Antimicrobial Safety: Focus on Fluoroquinolones

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Background/purpose. Infrequent toxicities associated with certain drugs and drug classes have recently gained much attention from different health-care perspectives. To protect the patient, continued surveillance of safety and tolerability data is essential. Data from preclinical testing, phase 1–3 trials, and postmarketing surveillance may be used to objectively assess the risks associated with a specific drug or family of compounds. This review summarizes safety and tolerability data for the quinolones.

Main findings. The most common adverse events associated with the quinolone class involve the gastrointestinal tract (nausea and diarrhea) and central nervous system (CNS) (headache and dizziness). These adverse events are usually mild and do not require discontinuation of therapy. Uncommon and potentially serious quinolone-related adverse events involve the cardiovascular system (rate-corrected electrocardiographic QT interval prolongation), musculoskeletal system (tendinitis and tendon rupture), endocrine system (glucose homeostasis dysregulation), renal system (crystalluria, interstitial nephritis, and acute renal failure), and the CNS (seizures). Severe idiosyncratic adverse events are specific to individual agents that may share some structural congruity, such as the 1-(2,4)-difluorophenyl group shared by trovafloxacin (associated with hepatitis), temafloxacin (associated with hemolytic-uremic syndrome), and tosufloxacin (associated with eosinophilic pneumonitis). Overall, discontinuation rates from clinical trials were <4% for the currently marketed quinolones. Quinolones with higher discontinuation rates, such as trovafloxacin (7.0%) and grepafloxacin (6.4%), are no longer available for general use.

Conclusions. The currently marketed quinolones are well tolerated, with safety profiles similar to those of other antimicrobial classes. Although adverse effects are unusual, some, including tendinitis and CNS-related effects, are more common with quinolones than with other antimicrobial classes. Rare adverse effects attributed to some members of the quinolone family (e.g., Torsades de Pointes, hepatotoxicity, and dysglycemias) are more likely to occur in select “susceptible” populations. These adverse events can often be circumvented by avoiding exposure to the specific quinolone. In some cases, the therapeutic value offered by a quinolone may outweigh its potential risks.

The safety and tolerability of pharmaceuticals have always been an interest and concern for those who receive and prescribe drugs. Antimicrobial agents are no exception, and with their great benefit comes the responsibility of clinicians and consumers to understand their risks. The exact incidence of specific adverse events is often impossible to assess, although clues are gathered from multiple sources. An initial sense of safety and tolerability is garnered from preclinical testing of animals and, ultimately, from data collected in phase 1–3 testing. After the approval of an agent for general use, the incidence of specific adverse events may be gathered from phase 4 postmarketing studies and from reports to the US Food and Drug Administration (FDA) of unusual and serious events. However, there are many difficulties in collecting accurate safety data.

It is important to note that rates of reporting adverse events can vary in clinical studies on the basis of the time of product approval and geography. For instance, rates of reporting low-frequency and/or poorly characterized adverse events may differ on the basis of new knowledge of toxicity, media attention, or improved diagnostic capabilities. Differences can also be noted on the basis of geography (purportedly because of patient stoicism); for instance, rates of reporting adverse events were 3-fold higher in phase 3 studies of levofloxacin conducted in the United States, compared with those conducted in Japan [1, 2]. Moreover, no adverse events were reported from sitafloxacin studies in Japan [3].
For postmarketing studies, safety monitoring is less stringent than it is in phase 2/3 trials, and such data as laboratory values or electrocardiograms (ECGs) are not collected as often or at all, and, when they are collected, the timing can be erratic. For evaluations of spontaneous adverse events reported to central databases (e.g., insurance claims databases and the FDA’s Adverse Event Reporting System [AERS] database), reports infrequently contain all of the information necessary to determine causality, and the reporting of older (versus newer) agents is usually far less frequent, because of a lack of prescriber and media attention (known as the “Weber effect”) [4]. In an AERS database review of Torsades de Pointes (TdP), Shaffer et al. [5] noted that actual ECG data were available for only 24%–36% of patients to support the diagnoses of TdP. In addition, up to 11% of the reports were also lacking vital demographic information, such as age and sex [5].

Because of the infrequency and/or, sometimes, the quality of data supporting causality for some identified serious adverse events (e.g., TdP, hyperglycemia, hypoglycemia, and tendon rupture), it can be difficult to distinguish some of the quinolones on the basis of data from clinical trials. Thus, nonclinical models or in vitro expression systems are relied on to supplement clinical trial and postmarketing experiential data. What can be gleaned from the culmination of these data is the identification of “susceptible” host populations who are at risk for serious adverse events [6]. Regardless of the antimicrobial to be used, a risk-benefit analysis should be used to weigh the risks of toxicity and antibiotic resistance against the intended therapeutic benefit.

This review will focus on the safety and tolerability of the quinolone compounds, with an emphasis on the newer agents. A discussion of commonly encountered adverse effects (e.g., gastrointestinal [GI] and CNS disturbances) and more rare adverse events, such as rate-corrected electrocardiographic QT (QTc) prolongation and glucose homeostasis abnormalities, will be addressed. In addition, the safety of quinolone use in certain susceptible populations of patients (e.g., pediatric patients) will also be reviewed.

PHARMACOPHORES

As a segue into clinical discussions of antimicrobial safety, the molecular aspects of the various quinolone- and naphthridone-based chemical structures have provided scientists with insight into a variety of toxicities. The bicyclic quinolone nucleus is presented in figure 1A. A derivative of the bicyclic quinolone structure is the naphthridone nucleus (e.g., nalidixic acid, trovafloxacin, and gemifloxacin), which differs from the quinolone nucleus only by the presence of a nitrogen atom at position 8 (figure 1A) [7]. Positions 1, 7, and 8 have been popular targets for substituent modification, resulting in the majority of clinically important refinements (figure 1B). For instance, the addition of a methoxy group to position 8 (e.g., gatifloxacin and moxifloxacin) has resulted in the virtual elimination of phototoxic potential (figure 1C), and modifications at position 7 have allowed for longer half-lives (figure 1C and 1D), improved gram-positive activity (figure 1C and 1D), and reduced seizure potential (figure 1C).

