Clinical Safety Profile of Fluoroquinolones

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Fluoroquinolones are considered safe and well-tolerated anti-infective agents that are commonly used to treat community-acquired and healthcare-associated infections. The most frequent reported adverse events (e.g. gastrointestinal and central nervous system [CNS] reactions) are usually transient and mild to moderate in severity. However, serious adverse reactions have led to the withdrawal of temafloxacin and grepafloxacin from worldwide markets, and restrictive and limited use of trovafloxacin in the United States. Rare and agent-specific adverse events have included alterations in glucose homeostasis (e.g. gatifloxacin), prolongation of QTc interval (e.g. moxifloxacin), and skin rash (e.g. gemifloxacin). High-dose therapy for serious infections or short-course therapy has been limited to ciprofloxacin and levofloxacin secondary to their excellent tolerability and lower rates of adverse events compared to other, currently available, fluoroquinolones.

Introduction

Fluoroquinolones have demonstrated comparable efficacy and rates of adverse events as β-lactam and/or macrolide agents in the treatment of community-acquired and healthcare-associated infections. Fluoroquinolones currently marketed are generally considered to have good safety profiles (1–5). However, post-marketing spontaneous adverse event reports have imposed updates in the precautions and warning sections of product package inserts of fluoroquinolones. In addition, higher rates of serious toxic reactions has resulted in restricted or suspended use of trovafloxacin, worldwide withdrawal of temafloxacin and grepafloxacin, and discontinued development of fleroxacin, BAY 3118, and clinafloxacin (4–8) (Table 1). The purpose of this paper is to review the adverse events associated with fluoroquinolone therapy, with an emphasis on safety profiles of ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin.

Relationships between molecular structure and adverse reactions

Potential adverse reactions have been associated with specific chemical modifications of the basic molecular structure of fluoroquinolones (9) (Figure 1). Phototoxicity and central nervous system (CNS) adverse events tend to be associated with modifications at positions 1, 5, 7, and 8. A greater incidence of phototoxic reactions appears when the substitution at position C-8 is a halogen, such as fluorine (lomefloxacin, sparfloxacin, fleroxacin) or chlorine (clinafloxacin, sitafloxacin) (Figure 2). Recent studies suggest that fluoroquinolone phototoxicity is also influenced by the substituent at position 1 (10).

Alterations of the molecular structure at position 7 seem to have the greatest influence on CNS effects (9). Unsubstituted piperazinyl and pyrrolidinyl moieties exhibit higher binding affinity to the gamma-aminobutyric acid (GABA) receptor site. A reduction in GABA-mediated inhibitory transmission may increase the excitability of the CNS.

Fluoroquinolones that have a 2, 4-difluorophenyl moiety at position C–1 (Figure 3) have been associated with unexpected and severe idiosyncratic drug reactions (e.g. hepatitis [trovafloxacin], hemolytic-uremic syndrome [temafloxacin], eosinophilic pneumonitis [tosufloxacin]) (3,4,7,8). No definitive study has confirmed a cause–effect relationship is associated with the similar C–1 molecular modifications of temafloxacin, trovafloxacin, and tosufloxacin.
Table 1. Selected landmarks in fluoroquinolones safety

<table>
<thead>
<tr>
<th>Date</th>
<th>Fluoroquinolone</th>
<th>Adverse event</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 1992</td>
<td>Temafloxacin</td>
<td>Hemolytic anemia, hypoglycemia, renal failure,</td>
<td>Withdrawn from worldwide market</td>
</tr>
<tr>
<td></td>
<td></td>
<td>abnormal liver function tests, coagulopathy</td>
<td></td>
</tr>
<tr>
<td>March 1993</td>
<td>Lomefloxacin</td>
<td>Phototoxicity</td>
<td>Product package insert warnings added</td>
</tr>
<tr>
<td>Mid-1990s</td>
<td>Various agents</td>
<td>Tendinitis, tendon rupture</td>
<td>Class language added to product package insert</td>
</tr>
<tr>
<td>December 1996</td>
<td>Sparfloxacin</td>
<td>Phototoxicity, QTc prolongation</td>
<td>Product package insert warnings added</td>
</tr>
<tr>
<td>June 1999</td>
<td>Trovafoxacin</td>
<td>Hepatic toxicity</td>
<td></td>
</tr>
<tr>
<td>October 1999</td>
<td>Grepafloxacin</td>
<td>Cardiovascular events</td>
<td>Withdrawn from worldwide market</td>
</tr>
<tr>
<td>November 1999</td>
<td>Clinafloxacin</td>
<td>Phototoxicity, CNS reactions</td>
<td>Clinical development discontinued</td>
</tr>
<tr>
<td>December 1999</td>
<td>Moxifloxacin, Gatifloxacin</td>
<td>QTc prolongation</td>
<td>Product package insert warnings added</td>
</tr>
<tr>
<td>Mid-2002</td>
<td>Gatifloxacin</td>
<td>Glucose homeostasis</td>
<td>Product package insert warnings added</td>
</tr>
</tbody>
</table>

