Fluoroquinolone Toxicity Profiles: A Review Focusing on Newer Agents

Benjamin A. Lipsky and Catherine A. Baker

From the Veterans Affairs Puget Sound Health Care System and University of Washington School of Medicine, Seattle, Washington; and Providence St. Vincent Medical Center, Portland, Oregon

Since their introduction in the 1960s with nalidixic acid, quinolone antimicrobial agents have undergone extensive synthetic and clinical development, resulting in improved antimicrobial activity, pharmacokinetic features, and toxicity profiles [1, 2]. Nalidixic acid had limited use and frequently caused adverse events [3]. The pyridopyrimidine and cinnoline derivatives introduced in the 1970s demonstrated broader antimicrobial spectra and better pharmacokinetic profiles. The most important breakthrough, however, was the development of the fluoroquinolones (FQs) in the 1980s, with broad antibacterial spectra, excellent pharmacological properties, and a low incidence of serious adverse events [2–4]. While the pharmacokinetics and efficacy of these agents have improved, a major ongoing goal has been to further reduce adverse events [4]. This paper will review the safety profile of FQ agents, assess differences among class members, and address the safety of these agents in special populations. We will focus on the newest FQs approved in the past 2 years by the U.S. Food and Drug Administration (FDA): levofloxacin,sparfloxacin, grepafloxacin, and trovafloxacin.

For 2 decades fluoroquinolones have been found to be generally well-tolerated and safe. Adverse events may be inherent to the class or influenced by structural modifications. The commonest adverse events are gastrointestinal tract (GI) and central nervous system (CNS) reactions; nephrotoxicity and tendinitis are infrequent, but agents differ greatly in phototoxic potential. Fluoroquinolones are safe in elderly, human immunodeficiency virus–infected, and neutropenic patients, but because of possible effects on articular cartilage, they are not currently recommended for children or pregnant women. Four new agents have recently been licensed. Levofloxacin causes few GI or CNS adverse events and is minimally phototoxic. Sparfloxacin infrequently causes GI or CNS effects but is associated with relatively high rates of phototoxicity and prolongation of the electrocardiographic QT interval (Q-T interval, corrected for heart rate). Grepafloxacin causes relatively high rates of GI effects, taste perversion, and QT interval prolongation, but it is minimally phototoxic. Trovafloxacin is associated with a moderate rate of GI effects and a relatively high incidence of dizziness but has low phototoxic potential.

General Overview of Toxicity of FQ Antimicrobials

With the exception of temafloxacin [5–7], FQs have proven to be a well-tolerated class of drugs [8, 9], especially when compared with other commonly prescribed antimicrobials [2, 10]. A review of safety results from 28 prospective, randomized, double-blind, placebo- or active-controlled clinical trials revealed that in 22, FQ agents were not significantly different from nonquinolone comparator agents or placebo in terms of the proportion of patients experiencing adverse events, and in 5 studies FQ agents were significantly superior to comparator agents [11]. Adverse events caused by various FQs are generally comparable, although for individual agents the incidence and type may differ [1, 12]. Reported rates of adverse events depend on definitions used and how information was obtained. Prospective comparative trials give the most reliable (and usually highest) rates. Table 1 summarizes the most frequently reported adverse events associated with FQ agents; the CNS and gastrointestinal (GI) tract are most commonly involved [1]. Toxic effects observed only in animal models or not shown to be clinically relevant include chondrotoxicity, reproductive and developmental toxicity, genotoxicity, and carcinogenicity [2, 4, 8, 11].
Table 1. Most frequently reported adverse events associated with fluoroquinolone (FQ) antibacterials.

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Specific adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, abdominal pain, diarrhea, anorexia</td>
</tr>
<tr>
<td>CNS</td>
<td>Headache, dizziness, sleep disorder(s), mood changes, confusion, delirium, psychosis, tremor, seizure</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transient rise in level of liver function enzymes, cholestatic jaundice, hepatitis, hepatic failure</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia, crystalluria, hematuria, interstitial nephritis, nephropathy, renal failure</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash, pruritus, photosensitivity, hemorrhagic bullae, leg pigmentation, urticaria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthropathy, tendinitis, tendon rupture</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, tachycardia, QT interval prolongation</td>
</tr>
<tr>
<td>Other</td>
<td>Drug fever, chills, serum sickness–like reaction, anaphylactoid reaction, anaphylaxis, angioedema, bronchospasm, vasculitis</td>
</tr>
</tbody>
</table>

NOTE. Occurrence and incidence of adverse events vary among the FQ agents. QT, interval = Q-T interval, corrected for heart rate.

Adverse effects such as GI symptoms and arthropathy do not appear to be affected by structural modification. Crystalluria, CNS symptoms, and phototoxicity are highly related to chemical changes [4, 13]. Chemical structures of various FQs are shown in figure 2.

Overview of Safety with the Newest FQs

Levofoxacin

Levofoxacin (Levaquin; Ortho-McNeil Pharmaceutical, Raritan, NJ), the active 1-isomer of racemate ofloxacin, is approximately twice as potent as ofloxacin against many susceptible pathogens [14]. It is available in both oral and parenteral formulations and has been approved for a broad range of indications, including infections of the upper and lower respiratory tract, skin and skin structure, and upper and lower urinary tract [15].