COMMON ADVERSE EVENTS

GI. GI toxicities have included, nausea, anorexia, vomiting, abdominal pain, diarrhea, and taste disturbance. The incidences of these toxicities generally are 2%–20%. On the basis of the relative probability of such toxicities occurring in association with specific agents, a list of agents with the highest to lowest associated probability is as follows: fleroxacin, grepafloxacin, trovafloxacin,sparfloxacin, pefloxacin, ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, enoxacin, and ofloxacin [1, 8–11]. Although these agents have been ranked in terms of general incidence, actual comparisons between agents are difficult to assess, because all agents have not been specifically compared with one another. An analysis of spontaneous adverse event reports from 3 Italian regions reported that the incidence of GI-related adverse events was similar between quinolones (10%) and other systemic antimicrobials (9.1%) [12]. As yet, there has been no correlation between chemical structure and GI toxicity. Of note, grepafloxacin was associated with relatively high incidences of GI-related adverse events, including vomiting (up to 10%) and metallic taste (9%-18%); these incidences are statistically greater than those of adverse events associated with grepafloxacin’s comparator, clarithromycin [1, 13]. The effects of grepafloxacin on the GI tract were dose related (between 200, 400, and 600 mg daily), with significantly higher GI toxicity occurring in association with grepafloxacin than with ciprofloxacin (500 mg q12h) [14]. In phase 2 and 3 studies of moxifloxacin (both intravenous [iv] and oral [po]), incidences of GI-related adverse events were low and are presented in table 1.

CNS. CNS symptoms following administration of quinolones occur at an overall incidence of 1%-2%. Of these, the more commonly reported symptoms have included dizziness, headache, and somnolence [1]. Other, less commonly reported, CNS events have included agitation, delirium, confusion, acute organic psychosis, and abnormal vision. Overall, quinolones with the potential for causing CNS-related adverse events may be listed, from greatest potential to least potential, as follows: fleroxacin, trovafloxacin, grepafloxacin, norfloxacin, sparfloxacin, ciprofloxacin, enoxacin, ofloxacin, pefloxacin, gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin [1, 8–11, 15]. Spontaneous adverse event reports indicate that the incidence of CNS-related adverse events was higher in association with quinolone use (12.2%) than with the use of other systemic antimicrobials (3.6%; P < .01) [12].
Figure 1. Structures of representative quinolones

Fleroxacin, which was not made available for use in the United States, has been associated with unacceptable frequencies of CNS-related adverse events, exceeding rates of 70% [16, 17]. Trovafloxacin was associated with an unusually high incidence of CNS-related adverse events, primarily dizziness (3%–11%), light-headedness (2%–4%), and headache (1%–5%) [18]. Interestingly, women <45 years of age appeared to be more susceptible to these CNS effects [1]. Such events are not commonly associated with the use of the newer quinolones, such as moxifloxacin (table 1).

Seizures, as referred to above, are rare and usually involve a susceptible population with underlying CNS disorders, such as epilepsy, cerebral trauma, or anoxia [15]. In some cases, coadministration of certain nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., fenbufen, because of its metabolite, 4-biphenylacetic acid) with quinolones or coadministration of theophylline with ciprofloxacin or enoxacin (because of cytochrome P450 [CYP] 1A2 interactions) potentiate the likelihood of seizures [1]. The exact mechanism by which quinolones induce seizures is controversial; however, there appears to be a strong
Table 1. Adverse drug reactions occurring in >1% of patients in phase 3 studies of intravenous/oral moxifloxacin, by drug administered.

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Moxifloxacin 400 mg (n = 550)</th>
<th>Comparators (n = 579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>6.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Liver function test abnormal</td>
<td>5.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.6</td>
<td>2.4</td>
</tr>
<tr>
<td>GGTP increased</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>0.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Rash</td>
<td>0.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

NOTE. Data are percentage of patients. Data were derived from Ball et al. [9]. GGTP, γ-glutamyl transpeptidase.

*Levofloxacin, trovafloxacin, and amoxicillin-clavulanate, with or without clarithromycin.

association between the similar chemical structures of certain subunits at position 7 of the quinolone nucleus and the chemical structure of γ-aminobutyric acid (GABA) [19, 20]. These select quinolones appear to displace GABA or compete with GABA binding at the receptor sites within the CNS, resulting in stimulation. Several researchers have demonstrated the associations between quinolones containing 7-piperazine (e.g., ciprofloxacin, enoxacin, and norfloxacin) and those containing 7-pyridoline (e.g., tosufloxacin and clinafloxacin) and increased epileptogenic potential [15, 19]. However, substituted (e.g., methylated) compounds containing 7-piperazinyl- or 7-pyridoline (e.g., levofloxacin, gatifloxacin, and sparfloxacin) are associated with reduced seizure-causing potential [19]. There exists one exception—lomefloxacin—that contains a substituted piperazine group at position 7 and has been linked to seizures [19]. This suggests a multifactorial contribution to this extreme form of toxicity. Quinolones with increased CNS penetration, coupled with unsubstituted piperazine or pyridoline groups at the 7 position, may be considered to be associated with a higher risk for seizures [21].

Gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin lack the specific structure-toxicity relationships noted to induce seizures; currently, only a single case report of a possible gatifloxacin-induced seizure exists [22]. In general, however, quinolones should be used with caution in patients with a history of seizure disorders, including epilepsy.

**QTc interval prolongation and TdP.** This topic has recently been extensively reviewed elsewhere [23]. A prolonged QTc interval >500 milliseconds overall or an increase in the QTc by 60 milliseconds from baseline has been associated with an increased risk of establishing an electrophysiologic milieu that predisposes to the occurrence of a polymorphic ventricular tachyarrhythmia, termed “TdP” [23]. The mechanism of most drug-induced (or acquired) QT interval prolongation is the blockade of the rapid component of the delayed rectifier K+ current (I_{Kr}). In the past, specific studies to determine the proclivity of a drug to block this current have lacked a uniform methodology and model, and studies may or may not have been conducted prior to the approval of a drug. To facilitate and provide standards for QT interval testing, the FDA’s International Conference on Harmonization S7B document has been developed to offer regulatory guidance [24]. The document recommends that new drugs undergo 3 preclinical tests: (1) human ether-a-go-go-related gene (HERG) studies, to examine the effect on the I\_Ks current; (2) canine Purkinje fiber studies, to determine the effect on the action potential; and (3) in vivo testing in the rodent model, to establish the drug’s influence on the ECG. Because the currently marketed quinolones have been approved at different times, most before the availability of this consensus document, differing qualities and quantities of cardiac toxicity studies have been available, creating concern among clinicians and researchers alike.

