Clinical Pharmacology of Gatifloxacin, a New Fluoroquinolone

Dennis M. Grasela

Gatifloxacin is an advanced-generation, 8-methoxy fluoroquinolone that is active against a broad spectrum of pathogens, including antibiotic-resistant Streptococcus pneumoniae. The drug has high oral bioavailability (96%), and, therefore, oral and intravenous formulations are bioequivalent and interchangeable. Gatifloxacin has a large volume of distribution (~1.8 L/kg), low protein binding (~20%), and broad tissue distribution and is primarily excreted unchanged in the urine (~80%). Gatifloxacin can be administered without dose modification in patients with hepatic impairment, in women, and in the elderly. In vitro experiments and clinical studies indicate that gatifloxacin does not interact with drugs metabolized by the cytochrome P450 enzyme family. At therapeutically relevant doses, gatifloxacin’s pharmacokinetically linked parameters (the ratio of maximum serum concentration to minimum inhibitory concentration and the ratio of the area under the curve to minimum inhibitory concentration) are similar to or better than those of other fluoroquinolones. Clinical studies show that gatifloxacin has limited potential to prolong the QT interval on the electrocardiogram and lacks the potential to cause photosensitivity reactions, to alter oral glucose tolerance, or to cause crystalluria.

Gatifloxacin is a new 8-methoxy fluoroquinolone that exhibits enhanced activity against clinically relevant pathogens, including such common respiratory pathogens as Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Moraxella catarrhalis, and Legionella spp. [1–10]. In recently completed clinical trials, gatifloxacin was shown to be effective in the treatment of acute respiratory infections, including community-acquired pneumonia, acute exacerbation of chronic bronchitis, and acute maxillary sinusitis [11–18]. Clinical cure rates in all trials of patients treated with gatifloxacin were ~90% or higher.

In addition to enhanced activity against many clinical isolates, gatifloxacin has been chemically engineered to optimize its safety and pharmacokinetic profiles. The absence of a halide at the C8 position minimizes the potential for photosensitivity reactions, and a methyl-substituted piperazinyl group at the C7 position provides metabolic stability and a long half-life (figure 1) [19–21]. Although gatifloxacin is administered as a racemate, there are no antibacterial or pharmacokinetic differences between the R- and S-enantiomers [19, 22]. At doses of 200–800 mg, the pharmacokinetics of gatifloxacin are linear, time-independent, and predictable, and have low intersubject variability, as evaluated in 40 healthy adult males [23].

The gatifloxacin clinical pharmacology program was an extensive effort to assess the safety, tolerability, and pharmacokinetics of oral and iv gatifloxacin in both single- and multiple-dose regimens. The program was also designed to study diverse populations: healthy white male volunteers, women, the elderly, people of diverse ethnic origin, patients with respiratory infections, hepatically impaired patients, renally impaired patients, and patients with noninsulin-dependent diabetes mellitus.

The pharmacokinetics of gatifloxacin were examined after iv administration in a randomized, double-blind, placebo-controlled sequential dose-escalation study (200, 400, 600, and 800 mg) with 40 white male subjects, aged 20–45 years [23]. Randomization included 4 groups of 8 subjects for treatment with either gatifloxacin or placebo in a 3:1 ratio. Single doses were administered by iv infusion over 1 h. The volume of distribution at steady state (VSS, 1.8 L/kg), total clearance (CLT, 190 mL/min), renal clearance (CLR, 150 mL/min), urinary recovery (UR, 80%), and elimination half-life (T1/2, 12.6 h) were each independent of dose. Figure 2 shows mean plasma concentrations compared with time profiles of gatifloxacin after a 1-h infusion. With multiple-dose administration of gatifloxacin once daily for 14 consecutive days, a predictable and modest accumulation of drug was observed (26%, ratio 1.2) [23]; steady state was reached by the third dose and maintained through the fourteenth dose. Approximately 80% of the dose was recovered, unchanged, in the urine. Both the maximum serum concentration (Cmax) and the area under the curve (AUC) increased proportional to the dose. VSS, CLT, CLR, UR, and T1/2 were each independent of dose and did not change with multiple dosing.