During phase II and III clinical trials, the safety and tolerability of levofloxacin among 5,388 patients were assessed. In dosage regimens ranging from 250 mg once daily for 7–10 days to 500 mg once daily for 14 days, the drug was generally well-tolerated and safe [16–25], with fewer GI, CNS, and dermatologic adverse events occurring than with use of ofloxacin [15, 26]. North American clinical trials of levofloxacin found an overall incidence of possible or probable drug-related adverse events of 2.0%–9.9% [16–25], with nausea (1%–3%) and diarrhea (1%–2%) the most common. Drug-related adverse events for comparators in nine trials ranged from 2.7% (for ciprofloxacin) to 21.2% (for amoxicillin/clavulanate) [16, 17–19, 21–25]. The reported incidence of phototoxicity for levofloxacin was 1/3,460 (0.03%), vs. 9/2,449 (0.36%) for comparator drugs. There were no clinically significant changes in laboratory test values, including liver and renal function, blood glucose, and hematologic parameters, in patients treated with levofloxacin.

Sparfloxacin

Sparfloxacin (Zagam; Rhône-Poulec Rorer Pharmaceuticals, Collegeville, PA) is a difluorinated oral quinolone that differs from other agents by having an amino group at the C-5 position of the quinolone ring. It has increased potency against aerobic gram-positive cocci, particularly Streptococcus pneumoniae, and has recently been approved for treatment of community-acquired pneumonia (CAP) and acute bacterial exacerbations of chronic bronchitis (ABECB) [27].

In a series of 1,040 patients treated for lower respiratory tract infections in European trials [28], sparfloxacin was at least as well tolerated as comparator antibacterials (amoxicillin, amoxicillin/clavulanate, ofloxacin with amoxicillin, and eryth-
The percentage of patients discontinuing therapy because of an adverse event was similar for patients treated with sparfloxacin and those treated with comparator agents.

To date, few published articles describe the toxicity profile of sparfloxacin, but data are available from abstracts and post-marketing surveillance. Adverse events were evaluated in six North American phase III trials of patients with respiratory or complicated skin and skin structure infections [29]. The most frequently reported drug-related adverse events that occurred at statistically significant different rates for sparfloxacin vs. one of several comparator agents (erythromycin, cefaclor, ofloxacin, clarithromycin, or ciprofloxacin) were photosensitivity reactions (7.9% vs. 0.9%; \( P < .001 \)); diarrhea (4.6% vs. 6.7%; \( P = .015 \)); nausea (4.3% vs. 10.3%; \( P < .001 \)); insomnia (1.9% vs. 5.6%; \( P < .001 \)); pruritus (1.8% vs. 0.8%; \( P = .024 \)); abdominal pain (1.8% vs. 3.5%; \( P = .004 \)); taste perversion (1.4% vs. 2.9%; \( P = .004 \)); prolongation of QT interval (Q-T interval, corrected for heart rate; 1.3% vs. 0.5%; \( P = .035 \)); and vomiting (1.3% vs. 2.6%; \( P = .019 \)). Adverse events that were serious or that led to discontinuation of therapy occurred in 2.7% and 6.6% of sparfloxacin-treated patients, respectively, and 3.5% and 8.9% of the comparators [29]. No clinically important laboratory abnormalities were detected. These results are similar to those previously reported from six similar European phase III comparative trials, except that the rate of sparfloxacin-associated phototoxicity was higher than in the European studies [30].

Although sparfloxacin prolonged the QT interval by a mean of 10 msec, there were no associated clinically significant cardiac arrhythmias. Because of reported incidents of torsades de pointes detected post-marketing, sparfloxacin is contraindicated for patients receiving other QTc interval prolonging drugs and should be avoided by those with a QTc interval prolonged for any other reason.

**Grepafloxacin**

Grepafloxacin (Raxar; GlaxoWellcome, Research Triangle Park, NC) is characterized by an N-1 cyclopropyl group, a C-5 methyl group, and a C-7 piperazinyl moiety with an attached methyl group. Grepafloxacin has enhanced activity against gram-positive organisms, particularly *S. pneumonie*, and atypical organisms. It is approved for oral treatment of mild to moderate infections, including ABECB, CAP, uncomplicated gonorrhea, and nongonococcal urethritis and cervicitis caused by *Chlamydia trachomatis* [31].

Grepafloxacin has been used by over 20,000 patients worldwide. In three double-blind comparative clinical trials involving patients with respiratory tract infections, the proportion of patients reporting adverse events was similar among patients treated with grepafloxacin (300–600 mg once daily for 7–14 days), ofloxacin, or amoxicillin. The most common events associated with grepafloxacin included nausea (≤9%), headache (≤3%), diarrhea (≤3%), dizziness (≤2%), and rash.
tients worldwide, therapy was discontinued for 5% because of ciprofloxacin (13.1%) [50, 51].

Trovafoxacin, which is rapidly converted to trovafloxacin in rates for sparoxacin that are similar to those of cefaclor [48]. Trovafoxacin is not soluble in aqueous solution; the intravenous formulation is alatrofoxacin, the L-Ala-L-Ala prodrug of trovafloxacin. Available data suggest trovafloxacin’s phototoxic potential is among the lowest of any FQ [40].

Toxic Effects of FQs on Specific Body Systems

GI Tract

Adverse events involving the GI tract occur with all FQs but are usually mild and seldom necessitate discontinuation of therapy [2, 4]. These effects are the most frequently reported, with estimated overall incidences ranging from 2% to 20% [1, 4, 9–11, 26, 27, 29, 42–45]. Reported symptoms include nausea, anorexia, and dyspepsia; abdominal pain, vomiting, and diarrhea are less frequent but more likely to necessitate discontinuation of therapy [9, 45]. Clostridium difficile–associated colitis is uncommon with FQs, perhaps because of their minimal effect on anaerobic flora [11, 42]. Based on data reported to manufacturers or derived from clinical trials, the estimated rank order for agents in causing GI adverse events is as follows: fleroxacin, grepafloxacin > trovafloxacin > sparoxacin > pefloxacin > ciprofloxacin, levofloxacin > norfloxacin > enoxacin > ofloxacin [10, 11, 15, 27, 31, 36, 46, 47]. To date, no one feature of the FQ structure has been associated with adverse GI effects [4].