The background incidence of TdP in the general population is unknown, although some researchers have suggested an incidence of ~8.6 cases/10 million individuals [25]. These are general incidences, as reported from the FDA AERS database; hence, inherent limitations germane to spontaneous adverse event reporting exist, as well as the limitations associated with quantifying the denominator (number of prescriptions per treatment course). An individual’s risk for TdP, aside from the risk associated with receipt of a QT interval–prolonging drug, may be amplified by the presence of the cofactors discussed below.

Knowledge of patient- and drug-related variables should be integrated to form a multidimensional understanding and assessment of antimicrobial-related TdP [26]. Simply put, it is often not as straightforward as TdP occurring moments after a drug is administered. To this end, arrhythmias do not occur in the vast majority of patients who receive QT interval–prolonging drugs. In fact, most drug-induced cases of TdP appear to occur in a so-called susceptible population [27]. The discovery that a mutation in KCNE2, a potassium channel regulatory gene that, when combined with HERG, forms the I_{Kr} channel, correlates with susceptibility to drug-induced QT interval prolongation is important [28]. Studies of patients with a diagnosis of clarithromycin-induced TdP actually identified that they carried a sporadic missense mutation in KCNE2, which made subunits of the I_{Kr} channel 3-fold more susceptible to clarithromycin than wild-type channels. There are now 7 identified genotypes of long QT syndrome (LQTS) [23]. These patients are at increased risk for TdP when drugs that prolong the QT interval are prescribed. Thus, most quinolones, mac-
rolides, and azole antifungal agents should be avoided for patients with diagnosed LQTS.

The term “repolarization reserve” was introduced by Roden [29] to describe repolarization adaptation to a variety of insults. This concept is central to the idea that the accumulation of multiple risk factors predisposes individuals to developing TdP. In the normal ventricle, there exists virtually no potential for TdP to develop; this is principally because of the purpose of the repolarizing currents, particularly the $I_{Kr}$ and the slow component of the $I_{kr}$, in maintaining a large repolarization reserve that encourages electrical stability. However, when multiple TdP risk factors accumulate (figure 2) [23], the repolarization reserve becomes exhausted, resulting in electrical instability within the ventricle.

In general, the quinolones benefit from the lack of pharmacokinetic risk factors that predispose other antimicrobials to an association with the risk for TdP. For instance, fluoroquinolones do not inhibit CYP3A4, 2C9, and 2C19 and are not characterized by nonlinear pharmacokinetics, which differentiates them from most macrolides, ketolides, and azole antifungal agents [23, 30]. Similar to the aforementioned antimicrobial classes, the quinolones do interact with the $I_{Kr}$ to varying degrees, and some require dose adjustments to avoid excessive concentrations in the presence of renal insufficiency [23, 31]. Susceptible populations of patients are considered to be those mentioned in figure 2, particularly patients receiving class IA and III antiarrhythmic agents.

An analysis of comparative phase 2/3 studies of moxifloxacin to determine surrogate markers of arrhythmias is presented in table 2 [32]. Several postmarketing studies have been completed as commitments by the manufacturers to collect additional safety data for gatifloxacin and moxifloxacin. The Avelox Clinical Experience Study evaluated the safety and efficacy of moxifloxacin for the empirical treatment of outpatients with acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and mild-to-moderate community-acquired pneumonia [33]. Moxifloxacin was prescribed for 10 days at a dose of 400 mg daily. Important exclusions included patients taking class IA or III antiarrhythmics or patients with a known prolongation of the QTc interval. Patients with cardiovascular disease who were taking other medications associated with QT interval prolongation were included in the study population. An independent and external safety committee evaluated all case reports flagged with one of the following surrogates for potential cardiac toxicity: TdP, ventricular arrhythmia, sudden death, cerebral vascular accident, syncope, palpitations, ECG recording, or hospitalization (nonelective and not solely because of worsening infection). Of the 18,374 patients, 297 experienced “possibly related” cardiovascular events that warranted closer examination by the safety committee. Upon review, no evidence of ventricular tachyarrhythmias was noted, but less than half ($n = 122$) of patients had ECG data available. Two sudden deaths were reported among patients with multiple comorbidities. Overall, the independent safety committee con-

Figure 2. Multifactorial risks contributing to increased host susceptibility to Torsades de Pointes. CHF, congestive heart failure; $I_{kr}$, delayed rectifier K+ current; LQTS, long QT syndrome; TMP-SMZ, trimethoprim-sulfamethoxazole.
Studies of intravenous moxifloxacin

Important exclusion criteria underlie cardiovascular disease and those receiving cardioprotective agents. ECG monitoring was not required for participation in the study; thus, limited electrophysiologic data were available. Among patients with cardiovascular disease, 0.3% experienced palpitations, <0.1% experienced syncope, and <0.1% experienced tachycardia.

Levofloxacin was initially approved prior to the close scrutiny of drugs associated with small changes in the QTc interval. Thus, large postmarketing studies for safety were not required. However, 17 case reports associating levofloxacin with QT interval–related toxicities, usually TdP (most often in patients with concurrent risk factors), have been published in the literature [23]. On the basis of these findings, the use of levofloxacin, like the use of all other quinolones, should be avoided in susceptible populations, from a patient safety perspective [23].

The quinolone most likely to cause TdP, sparfloxacin, is no longer marketed in the United States. Because of the relatively few numbers of patients treated with grepafloxacin, it is difficult to ascertain its overall risk, although it does appear to inhibit IKr to a lesser degree than does sparfloxacin [23]. Ciprofloxacin remains the safest quinolone to date, as confirmed through in vitro and in vivo models and from postmarketing experience. A single case of TdP has been reported in association with administration of ciprofloxacin [34]. With regard to gatifloxacin, levofloxacin, and moxifloxacin, these agents have been associated infrequently with TdP, regardless of route of administration, and are considered to be interchangeable from a cardiac safety perspective [23]. Postmarketing studies of gatifloxacin and moxifloxacin in the United States have added to the overall confidence level. Nonetheless, patients with a reduced repolarization reserve (particularly those receiving concurrent class IA or III antiarrhythmic agents) should not receive gatifloxacin, levofloxacin, moxifloxacin, or gemifloxacin. Although gemifloxacin appears to be similar to the currently available quinolones with respect to cardiac safety, fewer postmarketing data are available. Thus, overall cardiotoxicity risk remains to be determined.

