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Gatifloxacin

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Contents

Abstract

▲ Gatifloxacin is a novel extended-spectrum fluoroquinolone with improved Gram-positive and anaerobe coverage compared with older agents such as ciprofloxacin. It has good activity (but is slightly less active than ciprofloxacin) against Enterobacteriaceae.

▲ Gatifloxacin is generally 2- to 4-fold more active than ciprofloxacin against staphylococci, streptococci and enterococci and 4- to 16-fold more active than ciprofloxacin against anaerobes, including *Clostridium* and *Bacteroides* spp.

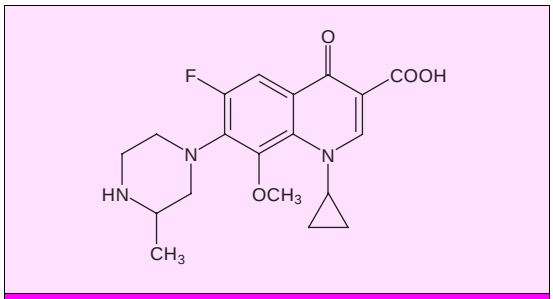
▲ In comparative clinical trials that included patients with lower respiratory tract, urinary tract, skin and soft tissue or gonococcal infections, clinical cure rates of ≥89% were achieved with oral gatifloxacin 400 mg/day for 7 to 14 days.

▲ Data from a subset of North American patients included in a multinational trial showed that oral gatifloxacin 400 mg/day produced a significantly higher clinical cure rate than cefuroxime axetil 250mg twice daily (89 *vs* 77%; p = 0.01) in patients with acute exacerbations of chronic bronchitis. The clinical efficacy of gatifloxacin was similar to that of clarithromycin or levofloxacin or ceftriaxone (with or without erythromycin) in the treatment of patients with community-acquired pneumonia.

▲ Oral gatifloxacin 400 mg/day showed clinical and bacteriological efficacy similar to that of levofloxacin in patients with skin and soft tissue infections. In patients with urinary tract infections, clinical cure and bacterial eradication rates achieved with a single 400mg oral dose of gatifloxacin were similar to those produced with ciprofloxacin.

▲ In a pooled analysis of tolerability data from trials that included 3021 patients treated with oral gatifloxacin 400 mg/day, the most commonly reported adverse events were nausea (8%), diarrhoea (4%), headache (4%) and dizziness (3%). The drug was reported to be well tolerated. Gatifloxacin does not appear to cause phototoxic effects.

Features and properties of gatifloxacin (AM 1155)	
Indications	
Treatment of bacterial infections	
Mechanism of action	
Fluoroquinolone antibacterial agent	Bacterial DNA gyrase and topoisomerase IV inhibitor
Dosage and administration	
Usual dosage in clinical trials	400 mg/day (oral)
Route of administration	Oral or intravenous
Frequency of administration	Once daily
Pharmacokinetic profile (400mg oral dose)	
Peak plasma concentration	4.21 mg/L
Time to peak plasma concentration	1h
Area under the plasma concentration-time curve	51.3 mg • L/h
Serum protein binding	≈20%
Elimination half-life	8h
Renal clearance	9.48 L/h
Drug interactions	
Interacts with gatifloxacin	Ferrous sulphate (reduced absorption of gatifloxacin)
Documented examples of no interactions with gatifloxacin	Digoxin, warfarin, glyburide, midazolam, cimetidine, theophylline
Adverse events	
Most frequent	Nausea, diarrhoea, headache, dizziness



Gatifloxacin (AM 1155)

Gatifloxacin is an 8-methoxy fluoroquinolone with a 3-methylpiperazinyl substituent at C7. It has an extended spectrum of antibacterial activity compared with the earlier fluoroquinolones, such as ciprofloxacin. Both oral and intravenous formulations of gatifloxacin are available; these 2 formulations are bioequivalent.[1]

1. Antibacterial Activity

In Vitro Activity

In this review, *in vitro* antibacterial activity refers to minimum inhibitory concentrations (MICs) determined by broth or agar dilution techniques (except in the case of some intracellular bacteria, which were tested in cell culture). MIC_{50} and MIC_{90} refer to minimum concentrations required to inhibit growth of 50 and 90% of strains, respectively.

