen (i.e. fluorine or chlorine) at this position, such as sparfloxacin and lomefloxacin, have a higher rate of phototoxic reactions than those with a different side chain at this position.[10,23] Notably, levofloxacin has a methoxy analogue at this position, which is not indicative of a significant risk of phototoxicity.[23] The rank order of the fluoroquinolones in terms of causing phototoxicity is as follows: lomefloxacin > fleroxacin > enoxacin > pefloxacin > ciprofloxacin > grepafloxacin > gemifloxacin > levofloxacin > norfloxacin > ofloxacin > moxifloxacin.[10,35-38] However, it is important to note that the incidence of phototoxicity, in the absence of excessive light exposure is generally very low for the fluoroquinolones, at <1% for ciprofloxacin.[10,39]

2.4 Cardiovascular Toxicity

The QT interval is a measure of the cellular ventricular action potential, generated by the

interplay of ionic currents through various ion channels.[40] Prolongation of this interval can occur with a variety of drugs because of their actions at these important ion channels. In some cases, this QT interval prolongation can lead to the development of torsades de pointes, which may degenerate into ventricular fibrillation and, potentially, sudden death.[41] The fluoroquinolones prolong the QT interval by blocking voltage-gated potassium channels, especially the rapid component of the delayed rectifier potassium current I_{Kr}, expressed by the *human ether-a-go-go*-related gene, HERG.[42]. All the fluoroquinolones act to antagonize this current, and QT interval prolongation varies dose dependently.[43] However, not all of the fluoroquinolones have the same magnitude of effect on the QT interval; this is partly due to structural differences between fluoroquinolones.[44-46] Furthermore, the average QT interval prolongation caused by fluoroquinolones (approximately 3–6 ms) has little clinical significance against the normal QT interval (450–470 ms).[47] It is thought to be the patients with excessive QT prolongation who are at most risk of developing torsades de pointes.[8]

Some fluoroquinolones have been withdrawn because of their prolongation of the QT interval: grepafloxacin, which caused torsades de pointes, and sparfloxacin, which prolonged the QT interval at low doses, increasing the risk for severe arrhythmia.

The risk of cardiac events with the fluoroquinolones appears to be dependent upon the degree to which the individual agents inhibit the I_{Kr}.[48,49] Notably, levofloxacin appears to be a less potent inhibitor of this channel than many other fluoroquinolones, including sparfloxacin, grepafloxacin, moxifloxacin and gatifloxacin.[44] In a study using patch clamp electrophysiology,[44] all of the fluoroquinolones tested (levofloxacin, sparfloxacin, ciprofloxacin, gatifloxacin, ofloxacin, grepafloxacin and moxifloxacin) were found to inhibit the HERG channel in a dose-dependent manner, although the potencies of each agent differed markedly. Moreover, agents that only weakly inhibited the HERG channel (levofloxacin, ciprofloxacin and ofloxacin) all lack C5 substituents, whereas sparfloxacin and grepafloxacin do have such substituents. Based on the HERG inhibition observed in this study, the potency of the fluoroquinolones in terms of QT interval prolongation can be considered to have the following rank order: sparfloxacin > grepafloxacin > moxifloxacin > gatifloxacin > levofloxacin > ciprofloxacin > ofloxacin. This is largely consistent with the rank order of the reported incidence of QT prolongation with the fluoroquinolones.[50]

Similarly, in a study conducted using the methoxamine-pretreated rabbit model, sparfloxacin and moxifloxacin had markedly higher antagonist potency against the I_{Kr} than the other fluoroquinolones tested (gatifloxacin and grepafloxacin).[46] In this study, these more potent I_{Kr} antagonists, moxifloxacin and sparfloxacin, were associated with an increased tendency towards prolongation of the QT interval and rhythm disturbances.