**Glucose homeostasis.** Like the insulin secretagogues, the quinolones, as a class, have demonstrated the capacity to close K⁺-ATP channels in the pancreatic β cell, resulting in release of insulin and subsequent hypoglycemia [35]. Historically, quinine has been shown to cause hypoglycemia by the same mechanism. Because quinine and the quinolone antibiotics are related by chemical structure (quinoline rings), their insulinotropic effects may be explained, at least in part, by this

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**Table 2. Adverse events considered to be surrogates for arrhythmias from comparative phase 2/3 studies.**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Oral moxifloxacin (n = 5407)</th>
<th>Comparatorsa (n = 5097)</th>
<th>Intravenous moxifloxacin (n = 550)</th>
<th>Comparatorsa (n = 579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
<td>42 (0.8)</td>
<td>35 (0.7)</td>
<td>16 (2.9)</td>
<td>13 (2.3)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>24 (0.4)</td>
<td>19 (0.4)</td>
<td>8 (1.5)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>19 (0.4)</td>
<td>21 (0.4)</td>
<td>11 (2.0)</td>
<td>8 (1.4)</td>
</tr>
<tr>
<td>Palpitation</td>
<td>13 (0.2)</td>
<td>11 (0.2)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>13 (0.2)</td>
<td>2 (&lt;0.1)</td>
<td>11 (2.0)</td>
<td>10 (1.7)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11 (0.2)</td>
<td>9 (0.2)</td>
<td>14 (2.6)</td>
<td>13 (2.3)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>11 (0.2)</td>
<td>1 (&lt;0.1)</td>
<td>0 (0.0)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Syncope</td>
<td>9 (0.2)</td>
<td>10 (0.2)</td>
<td>2 (0.4)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (&lt;0.1)</td>
<td>3 (&lt;0.1)</td>
<td>2 (0.4)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>QT interval prolongation</td>
<td>4 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td>7 (1.3)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (&lt;0.1)</td>
<td>5 (0.1)</td>
<td>2 (0.4)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>...</td>
<td>...</td>
<td>5 (0.9)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients. Data were derived from Ball et al. [32]. ECG, electrocardiogram.

a Levofloxacin, trovafloxacin, and amoxicillin-clavulanate, with or without clarithromycin.
commonality. However, the mechanism for hyperglycemia remains poorly understood.

Product labels for ciprofloxacin, gatifloxacin, levofloxacin, and moxifloxacin mention the possibility of hypoglycemia and hyperglycemia, whereas the product label for gemifloxacin mentions hyperglycemia only [36–40]. Although glucose disturbances appear to be a class effect, it is clear that some of these agents can be differentiated. For instance, early studies of clinafloxacin exposure in healthy volunteers demonstrated a substantial increases (165%–235%) in insulin levels from baseline measurements, resulting in a 47%–51% decrease in the blood glucose level [41]. These effects ostensibly resolved ~4 h after administration. In phase 2 and 3 studies, clinafloxacin was associated with a 4% incidence of hypoglycemia (vs. an incidence of 1.1% in comparator-treated patients) [42].

CYP drug interactions do not explain interactions that would result in pharmacokinetic changes in most medications used to treat type 2 diabetes. Of the quinolones, only ciprofloxacin, clinafloxacin, enoxacin, grepafloxin, pefloxacin, and trovafloxacin inhibit CYP 1A4 isoenzymes [43]. Few drugs are metabolized by these isoenzymes, but important drugs include the methylxanthines (theophylline and caffeine) and warfarin. Displacement of glyburide from human proteins may result in increased drug effect, but this usually occurs with the coadministration of such drugs as trimethoprim-sulfamethoxazole, certain NSAIDs, salicylates, chloramphenicol, and β-adrenergic–blocking agents [44]. The quinolones have relatively lower degrees of protein binding, and those with higher degrees of protein binding (e.g., trovafloxacin and gemifloxacin) have not appeared to be associated with greater incidences of hypoglycemia than have drugs with lower degrees of protein binding (e.g., levofloxacin and gatifloxacin).

Twelve patients with type 2 diabetes who were concurrently receiving ciprofloxacin and glyburide were reported to have increased glyburide levels, but this did not result in dysglycemia [44]. Despite this purported interaction, only a few case reports describing hypoglycemia associated with the coadministration of ciprofloxacin and glyburide exist in the literature, although the product labels for each drug do indicate a potential interaction [45, 46].

Gatifloxacin also has been studied in patients with type 2 diabetes who are concurrently receiving glyburide, and it has been shown to result in no pharmacokinetic interactions or glucose-related adverse events [47]. In another study, gatifloxacin was compared with ciprofloxacin and placebo in patients with type 2 diabetes maintained by diet and exercise [48]. Important findings included the following: (1) fasting glucose levels 0–6 h after administration of gatifloxacin on days 1–10 of treatment showed a downward trend in glucose similar to that seen after administration of ciprofloxacin but not statistically different than that associated with placebo, and (2) gatifloxacin resulted in modest and transient release of insulin (short-term, but not long-term, effect), whereas ciprofloxacin resulted in a modest increase in insulin over the long term but not the short term [48]. Moxifloxacin also has been studied in combination with glyburide, and it has been found to have no effect on insulin concentrations [49]. However, coadministration of these drugs did result in small but statistically significant increases in blood glucose, as measured by 7% and 6% increases in blood glucose area under the curve (AUC) and peak concentrations 0–6 h after administration, respectively [49]. These changes were stated to be clinically unimportant [49].