GI disorders were the most common drug-related adverse events in clinical trials of levofloxacin (5.1%); specific complaints included diarrhea (1.2%), nausea (1.2%), flatulence (0.5%), abdominal pain (0.3%), dyspepsia (0.3%), taste perversion (0.2%), and vomiting (0.2%) [15–25]. In clinical trials of sparoxacin, the most frequently reported GI adverse events were diarrhea (4.6%), nausea (4.3%), dyspepsia (2.3%), abdominal pain (1.8%), vomiting (1.3%), and flatulence (1.1%) [27]. Comparative trials have demonstrated adverse GI event rates for sparoxacin that are similar to those of cefaclor [48] and 2.5- to 5-fold lower than for erythromycin [49]. The incidence of nausea with sparoxacin (4.0%–4.4%) was found to be approximately one-third as high as for ofloxacin (10.2%) or ciprofloxacin (13.1%) [50, 51].

GI adverse events are also the most frequently reported in grepafloxacin clinical trials and include nausea (11%–16%), diarrhea (3.5%–4%), abdominal pain (2%), vomiting (2%–6%), dyspepsia (1.5%–3%), anorexia (1%–2%), and constipation (1%–2%) [31]; a metallic taste was reported by 9% and
18% of patients receiving 400 mg and 600 mg daily, respectively. The manufacturer noted trends suggesting a reduced incidence of nausea and taste perversion if the dose is administered in the evening [33]. Trovafloxacin is associated with a relatively low incidence of adverse GI events, with nausea (4%–8%), vomiting (1%–3%), diarrhea (2%), and abdominal pain (1%) the most frequently reported [36].

CNS

CNS disturbances are the second most commonly reported adverse events with FQs [4, 11], with an overall incidence of 1%–2% [10, 26, 27, 52]. Symptoms include headache, dizziness, and drowsiness, which usually occur on the first day of therapy and resolve after discontinuation of the drug therapy [10]. Other reported CNS effects include abnormal vision, restlessness, sleep disorders, agitation, acute organic psychosis, confusion, and delirium [4, 10, 45]. Convulsions and seizures have occurred rarely, and usually in the setting of predisposing factors (e.g., epilepsy, cerebral trauma, or anoxia), metabolic imbalance, or concomitant therapy with interacting agents (e.g., theophylline or nonsteroidal anti-inflammatory drugs) [1, 10–12, 53]. Convulsions during FQ therapy usually develop 3–4 days after the start of treatment and resolve with its discontinuation [42]; they have occurred during treatment with enoxacin, pefloxacin, ofloxacin, ciprofloxacin, and norfloxacin [12, 45].

The reported overall trend in incidence of drug-related CNS adverse events is as follows: fleroxacin > trovafloxacin > grepafloxacin > norfloxacin > sparfloxacin > ciprofloxacin > enoxacin > ofloxacin > pefloxacin > levofloxacin [10, 11, 15, 27, 29, 31, 36, 46, 47]. Symptoms vary somewhat for individual agents. Acute psychosis has been associated with ofloxacin [54] and ciprofloxacin [55, 56], and two cases of confusion and delirium have been attributed to pefloxacin [57].

Recent studies [18, 20–22, 24, 25] have shown a low incidence (0.2%–1.1%) of CNS adverse events associated with levofloxacin and a slightly higher rate with sparflloxacin (1.9% to 4.2%) [27, 29]. The North American trials showed sparfloxacin was associated with somewhat lower rates of dizziness and insomnia but a higher rate of headaches than were comparators [29]. In direct comparisons with ofloxacin, sparfloxacin was associated with a lower rate of headaches (4.2% vs. 2.9%) [58] and insomnia (4.7% vs. 1.1% in one study and 14.9% vs. 1.5% in another) [50, 58]. CNS effects of grepafloxacin include dizziness (4.3%–5.4%), somnolence (1%–1.5%), and nervousness (0.6%–1.7%) [31]. Trovafloxacin has a higher rate of CNS effects, including dizziness (3%–11%), lightheadedness (2%–4%), and headache (1%–5%) [36]. These symptoms are generally mild, last only a few hours, and may resolve with continued dosing; the incidence may be reduced if trovafloxacin is taken at bedtime or with food. CNS symptoms with trovafloxacin have occurred more frequently in women and subjects younger than age 45 years. Reports of patients over 65 years of age indicated a lower incidence of dizziness (3.1%) and lightheadedness (0.6%).

The mechanism of quinolone-associated CNS toxicity has not been fully elucidated but may involve gamma-aminobutyric acid (GABA). Inhibition of binding of GABA to GABA<sub>A</sub> receptors in the CNS results in CNS stimulation [1]. This characteristic, however, is not unique to the quinolones; penicillins, cephalosporins, and carbacephems also antagonize this neurotransmitter, causing neurotoxic effects [52]. Experiments in mice show binding of FQs to GABA receptors is enhanced by 4-biphenylacetic acid, an active metabolite of the nonsteroidal anti-inflammatory drug fenbufen [59].

The primary excitatory effects of FQs in the CNS may also operate via N-methyl-D-aspartate and adenosine-receptor mechanisms or by activation of excitatory amino acid receptors. Preclinical studies in mice showed the following trend in epileptogenic activity: enoxacin > norfloxacin > ciprofloxacin > ofloxacin > levofloxacin [1, 60]. Neither grepafloxacin nor trovafloxacin or alatrofloxacin induced convulsions in mice when administered in high doses in conjunction with fenbufen [32, 36]. No single model for predicting epileptogenic activity of the FQs has completely predicted clinical experience.