Abbreviation: CNS = central nervous system.

Figure 1. Adverse events associated with the molecular structure of fluoroquinolones.

Figure 2. Molecular structure of fluoroquinolones associated with higher rates of phototoxicity.

Abbreviation: GABA = gamma-aminobutyric acid.
Adapted from reference (9).
Adverse effects of fluoroquinolones
Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin are currently the most commonly marketed fluoroquinolones. These agents are well tolerated and appear to be free of severe immunologically mediated adverse drug reactions. The most common drug-related adverse events are gastrointestinal (GI), CNS, and dermatologic reactions. These adverse events are usually considered mild to moderate in severity and rarely result in a discontinuation of fluoroquinolone therapy (1–5) (Table 2). Rare adverse events have been reported (e.g. torsades de points, glucose homeostasis abnormalities, severe skin reactions), but are more likely associated with specific agents and patient populations.

GI reactions
The most common drug-related adverse events caused by fluoroquinolone therapy involve the GI tract (1–5) (Table 2). The incidence of drug-related GI events among currently used fluoroquinolones is 2–20% (1–3). The most frequently reported reactions are nausea, vomiting, and diarrhea; while abdominal pain, anorexia, dyspepsia, and constipation have also been reported (11–15). Fluoroquinolone-associated GI effects tend to be mild in severity and rarely require the discontinuation of therapy. The fluoroquinolones most likely to cause adverse GI events (fleroxacin, grepafloxacin, trovafloxacin, sparfloxacin) are not available for clinical use. Grepafloxacin, for example, caused dose-related GI adverse reactions, including a high incidence of metallic taste (9–18%) and vomiting (up to 10%) (16,17).

CNS reactions
Reactions involving the CNS are the second most frequently reported adverse events during fluoroquinolone therapy. Headache, dizziness, and insomnia are the most commonly reported events (1–5). The incidence of these drug-related CNS reactions ranges from 1% to 2%, and severity is usually mild to moderate. However, a wide range of other CNS adverse effects have been reported including restlessness, agitation, drowsiness, light-headedness, tremors, and confusion. Delirium, acute psychosis, and convulsions have been described in rare and selected instances (1–3,18). Most CNS effects occur early in therapy and usually resolve with discontinuation of the drug.

There is a higher probability of CNS adverse events among fluoroquinolones that are no longer used (e.g. BAY 3118, fleroxacin, trovafloxacin,

| Table 2. Comparative adverse events and discontinuation rates (%) for selected fluoroquinolones |
|-----------------------------------------------|------------------|------------------|------------------|------------------|------------------|
| Gastrointestinal effects                     | Ciprofloxacin    | Levofloxacin     | Gatifloxacin     | Moxifloxacin     | Gemifloxacin     |
| Nausea                                        | 5.0              | 1.0              | 3.0–6.0          | 7.2              | 2.7              |
| Vomiting                                      | 2.0              | 0.2              | 2.0              | 1.0–2.0          | 0.9              |
| Diarrhea                                      | 2.0              | 1.0              | 3.0–6.0          | 5.7–8.0          | 3.6              |
| Abdominal pain                                | 2.0              | 0.3              | < 3.0            | 2.0              | 0.9              |
| CNS effects                                   |                  |                  |                  |                  |                  |
| Dizziness                                     | 1.0–2.0          | 0.3              | 1.0–2.0          | 3.0              | 0.8              |
| Headache                                      | 1.0              | 0.1              | ≥ 0.1–< 3.0      | 2.0–8.0          | 1.2              |
| Dermatologic effects                          | < 1.0            | 0.3              | ≥ 0.1–< 3.0      | ≥ 0.1–< 2.0      | 2.8              |
| Discontinuation rate                          | 1.2–3.5          | 1.3–3.7          | 3.0–5.0          | 2.0–5.0          | 2.2              |

Abbreviation: CNS = central nervous system.
Adapted from reference (2,11–15).
Dermatologic reactions
The incidence of dermatologic adverse effects resulting from fluoroquinolone therapy ranges from 0.5% to 3% (1–5). Most of these skin reactions are reported as mild, self-limiting skin rashes and pruritus.

