

Review Article

Efficacy and Safety of Levofloxacin in the Context of Other Contemporary Fluoroquinolones: A Review

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ABSTRACT

Background: In recent years, fluoroquinolone research has focused on achieving several goals, including (1) enhanced potency against gram-positive cocci, notably *Streptococcus pneumoniae*, and anaerobes, while (2) maintaining potency against gram-negative pathogens, (3) optimizing pharmacokinetics and pharmacodynamics (PK/PD), and (4) minimizing potential adverse drug reactions through recognition and avoidance of structural configurations that have characterized earlier, reactive compounds.

Objective: This review examines the efficacy and safety of fluoroquinolones and the specific clinical evidence regarding levofloxacin.

Methods: Using published literature collected over time by the author, a review was conducted, focusing on the efficacy and safety profile of levofloxacin and other fluoroquinolones.

Results: The newer fluoroquinolones have fulfilled many of the research goals described above. Levofloxacin has improved anti-gram-positive potency, PK/PD properties, a proven clinical trial record (particularly for community-acquired pneumonia [CAP]), and an excellent safety profile—in the context of the treatment of >250 million patients worldwide in the past decade. It is licensed for management of drug-resistant *S pneumoniae* infections in the United States and has gained widespread formulary acceptance and guideline inclusion. Studies assessing levofloxacin for CAP therapy show significant advantages over standard therapy, such as trends toward reduced IV therapy and length of hospitalization, reduced mortality, and significant associated cost reduction. In addition, levofloxacin has proved highly effective in acute exacerbations of

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chronic bronchitis (AECB), with excellent clinical and bacteriologic results, typical of the class, and significant advantages—in terms of clinical response, overall pathogen eradication, extension of the symptom-free period, and trends toward a reduction in the number of consultation visits and hospitalizations—over standard agents, such as the oral cephalosporins.

Conclusions: Levofloxacin offers a combination of documented efficacy and tolerability, and provides an important option for the treatment of bacterial infections, including CAP and AECB, compared with standard agents used in the management of lower respiratory tract infections. (*Curr Ther Res Clin Exp*. 2003;64:646–661) Copyright © 2003 Excerpta Medica, Inc.

Key words: acute exacerbations of chronic bronchitis, community-acquired pneumonia, fluoroquinolones, gram-positive bacteria, nosocomial pneumonia, respiratory tract infections, resistance.

INTRODUCTION

Over the past decade, the development of successive generations of fluoroquinolones, such as levofloxacin, grepafloxacin, sitafloxacin, sparfloxacin, trovafloxacin, moxifloxacin, gatifloxacin, and gemifloxacin,¹ has been prompted primarily by the lesser in vitro potency of the original second-generation agents, such as ciprofloxacin, against *Streptococcus pneumoniae*.^{1–4} Earlier fluoroquinolones remain the agents of choice for gram-negative infections, both superior and inferior to the diaphragm, but the newer class members have become the drugs of choice for lower respiratory tract infections (LRTIs), notably community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB).⁴ Newer fluoroquinolones appear to be the drugs of the future for these indications,^{4,5} at a time when standard therapy is increasingly compromised by bacterial drug resistance.⁶ Many newer fluoroquinolones are available in IV and PO formulations, allowing flexibility in administration and offering the potential for IV-PO switch once the patient improves.

Beta-lactam and macrolide resistance in *S pneumoniae* now threatens routine management of CAP,^{7,8} and beta-lactamase production in *Haemophilus influenzae* and *Moraxella catarrhalis* has compromised the use of beta-lactams in AECB. The fluoroquinolones offer potent, first-choice alternative therapies to traditional agents. The newer fluoroquinolone agents—which have enhanced activity against *S pneumoniae*, including drug-resistant *S pneumoniae*—are increasingly prominently represented in CAP guidelines in the West^{9–11} and in Japan.¹² The newer fluoroquinolones also are considered among the agents of first choice for patients with AECB who are at risk for poor therapeutic outcome.^{13–15}

This review examines the efficacy and safety of fluoroquinolones and the specific clinical evidence regarding levofloxacin.