In postmarketing studies of gatifloxacin for the treatment of respiratory tract infections, associations with hyperglycemia were rare and were increased in elderly patients (age <65 years, <0.1%; age 65–79 years, 0.2%; and age ≥80 years, 0.6%; P < .001) [11]. In patients with diabetes treated with gatifloxacin, the overall incidence of hypoglycemia was 0.4%, 0.7%, and 1.6% for patients <65, 65–69, and ≥80 years old, respectively; corresponding incidences of hyperglycemia were 1.0%, 1.6%, and 3.3%, respectively [11]. Despite a low incidence, case reports of hypoglycemia and hyperglycemia associated with the use of gatifloxacin have surfaced, and the FDA-approved prescribing information has been changed to include a stronger precautionary section related to glucose homeostasis [50, 51]. According to the product label of gatifloxacin, hypoglycemic events are more likely to occur within the first 3 days of therapy, whereas hyperglycemia is more likely to develop during days 4–10 of treatment. In view of the absence of pharmacokinetic drug interactions, these events appear to be occurring in a potentially susceptible population described as older patients with type 2 diabetes and renal insufficiency who are receiving glucose-lowering agents, such as glyburide. The metabolites of glyburide can accumulate in patients with renal insufficiency, which, in concert with the failure to adjust the dose of gatifloxacin in this scenario, may indeed create a vulnerable population [46]. In fact, when exposure to gatifloxacin was simulated in patients with severe hyperglycemia, AUC values were 2–3 times those observed in patients with normal renal function [52]. On the basis of their findings, the authors suggest empirically adjusting the dose of gatifloxacin to 200 mg daily for patients aged >65 years with community-acquired respiratory tract infections.

In a pooled analysis of 30 oral and 2 iv/po phase 2/3 clinical studies of moxifloxacin, the frequency of hyperglycemic-hypoglycemic episodes and glucose-related adverse events and adverse reactions (i.e., those considered to be drug-related), compared with the frequency of such episodes, events, and reactions associated with comparator antimicrobials (i.e., penicillins, cephalosporins, macrolides, doxycycline, and fluoroquinolones), was evaluated [53]. Similar evaluations were conducted on data pooled from 5 postmarketing surveillance studies.
The phase 2/3 database comprised 14,731 patients (8474 receiving moxifloxacin and 6257 receiving comparator antimicrobials). There were no drug-related hypoglycemic adverse events reported in association with moxifloxacin in either the oral or iv/po database. Drug-related hyperglycemic adverse events were reported in 7 moxifloxacin-treated patients (<0.1%) in the oral study database; none of these cases was considered to be serious, and 6 of the 7 moxifloxacin-related cases were graded as mild and required no countermeasures. There were no cases of drug-related hyperglycemic events in any patient enrolled in the iv/po studies. In addition, data from 5 postmarketing studies of moxifloxacin (involving >46,000 subjects) reported no episodes of hypoglycemia and 2 non–drug-related episodes of hyperglycemia [53]. On the basis of this analysis of the data pool for phase 2/3 clinical trials and postmarketing studies of moxifloxacin, it appears that administration of moxifloxacin has no clinically relevant effect on blood glucose homeostasis, similar to most other agents within this class.

A search of the FDA's New Drug Applications database [54] for gatifloxacin, levofloxacin, and moxifloxacin through the Freedom of Information Act has revealed an incidence of glucose homeostasis–related adverse effects of <2% (table 3). The incidence of hyperglycemia due to gemifloxacin has been reported as 1.4%, and further experience will better define the safety profile of this drug.

Some caution should be used when interpreting low-incidence adverse events. Quinolone-associated effects on blood glucose in patients with type 2 diabetes are rare and usually occur in patients with concurrent risk factors for dysglycemia; thus, causality is difficult to ascertain in most cases. It should be remembered that elderly patients without diabetes can be susceptible to blood glucose disturbances. For instance, in one study, hypoglycemia was reported to have occurred in 0.5% of hospitalized elderly patients without diabetes [55]. Statistically significant risk factors for symptomatic hypoglycemia, as determined by multivariate logistic modeling in this population, were not evidently drug related but, rather, were due to low plasma albumin levels, liver disease, malignancy, and congestive heart failure [55]. A more recent study reported similar risk factors. Hospitalized patients >70 years old with hypoglycemia were compared with a similar group of elderly patients without hypoglycemia [56]. Diabetes was known to be present in only 42% of the patients with hypoglycemia. Multivariate analysis revealed that sepsis, albumin level, alkaline phosphatase level, creatinine level, sulfonylurea use, insulin treatment, and female sex were all independent risk factors for developing hypoglycemia [56].

In summary, glucose homeostasis abnormalities have been reported for most of the quinolones, as well as a number of medications, including other antimicrobials. Such abnormalities occur rarely, and their exact causes are not completely known. For quinolones that rely significantly on renal pathways for clearance (gatifloxacin and levofloxacin), it is prudent to consider dose adjustment for elderly patients with type 2 diabetes, to reduce the risk of hypoglycemia and hyperglycemia.

### Arthropathies and tendinitis

Analysis of reports of spontaneous adverse events indicate that general musculoskeletal-related adverse events occur more frequently in association with quinolones (incidence, 14.7%) than with other systemic antimicrobials (incidence, 0.3%; P < .01) [12]. Among the quinolones, significant differences were observed between agents, with levofloxacin and pefloxacin being associated with more reports than were ciprofloxacin, enoxacin, moxifloxacin, and rufloxacin (P < .01).

In clinical studies, quinolone-associated arthropathy, primarily in weight-bearing joints, has been reported to occur in ~1% of patients who receive quinolones [1]. Arthropathy usually presents as pain, stiffness, and swelling of the involved joints within the first few days of therapy and resolves within days to weeks after discontinuation of therapy. The leading postulate for the mechanism of quinolone-associated arthropathies is the chelation of magnesium, resulting in altered functionality of chondrocyte surface integrin receptors [57]. However, some in vitro data suggest that defective proteoglycan and procollagen synthesis may be involved [58].