Clinical trials have been conducted to investigate the effect of the fluoroquinolones gemifloxacin, levofloxacin, ofloxacin, ciprofloxacin and moxifloxacin on QT interval prolongation (table II).[51-55] Available evidence suggests that, of the most widely used fluoroquinolones, moxifloxacin has the greatest potential to cause QT interval prolongation.[46,51,55] However, current US labelling states that QT interval prolongation with moxifloxacin treatment has not been associated with cardiovascular morbidity or mortality.[16]

In a study conducted in healthy volunteers ($n = 18$), a single dose of moxifloxacin 400 mg was shown to prolong the QT interval, although the association with torsades de pointes was low.[55] Another study of healthy volunteers also revealed an association between moxifloxacin intake and prolongation of the QT interval. In this study, 7 days' treatment with moxifloxacin 400 mg/day was associated with a significant increase from baseline in the heart-rate corrected QT interval (QTc) of 6 ms ($p = 0.022$).[51] In contrast, neither levofloxacin nor ciprofloxacin were associated with any changes in the QTc interval. A consistently greater effect of single doses of moxifloxacin than of either ciprofloxacin or levofloxacin on both QT and QTc interval was also shown in healthy volunteers by Noel et al.,[54] although this study used high doses of the three agents (800 mg for moxifloxacin, 1500 mg for ciprofloxacin and 1000 mg for levofloxacin).

Table II. Summary of clinical trials examining the effect of fluoroquinolones on QTc prolongation (reproduced from Falagas et al.,[43] with permission from Elsevier)

Study	Design	No. of subjects	Study population (mean age [y])	Treatment	Effect on QTc	Mean QTc increase
Tsikouris et al.[51]	Randomized, open-label, crossover study	13	Healthy volunteers (34)	Ciprofloxacin 500 mg twice daily, 7 days	No effect	NS
				Levofloxacin 500 mg once daily, 7 days	No effect	NS
				Moxifloxacin 400 mg once daily, 7 days	Prolongation at day 7	6 ms (from baseline); $p = 0.022$
Makaryus et al.[52]	Prospective clinical trial	38	Patients with RTI or UTI without arrhythmia or not receiving QT interval-prolonging medication (65)	Ciprofloxacin 250 mg twice daily	No effect	NS
				Levofloxacin 500 mg once daily or 250 mg once daily for patients with UTI	No effect	NS
Noel et al.[53]	Double-blind, randomized, placebo-controlled, four-period, four-sequence, crossover study	47	Healthy volunteers (47.1)	Levofloxacin single 500 mg dose	No effect	NS
				Levofloxacin single 1000 mg dose	Prolongation at 24 h	From 1.5 to 3.9 ms; $p \leq 0.05$
				Levofloxacin single 1500 mg dose	Prolongation at 24 h	From 6.4 to 7.7 ms; $p \leq 0.001$
Noel et al.[54]	Double-blind, randomized, placebo-controlled, four-period, four-sequence, crossover study	47	Healthy volunteers (47.6)	Placebo	No effect	NR
				Moxifloxacin 800 mg once daily	Prolongation at 24 h	From 16.3 to 17.8 ms; $p < 0.001$
				Levofloxacin 1000 mg once daily	Prolongation at 24 h	From 3.5 to 4.9 ms; $p < 0.05$
				Ciprofloxacin 1500 mg once daily	Prolongation at 24 h	From 2.3 to 4.9 ms; $p < 0.05$
Demolis et al.[55]	Double-blind, randomized, placebo-controlled, crossover trial	18	Healthy volunteers (23.8)	Placebo	No effect	NR
				Moxifloxacin 400 mg once daily	Prolongation at 2 h	$4.0 \pm 5.1\%$; $p < 0.05$
				Moxifloxacin 800 mg once daily	Prolongation at 2 h	$4.5 \pm 3.8\%$; $p < 0.05$

NR = not reported; **NS** = non-significant; **RTI** = respiratory tract infection; **UTI** = urinary tract infection.