The relative incidence of CNS adverse events of FQs may be related to their chemical structures. The R<sub>7</sub> substituent appears to have the greatest influence on the degree of CNS effects [4]. Acute psychosis has been associated with ofloxacin [54] and ciprofloxacin [55, 56], and two cases of confusion and delirium have been attributed to pefloxacin [57].

Liver

Liver enzyme abnormalities have been noted in 2%–3% of patients receiving FQ therapy [11, 46]. Elevations in serum transaminase and alkaline phosphatase levels are most common [11, 61]; these are usually mild and reversible with discontinuation of the therapy. On the basis of crude pooled estimates of data supplied by manufacturers, elevated levels of serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase occurred in 24.9, 24.0, and 17.8 patients per 1,000 treated with ciprofloxacin, ofloxacin, and pefloxacin, respectively [46]. These liver enzyme abnormalities rarely led to discontinuation of therapy.

The largest safety database available for any FQ is that for ciprofloxacin, which has been administered to nearly 80,000 patients in clinical trials and, as of 1993, had been prescribed to ~80 million patients [8]. Spontaneous reports showed that 144 ciprofloxacin-treated patients had serious abnormalities in liver function test values; small numbers of patients also developed hepatitis, liver necrosis, or hepatic insufficiency or failure. Two cases of cholestatic jaundice, possibly induced by ciprofloxacin, have been reported [62, 63], and hepatotoxicity
has been observed during therapy with enoxacin [64], norfloxacin [65], and ofloxacin [66].

Clinical trial data for levofloxacin indicate a very low frequency (0.3%) of abnormal liver function test values [15], none of which necessitated discontinuation of therapy. Elevated transaminase levels were found in ~2% of patients treated with sparfloxacin in North American trials [29]. Clinical trial data for 2,500 patients treated with grepafloxacin demonstrated increased levels of hepatic transaminases, gamma-glutamyl transpeptidase, and alkaline phosphatase in <1% [31]. Among 140 patients treated with trovafloxacin for 28 days, 9% had asymptomatic increases in hepatic transaminase levels to ≥3 times normal, but they returned to normal within 2 months following discontinuation of therapy [36].

**Urinary Tract**

Nephrotoxicity as a consequence of FQ therapy is uncommon [4, 11, 12], but there have been some reports of hematuria, interstitial nephritis, or acute renal failure [11, 61]. Nearly all reported cases of acute renal failure have involved patients over 50 years of age, and in most instances the patients were >65 years of age [45]. Renal failure may be due to a hypersensitivity reaction, as reported for ciprofloxacin, or a direct toxic effect, as reported for norfloxacin [45]. Adverse renal reactions to ciprofloxacin are uncommon [8] but have included renal failure (91 patients, of whom 12 required dialysis); elevated serum creatinine and blood urea nitrogen levels (63 patients); nephritis (23 patients, including 2 with consequent renal failure); and a renal tubular disorder (1 patient). The incidence of an elevated serum creatinine level related to therapy with ciprofloxacin, norfloxacin, ofloxacin, and pefloxacin ranges from 0.2% to 1.3% [11]. The rate for ofloxacin (1.3%) was slightly higher than for the other FQs (0.2%–0.8%). Incidences of azotemia with ciprofloxacin, ofloxacin, and pefloxacin ranged from 1.8 to 13.1 per 1,000 patients treated [46].

Crystalluria has been linked to FQ solubility in urine, which is pH-dependent. It has been observed in rats and monkeys, under urinary pH conditions that do not usually exist in humans [12]. In the normally acidic urine of humans, crystalluria is rare [42] and not necessarily a cause of renal damage [4, 11, 12, 45]. Nonetheless, patients should be well hydrated, and alkalinity of urine should be avoided during FQ therapy. Nearly all FQs are zwitterionic, owing to a basic amine group in the R$_3$ side chain, making them least soluble at physiological pH [4].

Changes in molecular structure aimed at improving water solubility in this pH range would minimize risk of crystalluria. These include alkyl substitution of the R$_2$ substituent and use of CF, CCI, CCF$_3$, and COMe as the X$_8$ substituent (figure 1) [4]. Crystalluria, interstitial nephritis, and acute renal failure have not been causally associated with levofloxacin, sparfloxacin, grepafloxacin, or trovafloxacin therapy.

**Skin**

Dermatologic adverse events with use of the available FQs occur at an overall rate of ~0.5%–3% [42]. While a variety of toxic effects on skin have been reported, photosensitivity reactions of two types have received the most attention. Phototoxic reactions, by contrast, are more common, can occur on initial exposure in anyone given a sufficient dose of the offending drug and a high enough ultraviolet (UV) exposure, and develop within a few hours [67]. The mechanism of photosensitivity appears to relate to photodegradability of individual FQs and their ability to induce oxygen singlets and free radicals [42]. These reactive species are thought to attack cellular lipid membranes, initiating the inflammatory process [68]. Persons with fair skin are more susceptible than those with darker skin.

Photosensitivity reactions have been reported for most FQs but differ in severity and incidence [4]. Clinical manifestations range from mild erythema of sun-exposed areas to extensive and severe bullous eruptions. Reactions may follow exposure to direct or indirect sunlight (e.g., through glass or in shade), as well as from UV (especially UVA) lamps. They generally appear within a few days of the start of therapy but can occur up to 3 weeks after its discontinuation, and they usually subside within 1 month [11, 12, 42, 45]. Topical sunblockers that screen against both UVA and UVB may afford some protection, but covering the skin with clothing or avoiding the outdoors is safer.