Table 1 shows mean pharmacokinetic parameter values that were estimated from data assembled after oral and iv administration of gatifloxacin during the gatifloxacin clinical pharmacology program. A review of the safety and pharmacokinetics of gatifloxacin is presented below.

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Absorption

Single-dose absorption. In 2 studies with published reports, single doses of oral gatifloxacin were administered to 53 healthy white male volunteers and to 30 healthy Japanese male volunteers [22, 24]. Gatifloxacin was rapidly absorbed by both study groups, with a time to maximum serum concentration (T_{max}) of 1–2 h after administration. Among the white males, mean maximum serum concentrations (C_{max}) of gatifloxacin were as follows for single doses: for 200 mg, 2.0 μg/mL; for 400 mg, 3.8 μg/mL; for 600 mg, 5.3 μg/mL; and for 800 mg, 7.0 μg/mL. Linear dose proportionality was noted for both the C_{max} and the area under the time-concentration curve, with a coefficient of correlation of 0.998 [24].

Multiple-dose absorption. In 6 healthy Japanese volunteers who received multiple doses of gatifloxacin (300 mg twice daily for 7 days), steady state was reached within 2 or 3 days [24]. These data were used to design a subsequent double-blind, placebo-controlled study in 36 healthy male white volunteers. Subjects received gatifloxacin (400 mg or 600 mg) once daily for 15 days. Blood and saliva samples were drawn up to 3 days after days 1 and 15 of gatifloxacin administration [25]. Modest plasma accumulation was reported with multiple dosing, with an accumulation ratio of ~1.2. When plasma concentrations of gatifloxacin on day 1 were compared with concentrations on day 15, the differences in C_{max} and T_{max} were not significant, and the steady-state peak was ~4 μg/mL. The trough serum concentration, observed at 24 h, was ~0.5 μg/mL.

Equivalence of oral and iv formulations. Oral and iv formulations of gatifloxacin were shown to be equivalent in a randomized, open-label crossover study with 24 healthy adults (12 male and 12 female) [26]. The subjects randomly received a single dose of gatifloxacin (400 mg) iv or orally. Doses were administered 1 week apart. The pharmacokinetic parameter values was analyzed primarily for treatment and sex interactions, in which the treatment effects were assessed by 2-way ANOVA, with the values of C_{max} and AUC_{0→∞} a priori log transformed. Figure 3 shows the mean plasma concentration time curves for these subjects. As expected, the C_{max} after iv administration was greater than after oral administration (figure 3). The iv administration was found to be bioequivalent to oral dosing of gatifloxacin with respect to AUC_{0→∞}. Like other new fluoroquinolones, gatifloxacin has high oral bioavailability, with an absolute bioavailability of 96% [26].

Effect of food and cation administration. The bioavailability of gatifloxacin was not affected by the presence of food. In one trial, 12 healthy white volunteers (5 men and 7 women) received single doses of oral gatifloxacin (400 mg) in a randomized, crossover fashion while fasting and after a high-fat meal [27]. Each dose was separated by 1 week. No statistically significant differences in C_{max} or AUC were observed between fasted and fed states. Although a somewhat prolonged T_{max} was observed in the fed state, the difference was not statistically significant or considered clinically relevant; nor was any statistically significant interaction observed between sex and type of treatment. In addition, no effect was found in 6 healthy Japanese male volunteers who received single-dose oral gatifloxacin (200 mg) during fasting and fed states [24] and, similarly, in 18 healthy White male volunteers who received a single 400-mg oral dose of gatifloxacin [28]. Together, the data from these studies indicate that gatifloxacin can be administered without regard to meals.