MATERIALS AND METHODS

Using published literature collected over time by the author, a review was conducted, focusing on the efficacy and safety profile of levofloxacin and other fluoroquinolones.

MICROBIOLOGIC CONSIDERATIONS

The modern fluoroquinolones have comprehensive activity against the major respiratory pathogens. They are highly active against *H influenzae*, in which species' resistance to fluoroquinolones is virtually nonexistent, and have good to excellent potency^{1,2} against *S pneumoniae* irrespective of coexistent resistance to beta-lactams or macrolides. The spectrum of activity also extends to *M catarrhalis*, atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, and *Legionella* species. Therefore, the fluoroquinolones are ideal candidates for the empiric management of moderate to severe LRTIs, in which the potential pathogens may be—at least initially—unidentified.

Fluoroquinolone resistance among *S pneumoniae* is appearing in some areas of the world, notably Hong Kong¹⁶ and Spain¹⁷ and, to a lesser extent, North America.¹⁸ Some evidence shows that bacterial resistance may lead to treatment failure.¹⁹ Such uncommon reports of treatment failure with levofloxacin have occurred mostly among predisposed hospitalized patients with chronic respiratory disease.²⁰ In most countries, levofloxacin resistance among *S pneumoniae* is <1%; the minimum inhibitory concentration for 90% of isolates (MIC₉₀) remains at 1 mg/L¹⁷; and, provided that optimized regimens are used, fluoroquinolones, including levofloxacin, remain highly effective against this pathogen. Levofloxacin is licensed for the management of drug-resistant *S pneumoniae* in the United States and has widespread formulary acceptance and guideline inclusion.

However, concerns have been expressed²¹ that continued widespread use of levofloxacin and ciprofloxacin may predispose to increasing fluoroquinolone resistance in *S pneumoniae*. There are limited clinical data to confirm or refute such suggestions. Most rapid emergence of resistance has been due to the selection and dissemination of ≥ 1 single clone, as in Hong Kong.¹⁶ It is unclear whether levofloxacin (which permits single-step resistance emergence) is more likely to select resistant strains than agents that require both topoisomerase and gyrase mutations, such as 8-methoxyquinolones. Although resistance-selection frequencies of levofloxacin are higher than those for moxifloxacin,²² 1 study²³ that attempted to assess potential for resistance selection in *S pneumoniae* while simulating human dosing and kinetics demonstrated that, despite lower MICs seen with moxifloxacin, the overall selection of resistance with levofloxacin did not differ significantly from that seen with moxifloxacin. Clearly, optimal dosing is required to eradicate pathogens rapidly before resistance develops.⁵ In this context, a study²⁴ of various pharmacodynamic (PD) end points demonstrated that levofloxacin and moxifloxacin

offered rapid and sustained bactericidal activity at clinically relevant concentrations.

PHARMACODYNAMIC PREDICTION OF OUTCOMES

PD assessment, integration of pharmacokinetic (PK) parameters with MICs, and correlating such resultants with clinical or bacteriologic outcomes (so-called *PK/PD modeling*) can assist in determining optimal regimens and dosages. However, many of the established serum concentration–dependent breakpoint parameters were established in gram-negative infections.²⁵ In the case of *S pneumoniae*, a maximal plasma concentration:MIC ratio of ~12 for levofloxacin equates with clinical efficacy.^{26,27} One assessment²⁸ of the area under the concentration–time curve (AUC):MIC ratios originally suggested a figure of 125 to predict clinical response. However, a review²⁹ of many models indicated AUC:MIC ratios of 35 to 50 to be more appropriate breakpoints for pneumococcal infection, which would explain the paradox between the clinically proven efficacy of levofloxacin and AUC:MIC ratios that may not attain the recommended figure of 125 in all patients.