The approximate order for phototoxic potential among the FQs is as follows: lomefloxacin, fleroxacin > sparfloxacin > enoxacin > pefloxacin > ciprofloxacin, grepafloxacin > norfloxacin, ofloxacin, levofloxacin, and trovafloxacin [4, 8, 13, 15, 27, 29, 31, 36, 69]. Marked differences in phototoxic potential are largely related to the X$_8$ substituent (figure 1) [4]. The highest frequency of photosensitivity occurs when this position is substituted by a halogen, especially fluorine; fleroxacin [70], lomefloxacin [71], and sparfloxacin [29] all have a CF group in the X$_8$ position [4]. In addition, FQs with a bulky side chain or a methyl group at R$_3$ are more likely to cause phototoxicity than would be predicted solely by the X$_8$ group [4].

Fleroxacin demonstrates a dose-related frequency of phototoxicity ranging from 0.6% at 200–400 mg daily to 16% with 800-mg doses [47]. Photosensitivity occurred in 2.4% of 2,869 lomefloxacin recipients and was judged to be drug-related in 1.7% of cases [72]. Pooled data for pefloxacin, which has a CH group in the X$_8$ position, indicate a phototoxicity frequency of 9.3 per 1,000 patients [46].

Phototoxicity has been the most frequent and important adverse event associated with sparfloxacin therapy. Studies conducted in Japan, usually at dosages of 100 mg daily, revealed phototoxicity in about 1%–2% of subjects. European clinical safety data [28, 30] from 1,040 patients revealed a 2.0% inci-
dence of phototoxicity with use of sparflaxacin (usually 100 or 200 mg daily), vs. a 0.2% incidence with comparators. Rates of photosensitivity were the same for the two sparflaxacin dosage regimens, and only one reaction was considered severe.

In the North American trials the overall rate of photosensitivity reactions to sparflaxacin was 7.9%, compared with a combined rate of 0.9% for five different comparators [29]. Most reactions were mild (4.2%) or moderate (3.4%), but a few (0.6%) were severe. Because of the potential for phototoxic reactions, patients must avoid exposure to direct or indirect sunlight or artificial UV light during and for 5 days following sparflaxacin therapy [27].

For levoflaxacin, data from preclinical and phase I–II studies indicate a minimal phototoxic potential, similar to that of ofloxacin and ciprofloxacin [14, 73]. Only one of 3,490 subjects had a potentially phototoxic reaction [73]. Studies of the relative phototoxic effect on mice of a 200-mg/kg dose of various FQs found evidence of toxicity with use of sparflaxacin, lomefloxacin, and to a lesser degree, enoxacin; ofloxacin, ciprofloxacin, and grepafloxacin had slight or no effects [74].

Clinical trial data for grepafloxacin regimens (400–600 mg daily) showed photosensitivity in <2% of patients [31]. Currently available data suggest grepafloxacin has weak photosensitizing potential, similar to that of ciprofloxacin [75]. In studies of mice, trovafloxacin caused only mild photosensitivity reactions, and preliminary evaluations in humans suggest a lower phototoxic potential for trovafloxacin than for lomefloxacin or even ciprofloxacin [68, 76]. Phototoxicity was observed in <0.03% (two of 7,096 patients treated with trovafloxacin [36] in clinical trials, making it among the least phototoxic FQ agents.

Other skin reactions during FQ treatment are uncommon. Occasionally reported reactions include rash, pruritus, urticaria, vasculitis, edema, blue-black pigmentation of the legs, eruptions with hemorrhagic bullae, and Henoch-Schönlein purpura [46, 61, 77, 78].

Immune System

Hypersensitivity reactions, often with skin manifestations, have occurred at a frequency of 0.6%–1.4% in FQ clinical trials [10]. Erythema, pruritus, urticaria, and rash may be caused by allergic reaction or a histamine-release phenomenon [79]. Fatal hypersensitivity vasculitis has occurred during ciprofloxacin and ofloxacin therapy [43, 80], and cutaneous erythema, itching, and a burning sensation have been reported to occur during intravenous infusion of ciprofloxacin [81]. Serum sickness–like illness has also been reported in association with ciprofloxacin use [82].

Anaphylactoid and anaphylactic reactions have been observed from 5 minutes to 1 hour following FQ administration, in an estimated 0.46 to 1.2 cases per 100,000 [42, 45]. History of hypersensitivity to one quinolone precludes or at least requires extreme caution with the use of another [12, 42].

Musculoskeletal System

FQ-induced arthropathy is noted in ~1% of patients [83, 84]. It most frequently affects weight-bearing joints in those <30 years of age and presents with pain, stiffness, and joint swelling. Onset is in the first few days of treatment, and the arthropathy usually resolves within a few days or weeks after discontinuation of the treatment [1, 84]. The potential for quinolone-induced arthropathy is a class effect, and structural modification may not reduce this risk [4]. Chondrotoxicity has been observed in animal studies, but there is little evidence of clinically important quinolone-induced arthropathy in humans [1, 4, 85].

More recently, the possibility of tendonitis and tendon rupture associated with FQs has been raised [85–90]. A survey conducted in France between 1985 and July 1992 found tendon disorders in 100 patients, including 31 with tendon rupture [89]. As of October 1994, 25 cases of FQ-associated tendon rupture were reported to the FDA, 22 of which had occurred outside the United States [88]. Few cases of Achilles tendonitis complicating FQ treatment in the Netherlands have been described [91]. Tendon disorders have most often involved the Achilles, with some occurring in the shoulder joint or hand [88–91]. Symptoms may begin from 1 to 42 days (average, 13 days) after the start of FQ treatment and may occur after the offending agent has been withdrawn [88–90].