In vitro studies investigating the effect of cations on gatifloxacin have indicated that the potential for chelation is greater with aluminum and lower with calcium than with iron [29]. An absence of interaction with calcium was supported by the findings of a randomized, open-label study in 32 healthy volunteers [29]. The study randomized patients to receive the concomitant gatifloxacin (400 mg) and either calcium carbonate (1000 mg) or ferrous sulfate (325 mg), or gatifloxacin (400 mg) either 2 h before or 2 h after the administration of calcium carbonate or ferrous sulfate. Patients were divided so that 16 received gatifloxacin with or without calcium carbonate and 16 received gatifloxacin with or without ferrous sulfate [29]. The calcium
supplement had no significant effect on the pharmacokinetics or systemic availability of gatifloxacin. Similarly, the administration of ferrous sulfate either 2 h before or 2 h after the administration of oral gatifloxacin had no effect on gatifloxacin pharmacokinetics or systemic availability [29]. These results suggest that concomitant administration of ferrous sulfate and gatifloxacin should be avoided, because it may cause a clinically significant decrease in systemic availability of the drug, but can be prescribed if patients are instructed to take the 2 agents at least 2 h apart.

On the basis of in vitro studies and data from other fluoroquinolones, some interaction between gatifloxacin and an aluminum-based antacid (Maalox; Novartis, Summit, NJ) was expected [20, 30]. In a clinical study with healthy volunteers, the administration of Maalox (20 mL) resulted in a 68% decrease in Cmax if administered at the same time as a single dose of gatifloxacin (400 mg) and a 45% decrease if administered 2 h before [31]. AUC was also significantly reduced by 64% with concomitant administration and by 42% when Maalox was administered 2 h before gatifloxacin. However, when Maalox was administered 2 h after a gatifloxacin dose, a statistically significant (albeit clinically irrelevant) reduction in AUC was observed. When the antacid was administered 4 h after a gatifloxacin dose, no pharmacokinetic changes were observed [31]. Therefore, the intake of Maalox ≥4 h after gatifloxacin administration is recommended [32].

Distribution

Gatifloxacin is well distributed in tissues and often achieves concentrations that exceed serum concentrations. In healthy volunteers, the volume of distribution at steady state has been found to be ~1.8 kg/L, and serum protein binding to be 20% [23, 24]. The concentration of gatifloxacin in selected tissues was measured over 24 h after administration of single (100 mg, 150 mg, 200 mg, 300 mg, or 400 mg) or multiple (150 mg or 200 mg, bid) doses of the drug [32]. The mean concentration in most tissues, including those in the respiratory tract (bronchial mucosa, lung epithelial lining, sinus mucosa), was ~1.5–2.0 times the mean serum concentration. The concentration of gatifloxacin was particularly high in alveolar macrophages and lung parenchyma (26.5 and 4.09 times the plasma concentration, respectively), which indicates good intracellular penetration and targeting of lung tissue. Compared with other fluoroquinolones, the concentration of gatifloxacin in cerebrospinal fluid was also high, at 0.36 times serum concentrations. In patients with meningitis, the distribution in cerebrospinal fluid is expected to be even higher [32].

Metabolism

Gatifloxacin is a metabolically stable compound; >80% of the drug is excreted in the urine unchanged [24, 25]. Up to 72 h after administration of single-dose gatifloxacin (400 mg), the

![Figure 3. Oral and iv equivalence of gatifloxacin in healthy male and female volunteers who received a single 400-mg dose [26]. The mean absolute bioavailability of gatifloxacin was 96% (90% CI, 88–104%). For females, the mean bioavailability was 90.4% (90% CI, 80–102%); for males, 101% (90% CI, 89–114%).](cid2000:S51_10815)

Table 1. Mean pharmacokinetic values for single and multiple doses of gatifloxacin (400 mg).a