In addition, serum-based PD parameters may not accurately predict activity in tissues and fluids. Fluoroquinolones are concentrated in various tissues and, for example, after a standard 500-mg dose, levofloxacin clearly achieves effective therapeutic concentrations in bronchial mucosa (~6 mg/L), epithelial lining fluid (~9 mg/L), and alveolar macrophages (>40 mg/L).³⁰

Thus, although they do not entirely explain the undoubted activity of levofloxacin, existing PD parameters certainly indicate that a high dose is required to ensure efficacy (and probably to avoid resistance emergence) and that, should an upward shift in MIC distribution in *S pneumoniae* be encountered, assessment of higher-than-currently-used doses should be investigated. The safety profile at the presently recommended dose³¹ of levofloxacin encourages this possibility.

FLUOROQUINOLONE EFFICACY IN COMMUNITY-ACQUIRED PNEUMONIA

The newer fluoroquinolones have been widely assessed in a number of recent clinical trials^{4,5} in CAP of varying severity. These studies usually have reported clinical cure rates >90%.^{4,5} For levofloxacin, cure rates in mild to moderate CAP have ranged from 94% to 98%,^{4,5,32} and in severe disease, 87%.³³ These studies have shown that levofloxacin compares favorably with ceftriaxone.

Two trials^{32,33} of IV-PO switch therapy compared levofloxacin with ceftriaxone followed by PO cephalosporin therapy. One study,³² a large series in predominantly ambulatory patients (half initially treated in the hospital), reported clinical success at 1 week after therapy in 96% of patients receiving levofloxacin (217/226), compared with 90% after cephalosporin therapy (ceftriaxone/cefuroxime axetil) (207/230). This difference was statistically significant (95% CI, -10.7

to -1.3). Bacteriologic eradication was 98% for levofloxacin compared with 85% for the cephalosporins (95% CI, -21.6 to -4.8), and, in pneumococcal disease, efficacy was 100% versus 94%, respectively, and eradication 100% versus 97%, respectively (95% CI, -10.8 to -4.6). This study was one of the first to show a significant advantage to fluoroquinolone therapy. A second study,³³ undertaken in more severe infections (hospitalized patients), reported clinical response in 87% of levofloxacin-treated patients (273/314) (vs 86% for cephalosporin therapy, 262/305) and bacterial eradication rates of 87% and 85% for levofloxacin- and cephalosporin-treated patients, respectively. These and 2 other Phase III trials^{34,35} in CAP were subsequently analyzed for the response of macrolide-resistant pneumococcal infections. Clinical success was reported in 26 of 27 patients (96%) infected with macrolide-resistant *S pneumoniae* strains.³⁴ PO therapy was similarly effective: efficacy of levofloxacin was compared with amoxicillin/clavulanic acid in CAP, and clinical efficacy in both groups was 95% (95% CI, -9.7 to 6.7), with 100% pneumococcal eradication.³⁵

CAP caused by atypical pathogens also responds well to levofloxacin therapy. In these trials,³²⁻³⁵ beta-lactam comparators usually were supplemented by additional macrolide therapy, whereas levofloxacin was used alone. In the large trial³² in predominantly ambulatory patients, clinical success rates of levofloxacin monotherapy in treating *M pneumoniae* (19/19 patients) and *C pneumoniae* (46/47 patients) infections were 100% and 98%, respectively. An overview meta-analysis³⁶ of results in 191 atypical infections reported a 96% response rate with levofloxacin therapy (94% for comparators [ceftriaxone, cefuroxime axetil, and amoxicillin/clavulanic acid]), *Mycoplasma* infections responded in 100% of cases, *Chlamydia* in 96%, and *Legionella* in 92% (vs 83% with comparator agents). The latter figure was confirmed by data from a large-scale (625 patients), non-comparative study³⁷ in the United States, where 24 of 26 patients (92%) with confirmed legionellosis were clinically cured by levofloxacin therapy.