In contrast to arthropathy, tendon disorders or rupture generally occurs in individuals >50 years of age [84], although reports include those from 25 to 84 years old [88, 89]. More men than women are affected, and concomitant use of corticosteroids appears to increase the risk [88, 89]. In the French series [89], the clinical course of patients with tendon disorders was usually favorable, although symptoms persisted for >2 months in one-third of cases. Among patients reported to the FDA, 11 of 25 were hospitalized, had surgical repairs, or had a prolonged period of disability [88].

Specific agents reported to cause tendon disorders include norfloxacin, ciprofloxacin, pefloxacin, enoxacin, and sparflaxacin [30, 90, 92]. During preclinical development studies with levoflaxacin, one case of possibly drug-related tendinitis was reported; tendon rupture was not reported for levoflaxacin in clinical trials [16–25]. Postmarketing surveillance in Japan and Europe has uncovered occasional cases of tendinitis and tendon rupture associated with sparflaxacin. In the French sparflaxacin pharmacovigilance data, estimated rates were 0.7 and 0.005 per 1,000 treated patients, respectively [30]. Postmarketing surveillance will be necessary to assess association with grepafloxacin or trovafloxacin. Until additional information is available, the FDA recommends that patients discontinue FQ therapy at the first sign of tendon pain or inflammation and refrain from exercise until the diagnosis of tendinitis can be confidently excluded [86–88]. MRI may be useful for early detection and monitoring of tendinitis or tendon degeneration [90].
Cardiovascular System

Systolic and diastolic hypotension has been noted in animals following rapid intravenous administration of most quinolones, probably as a result of histamine release [12]. In humans, hypotension, tachycardia, syncope, and migraines have followed oral administration of quinolones [12, 43]. Because QTc interval prolongation [93] was noted during preclinical development of sparfloxacin, careful electrocardiographic evaluation was conducted in subsequent clinical trials. These revealed that 1.2% to 3% of sparfloxacin-treated patients experienced a potentially clinically important QTc interval prolongation, to ≥500 msec [29, 94, 95]. The magnitude of change appears dose-related, with a mean prolongation of QTc interval of 2%--8% associated with doses from 100 mg daily to 400 mg daily, respectively. This appears less than that associated with erythromycin therapy [92, 94], and QTc interval prolongation due to sparfloxacin generally has not been associated with clinical symptoms, cardiac arrhythmias, or other cardiovascular events. One case of torsades de pointes leading to cardiopulmonary resuscitation was reported as probably associated with sparfloxacin therapy [96].

An international safety board reviewed data collected from ~750,000 patients treated with sparfloxacin as of May 1995 [94]. Seven serious adverse cardiovascular events were reported, all in patients with an underlying cardiac condition. The adverse cardiovascular event rate was not significantly different between sparfloxacin-treated patients and those who received comparator antibacterials. The international safety board concluded that the QTc interval prolongation was not a cause for concern, but coadministration of sparfloxacin with medications known to increase the QTc interval or to induce bradycardia should be avoided, and concomitant administration of amiodarone or sotalol was contraindicated.

In preclinical and clinical studies, levofloxacin was not associated with QTc interval prolongation. Grepafloxacin caused QTc interval prolongation in clinical trials [31], but the magnitude of effect is unclear. Presently, grepafloxacin is contraindicated in patients with known QTc interval prolongation or those concomitantly treated with other medications that may increase the QTc interval or induce torsades de pointes, unless appropriate cardiac monitoring is available. It is not recommended for use in patients with ongoing proarrhythmic conditions. One study found no clinically significant abnormal vital signs or electrocardiographic changes during intravenous infusion of alatrofloxacin in doses up to an equivalent dose of 300 mg of trovafloxacin [37]. Clinical trials data cited in trovafloxacin product information do not include occurrences of a prolonged QTc interval.

Special Patient Populations

Pediatric

Because FQ-treated juvenile animals develop lesions in the articular cartilage, these agents are not recommended for children and growing adolescents [1, 88, 97, 98]. The mechanism of this chondrotoxicity is largely unknown [1, 85, 97, 99].

Despite concerns about toxicity, pediatric patients have received FQ therapy on a compassionate basis and in clinical trials in special situations [97, 100, 101]. In one analysis, comprehensive clinical, MRI, and histopathologic monitoring of 18 patients aged 6–24 years for up to 22 months after a 3-month course of ciprofloxacin therapy demonstrated no evidence of FQ-induced arthropathy [97]. Review of several published pediatric clinical trials involving >1,000 prepubertal children revealed good to excellent efficacy, with mild and reversible adverse events in 5%–15% of patients [101]. Reversible arthropathies were reported to occur in young patients with cystic fibrosis treated with ciprofloxacin (8 of 634; 1.3%) or pefloxacin (9 of 63; 14%). Some patients who had joint manifestations with pefloxacin therapy later tolerated ofloxacin without problems [85].

The 1991 worldwide ciprofloxacin compassionate-use protocols involved 634 children aged 3 days to 17 years [100], most of whom had an acute pulmonary exacerbation of cystic fibrosis. Mean oral and intravenous daily doses of ciprofloxacin were 25.2 mg/kg and 7.0 mg/kg, respectively. Eight children (1.3%), all of whom had cystic fibrosis, had arthralgia that was reversible upon discontinuation of treatment. In the 1997 cumulative data from worldwide ciprofloxacin compassionate-use protocols involving 1,795 case reports, 26% of the patients were 12–17 years of age, and 28% had cystic fibrosis. Arthralgia occurred in 31 (1.5%) of 2,030 treatment courses, but no unequivocal case of ciprofloxacin-induced arthropathy was documented [85]. In another ciprofloxacin treatment study [102], only five of 202 children with cystic fibrosis under 18 years of age experienced arthralgia. Arthralgias have been reported by cystic fibrosis patients treated with antimicrobials other than FQs and may also be due to underlying disease processes [100, 101].