Overall, neither levofloxacin nor ciprofloxacin appear to be associated with a clinically significant risk of any clinically significant increases in QT interval. For example, in a prospective investigation of a cohort of patients (n = 38) receiving levofloxacin or ciprofloxacin at standard doses, average changes in longest QT interval of 0.01 and −0.01 seconds were seen.[52] Furthermore, according to prescribing data, approximately 15 million prescriptions for levofloxacin were dispensed in the US between March 1997 and March 2000, during which time there was less than one reported case of QT prolongation or torsades de points per million prescriptions.[52,56] Similarly for ciprofloxacin, with experience of use in over 250 million patients, the reporting rate of possible associated serious cardiac dysrhythmias was one case per million treatments.[52,57]

A study conducted in healthy volunteers (n = 50) also failed to show any effect of levofloxacin 500 mg, 1000 mg or 1500 mg on QT interval at 4 hours post-treatment, although levofloxacin was associated with dose-dependent increases in heart rate.[53] This study suggests that any increase in QT interval with levofloxacin is likely to be mediated by an effect on heart rate rather than prolongation of ventricular repolarization, as seen with other drugs associated with prolongation of the QT interval. Notably, in this study, only the 1500 mg dose, which is twice the maximum recommended dose in the US,[7] was associated with a statistically significant effect on the QTc interval. The magnitude of this effect varied with the method used to correct for heart rate.

However, not all studies are consistent, with a randomized controlled trial failing to show any difference in cardiac rhythm safety between moxifloxacin and levofloxacin in elderly patients.[58] It should be noted that this study excluded patients with known QTc prolongation or those receiving class IA or III antiarrhythmics.

A search of the FDA database for reports of torsades de pointes associated with the fluoroquinolones ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin and moxifloxacin between January 1996 and May 2001 revealed a total of 37 individual cases, with concomitant use of other drugs known to prolong the QT interval reported in the majority of cases.[59] For 2001 data, reporting rates for fluoroquinolone-induced torsades de pointes per 10 million prescriptions were 0 for moxifloxacin, 0.3 for ciprofloxacin, 2.1 for ofloxacin, 5.4 for levofloxacin and 27 for gatifloxacin (table III).[59,60] However, under-reporting is a well known issue with such data and it must therefore be interpreted with caution.[61,62]

Overall, current evidence suggests that neither levofloxacin nor ciprofloxacin significantly prolong QT interval in the vast majority of patients, whereas other agents such as moxifloxacin do appear to be associated with QT interval prolongation, although this may not lead to increased cardiovascular morbidity or mortality.

2.5 Dysglycaemia

Disruption of glucose homeostasis can occur with any of the fluoroquinolones,[39] and disordered glucose regulation is now recognized as one of the most clinically important adverse events associated with fluoroquinolone treatment.[63] This can present as hypoglycaemia or hyperglycaemia – the latter may be due to a Somogyi response to the initial insulin secretion and decreased glucose, resulting in a rebound of the glucose to a high level.

Dysglycaemia appears to be more common with the fluoroquinolones than with other antibacterials such as cephalosporins and macrolides.[63,64] However, not all fluoroquinolones are associated with the same risk of dysglycaemia, with a number of studies indicating that the different fluoroquinolones have varying effects on glucose metabolism.[63-69]

Fluoroquinolone-associated disturbances in glucose metabolism are likely to be mediated by the action of the drugs on glucose transporter type 1 (GLUT1), a protein responsible for transport of glucose into the CNS as well as peripheral tissues.[70] Gatifloxacin is known to disturb GLUT1 function, reducing GLUT1 messenger RNA (mRNA) expression (leading to the development of dysglycaemia)[71] and also acts to stimulate insulin secretion and suppress insulin biosynthesis.[72] In 2006, gatifloxacin was withdrawn from the market because of severe glycaemic side effects.