<table>
<thead>
<tr>
<th>Formulation, dose</th>
<th>Cmax, µg/mL ± SD</th>
<th>Median AUC, µg h/mL ± SD</th>
<th>T1/2, h range</th>
<th>Tmax,b h ± SD</th>
<th>T1/2, h ± SD</th>
<th>CLR, mL/min ± SD</th>
<th>Urinary recovery % ± SD</th>
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</thead>
<tbody>
<tr>
<td>Oral formulation</td>
<td></td>
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<td></td>
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<tr>
<td>Single dose (n = 202)</td>
<td>3.79 ± 0.40</td>
<td>33.9 ± 6.2</td>
<td>1.00 (0.05, 6.00)</td>
<td>7.77 ± 1.31</td>
<td>151.4 ± 46.3</td>
<td>72.4 ± 18</td>
<td></td>
</tr>
<tr>
<td>Multiple dose (n = 18)</td>
<td>4.23 ± 1.3</td>
<td>34.4 ± 5.7</td>
<td>1.50 (0.5, 4.0)</td>
<td>7.1 ± 0.60</td>
<td>158.7 ± 34.4</td>
<td>80.2 ± 12.1</td>
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</tr>
<tr>
<td>Multiple dose (n = 140)</td>
<td>4.21 ± 1.9</td>
<td>51.3 ± 20.4</td>
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<td></td>
<td></td>
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<tr>
<td>Iv formulation</td>
<td></td>
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<tr>
<td>Single dose (n = 30)</td>
<td>5.52 ± 0.99</td>
<td>35.1 ± 6.7</td>
<td></td>
<td>7.4 ± 1.6</td>
<td>123.7 ± 40.9</td>
<td>62.3 ± 16.7</td>
<td></td>
</tr>
<tr>
<td>Multiple dose (n = 5)</td>
<td>4.56 ± 0.61</td>
<td>35.4 ± 4.6</td>
<td></td>
<td>13.9 ± 3.9</td>
<td>161.0 ± 42.6</td>
<td>83.5 ± 13.9</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. AUC, area under the time-concentration curve; Cmax, maximum serum concentration; T1/2, serum half-life; CLR, renal clearance.

a For single iv dose, AUC0–72 and 72 h urinary recovery collection interval.

b For multiple iv dose, AUC0–24 and 24 h urinary recovery collection interval.
amounts of ethylenediamine and methylethylenediamine metabolites recovered were each 0.03% of the total administered dose [24]. The amino metabolite and the glucuronide conjugate of gatifloxacin that have been observed in animals were not detected in human urine [24].

**Elimination**

The elimination half-life (T1/2) of gatifloxacin ranged from 7 to 14 h, with a mean T1/2 of ~8–10 h [22, 24, 25]. The T1/2 was independent of dose, regimen, or administration route.

Gatifloxacin is primarily excreted in the urine unchanged via glomerular filtration and not tubular secretion [22, 24, 25]. In healthy male volunteers who received either single-dose or multiple-dose oral gatifloxacin, recovery of unchanged drug ranged from ~80% to 95% of the administered dose. The renal clearance rate of gatifloxacin was ~150 mL/min and was independent of dose [22, 23, 24, 25]. Concomitant dosing with probenecid resulted in decreased clearance rates and decreased recovery of gatifloxacin in urine, which suggests that net tubular secretion may also be a mechanism of elimination [24].

As expected with high urinary excretion, fecal elimination of gatifloxacin is low. For subjects who received either single or multiple doses of oral or iv gatifloxacin, ~5% of the administered dose was recovered in feces [22, 24, 25].

**Special Populations**

**Race, age, and sex.** When gatifloxacin was administered to other healthy populations, the pharmacokinetics of the drug were similar to those found with healthy White and Japanese male volunteers (table 2) [24, 25]. Neither sex nor age had any clinically significant effect on the AUC or mean plasma concentrations for gatifloxacin (400 mg; see figures 3 and 4) [26, 33]. Modest pharmacokinetic differences that were noted between young and elderly adults were consistent with age-related decreases in renal function. The pharmacokinetics of gatifloxacin with respect to race have not been specifically studied; however, no differences were observed in populations of either African or Hispanic descent as determined in a study of the population pharmacokinetics of gatifloxacin in adults with acute bacterial exacerbation of chronic bronchitis [35].