Postmarketing data have revealed cases of quinolone-associated tendinitis and tendon rupture, primarily affecting the Achilles tendon, as well as cases occurring in the shoulders and hands. In up to 50% of patients, symptoms appear bilaterally [59]. Symptoms emerge, on average, 13 days after initiation of quinolone therapy (range, 1–152 days) and may not subside for >2 months after discontinuation [1, 59]. In addition, corticosteroids appear to enhance the risk of tendinitis during quinolone therapy. Although initial reports from France implicated pefloxacin, other drugs within the class have been associated with this rare adverse event [60]. In a recent review of a spontaneous adverse event reporting database in Italy, serious tendon disorders occurred in 16 patients over a 2-year period (median patient age, 72 years; range, 33–80 years); 31% of the patients were also receiving steroids [12]. Among the quinolones, levofloxacin was associated with the highest rate

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Blood glucose level, mg/dL[^a]</th>
<th>Total no. of patients (% of patients with hypoglycemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gatifloxacin</td>
<td>&lt;60</td>
<td>3000 (1.7)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&lt;70</td>
<td>2386 (1.9)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>&lt;50</td>
<td>2613 (0.65)</td>
</tr>
</tbody>
</table>

[^a]: Used to define hypoglycemia.
of tendinitis in this series (11.3 reports/daily defined dose/100 inhabitants/day) [11]. Reports to the FDA AERS database indicate that crude frequencies of ciprofloxacin- and levofloxacin-related tendon disorders are 0.5 and 0.6 cases/100,000 treatments, respectively [1]. A case-controlled study indicated that the risk of Achilles tendinitis or rupture associated with quinolone therapy was 3.2 cases/1000 patient treatment–years [61]. A recent population-based case-control study also confirmed a previous risk factor for quinolone-associated Achilles tendon ruptures to be older age, especially among patients receiving concurrent corticosteroids [62]. The mechanism of injury appears to resemble that of quinolone-related arthropathies; in animal models, magnesium-deficient animals showed a more pronounced injury to tendocytes after treatment with ofloxacin [63].

The FDA recommends discontinuation of quinolone therapy at the first sign of tendon pain and to refrain from exercise until tendinitis can be excluded [1]. MRI may be useful in diagnosing tendinopathies. As with other rarely occurring quinolone-related adverse events, it appears to be difficult to distinguish more or less likely culprits between the class members (with the exception of pefloxacin, which has been associated with more cases, regardless of patient age). The populations of patients most susceptible to tendon disorders, who are at risk when quinolones are administered, include those receiving corticosteroids, particularly elderly patients and athletes in training.

Phototoxicity. Phototoxicity is a dramatic and unusual dermatologic complication of quinolone therapy ranging from mild to severe reactions that usually occur within hours of exposure to a UV light source. Singlet oxygen molecules and other free radicals are generated when UV light comes in contact with certain quinolone compounds. Under these circumstances, the resulting products are believed to attack cellular components, including lipid membranes, resulting in a severe inflammatory process [20, 64, 65]. These reactions are more commonly associated with specific agents, particularly lomefoxacin, sitafloxacin, and sparflloxacin, and are inextricably related to the chemical structure [20]. Halogenation (chlorine, fluorine) of position 8 in concert with the fluorination of position 6 (i.e., the so-called double-halogenated quinolones) has demonstrated significant phototoxic potential [15]. The aforementioned compounds, along with several other agents that were abandoned during development (e.g., BAY y 3118 and clinafloxacin) exemplify this strong association between structure and phototoxicity. For perspective, phase 2 and 3 trials for clinafloxacin revealed relatively high rates of phototoxicity (po, 16.1%; iv, 1%) [42].

With regard to the use of other quinolones, including ciprofloxacin and trovafloxacin, phototoxicity is an uncommon adverse reaction and has not been reported in association with gatifloxacin or moxifloxacin in clinical trials. The reason for the notable absence of phototoxicity has been determined to be the presence of the 8-methoxy group, which is possessed by both gatifloxacin and moxifloxacin (figure 1C) and is a significant advancement in safety for this class of agents. The overall phototoxic-potential ranking of certain quinolones, from greatest phototoxicity to least, is as follows: lomefoxacin, fleroxacin, clinafloxacin, sparflloxacin, enoxacin, pefloxacin, ciprofloxacin, grepfoxacin, gemifloxacin, levofloxacin, norfloxacin, ofloxacin, trovafloxacin, gatifloxacin, and moxifloxacin [1, 8–10, 15]. In addition, susceptible patient populations include those receiving moderately phototoxic quinolones and those who are exposed to significant outdoor sunlight or UV light from indoor tanning facilities.

Anaphylaxis. Anaphylaxis (type I, IgE-mediated reactions occurring within 1 h of administration) more rarely occurs in association with quinolone use than with the use of other antimicrobial classes, such as the β-lactams [66]. Forms of type I reactions reported in association with quinolone use include urticaria, angioedema, and anaphylactic shock. These reactions have been associated with quinolone-specific IgE, and there appears to be substantial cross-reactivity among various quinolones, suggesting that the class should be avoided for patients with a history of immediate hypersensitivity reactions to the class [67]. Unfortunately, the reliability of skin testing has been considered to be poor because of the number of false-positive results for healthy control subjects (purportedly because of direct histamine release caused by the quinolones) [68]. Thus, the only definitive test to diagnose quinolone-induced immediate hypersensitivity is a challenge with the drug itself, which is a risky proposition, because fatalities have been reported [66, 69]. Although challenges and desensitizations have been successfully administered to patients who required therapy with a quinolone [70, 71], quinolones are contraindicated in patients who exhibit hypersensitivity reactions.

Immune-related idiosyncratic reactions. A number of relatively uncommon immune-related toxicities have been linked with quinolone use, including hemolytic-uremic syndrome, hemolytic anemia, thrombocytopenia, leukopenia, acute interstitial nephritis, acute hepatitis, acute cholestatic jaundice, Stevens-Johnson and Lyell syndromes, fixed drug eruption, cutaneous vasculitis, macular-papular exanthema, acute pancreatitis, serum sickness–like disease, angioimmunoblastic lymphadenopathy, acute exanthematous pustulosis, and eosinophilic meningitis [66]. Ostensible immune-mediated reactions, such as hepatitis, pancreatitis, interstitial nephritis, hemolytic anemia, and hemolytic-uremic syndrome, may be due to combined antibody and T cell interaction with the drug and host. Maculopapular exanthema has been associated with noncovalent interactions with T cell receptors and major histocompatibility complex. Quinolones are associated with a nonspecific capacity to cause mast cells and basophils to release histamine, on the basis of animal studies
measuring plasma histamine levels and the appearance of a generalized rash [72]. This may be, at least in part, a potential mechanism for some immune-mediated adverse reactions. Rash appears to be more common with gemifloxacin use, particularly in younger women (<39 years old) treated for 7 days (12%) versus those treated for only 5 days (2.1%) [8]. The fact remains that, apart from the elucidated mechanisms of cellular injury, the majority of these adverse reactions remain poorly understood.