Table III. Reporting rate of torsades de pointes induced by fluoroquinolones (2001 data)[59,60] [reproduced from Van Bambeke and Tulkens,[18] with permission from Adis, a Wolters Kluwer business (© Adis Data Information BV 2009). All rights reserved]

Drug	No. of US cases reported to the US FDA	No. of estimated total US prescriptions (millions)	No. of cases/10 million prescriptions (95% CI)
Moxifloxacin	0	1.4	0 (0, 26)
Ciprofloxacin	2	66	0.3 (0.0, 1.1)
Ofloxacin	2	9.5	2.1 (0.3, 7.6)
Levofloxacin	13	24	5.4 (2.9, 9.3)[a]
Gatifloxacin	8	3	27 (12, 53)[b,c]

a $p < 0.001$ for levofloxacin vs ciprofloxacin (Fisher's exact test).

b $p < 0.001$ for gatifloxacin vs ciprofloxacin (Fisher's exact test).

c $p = 0.001$ for gatifloxacin vs levofloxacin (Fisher's exact test).

The risk of gatifloxacin-associated hyperglycaemia was shown to be elevated by concomitant use of medications such as corticosteroids, and by use of higher-than-recommended gatifloxacin doses.[73] Data suggest that this is a dose-dependent adverse event.[74]

Both ciprofloxacin and levofloxacin have also been shown to decrease GLUT1 mRNA expression and glucose uptake.[75] After 20 hours' incubation with ciprofloxacin, GLUT1 mRNA expression in Hep-2 cells, measured by real-time polymerase chain reaction, has been shown to decrease in a dose-dependent manner, with a glucose transport assay revealing a dose-dependent decrease in 2-deoxy-d-glucose uptake; similar results were seen for levofloxacin.[75] Results of this study indicate that the potency of these compounds in terms of reducing cellular transport of glucose, at 41% with gatifloxacin, 28% with levofloxacin and 21% with ciprofloxacin, mimic the ranked potential for these agents to induce dysglycaemia.[75]

In a pooled analysis of all completed phase II/III trials of moxifloxacin (n = 32), no moxifloxacin-related hypoglycaemic adverse events were reported.[69] In this analysis, which included a total of 7924 moxifloxacin-treated patients and 5678 patients treated with a comparator antimicrobial, there were two reports of drug-related hypoglycaemia in patients receiving levofloxacin, both of which were mild in severity. There was also one report of hypoglycaemia in a patient after receiving trovafloxacin. In contrast, there were seven reports of moxifloxacin-associated hyperglycaemia (<0.1%), with only one such event among patients receiving comparator antimicrobials (cefalexin).

Postmarketing data also indicate a very low dysglycaemic potential for moxifloxacin, with no episodes of hypoglycaemia and only two of hyperglycaemia (not considered drug related) in five postmarketing studies enrolling a total of 46 130 patients.[69]

In an *in vitro* study investigating the effects of levofloxacin, temafloxacin and gatifloxacin on insulin secretion as well as activity of the pancreatic β-cell ATP-sensitive potassium channel, levofloxacin was shown to have only a small effect.[67] In contrast, both gatifloxacin and temafloxacin increased insulin secretion and were also shown to inhibit the potassium channel in a dose-dependent manner. In a case-control study in an inpatient setting, the incidence of hypoglycaemia between levofloxacin and gatifloxacin was compared, and levofloxacin was again shown to have less hypoglycaemic potential than gatifloxacin.[66] In this 7287-patient study, the formulary fluoroquinolone was levofloxacin from November 2000 to October 2001, after which time levofloxacin was replaced with gatifloxacin; the odds of developing hypoglycaemia were found to be 2.81 (95% CI 1.02, 7.70) times higher for gatifloxacin than levofloxacin. Similar results were observed in another study in which the formulary fluoroquinolone was changed from levofloxacin to gatifloxacin.[68] Lodise et al.[68] showed that, in an elderly inpatient population with normal baseline glucose levels, gatifloxacin was again associated with higher risks of both hypoglycaemia and hyperglycaemia than levofloxacin. Another case-control study of 788 patients showed a significantly higher risk of hypoglycaemia among patients receiving gatifloxacin compared with a macrolide antibacterial (OR 4.3 [95% CI 2.9, 6.23]) with a smaller, although still significant, risk with levofloxacin (OR 1.5 [95% CI 1.2, 2.0]), with no such increase in hypoglycaemia risk observed for either moxifloxacin or ciprofloxacin.[63] In this study, gatifloxacin was also associated with an increase in risk of hyperglycaemia (OR 16.7 [95% CI 10.4, 26.8]) compared with a macrolide.