THE CASE FOR COST-EFFECTIVENESS

Fluoroquinolones are expensive drugs; therefore, their use must be justified by improved outcomes that indicate overall cost-effectiveness. The CAPITAL study (Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin),³⁸ which assessed treatment of 1743 patients with CAP in 19 Canadian hospitals for 6 months during 1998, compared conventional management (in 10 institutions) with a critical pathway (9 institutions), consisting of levofloxacin therapy and practice guidelines. Hospitals using the critical pathway reported a significant 1.7-day reduction in bed-days per patient managed (4.4 days vs 6.1 days, respectively; $P = 0.04$) and an 18% decrease in admissions of low-risk patients compared with the conventional treatment group (31% vs 49%, respectively; $P = 0.01$). Interestingly, inpatients at critical-pathway hospitals had more severe disease but required fewer days of IV therapy than those receiving conventional therapy (4.6 days vs 6.3 days, respectively; $P = 0.01$),

and were more likely to remain on monotherapy (64% vs 27%, respectively; $P < 0.001$). Thus, the use of the critical pathway (incorporating levofloxacin and practice guidelines) reduced resource utilization (thereby reducing costs, estimated at US \$1700/patient) without affecting outcomes.

In some cases, mortality also is reduced after levofloxacin treatment. In 1998,³⁹ a Toronto hospital added levofloxacin to the formulary and implemented the new CAP guidelines. The progress of 2 cohorts of elderly patients (median age, 77 years)—167 patients admitted with CAP before these changes (October 1997–September 1998; early cohort) and 334 thereafter (October 1998–June 2000; late cohort)—were subsequently analyzed. The guideline compliance was high (88% for the early cohort and 92% for the late cohort). Overall, the late cohort had a median of 1 day of parenteral therapy, compared with 4 days in the early cohort ($P < 0.001$). Multivariate analysis demonstrated guideline-compliant patients to have had significantly lower mortality (relative risk, 0.43; 95% CI, 0.29–0.83), a 2.7-day shorter duration of IV therapy, and reduced median antibiotic costs (US \$70/patient). Analysis of the effect of levofloxacin showed significantly shorter parenteral treatment duration (0.9 days vs 2.7 days, respectively) and reduced costs (US \$55/patient), without adversely affecting mortality or length of stay.

FLUOROQUINOLONES IN ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS

Bacterial pathogens, primarily *H influenzae* but also *M catarrhalis*, *S pneumoniae*, and others, are associated with 50% to 75% of AECB worldwide. Fluoroquinolones, potent against all of these potential pathogens, are the agents of choice for this indication, notably among those with risk factors for poor outcome.^{1,13,14} In patients with mild to moderate AECB, clinical success rates of $\geq 90\%$ can be expected.⁴ Even in severely ill patients, success rates approach 80% with agents such as levofloxacin.⁴⁰

An initial clinical study⁴¹ assessing the use of levofloxacin in mild to moderate AECB therapy (500 mg once daily for 5–7 days) showed clinical response in 92% of patients. In somewhat more severe AECB, studies assessing moxifloxacin^{42,43} (400 mg once daily for 5 days) or gatifloxacin (400 mg once daily for 5 days)⁴⁴ as AECB treatment reported response rates of 89% and 91%, respectively. Such excellent results are to be expected with agents that penetrate well into the site of infection and are highly active against the causative pathogens of AECB. However, the real advantages of agents such as levofloxacin—in terms of clinical response, overall pathogen eradication, extension of the symptom-free period, and trends toward a reduction in the number of consultation visits and hospitalizations—can best be demonstrated in patients with more severe infections. Thus, in severely ill patients (peak flow ≤ 300 L/min), 84 of 112 patients (75%) receiving PO levofloxacin (500 mg once daily) responded, compared with 74 of 117 patients (63%) receiving PO cefuroxime axetil.⁴⁰ In patients

who were hospitalized or receiving concomitant steroids and theophylline, response rates were 76% (48/63) and 60% (34/57), respectively. Overall pathogen eradication in the per-protocol population was superior for levofloxacin-treated patients compared with cefuroxime axetil-treated patients (77% [98/127] vs 68% [84/124], respectively). In another study,⁴⁵ the response rate in patients with >4 AECB in the previous year was 71%, and even after only 5 days of levofloxacin therapy, the overall response rate in the group assessed as severe was 86%.