Less information is available for other FQs. No arthropathies were observed among 37 patients from 2 to 20 years of age treated with ofloxacin [45]. At least one case of destructive polyarthropathy has been reported, involving a 17-year-old atopic boy who received pefloxacin (800 mg/d for 3 months) [103]. A review of FQ use in more than 7,000 skeletally immature patients [85] concluded that reversible episodes of arthralgia do not lead to long-term sequelae when treatment with the offending agent is discontinued. Thus, prospective studies of selected quinolone agents for therapy in children seem justified, and the FDA has encouraged such studies [104].

Geriatric

In the elderly, FQ bioavailability—and thus maximal serum concentration—may be increased by diminished first-pass metabolism or by concurrent medications. Furthermore, area under the concentration vs. time curve may be increased by diminished drug clearance caused by age-related decline in renal or
hepatic function. There is relatively little published information regarding toxicity of FQs for patients >55 years of age, but it is likely that they are safe. In a summary of clinical data for oral ciprofloxacin [105], nearly one-fourth of the 1,652 patients were >70 years old. There was a tendency for all adverse events to occur more frequently in elderly patients than in younger ones, and three of four episodes of hallucinations were reported by elderly patients. A reported case of acute delirium associated with ciprofloxacin therapy occurred in a hospitalized elderly patient [106].

Tendon disorders may also occur more frequently in older patients. In the French series [89] of 100 patients with tendon disorders or ruptures, the mean age of the affected patients was 63 years, within a range of 25–84 years. One American case report described bilateral Achilles tendinitis in an 85-year-old patient with polymyalgia rheumatica who was receiving both steroid and enoxacin therapy [87]. Caution seems prudent in such situations.

Results of sparfloxacin clinical trials conducted in Europe demonstrated no difference in incidence of drug-related adverse events or rate of treatment discontinuation among the one-third of patients who were older than 65 years, vs. among those who were younger [28]. A recent study investigated the effect of age on single-dose pharmacokinetics in healthy young volunteers (18–40 years of age) as compared with elderly volunteers (>65 years of age) [107] and found no difference in incidence of adverse events following an oral dosing of 500 mg of levofloxacin.

No dosage adjustment is required for either grepafloxacin or trovafloxacin for elderly patients. In healthy patients aged 64–81 years who received grepafloxacin (400 mg/d for 7–9 days), volume of distribution and clearance were decreased, resulting in a 48% increase in the area under the curve compared to that for younger subjects [32]. For both agents renal excretion is minimal, with hepatic and biliary systems predominantly involved in metabolism and clearance [31, 39]. In multiple-dose clinical trials with trovafloxacin, the overall incidence of drug-related adverse events in the 27% of patients who were at least 65 years of age was actually less than that among younger age groups [36].

HIV-Infected

Patients infected with HIV may experience adverse events associated with their disease that are difficult to distinguish from those that are drug-induced [108]. Some data suggest the frequency of anaphylactic reactions during ciprofloxacin therapy may be increased in HIV-infected patients [45]. In the cases reported, the reaction usually occurred after the second exposure to an FQ [109–111]. Acute renal failure in one patient with AIDS who was treated with ciprofloxacin has been reported [112].

In two studies of patients with asymptomatic HIV infection [108, 113], subjects received single and multiple 350-mg doses (three times daily) of levofloxacin. Among 10 HIV-infected subjects who were not receiving concomitant zidovudine treatment [108], the most commonly reported adverse events were equally frequent in the levofloxacin and placebo groups and involved the GI tract (9 subjects in each group), CNS (3 patients in each group), and skin (2 levofloxacin-treated and 4 placebo-treated subjects). Transient elevations in hepatic transaminase levels also occurred in both groups. No subjects were withdrawn because of adverse events. In 16 subjects whose CD4 cell counts ranged from 100/mm³ to 550/mm³ and who were taking zidovudine concomitantly, there were no clinically significant differences in adverse clinical or laboratory events between the levofloxacin and placebo groups, nor did any adverse event require discontinuation of therapy or dosage reduction [113].

Neutropenic

Neutropenic patients may be exposed to higher doses and more prolonged courses of antibiotic prophylaxis with FQs than nonneutropenic patients [114]. Prolonged therapy or an increased dosage may be associated with a higher incidence of adverse events with quinolones. Little safety information on FQs has been derived from studies of neutropenic patients, in whom occurrence of potential adverse events is confounded by many factors.

A meta-analysis examined international safety data from 29 studies of neutropenic patients who received FQ therapy (16 studies) or prophylaxis (13 studies) [114]. The FQs were compared with several nonquinolone antibiotics or placebo. Rash and GI tract disorders were the most common adverse events with FQs. The incidence of adverse events was significantly higher ($P < .05$) among neutropenic patients receiving treatment with FQ monotherapy than among nonneutropenic patients (12.6% vs. 6.4%, respectively). In addition, the overall incidence of adverse events was significantly higher ($P < .05$) when FQs were used as therapy, generally at higher doses, than when used as prophylaxis. In all prophylaxis studies except one, the incidence of adverse events associated with trimethoprim-sulfamethoxazole was higher than that with FQs. In studies evaluating monotherapy, there was no statistically significant difference in incidence of adverse events between FQs (12.6%) and comparator agents (10.3%).