However, not all studies have consistently shown a statistically significantly lower rate of hypoglycaemia with levofloxacin than with gatifloxacin. In a retrospective chart review of 17 108 patients receiving at least one dose of levofloxacin, gatifloxacin, ciprofloxacin or ceftriaxone, 101 patients experienced an abnormal glucose concentration within 72 hours of drug administration.[64] None of these events occurred in patients receiving ciprofloxacin, 76 were receiving gatifloxacin, 11 levofloxacin and 14 ceftriaxone, corresponding to rates of 0%, 1.01%, 0.93% and 0.18%, respectively. The rate of dysglycaemia did not differ with gatifloxacin and levofloxacin (relative risk 1.07, 95% CI 0.62, 1.86, $p = 0.8$).[64] Notably, most patients who experienced glucose abnormalities already had dysglycaemia prior to receiving the antibacterial, with 91% of the 101 patients having type 2 diabetes mellitus.

In a study conducted in mice, neither ciprofloxacin nor levofloxacin were found to cause reductions in glucose levels in either fasted or glucose-loaded animals.[65] In contrast, intraperitoneal administration of lomefloxacin, enoxacin or gatifloxacin, at both high and low doses, resulted in reductions in plasma glucose levels in glucose-loaded mice.

Overall, currently available data suggest that, while some agents in this class of drugs carry an unacceptable risk of dysglycaemia, there are marked differences in the potential of the fluoroquinolones to induce clinically relevant changes in blood glucose. While there have been reports of symptomatic hyper- and hypoglycaemia with levofloxacin, the preponderance of studies suggest the risk of such events is relatively low, particularly when compared with gatifloxacin.[39,66,68,76] Blood glucose levels should be carefully monitored in patients with diabetes who are receiving concomitant therapy with an oral hypoglycaemic agent such as glibenclamide (glyburide) or with insulin.[39]

2.6 Hypersensitivity and Skin Disorders

Spontaneous adverse drug reaction reports provide an estimate of the frequency of fluoroquinolone-associated anaphylaxis of 1.8–23 per million days' treatment.[77] However, data are inconsistent regarding the risk of anaphylaxis and/or allergic reactions with each of the fluoroquinolones, suggesting that there may not be marked differences in the propensity of these agents to induce such reactions.[77-79]

In a study of German fluoroquinolone-associated adverse drug reaction reports[78] there were a total of 204 reports of anaphylaxis, anaphylactic shock or anaphylactic/anaphylactoid reaction between 1 January 1993 and 31 December 2004. Of these reports, 166 were considered to have a relationship with the fluoroquinolone of at least 'possible'. The majority of cases were associated with moxifloxacin (54%), a finding that could not be explained by greater exposure to this agent relative to other fluoroquinolones. Rates per million daily doses for moxifloxacin, levofloxacin, ciprofloxacin and ofloxacin were 3.3, 0.6, 0.2 and 0.2, respectively.

A cohort study of antibacterial users in a large US health insurance claims database indicated similar rates of anaphylaxis for moxifloxacin, levofloxacin, gatifloxacin and ciprofloxacin, at an incidence of approximately 0.1–0.3 per 10 000 dispensings.[79] These rates compared with a rate of 0.2 for cephalosporins and 0.1 for penicillin.

Adverse reactions involving the skin are the most common drug-related adverse events.[80] Antibacterials are often associated with such adverse reactions, although there are large variations in the incidence between antibacterial drug classes. Regarding the fluoroquinolones, the incidence of adverse skin effects differs between agents in this class. Separately published reviews suggest an incidence of 0.2% for levofloxacin,[9] 2.0% for moxifloxacin[81] and 5.1% for sparfloxacin.[82] This elevated rate of adverse skin reactions for sparfloxacin may be a reflection of the high rate of phototoxicity seen with this agent. Clinical data from Europe and North America reported incidences of phototoxicity with sparfloxacin of 2.0%[82] and 7.9%,[83] respectively. In contrast to the generally low rates of hypersensitivity and adverse skin effects seen for the fluoroquinolones other than sparfloxacin, various other classes of antibacterials are associated with substantially higher rates. For example, the patient-reported allergy rate with the β-lactams may be as high as 15%,[84] with a rate of around 3% for

sulfonamides in the general population,[85] increasing to more than 7% for hospitalized patients.[84]