The overall rate of skin rash for gemifloxacin has been reported as 2.8%, which is approximately two to three times higher than comparator agents, including other fluoroquinolones (15). The severity of this drug-related rash has usually been described as mild to moderate, however up to 10% of patients have experienced a rash of severe intensity. The rash usually resolves in 60–80% of patients within 7–14 days after discontinuation of gemifloxacin therapy.

Rash has been described as an uncomplicated exanthematous (morbilliform) skin reaction, and has not been associated with eosinophilia or severe or toxic manifestations (e.g., Stevens-Johnson Syndrome, mucous erythema multiforme, toxic epidermal necrolysis). The rash most commonly occurs after 8–10 days of therapy, in female patients younger than 40 years of age, and postmenopausal women receiving hormone replacement therapy (Figure 4). Prolonged therapy (> 7 days) should be avoided and gemifloxacin should be discontinued in patients who develop a rash.

Photosensitivity is an uncommon, but distinctive adverse reaction specific to individual fluoroquinolones. Two types of photosensitivity have been described: photoallergy and phototoxicity. Photoallergic reactions are rare and require prior exposure to a fluoroquinolone; it is thought to be a manifestation of cell-mediated immunity (23). Phototoxicity is generally considered uncommon (< 0.1%) for ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin (11–15). However, significant rates (1–16%) of phototoxic reactions have been associated with previously available (lomefloxacin, sparfloxacin) or investigational (fleroxacin and clinafloxacin) agents (1–5). As previously discussed, all of these agents have had a halogen such as fluorine or chloride substituted in the X–8 position of the agent’s bicyclic ring (9) (Figure 2). It is recommended that extensive exposure to ultraviolet light should generally be avoided during therapy with any fluoroquinolone, and that therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

The intravenous administration of fluoroquinolone has been associated with injection site reactions and pain in 3.5–5% of patients. The recommended intravenous infusion period for injectable fluoroquinolones is 60 minutes, while the infusion period should be extended to 90 minutes for the 750 mg dose of levofloxacin (12).

Anaphylactoid and anaphylactic reactions
Anaphylactoid and anaphylactic reactions have
been reported to occur with all fluoroquinolones (24). The estimated rate of anaphylactoid reactions for ciprofloxacin is 1.2 per 100,000 prescriptions (25). A quinolone-specific immunoglobulin E (IgE) has been associated with the various forms of type I reactions (e.g. urticaria, angioedema, and anaphylactic shock) (26). Desensitizations have been shown to be successful administered (27,28). However, the use of fluoroquinolones should be avoided in any patient who has previously experienced an immediate hypersensitivity reaction because of significant cross-reactivity and similar chemical structures among the various agents.

Musculoskeletal reactions

Adverse events associated with the musculoskeletal system are either arthropathy or tendinopathy (1–4). In humans, the incidence of fluoroquinolone-induced arthropathy is less than 1%. It has typically involved the weight bearing joints and is more common in patients < 30 years of age (2,3). The clinical presentation includes pain, stiffness, and synovial swelling. The onset of symptoms occurs during the first few days of treatment and usually resolves within a few days or weeks after discontinuation of drug therapy.

Concern about fluoroquinolone-induced arthropathy is a result of observation studies restricted to juvenile animals, except for pefloxacin where data exists for both skeletally mature and immature dogs (4,29). A comprehensive review of the published literature concluded that observed fluoroquinolone-induced arthropathy in animals does not correlate with the use of these agents in children and adolescents (30). Reports on the use of ciprofloxacin, norfloxacin, ofloxacin, and nalidixic acid in more than 7,000 skeletally immature patients have not demonstrated the development of arthralgia beyond what might be expected as a result of an underlying disease. In addition, several recent reports involving gatifloxacin provide further evidence of the safety profile in pediatric patients (31–33). The United States Food and Drug Administration (FDA) has recently approved ciprofloxacin for the treatment of infections in children (11). Despite the increasing evidence on the safety of fluoroquinolones for treating pediatric patients, the appropriate use and increasing selective pressure that favors drug-resistant microorganisms remains controversial.