When FQs were used in combination therapy, the incidence of adverse events (14.9%) was not significantly different from that associated with monotherapy (11.6%) or with comparator agents (13.6%). Nephrotoxicity was more frequent with FQ combination regimens than with FQ monotherapy. While the incidence of adverse events is higher than that observed for nonneutropenic patients, the general profile of events is similar, and FQs appear to be at least as safe as other antibiotics.

Pregnant and Nursing Women

FQs are not recommended for pregnant or nursing women, mainly because of the theoretical potential for causing arthropa-
thies in children. Additional concerns based on preclinical data include their ability to impair bacterial DNA synthesis through inhibition of DNA gyrase (topoisomerase II) and abortifacient effects when administered at maternally toxic doses [8, 115]. Maternally nontoxic doses of ciprofloxacin administered to pregnant cynomolgus monkeys caused no increase in abortions, nor was there any effect on development of the embryo or fetus [115]. Other animal studies, however, have demonstrated fetal wastage and embryotoxic effects such as malformations with large doses of ciprofloxacin, ofloxacin, norfloxacn, trovafloxacin, and temafloxacin [11, 36, 61].

In a clinical study involving 38 pregnant women who received either norfloxacin or ciprofloxacin during pregnancy, there was no evidence of increased risk of infant malformations or musculoskeletal problems when compared to the outcome of a matched control group [116]. Most women in the study were being treated for a urinary tract infection and most were in the third trimester of pregnancy. Cesarean delivery (45%) and fetal distress (40%) were significantly more common among women treated with an FQ, and mean birth weight of infants born to FQ-treated mothers was 8.5% higher than that of infants born to mothers in the control group. There was no evidence of infant musculoskeletal problems.

In a recent prospective study, 200 pregnant women exposed to an FQ (mostly ciprofloxacin or norfloxacin) were matched with 200 controls who were treated for various infections with an antibiotic known to be nonteratogenic and nonembryotoxic [117]. Quinolone-treated women had therapeutic abortions at a higher rate, but rates of congenital malformations and other measures of pregnancy outcome and infant health did not differ for the two groups. While the authors of this large multicenter trial concluded that use of FQs during embryogenesis appeared safe, it seems prudent for pregnant or nursing women to avoid these drugs unless the potential benefit clearly outweighs the potential risk [8].

High-Risk FQs

Some FQs are notable for a relatively high level of toxicity. In addition to temafloxacin, another agent associated with an unexpectedly high incidence of adverse experiences is fleroxacin, a trifluorinated compound [10, 118]. The overall incidence of reported adverse events with fleroxacin was 84% in 79 subjects, with severe reactions in 48%. The incidence and severity of adverse events were dose-related; such events occurred in 69%, 85%, and 96% of patients treated with doses of 400 mg, 600 mg, and 800 mg, respectively. The most common events were those involving the CNS and GI tract. Dose-related phototoxicity with fleroxacin was mentioned earlier. This unusually high frequency of adverse events may be related to three fluorine atoms in the fleroxacin molecule [10].

Phototoxicity is a problem with sparfofloxacin. The reaction is avoidable, usually only mild to moderate, and fully reversible. Nevertheless, the manufacturer of sparfofloxacin made the admi-

rable decision to apply for FDA approval only for the most-needed indication for this agent, i.e., lower respiratory tract infections.

Summary

The important advance in antibacterial activity ushered in by FQs has fortunately been accompanied by a generally excellent safety record. Ongoing research in the development of new FQ agents is aimed at further improvement in the safety profile, while maintaining or enhancing antimicrobial efficacy. As new agents become available, certain predictions can be made regarding possible adverse events, on the basis of their molecular structure. The four newly approved agents demonstrate the importance of an agent’s safety profile in selecting an FQ for therapy. All represent an advance in therapeutic efficacy over previously available agents, but the adverse event profiles for sparfofloxacin and grepafloxacin are likely to limit their use compared with use of levofloxacin and trovafloxacin.

Levofloxacin appears to be at least as safe and well tolerated as other agents in its class. It has demonstrated a low incidence of GI and CNS adverse events, very little phototoxicity, and no cardiotoxicity. While the rates of most adverse events with sparfofloxacin are similar to or lower than those with other agents, it is hampered by a relatively high rate of phototoxicity and QTc interval prolongation. The most frequently reported adverse events with grepafloxacin are GI symptoms and taste perversion, particularly at high doses. Grepafloxacin has been associated with QTc interval prolongation, but the incidence of associated phototoxicity appears less than that with sparfofloxacin.

Trovafloxacin appears to cause an increased rate of mild CNS effects, mainly dizziness, but it has not been reported to prolong the QTc interval and has a low phototoxic potential. The implications of trovafloxacin’s structure with respect to temafloxacin-like adverse events are uncertain, but no problems were noted in >200,000 subjects in clinical trials. These latest FQ additions further advance this group of relatively safe and highly effective antimicrobials that are now widely used in clinical practice.

Acknowledgment

The authors thank Tina Torey, of the Antibiotic Research Clinic (Seattle), for her help in preparing the manuscript.

Addendum

After this manuscript was accepted for publication, additional post-marketing surveillance data for trovafloxacin became available that revealed the potential for liver enzyme abnormalities and/or symptomatic hepatitis during short- or long-term therapy [36]. In addition, symptomatic pancreatitis was reported. It is recommended that clinicians monitor liver function tests and pancre-
atic function tests in patients who develop symptoms consistent with hepatitis and/or pancreatitis, as clinically indicated.

References

5. Finch RG. The withdrawal of temafloxacin: are there implications for acinet in North American phase III clinical trials [abstract no LM-57].
7. Finch RG. The withdrawal of temafloxacin: are there implications for acinet in North American phase III clinical trials [abstract no LM-57].


Lipsky and Baker

CID 1999;28 (February)