Severe drug-related reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the fluoroquinolones. However, such reactions are extremely rare, with no published reports of SJS for moxifloxacin or levofloxacin and 9 for ciprofloxacin, with 1, 4 and 17 cases of TEN reported with moxifloxacin, levofloxacin and ciprofloxacin, respectively.[86,87] The OR for SJS or TEN for exposed cases compared with non-exposed patients in a global analysis study, including data from clinical trials, meta-analyses, postmarketing studies, spontaneous report systems and case reports, was 10 for the fluoroquinolones as a class, compared with 14 for the cephalosporins and 170 for the sulfonamides.[88]

2.7 Hepatic Toxicity

The fluoroquinolones are known to be associated with mild, usually transient, elevations in hepatic enzymes.[89] More specifically, the incidence of acute liver injury in recipients of fluoroquinolones has been estimated at <1 per 100 000 users.[90] The corresponding rate for amoxicillin/clavulanic acid, the antibacterial most frequently implicated in hepatotoxicity, is approximately 20 per 100 000 users,[91] while the rate for erythromycin is 2 per 100 000 users.[92]

Clinical trial data for levofloxacin gives an incidence of 0.1–1% for hepatobiliary disorders (abnormal hepatic function, increased hepatic enzymes and increased alkaline phosphatase).[7] Additionally, acute liver failure reporting rates using FDA data per 10 million prescriptions have been given as 2.1 for levofloxacin, compared with 6.6 for moxifloxacin, 6.0 for gatifloxacin and 58 for trovafloxacin.[18] The differences may be explained, at least in part, by the structural differences between the various fluoroquinolones. There is evidence to suggest that, while hepatotoxicity associated with the fluoroquinolones remains largely unpredictable, molecules with substituents that generate reactive intermediates, including temafloxacin and trovafloxacin, are associated with a higher incidence of hepatotoxicity.[18] Notably, temafloxacin and trovafloxacin share a difluorophenyl side chain, which may play a role in the adverse effects specific to these agents, including hepatotoxicity, via an unknown mechanism.[89] In 2008, the safety of moxifloxacin was reviewed in the EU following concerns over liver safety. The European Medicines Agency recommended restricting the use of moxifloxacin and strengthening warnings in product information.[93]

2.8 Tendon and Joint Toxicities

Although rare, tendinitis and tendon rupture, due to collagen damage, have been reported with the quinolones, including the fluoroquinolone levofloxacin.[94] Estimated incidence rates for the fluoroquinolones range from 0.14% to 0.4%.[39] The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is elevated in older patients, usually those over 60 years of age, and in patients taking corticosteroid drugs.[95]

Spontaneous reporting system data show a higher rate of reporting of tendon disorders for levofloxacin than ciprofloxacin or norfloxacin,[96,97] and isolated cases have also been reported for moxifloxacin.[98] However, limitations of data obtained from spontaneous reports do not allow direct comparisons between agents.[97]

Despite being a rare event with the quinolones, the available evidence does suggest a causal relationship between these agents and tendon/joint disorders, given the often sudden onset, sometimes after only a single dose, suggesting a toxic effect on the collagen fibres.[95] As a result, product labelling in the US and Europe for all currently available fluoroquinolones, including levofloxacin, moxifloxacin, ciprofloxacin and ofloxacin, carry warnings regarding this risk. US product labelling for all fluoroquinolones, including levofloxacin, also includes a black-box warning regarding the risk of tendinitis and tendon rupture.[7,15,16]

3. Toxicity Issues in Specific Populations

3.1 Use in the Paediatric Population

During 2002 in the US, 520 000 prescriptions for fluoroquinolones were written for children and adolescents despite the only approved indication in

this patient population at this time for these agents being post-exposure treatment for anthrax inhalation.[99]