Fluoroquinolone-associated tendinopathy has included tendinitis and tendon rupture, with approximately 90 cases reported in the literature (34). The suggested incidence of fluoroquinolone-induced tendon injury in the healthy patient population is rare (approximately 0.14–0.4%). However, this incidence may be higher in patients with select risk factors such as renal transplantation, renal failure, hemodialysis, use of corticosteroids, age > 50, and male athletes (34,35). Although the onset of symptoms usually occurs within 1–2 weeks after starting therapy, reports have described onset as long as months after discontinuation of the fluoroquinolone. The majority of reports involve injuries to the Achilles tendon and ruptures occur in approximately 50% of these cases. Recovery from the injury usually requires rest and immobilization for 1–2 months. The most frequent reports have come from France and are attributed to pefloxacin, which is commonly used in that country (it is unavailable in the US). Although ciprofloxacin was the second most commonly reported antimicrobial associated with these tendon injuries, they are considered a class effect for all fluoroquinolones.

Renal and hepatic reactions

Adverse events to the liver and kidneys are uncommon reactions with fluoroquinolones (36,37). In general, liver enzyme elevations occur in 2–3% of patients during treatment with fluoroquinolones. The increases in transaminases and alkaline phosphatase are usually two to three times the upper limit of normal levels. These ranges generally return to normal laboratory values once the agent is discontinued. There are limited case reports of severe liver abnormalities including cholestatic jaundice, hepatitis, liver necrosis, and hepatic insufficiency or failure (2,8). For renal injury, there are reports of crystalluria, hematuria, interstitial nephritis, and acute renal failure (2,7).

The obvious exceptions with fluoroquinolone-associated renal and/or hepatic reactions have been temafloxacin and trovafloxacin (2,7,8). Temafloxacin was withdrawn shortly after its initial market approval because of “temafloxacin syndrome”, which consisted of hemolytic anemia, renal failure, abnormal liver functions test, hypoglycemia and/or coagulopathy (7). In comparison, trovafloxacin was placed on restrictive use in the United States and removed from the market in Europe within two years after its approval. Trovafloxacin therapy resulted in more than 100 reported cases of clinically symptomatic and severe liver toxicity. The public health advisory issued by the FDA stated that 14 cases of acute liver failure had been reported, with five deaths due to liver-related illnesses and four patients requiring liver transplantation (one of whom subsequently died) (8). The mechanisms of these higher incidence and severity of renal and hepatic adverse reactions remains unknown.
Glucose homeostasis reactions

The incidence of glucose homeostasis reactions (e.g. hypoglycemia and hyperglycemia) among currently available fluoroquinolones is considered extremely low (< 2%) (38). The product package insert outlines the potential for symptomatic hypoglycemia and/or hyperglycemia reactions (11–15). In general, the product information has included class precautions and suggests that these reactions usually occur in diabetic patients receiving concurrent treatment with insulin or an oral hypoglycemic agent (e.g. glyburide or glibenclamide). It is recommended that careful monitoring of blood glucose is needed in patients at risk of these reactions. Fluoroquinolone therapy should be discontinued and appropriate treatment started immediately if a hypoglycemic reaction occurs.

It does appear that some fluoroquinolones are more commonly associated with higher rates of serious glucose homeostasis reactions in susceptible patient populations. Historically, lomefloxacin, enoxacin, and temafloxacin were associated with hypoglycemia in elderly patients (2). The incidence of hypoglycemia events during Phase II and III clinical trials was much higher in patients treated with clinafloxacin (4%) versus comparator agents (1.1%) (4). In addition, clinafloxacin was associated with significant decreases in blood glucose levels in healthy subjects secondary to extensive increases in insulin concentrations (39). More recently, retrospective studies, case reports, and post-marketing surveillance have indicated that hypoglycemia and hyperglycemia occur more often with gatifloxacin than with other commonly used antimicrobial agents, including fluoroquinolones (13,38,40–45).

Frothingham has recently obtained and reviewed the FDA spontaneous adverse event reports for ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin during the period November 1997 to September 2003 (45). Gatifloxacin accounted for 80% (453, n = 568) of all adverse event reports for glucose homeostasis abnormalities and 68% (17, n = 25) of reported fatalities. In addition, glucose homeostasis reactions accounted for 24% of all reported adverse event reports for gatifloxacin, significantly higher ciprofloxacin (1.3%), levofloxacin (1.6%), and moxifloxacin (1.3%). The exact reasons why gatifloxacin is associated with a higher frequency of disturbances to blood glucose are not known. It has been hypothesized that blockade of ATP-sensitive potassium channels in pancreatic beta cells may result in a dose- or concentration-related increase or decrease in insulin release (46–49). In vitro studies support the clinical findings that temafloxacin and gatifloxacin have a much greater likelihood of inducing these changes compared to levofloxacin or moxifloxacin.