Trifluorinated quinolones (e.g., temafloxacin, tosufloxacin, fleroxacin, and trovafloxacin) also appear to pose greater risks for potentially fatal immune-based toxicities. All of the trifluorinated quinolones mentioned contain a 1-(2,4)-difluorophenyl group, with the exception of fleroxacin. The most serious immune-related reactions that are recognized include temafloxacin syndrome and trovafloxacin-associated hepatotoxicity [15, 73]. Temafloxacin syndrome is characterized by hemolysis, renal failure, and thrombocytopenia [73] and occurs at an estimated incidence of 1 case/5,000 prescriptions [74]. Reports of hepatic-related injury involving eosinophilic infiltration, hepatocellular vacuolar degeneration, and necrosis associated with trovafloxacin were recognized soon after the drug became available for general use [74]. Severe hepatic reactions were reported in 140 patients only after ~2.5 million courses of therapy were administered [75]. The high frequency of adverse events associated with fleroxacin (e.g., 84% in a study of 79 patients, with 48% of adverse events being severe), has been suggested to be related to the trifluorinated chemical configuration of this agent [15]. Tosufloxacin has been associated with eosinophilic pneumonitis in a report from Japan [75].

Clostridium difficile-associated diarrhea (CDAD). The use of antimicrobials in general, in conjunction with exposure to the organism (usually through hospitalization or a stay at a long-term care facility), are primary risk factors for infection caused by C. difficile. In fact, all antimicrobials mention the risk of C. difficile infection in their product labels. Overall rates of diarrhea associated with use of the newer fluoroquinolones, although not specific for CDAD, were comparable in phase 2/3 studies (4%, 5.2%, and 6% for gatifloxacin, moxifloxin, and levofloxacin, respectively) [32].

A recent report demonstrated the effect of a fluoroquinolone formulary change (i.e., from levofloxacin to gatifloxacin) at a long-term care facility on the rates of CDAD [76]. Rates of CDAD were assessed during two 9-month periods. Ten levofloxacin-associated cases of CDAD were identified in the preinterchange period, compared with 14 gatifloxacin-associated cases of CDAD during the postinterchange period, constituting the ostensible outbreak. Calculated attack rates were higher for the gatifloxacin-associated cases (30%) than the levofloxacin-associated cases (17%). Overall, the rates were high for both groups and were confounded by the fact that many patients received ≥1 antimicrobial prior to developing CDAD. Nonetheless, when the facility switched back to levofloxacin, the number of cases of CDAD declined. The authors of the report postulated that the anaerobic activity of gatifloxacin stimulated the outbreak of CDAD [76].

Interestingly, just prior to the conversion back to the use of levofloxacin, sodium hypochlorite (a sporidical cleaning agent) was used to clean the long-term care facility, and handwashing and hygiene techniques were emphasized. Quaternary ammonium–based detergents commonly used to clean patient rooms in hospitals are not sporidical and, in fact, can actually increase the spore burden in the environment [77]. Interventions that selectively replaced quaternary ammonium–based cleaning agents with chlorine-based disinfectants (sodium hypochlorite) have alone resulted in significant reductions in cases of CDAD, as well as the environmental spore burden [77, 78]. High rates of C. difficile may warrant that locations change their use of products to hypochlorite-based products because of the more reliable sporidical activity of such products [79]. It is important to emphasize that acquisition of CDAD is a multifactorial process consisting of exposure to the organism in the environment [80], prior use of any antimicrobial agent [81] (perhaps compounded by the prior use of antimicrobials that are specifically inactive or have borderline activity against C. difficile [82]), host levels of serum immunoglobulins [83], advanced age [84], and severity of the underlying illness of the host [84]. With regard to the theory that antianaerobic regimens contribute to CDAD, antimicrobials lacking activity against obligate anaerobes (i.e., most cephalosporins, levofloxacin, and ciprofloxacin) have been significantly associated with CDAD [85–90], whereas such agents as piperacillin-tazobactam have been shown to be relatively protective against CDAD [91]. This result is contrary to the proposed assumption in the fluoroquinolone trial described above. Nonetheless, regardless of their activity against anaerobes, quinolones should be used judiciously to minimize such complications as CDAD.

Effect on bowel microflora. Antimicrobial agents, including the quinolones, can have a selective effect on the normal ecology of the human intestine [92]. Suppression, chiefly among aerobic gram-negative organisms, occurs in association with this class of drugs, whereas enterococci and anaerobes can also be reduced. In one study [92], the reconstitution of normal flora was similar between ciprofloxacin, levofloxacin, and moxifloxacin use and occurred at 14 days after discontinuation of treatment. For gatifloxacin, the return of normal microflora was noted to occur 40 days after discontinuation [92]. The clinician should be cognizant that drugs and food additives can be modified by intestinal anaerobes. For instance, Escherichia coli, which is a gram-positive anaerobic bacilli constituent of the bowel flora, can reduce digoxin to an inactive form. Approximately 10% of the general population and up to 30% of urban populations have E. coli as part of their fecal flora.

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and typically require increased dosages of digoxin. For this reason, the administration of antibiotics that have activity against this organism may result in up to a 2-fold increase in digoxin levels [93]. Like macrolides and tetracyclines, quinolones as a class have activity against this bacterium [94–96]. Because all antimicrobial agents affect normal flora as well as the targeted pathogens, infection-appropriate durations of therapy (particularly short courses, when applicable) should be prescribed.

USE IN SPECIAL POPULATIONS

Pediatric patients. Ciprofloxacin recently received FDA approval for the treatment of infections in children, and gatifloxacin has also been examined in large-scale studies of pediatric patients. Apprehensions related to the use of quinolones in the pediatric population have centered around 2 issues—the development of antimicrobial resistance and safety. In terms of the latter issue, data regarding quinolone-induced damage to weight-bearing cartilage and joints in juvenile animals led to concerns that these effects may manifest more commonly in human children than adults. Thus, when ciprofloxacin was approved in 1989, it was not approved for use in children. As time advanced, the risks were outweighed by benefits in specific therapeutic pediatric arenas, such as the treatment of exotic or typically resistant bacteria in patients with cystic fibrosis or severe infections in immunocompromised hosts.