The main reason for the limited approval for the fluoroquinolones in children is their potential to induce arthropathy, as observed in juvenile animals when administered at high doses;[100-102] however, data from the use of fluoroquinolones in children, in clinical trials and from compassionate use, appear to indicate that these agents may be safer in children than in juvenile animals.[103,104]

In a study investigating the occurrence of tendon or joint disorders in children, the incidence of such disorders with fluoroquinolones (ofloxacin, levofloxacin or ciprofloxacin) was <1% and was comparable to that seen with the reference drug azithromycin.[105] However, in a subset of children in clinical trials enrolled in a prospective long-term surveillance study, children treated with levofloxacin had a statistically significantly higher incidence of musculoskeletal disorders than those receiving non-fluoroquinolone agents.[7]

The US package insert for levofloxacin cautions that children have a higher chance than adults of bone, joint or tendon problems, and that the safety of levofloxacin has not yet been established in children for periods of use longer than 14 days, or for use in children under the age of 6 months.[7] Similar warnings regarding use in children are also included in the US package inserts of other fluoroquinolones, including ciprofloxacin and moxifloxacin.[15,16] EU and UK prescribing information for moxifloxacin and levofloxacin state that these drugs should not be used in children.[106,107] In the UK, package inserts for ciprofloxacin (intravenous and oral) state that this agent should generally only be used for the approved indications, and physicians that initiate the drug should be experienced in treating children with these conditions.[108,109]

As with adult patients, gastrointestinal events, specifically vomiting and diarrhoea, appear to be the most frequently reported adverse events in children receiving levofloxacin.[7]

3.2 Use in the Elderly Population

While advancing age alone does not seem to increase the risk of fluoroquinolone toxicity, a review suggests that decreasing organ function and the greater likelihood of certain degenerative conditions should be considered when using fluroquinolones in the elderly.[110] There is evidence to suggest that the elderly population is at elevated risk of fluoroquinolone-associated tendon disorders, with this risk further increased among patients receiving concomitant corticosteroid treatment.[95] Elderly patients may also be at increased risk of QT interval prolongation.[18] Furthermore, the elderly are at a higher risk of having seizures; this risk increases with age.[111] There is also the possibility that less dramatic fluoroquinolone neurotoxicities such as confusion, anorexia or tremor may be mistaken for manifestations of aging.[110]

US prescribing information for levofloxacin recommends caution in prescribing the agent to elderly patients, particularly those receiving corticosteroids, as well as those receiving concomitant drugs that can result in QT interval prolongation. Additionally, because of the likelihood of decreased renal function in older patients, care should be taken with dosage selection; monitoring of renal function may be useful.[7] Similar warnings regarding use in the elderly are also included in the UK package insert for levofloxacin[107] and in the package inserts for moxifloxacin and ciprofloxacin in the US, EU and UK.[15,16,106,108,109]

3.3 Use in Pregnant Women and Nursing Mothers

Levofloxacin has been classified by the FDA as a pregnancy category C agent. Agents are classified in this category when animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, or when no data are available in pregnancy for either humans or animals.[112] Use of agents with a category C rating, such as levofloxacin, should therefore only be used in pregnancy if the potential benefits outweigh the potential risk to the fetus.[7] Moxifloxacin and ciprofloxacin are also classified as pregnancy category C agents.[15,16] Similarly, prescribing information from the EU and UK for

levofloxacin, ciprofloxacin and moxifloxacin state that because of the absence of human data, these drugs should not be used in pregnant women.[106-109]

However, in a meta-analysis, first-trimester exposure to any quinolone or fluoroquinolone was not associated with any increase in risk for major malformations or for delivering stillborn, premature or low birthweight babies.[113] Nevertheless, while these data may suggest that the fluoroquinolones appear to be relatively safe for use in pregnancy, the limited availability of more conclusive evidence indicate that a conservative approach to the use of these agents in pregnant women remains necessary.