These results are highly encouraging for patients with advanced disease and justify the selection of fluoroquinolones as first-choice agents in guidelines for AECB. However, the effect of such active agents on the apparently relentless progression of this chronic disease, while anticipated, has yet to be proved. On the basis of historical comparisons, though, fluoroquinolones may influence the long-term outcomes by extending the infection-free interval between AECB, thus reducing active bronchial damage,^{15,45–47} consultation visits, and, potentially, hospitalizations. These positive effects may be related to the efficacy of fluoroquinolones in eradicating (or at least minimizing) the endobronchial bacterial load, which is associated with extended symptom-free intervals and health care cost savings.^{48,49} Fewer exacerbations predict better long-term outcomes.^{50,51} Reduced hospital admission rates also have been reported in some studies.^{15,52}

ADVERSE EFFECTS

Fluoroquinolone development over the past 15 years has not been without problems. Various agents—notably, temafloxacin, trovafloxacin, and grepafloxacin—have been withdrawn or suspended due to serious, although rare, idiosyncratic reactions encountered during postmarketing surveillance (PMS). Others, such as Bay y 3118 and clinafloxacin, have been withdrawn or suspended during clinical trial development. However, many fluoroquinolones have shown efficacy and tolerability when used to treat large numbers of patients worldwide. Ciprofloxacin has been used to treat ≥ 350 million patients⁵³; levofloxacin, >250 million (unpublished data, Aventis, 2003); moxifloxacin, >13 million⁵⁴; and gatifloxacin, >7 million patients (unpublished data, Bristol-Myers Squibb, 2003).

Adverse drug reactions (ADRs) common to all types of fluoroquinolone therapy can be summarized as class effects, subdivided into common and rare class reactions and potentially serious idiosyncratic reactions, as follows. Common-class ADRs include effects on the central nervous system (CNS) and the gastrointestinal (GI) system, and on the skin. These effects occur at varying rates relevant to individual agents but are rarely serious. Rare-class ADRs include phototoxicity, QTc (heart rate–corrected QT) prolongation and associated cardiac arrhythmias, tendonitis, and, rarely, target organ damage. Idiosyncratic effects are peculiar to certain agents or groups of agents with specific side-chain/nuclear constituents.

The overall frequency of ADRs in agents investigated in the latter part of the past decade have averaged 25% to 30%.^{55,56} Comparisons between agents also may be influenced by the period of investigation, with agents assessed in the period before intensive examination of ADRs having significantly lower rates than those assessed afterward. For example, ciprofloxacin (PO and IV) ADR rates derived from ~1985 to 1995 were ~5% to 7%,⁵⁷ and levofloxacin, <3% in Japanese patients and ≤9.9% in North Americans.^{56,58} These findings contrast with those of PO moxifloxacin (25% in US and German trials) and gatifloxacin (29% in US trials), which were investigated in the late 1990s.^{59,60} Later (Phase IV) studies of levofloxacin in generally sicker and older patients (eg, those with AECB) report rates of 19% to 21% in Europe,^{40,45} South America,^{40,45} and South Africa.⁴⁰

For common-class ADRs, rates for levofloxacin appear to be among the lowest of the class, irrespective of racial, geographic, or chronologic factors.^{55,56} Thus, rates for GI reactions are 5.1% (class range, 3.4%–15%); CNS reactions, 0.2% to 1.1% (class range, 0.2%–5.4%); and dermatologic reactions, 0.2% (class range, 0.2% to exceptionally 5%).⁵⁵

Fluoroquinolone ADR-associated discontinuation rates average ~3% to 4% (levofloxacin is class mean, 3.7%), with exceptions being trovafloxacin (related to dizziness) and grepafloxacin (GI disturbance) at ~6% to 7%.^{55,56}