Animal models support the notion that quinolone-associated damage begins in the articular-epiphyseal-cartilage complex [57]. This toxicity has been limited to juvenile animals for the studied quinolones, with the exception of pefloxacin, in which the toxicity extends to mature animals as well [57]. Arthropathies have been reported in children receiving quinolones, particularly pefloxacin, as well as in adults. In fact, 7 of the 10 cases reported in children occurred during treatment with pefloxacin, and arthropathy manifested as joint pain or swelling [57]. Apart from these 7 cases, a review of >7000 children who had received quinolones showed no signs of arthropathy [57]. A database of children with cystic fibrosis treated with ciprofloxacin revealed 31 cases of arthralgias in >2000 treatment courses [97]. These cases were reported to be reversible after discontinuation of the drug, and no evidence of arthropathy was found.

Data excerpted from a global clinical database of patients <18 years old who were treated with ciprofloxacin were recently published (n = 2622) [98]. The incidences of arthralgia and arthritis as a function of duration of therapy were 1% and <1% at 1–29 days, 4% and 1% at 30–59 days, and 4% and 0% at >60 days of therapy, respectively [94]. From a similar database, albeit from comparative studies, of information on ciprofloxacin (n = 462) and control agents (n = 456), incidences of joint disorders (5% for ciprofloxacin and 8% for control agents) and arthralgias (3% for ciprofloxacin and 3% for control agents) were reported [98]. Control agents included aminoglycosides, trimethoprim-sulfamethoxazole, and β-lactams. To a lesser extent, the use of gatifloxacin in children with no reports of arthropathies has been studied [99]. Overall, the manifestation of arthropathies in children is rare and does not appear to be different than nonquinolone comparators. In the arthralgia cases that have been reported, the symptoms have been mild and transient and have dissipated after discontinuation of therapy [98]. The compelling rationale for avoidance of general use in children, chiefly the minimization of development of resistance to quinolones, still exists.

Elderly patients. Although adverse events associated with quinolones have not been reported in greater frequency in elderly patients (in general), large trials specifically enrolling elderly patients are not widely conducted [100]. As a surrogate, although pharmacokinetics do not change in elderly patients per se, the pharmacokinetics of many drugs are affected by renal function and body weight. In general, elderly patients are of smaller body mass than are younger individuals, and their kidney function is diminished by comparison. In humans, an ~1-mL/min/year reduction in the glomerular filtration rate occurs after the age of 30 years [101]. This correlates well with findings that creatinine clearance is decreased by ~40% in individuals >80 years of age (despite serum creatinine values that appear to be normal) [102].

For those quinolones that are primarily eliminated through the kidneys, studies comparing the pharmacokinetics of ofloxacin [103], levofloxacin [104, 105], and gatifloxacin in elderly versus younger adults [97, 105] indicate that there are pharmacokinetic differences between these populations. However, the differences were attributed again to differences in renal function and not specifically to age.

Moxifloxacin relies the least on renal function for its elimination and currently is the only drug class representative used for systemic infections that does not require dosing adjustments for any degree of renal insufficiency [38, 106]. Because renal impairment does not influence the pharmacokinetics of moxifloxacin, age-related changes in renal function do not affect its pharmacokinetics in elderly patients. A recent retrospective analysis of phase 2/3 studies of oral moxifloxacin stratified adverse events according to patient age (<65, 65–74, or ≥75 years) [9]. The incidence of moxifloxacin-related adverse events was similar across all age groups (27.2%, 21.7%, and 22.7%, respectively) [9]. Moreover, the rates of both total and serious adverse events were comparable among patients who received moxifloxacin and those who received comparators. Among patients ≥65 years old, nausea was reported in 4% of patients in each treatment group, whereas diarrhea was seen in 5% of patients who received moxifloxacin and in 4% of patients who received comparators. In addition, the incidence of cardiovascular adverse events (e.g., tachycardia, vasodilation, and pal-
concentration) was 0.8% in association with both moxifloxacin and comparator use in patients aged <65 years, whereas the incidence among patients aged ≥65 years was 1.4% for patients who received moxifloxacin and 1.5% for those who received comparators [9].

For ciprofloxacin, studies of elderly patients and studies of younger adults have shown comparable pharmacokinetics [100], with the exception of one study that enrolled elderly patients with severe renal insufficiency [107]. Exposures in this study revealed a half-life that was 2-fold longer in elderly patients with severe renal insufficiency [107].

Dose-related toxicities can be avoided by identifying populations of patients with diminished renal function or for whom higher drug exposures may be expected (e.g., elderly patients with low body mass). Proactive dose reductions for quinolones that are eliminated primarily through the kidneys may reduce the likelihood of exaggerated drug exposures and, thus, toxicities in this population.

**CONCLUSIONS**

Overall, the currently marketed quinolones are well tolerated and safe, with safety profiles similar to those of other antimicrobial classes. Although rare, some adverse effects are more common in association with quinolones than with other antimicrobial classes, including tendinitis and CNS-related effects. Fortunately, quinolones associated with rare and potentially life-threatening toxicities have been removed from the market or never became available. No perfect data source is reliable on its own to quantify risk assessment, because preclinical testing, phase 1–3 trials, and postmarketing surveillance all have limitations in their ability to identify true quinolone-related toxicities. Despite their inadequacies, data from all of these sources may be used to objectively assess the risks associated with antimicrobial therapy for formulary status or individual patient treatment decisions.

With recent given attention to quinolone-related adverse events, susceptible populations of patients have been further characterized. Gatifloxacin, levofloxacin, and moxifloxacin should not be used in patients receiving class IA and III antiarrhythmic agents or in patients with diagnosed LQTS or a history of a prolonged QT interval. In terms of glucose-related adverse events, avoidance of overexposure to quinolones in patients with type 2 diabetes (e.g., by adjusting the dose of those agents that are eliminated through the kidneys) is warranted, and adherence to precautionary and warning labels is needed. In addition, the consideration of an empirically lower dose of gatifloxacin for elderly patients is de rigueur. The concurrent administration of ciprofloxacin with glyburide has resulted in elevated glyburide concentrations, with or without symptomatic hypoglycemia, and the combination should be used only if no other alternative therapies are available. Patients with a history of a seizure disorder, including epilepsy, should not receive quinolones (or should receive them with caution). Athletes in training should not receive quinolones, and quinolones should be used with caution for elderly patients receiving corticosteroids, to avoid tendinitis or tendon rupture.

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