Several safety-related changes have occurred in the labeling of the FDA-approved product package insert for gatifloxacin (13) (Table 3). Similar to previous reports, the hypoglycemic reactions tend to occur in diabetic patients, while hyperglycemic episodes occurred in patients not previously diagnosed with diabetes. Caution should be exercised when prescribing gatifloxacin in patients with diabetes mellitus or in elderly patients. The latter recommendation is supported, in part, by the observations that elderly patients (≥ 65 years) are at an increased risk of severe hyperglycemia second-

### Table 3. Warning statements regarding gatifloxacin and disturbances in blood glucose

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Warning statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic episodes</td>
<td>“Hypoglycemic episodes, in some cases severe, have been reported in patients with diabetes mellitus treated with either sulfonylurea or non-sulfonylurea oral hypoglycemic medications.”</td>
</tr>
<tr>
<td></td>
<td>“These events frequently occurred on the first day of therapy and usually within 3 days following the initiation of gatifloxacin.”</td>
</tr>
<tr>
<td>Hyperglycemic episodes</td>
<td>“Hyperglycemic episodes, in some cases severe and associated with hyperosmolar non-ketotic hyperglycemic coma, were reported in diabetic patients, mostly between 4 and 10 days following the initiation of gatifloxacin therapy. Many of these patients had other underlying medical problems and were receiving concomitant medications that may have contributed to the glucose abnormality.”</td>
</tr>
<tr>
<td></td>
<td>“Episodes of hyperglycemia, including hyperosmolar non-ketotic hyperglycemic coma, also occurred in patients not previously diagnosed with diabetes mellitus.”</td>
</tr>
<tr>
<td></td>
<td>“Elderly patients who may have unrecognized diabetes, age-related decrease renal function, underlying medical problems, and/or are taking concomitant medications associated with hyperglycemia may be at particular risk for serious hyperglycemia.”</td>
</tr>
</tbody>
</table>

Adapted from reference (13).
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Cardiovascular reactions
The prolongation of electrographic QTc intervals and its potential complications have emerged as safety issues for fluoroquinolones (51,52). Historically, cardiac-related fatalities and life-threatening ventricular arrhythmias have been associated with sparfloxacin and grepafloxacin. In part, these adverse events led to the withdrawal of grepafloxacin from the worldwide market and contributed towards sparfloxacin’s withdrawal from the US market (2–4).

Numerous in vitro and animal models have clearly demonstrated that fluoroquinolones are inhibitors of the human ether-a-go-go-related gene (HERG) potassium channel and these agents can be associated with cardiac arrhythmias (53–55). All fluoroquinolones produce a dose-dependent prolongation of the QTc interval and differences in the potency for potassium channel blocking properties among these agents exist. Almost all studies conclude that sparfloxacin and grepafloxacin are the most potent HERG potassium channel inhibitors, while ciprofloxacin is one of the weakest (51). The potency of fluoroquinolones has been ranked and, in general, typical findings suggest the following order: sparfloxacin > grepafloxacin ≥ moxifloxacin = gatifloxacin >> levofloxacin, ciprofloxacin (22).

A limited number of studies have evaluated effects of the currently available fluoroquinolones on the prolongation of the QTc interval in healthy subjects (56–58). A double-blind, randomized, placebo-controlled, crossover study comparing single doses of levofloxacin demonstrated that the mean QTc values after drug administration were not significantly different from placebo at the 500 mg and 1000 mg dose levels (56). Mean QTc interval prolongation was significantly greater for levofloxacin 1500 mg compared to the placebo.