Phototoxicity

Phototoxicity is a potential risk with all contemporary fluoroquinolones,⁵⁵ notably those with multiple fluorine side-chain substitution (floxacin, sparfloxacin) and those with a chlorine substituent at the 8-position (clinafloxacin, Bay y 3118).⁶¹ In contrast, levofloxacin (1,8 cyclic) and the 8-methoxyquinolones pose minimal risk,^{62–65} probably related to their differentially lesser ability to generate free oxygen radicals in the skin.⁶⁴ For these latter agents, phototoxicity, which amounts to no more than mild sunburn, occurs in <0.05% of patients.^{55,56}

QT Interval Prolongation and Ventricular Arrhythmia

Prolongation of the QTc by fluoroquinolones and their potential for precipitation of ventricular arrhythmia is a concern.^{3,66} QT prolongation, which follows blockade of the physiologic human ether-a-go-go related gene (hERG) channel (delayed rectifier potassium current: *IKr*), is a class effect.³ However, the average QTc prolongation induced by fluoroquinolone therapy, ~3 to 6 ms, is of little clinical significance against the normal QT interval, 450 to 470 ms, which varies throughout the day.⁶⁷ A few outlier patients with excessive QT prolongation may be at risk for torsades de pointes. The Committee for Proprietary Medicinal Products guidelines⁶⁸ states that increasing QTc prolongation predicts a significant risk for arrhythmia and suggests that a QTc >60 ms or a QT interval >500 ms should raise clear concern. However, development of torsades de pointes under such circumstances usually is associated with concomitant risk factors, ≥1 of which may exist within individual patients. These risk factors include female sex,

advanced age, underlying heart disease, bradycardia, electrolyte imbalance, congenital prolonged QT syndromes, and, notably, cotherapy with other agents known to prolong the QT interval (especially type I/III antiarrhythmics).⁶⁹

Torsades de pointes and other ventricular arrhythmias have been reported with all contemporary fluoroquinolones.^{3,70–76} The ability of models investigating differential blockade by fluoroquinolones of the hERG potassium channel to predict QT prolongation and the risk for arrhythmia in humans is controversial.^{3,66,77} Some data³ suggest that ciprofloxacin and levofloxacin may have lesser effects than later, third-generation agents. However, in clinical trials, the number of fluoroquinolone-treated patients in whom extreme QT changes occur is in any case <0.5%, and reported episodes of torsades de pointes during PMS are rare—an average of ~1 per 1 million treatment courses in the 1990s.⁵ Human data are difficult to interpret,⁷⁸ but contemporary analyses, including US data on levofloxacin and gatifloxacin,^{73–75} suggest the rate of occurrence of torsades de pointes to be 0.2 to 0.5 per 1 million treatment courses. Moxifloxacin data analysis,⁵⁹ including European experience,⁵⁹ indicates a similar frequency of ~0.5 per 1 million courses. Such fluoroquinolone therapy-associated cases have occurred almost invariably in highly predisposed patients. If coexistent (and often multiple) risk factors are considered, few reports can be considered unequivocally causally related to fluoroquinolone use.

Thus, there has been some overreaction to what appears to be a rare event. Fluoroquinolones have a minimal risk for provoking torsades de pointes in most patients and should be considered tolerable for routine patient management.^{3,66} The use of these agents in patients with risk factors should be avoided, but if risk factors are present, there is probably little difference in the risk for torsades de pointes between the fluoroquinolones.

Tendonitis and Tendon Rupture

Quinolone-related tendonitis and tendon rupture, caused by collagen damage and possibly relating to hypomagnesemia,⁷⁹ are rare events. They may be bilateral and often affect the Achilles tendon.^{80,81} Tendonitis and tendon rupture are class effects and, as such, have been reported with levofloxacin.⁸² Such events probably affect <1 in 5000 patients receiving fluoroquinolones,⁸³ and the adjusted relative risk compared with the incidence in the general population is ~3.7%.⁸⁴ The overall incidence is calculated at 3 cases per 1000 patient-years.⁸⁵ However, certain fluoroquinolones, such as pefloxacin, may pose an increased risk.^{84,86} Predisposing factors include consistently advanced age (risk increases with age after 60 years) and concurrent corticosteroid therapy.^{80,85,86} Symptoms usually resolve within a few weeks but may persist. Treatment, except for withdrawal of fluoroquinolone therapy and rest, usually is not required except in some cases of Achilles tendon rupture, which may require surgical intervention.