**Infected patients.** Pharmacokinetic data were also collected from various patient populations. In a phase II study, patients with acute exacerbation of chronic bronchitis were treated with oral gatifloxacin, 400 mg once daily for up to 10 days [34]. Pharmacokinetic data from these patients were similar to data from healthy volunteers in phase I studies (table 2). After accounting for differences in creatinine clearance and body weight, similar estimates of gatifloxacin clearance and volume of distribution were found for patients with acute exacerbation of chronic bronchitis and healthy volunteers, with no effects due to sex, race, or age. The population pharmacokinetics of gatifloxacin for individual infected patients were shown to be well estimated from the data obtained from the sparse sampling strategy.

**Hepatic impairment.** A single dose of gatifloxacin (400 mg) was administered to 8 patients with hepatic impairment (Child-Pugh Classification B or C) and to 8 control volunteers matched for age, weight, and sex [35]. Mean Cmax and AUC values in the patient group were slightly higher than the values in the control group. However, the treatment effect for the higher AUC was normal, and no dose adjustment was warranted in

### Table 2.

<table>
<thead>
<tr>
<th>Population</th>
<th>Differences</th>
<th>Special dosing considerations</th>
</tr>
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<tbody>
<tr>
<td>Women</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Geriatric</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nonwhite (Asian, African, or Hispanic)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patients with respiratory infections</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patients with hepatic impairment</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Patients with renal insufficiency</td>
<td>Reduced clearance</td>
<td>Reduce gatifloxacin dosage for patients with creatinine clearance &lt;40 mL/min</td>
</tr>
<tr>
<td>Patients with diabetes receiving insulin or other hypoglycemic agent</td>
<td>Decreased serum insulin concentration</td>
<td>Monitor patient glucose levels</td>
</tr>
</tbody>
</table>
hepatically impaired patients; differences in AUC values were within the statistical limit (based on an AUC point estimate of 1.23 and the 90% CI for ratio of means [1.07–1.40]; table 2) [35]. Other pharmacokinetic parameters, including CLR, T1/2, UR, and VSSF, were not statistically different between treatment groups.

Renal impairment. In patients with renal insufficiency, the systemic exposure to gatifloxacin was higher and clearance of gatifloxacin was lower than in patients with normal renal function (table 2) [19, 36]. A direct relationship between total clearance and creatinine clearance was noted. A population pharmacokinetic model of gatifloxacin was developed to fit the plasma time-concentration data obtained from patients with normal renal function and with selected degrees of renal impairment. To evaluate the systemic exposure to gatifloxacin in patients with varying degrees of renal impairment, we performed pharmacokinetic simulations based on the population model and parameter estimates. The safety and drug exposure data indicated that AUC values of $\sim 70$ µg-h/mL and $C_{\text{max}}$ of $\sim 7.0$ µg/mL are allowable before recommending dose modifications. Dose modifications are suggested for patients with a creatinine clearance $< 40$ mL/min [32].

Type II diabetes mellitus. In a diabetic population controlled with diet and exercise, gatifloxacin had no effect on glucose tolerance or homeostasis [37]. A second randomized, double-blind, placebo-controlled study of 34 patients has assessed the effects of oral gatifloxacin (400 mg) on oral glucose tolerance, glucose and insulin homeostasis, and glyburide pharmacokinetics. Gatifloxacin was found to have no effect on oral glucose tolerance or on glucose and insulin homeostasis in patients with type 2 diabetes mellitus that was controlled by glyburide therapy; however, a modest decrease in insulin production could not be ruled out [38]. Similar results for serum glucose were observed in a randomized, double-blind, placebo-controlled study of iv gatifloxacin at 200, 400, 600, and 800 mg in healthy volunteers [23]. Mean changes in fasting glucose and insulin levels were comparable across treatment groups and were unrelated to gatifloxacin dose. A mild, transient decrease in fasting serum glucose values at the end of infusion was observed; however, glucose tolerance testing found no apparent effect on glucose or insulin $C_{\text{max}}$ or on AUC values, which suggests that gatifloxacin administration is not associated with clinically important changes in glucose tolerance. In addition, gatifloxacin can be administered with glyburide without an apparent risk of pharmacokinetic or pharmacodynamic interaction [38].