In a second comparative study involving single oral doses of ciprofloxacin 1500 mg, levofloxacin 1000 mg, moxifloxacin 800 mg (each of these doses were twice the FDA-recommended dose at that time), the mean changes in QTc intervals at several end points were significantly greater for moxifloxacin than those with placebo, ciprofloxacin or levofloxacin (57). The effect of single 400 mg and 800 mg oral doses of moxifloxacin has also been evaluated in healthy subjects (58). The increase in QT interval duration compared to placebo ranged from 2.3% to 4.5% across the entire RR intervals evaluated. A significant correlation between the percent change of QT interval and moxifloxacin plasma concentrations was observed ($r = 0.72, p < 0.001$). Finally, moxifloxacin has more recently been used as a positive control in several comparative trials evaluating prolongation of the QTc intervals with various therapeutic agents (59, 60).

Only a few cases of drug-associated cardiac dysrhythmias (including torsades de pointes) have been reported among the currently marketed fluoroquinolones (52,61–64). However, the product package inserts of gatifloxacin, moxifloxacin, and gemifloxacin have extensive warnings about the limited clinical experiences of these agents in patients at high risk of QTc prolongation, electrolyte (potassium) disorders, and concurrent treatment with drugs (antipsychotics, tricyclic antidepressants, Class IA [e.g., quinidine, procainamide] or Class III [e.g., amiodarone, sotalol] antiarrhythmic agents) known to prolong the QTc interval (13–15). In addition, the recommended dose (400 mg once daily) or intravenous infusion rate (60 minutes) of moxifloxacin should not be exceeded since the effects on prolongation of QTc interval are dose- and/or concentration-dependent (14,58).

In contrast, no warnings appear in the ciprofloxacin package insert, while precaution statements for levofloxacin indicate that rare cases of torsades de pointes may occur in patients with concurrent medical conditions or medications (11,12). Overall, cases of torsades de pointes have rarely been reported among currently used fluoroquinolones, especially in patients without risk factors for QTc interval prolongation. The multiple risk factors for QTc interval prolongation and torsades de pointes must be carefully evaluated before prescribing fluoroquinolones in susceptible patient populations.

Safety of high-dose fluoroquinolone therapy
Ciprofloxacin and levofloxacin have established safety profiles in a broad range of clinical indications and daily doses. The FDA-approved clinical indications for ciprofloxacin include mild, moderate, and severe infections caused by susceptible strains of pathogens (11). The oral and intravenous doses of ciprofloxacin for mild to moderate infections are 250–500 mg every 12 hours and 400 mg every 12 hours, respectively. An oral dose of ciprofloxacin 750 mg every 12 hours and 400 mg intravenously every 8 hours is recommended for severe and/or complicated skin and skin structure infections, bone and joint infections, and nosocomial pneumonia. The higher intravenous dose of ciprofloxacin 400 mg every 8 hours was based...
on, in part, the long-term safety data of oral ciprofloxacin 750 mg every 12 hours, as well as similar systemic exposure parameters (maximum plasma concentration [C\text{max}] and area under the curve [AUC\text{0–24}]) associated with these two dosing regimens (65,66). Overall, the incidence and type of adverse events have been similar across all dose ranges of ciprofloxacin.

The recommended daily doses of levofloxacin have included 250 mg for the treatment of urinary tract infections and 500 mg for uncomplicated skin and skin structure infections, acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP), acute maxillary sinusitis, and chronic bacterial prostatitis (12). The initial indications for a higher dose (750 mg once daily) of levofloxacin included more serious infections such as nosocomial pneumonia and complicated skin and skin structure infections (67,68). Comparable rates of treatment-emergent, drug-related, and serious adverse effects have been demonstrated regardless which once-daily dosing regimen (250 mg, 500 mg or 750 mg) of levofloxacin is used (12). For the treatment of nosocomial pneumonia, a slightly higher rate of adverse and serious events were observed with the 750 mg once-daily dose of levofloxacin, however this might be more reflective of the severe underlying conditions and concomitant antimicrobial therapy in patients with this type of infection (67). Overall, the safety profile for levofloxacin has remained the same for dose ranges of 250 to 750 mg (12).

One of the most recent trends in antimicrobial therapy is the use of higher doses with shorter duration of therapy. The World Health Organization has encouraged drug development programs to focus on optimizing treatment regimens with regards to safety, efficacy, and the prevention of selecting resistant microorganisms (69). One of the considerations has been shorter courses of antimicrobial therapy in an attempt to reduce the disruption of the normal flora, decrease the selective pressure that favors drug-resistant microorganisms, and encourage patient adherence.

In multicenter, noninferiority studies involving adults with either CAP or acute bacterial sinusitis, a short course of 750 mg of levofloxa-
Review Article: Levofloxacin – An Efficacious, Multipurpose Antimicrobial


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