Regarding nursing mothers, limited available data suggest that levofloxacin will be excreted in human milk; therefore, a decision should be made whether or not to discontinue the drug during nursing, taking into account the clinical importance of the drug to the mother.[7] The same recommendation is made in the labelling for both ciprofloxacin and moxifloxacin.[15,16] The EU and UK prescribing information for levofloxacin, ciprofloxacin and moxifloxacin state that these drugs should not be used in breast-feeding women.[106-109]

3.4 Patient Screening and Education

Many of the fluoroquinolone-associated adverse reactions occur more frequently in patients with pre-existing risk factors or in certain subpopulations. Because of this, many adverse reactions with these agents could be prevented by improving patient screening and education.

Taking QT prolongation as an example, female sex has been shown to increase this risk.[114] Other non-pharmacological risk factors include cardiac arrhythmias such as bradycardia and heart failure, as well as electrolyte abnormalities (hypomagnesaemia, hypokalaemia, hypocalcaemia) and hepatic dysfunction.[114,115] The risk is also increased in patients receiving concomitant medications with the potential to prolong the QT interval.

Prevention can be achieved by not exceeding recommended doses of QT interval-prolonging drugs, given that this is usually a dose-dependent effect, as well as avoiding concomitant administration with drugs that also prolong the QT interval and cause electrolyte disturbances. Drugs that inhibit the cytochrome P450 (CYP) 1A2 isoenzyme should also be avoided as some fluoroquinolones, including ciprofloxacin (but not levofloxacin or moxifloxacin) inhibit the CYP1A2 isoenzyme.[116] Significant interactions between fluoroquinolones and drugs that inhibit other isoenzymes such as CYP3A4 are, however, not likely.[116] It may also be advisable to routinely monitor patients before and after administration of a fluoroquinolone or a dose increase,[115] particularly in patients at increased risk of such an adverse event.

Concurrent use of fluoroquinolone antibacterials with anticoagulants can increase the frequency of excessive anticoagulation and cause bleeding.[117] This occurs via suppression of bowel flora and decreased bacteria-associated vitamin K absorption. Patients on anticoagulants should be cautioned to watch for easy bruisability and/or frank bleeding, and have clotting parameters checked more frequently than usual while receiving fluoroquinolones.

Moreover, obtaining allergy histories from patients, as well as differentiating intolerance from true allergy, and emphasizing careful use of the fluoroquinolones in patients with renal insufficiency, patients who are immunosuppressed, such as transplant patients, and in patients at risk of seizure, diabetes or liver disease, also has the potential to lead to a marked reduction in adverse events with these agents.

The incidence of insomnia can be minimized in the case of fluoroquinolones dosed on a daily basis by advising use earlier in the day when possible. This allows drug levels to decrease prior to bedtime.

Patient education is also important, particularly for minimizing the impact of any adverse reactions should they occur. This would include counselling about diarrhoea (including potentially severe CDAD and colitis), phototoxicity and tendinitis.

Furthermore, to enhance patient screening and education efforts, greater vigilance for and

reporting of specific adverse events associated with the fluoroquinolones by groups such as Pharmacy and Therapeutic Committees and Hospital Safety Groups has the potential to greatly enhance our understanding of the particular safety issues associated with the fluoroquinolones as a class, as well as differences in the safety profiles of the individual agents within this class.

4. Conclusions

The fluoroquinolones are a frequently used class of drug for the treatment of a variety of infectious diseases. They are popular agents with a broad-spectrum and rapid bactericidal action.[1-18] While the fluoroquinolones are, as a class, associated with a number of well characterized tolerability issues, there do exist substantial variations in the tolerability profiles of the various agents within this class.

Furthermore, as many of the risk factors associated with particular fluoroquinolone-related adverse events have been identified, it would appear prudent to improve both patient education and patient screening to further reduce the risk of fluoroquinolone-associated adverse events.

Overall, it appears that levofloxacin is relatively well tolerated, with low rates of clinically important adverse events such as CNS toxicity, cardiovascular toxicity and dysglycaemia.

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