Tolerability and Safety

The safety and tolerability of gatifloxacin were assessed in 107 healthy white volunteers who had received either single or multiple doses of oral gatifloxacin in phase I trials [29]. In addition, the overall safety profile of gatifloxacin at a dose of 400 mg was retrospectively analyzed from studies in the clinical development program for gatifloxacin [19]. The pooled data of $> 5000$ subjects was analyzed; adverse events were evaluated and compared with those in patients who received other fluoroquinolones, cephalosporins, and macrolides.

Vital signs. No changes in vital signs, electrocardiogram, electroencephalogram, spirometry, or psychometric testing were noted in healthy volunteers who received gatifloxacin at doses from 200 to 800 mg [23, 29, 39]. Results from liver function tests were similar to those for patients who received other agents, and no clinically relevant liver enzyme elevations were found. In comparative clinical trials with gatifloxacin, the most frequently reported adverse events included nausea (9% of patients), diarrhea (4%), headache (4%), and vaginitis (5% of women) [19]. The incidence of adverse events was slightly higher in patients aged $\geq 75$ years. Women also reported more nausea than men (11% vs. 5%, respectively) [19]. In addition, more women (33%) than men (24%) experienced an adverse event that was defined as definitely, probably, or possibly related—a difference that has been previously noted with other fluoroquinolones [21].

$QTc$ interval. Serial electrocardiograms were recorded in volunteer subjects receiving multiple doses (200–800 mg once daily for 14 days) of iv gatifloxacin [23]. No changes in QTc interval ($QTc$ interval corrected for heart rate) were noted for any subject enrolled in a comparative or noncomparative trial with gatifloxacin [19].

Phototoxicity. The presence of a methoxy group rather than a halide at the C8 position has been associated with a reduced potential for photosensitivity [20, 40, 41]. Recently, the in vitro phototoxic potential of gatifloxacin, a C8-methoxy fluoroquinolone, was compared with that of enoxacin, sparfloxacin, fleroxacin, and ciprofloxacin [42]. After ultraviolet A irradiation, the rate of DNA strand breaks was 3% for gatifloxacin and 23%–54% for the other quinolones. The generation of reactive oxygen species (singlet oxygen, hydroxy radical, superoxide anion, and hydrogen peroxide) was also measured. Compound stability was negatively correlated with singlet oxygen production. Gatifloxacin was found to be stable, with a decomposition half-life of 2 h and no evidence of singlet oxygen production.

The phototoxic potential of gatifloxacin was also investigated clinically. In a double-blind, placebo- and positive-controlled study of 48 healthy volunteers, gatifloxacin (400 mg once daily for 7 days) did not exhibit phototoxic potential [43]. Skin photosensitivity in subjects receiving gatifloxacin was the same as in subjects receiving placebo (figure 5). By comparison, administration of either ciprofloxacin or lomefloxacin resulted in a significant change in the phototoxic index ($P < .05$). Overall, gatifloxacin has not been associated phototoxic effects in experimental animals, healthy human volunteers, or subjects in clinical studies [19].

Glucose tolerance. In healthy volunteers and patients with
Increases in the Cmax (12%) and AUC (19%) of digoxin [45].

(0.25 mg once daily for 7 days) resulted in geometric mean oral gati®oxacin (400 mg once daily for 7 days) and digoxin of 12 healthy volunteers, the concomitant administration of midazolam, or glyburide [38, 39, 44]. In an open-label study likely to affect the pharmacokinetics of theophylline, warfarin, studies with healthy volunteers indicate that gati®oxacin is not bolically based drug-drug interactions. In vitro studies and unchanged in urine; therefore, it has a low potential for meta-

ment [19].