PMS reports on fluoroquinolones in the United States (MedWatch, unpublished data, 1998–2000) indicate that tendonitis occurs in ~1 per 100,000 patients

receiving levofloxacin. Registration authorities in France have drawn attention to the higher risk for tendonitis in elderly patients receiving fluoroquinolones and concomitant steroid therapy.⁸⁷

Hepatitis and Liver Failure

Mild, transient elevation of hepatic enzymes occurs with all fluoroquinolones (at a rate of 2%–5%), but hepatitis and liver failure are rare.^{55,56,88,89} Reports of significant levofloxacin-associated hepatotoxicity are extremely rare.⁹⁰ More severe adverse effects (AEs) were reported with trovafloxacin (a fluoronaphthyridone) during PMS, with treatment leading to liver failure,⁹¹ the necessity for transplantation,⁹¹ and a small number of deaths⁹¹; these AEs may have been related to a hypersensitivity reaction and perhaps associated with neoantigen formation induced by the 1-[2,4]-difluorophenyl side chain.^{55,92} These findings led to the suspension/withdrawal of trovafloxacin in June 1999.⁹³ The 1-[2,4]-difluorophenyl side chain also characterized temafloxacin (a fluoroquinolone), which was associated with the syndrome of hemolysis, uremia, and (in 50%) hepatitis and which led to its withdrawal in the early 1990s.⁹⁴ More recently, PMS identified a background incidence of hepatitis with gatifloxacin.⁹⁵ The latest (2001) data from PMS suggest that levofloxacin and moxifloxacin are associated with hepatitis in ~1 per 100,000 patients.^{89,96} In clinical trials, the reported incidence of transient serum alanine aminotransferase elevation was highest with trovafloxacin, at 9.0% (after extended therapy), compared with gatifloxacin, at 1.3%; levofloxacin, at 2.0%; and ciprofloxacin, at 2.5%.⁵⁵

POSTMARKETING SURVEILLANCE

Spontaneous reports of drug toxicity in the postmarketing phase are often incomplete; occur against a poorly defined, chronologically asynchronous denominator population; and involve considerable observer error^{57,78} in relation to the compound, severity of response, requirement for corrective or therapeutic action, and contribution of comorbidity and concomitant therapy. Nonetheless, interesting comparisons can be made in terms of the rate of spontaneous reports during the immediate postlaunch period (4 and 15 months after launch). For example, reports to the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) on trovafloxacin and temafloxacin occurred at a rate of 98 to 108 per 100,000 patients (serious AEs, 15–28 per 100,000), compared with 16 per 100,000 (4.5 serious AEs per 100,000) for levofloxacin, a rate almost identical to that of ciprofloxacin⁹⁷ (also Ball P, personal analysis of US FDA AERS spontaneous reports [15 months/3 million prescriptions surveillance of levofloxacin and trovafloxacin—5 months, 0.4 million prescriptions], 1999). Of these, 4 per 100,000 affected the CNS, ~2.5 per 100,000 affected the GI tract, and <2 per 100,000 affected the skin or were associated with hypersensitivity phenomena.

More than 250 million patients have now been treated with levofloxacin, and the pattern of PMS reports remains similar to those observed with the other fluoroquinolones.

CONCLUSIONS

Levofloxacin has established itself as one of the leading fluoroquinolone agents during the past 5 years. It has shown clinical efficacy in CAP similar to that of gatifloxacin, and is at least as efficacious as the third-generation cephalosporins. Extensive clinical data confirm the good tolerability profile of levofloxacin without the phototoxicity or hepatic and cardiac AEs found with some other newer fluoroquinolone drugs. Therefore, levofloxacin offers a combination of documented efficacy and tolerability, and has an established place in the routine treatment of bacterial infections, including CAP and AECB.

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