Crystalluria. Microscopic examination of urine collected from volunteers receiving single-dose or multiple-dose oral or iv gati®oxacin (200–800 mg) revealed no evidence of crystalluria, although the gati®oxacin concentration in urine was very high [23, 24]. Crystalluria was also undetectable in the urine of patients with renal dysfunction who received therapeutically relevant doses of gati®oxacin [36]. In clinically evaluable patients, crystalluria was not associated with gati®oxacin treatment [19].

Drug-drug interactions. Gati®oxacin is primarily excreted unchanged in urine; therefore, it has a low potential for metabolically based drug-drug interactions. In vitro studies and studies with healthy volunteers indicate that gati®oxacin is not likely to affect the pharmacokinetics of theophylline, warfarin, midazolam, or glyburide [38, 39, 44]. In an open-label study of 12 healthy volunteers, the concomitant administration of oral gati®oxacin (400 mg once daily for 7 days) and digoxin (0.25 mg once daily for 7 days) resulted in geometric mean increases in the Cmax (12%) and AUC (19%) of digoxin [45]. Since no changes in renal elimination were observed, the digoxin Cmax and AUC may have increased, because the presystemic degradation of digoxin by gastrointestinal flora such as Eubacterium lentum increased the drug’s bioavailability [46–48]. Although a priori dose reduction of gati®oxacin is not warranted, monitoring of digoxin serum levels is suggested.

In vitro and in vivo studies also indicate that gati®oxacin does not interact with heptatically metabolized substances. In vitro studies with animal and human liver microsomes found that gati®oxacin did not inhibit a number of hepatic enzymes (CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A4), which suggests a low potential for interaction with agents that are biotransformed by these enzymes (theophylline, cyclosporine, warfarin, midazolam). The in vitro data are supported by an in vivo study that found no effect of gati®oxacin on the pharmacokinetics of theophylline and midazolam [39, 44]. An open-label study of 14 healthy male subjects assessed the pharmacokinetics of midazolam, a model substrate of CYP3A, with and without concomitant gati®oxacin administration [39]. Subjects received iv midazolam (0.0145 mg/kg) 24 h before the dose of oral gati®oxacin (400 mg), which continued for 5 days. A second 1-h infusion of midazolam was administered after the last dose of oral gati®oxacin. Mean values for CLT, T1/2, and VSS were not statistically different for the 2 doses of midazolam. All reported adverse events were mild to moderate and resolved before the patients were discharged from study, which suggests that multiple doses of gati®oxacin can be safely administered with iv midazolam. Midazolam had no effect on the steady-state pharmacokinetics of gati®oxacin, and no clinically important pharmacokinetics interactions are likely to occur with coadministration of gati®oxacin and drugs metabolized by CYP3A.

Conclusion

The clinical pharmacology program for gati®oxacin was an extensive effort to evaluate the safety and pharmacokinetics of this new fluoroquinolone. Male and female volunteer subjects of various ages and races and several patient populations were included in the program. They received single-dose or multiple-dose regimens of gati®oxacin (oral or iv). In these subjects and patients, as well as in >6200 patients enrolled in double-blind, randomized clinical-trials, gati®oxacin has proved to be both safe and well tolerated, with no reported incidence of phototoxicity, cardiac disturbance, tendinitis, or crystalluria. In addition, gati®oxacin has a predictable pharmacokinetic profile, with equivalent oral and iv formulations, rapid absorption, a half-life sufficiently long to warrant once-daily dosing, low serum binding, and only modest accumulation with multiple dosing. The favorable pharmacokinetic and safety profile of gati®oxacin, coupled with its potent antibacterial activity (particularly against the gram-positive cocci), makes this agent an excellent addition to the therapeutic armamentarium for infectious diseases.

References

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