The proposed MIC susceptibility breakpoint for gatifloxacin is ≤2 mg/L. This includes *Haemophilus influenzae*,[2] but not *Neisseria gonorrhoeae* (≤0.125 or ≤0.25 mg/L).[3] Breakpoints for ciprofloxacin are as follows: susceptible MIC ≤1 mg/L; intermediately susceptible MIC 2 mg/L and resistant MIC ≥4 mg/L for organisms other than *N. gonorrhoeae* (susceptible MIC ≤0.06 mg/L) and *Streptococcus* spp. (not recommended).

Mechanism of Action

- Gatifloxacin was more potent than several other quinolones (including sparfloxacin, ofloxacin and levofloxacin but not ciprofloxacin and clinafloxacin) in inhibiting DNA gyrase from *Escherichia coli* and topoisomerase IV from *Staphylococcus aureus* [IC_{50} (concentration required for 50% inhibition) 0.1 and 13.8 mg/L, respectively, for gatifloxacin]. However, gatifloxacin had the lowest activity of all compounds tested against mammalian topoisomerase II (IC_{50} 265 mg/L), indicating good selectivity for target bacterial enzymes.[4]

- At 4 to 8 × MIC, gatifloxacin was able to kill nondividing methicillin-resistant *S. aureus* (MRSA) and *E. coli* strains in the absence of protein or RNA synthesis ('mechanism B').[5]

Gram-Negative Bacteria

- Most Enterobacteriaceae were inhibited by gatifloxacin at MIC_{90}s of ≤1 mg/L (figs. 1 to 3). Gatifloxacin was generally 2-fold less active than ciprofloxacin and 4-fold less active than clinafloxacin, against Enterobacteriaceae in a European study.[6]

- All strains of Enterobactericeae (including *Proteus mirabilis* and *E. coli*) cultured from the urine of patients with complicated and/or hospital-acquired urinary tract infections were susceptible to gatifloxacin (MIC_{90} ≤0.125 mg/L).[11]

- Gatifloxacin showed activity against most Gram-negative organisms (MIC_{90} 2 mg/L against all tested Gram-negative organisms combined) isolated from patients with nosocomial or community-acquired bloodstream infections (a total of 4267 infections) in SENTRY hospitals in Canada, the US (fig. 2) and Latin America.[8] 41% of isolates were *E. coli*, 17.9% were *Klebsiella* spp., 10.6% were *Pseudomonas aeruginosa* and 9.4% were *Enterobacter* spp.[8]

- In a European study, gatifloxacin showed good activity against *Acinetobacter* and *Aeromonas* spp. (MIC_{90} ≤0.25 mg/L) and ampicillin-susceptible and -resistant strains of *H. influenzae* and *N. gonorrhoeae* (MIC_{90} 0.016 mg/L).[6] It was less active against ampicillin- and ceftazidime-resistant *E. coli*, ceftazidime-resistant *Klebsiella pneumoniae* and *Serratia marcescens* (MIC_{90} 4 to 8 mg/L).[6]

- Gatifloxacin was active against 131 strains of *N. gonorrhoeae* (including 46 isolates with reduced fluoroquinolone susceptibility); MIC_{50} and MIC_{90} values were 0.008 and 0.06 mg/L, respec-

tively. Corresponding values for ciprofloxacin were 0.008 and 0.25 mg/L.[3] Gatifloxacin showed good activity against clinical isolates of *H. influenzae* (1200 strains) [MIC ≤0.03 mg/L] and *Moraxella catarrhalis* (600 strains) [MIC ≤0.03 mg/L].[2]

• Gatifloxacin was less active than ciprofloxacin against *P. aeruginosa* (MIC_{90} 32 *vs* 8 mg/L) and other *Pseudomonas* spp.[6] However, gatifloxacin, moxifloxacin and trovafloxacin were the most active of several quinolones tested against *Stenotro-*

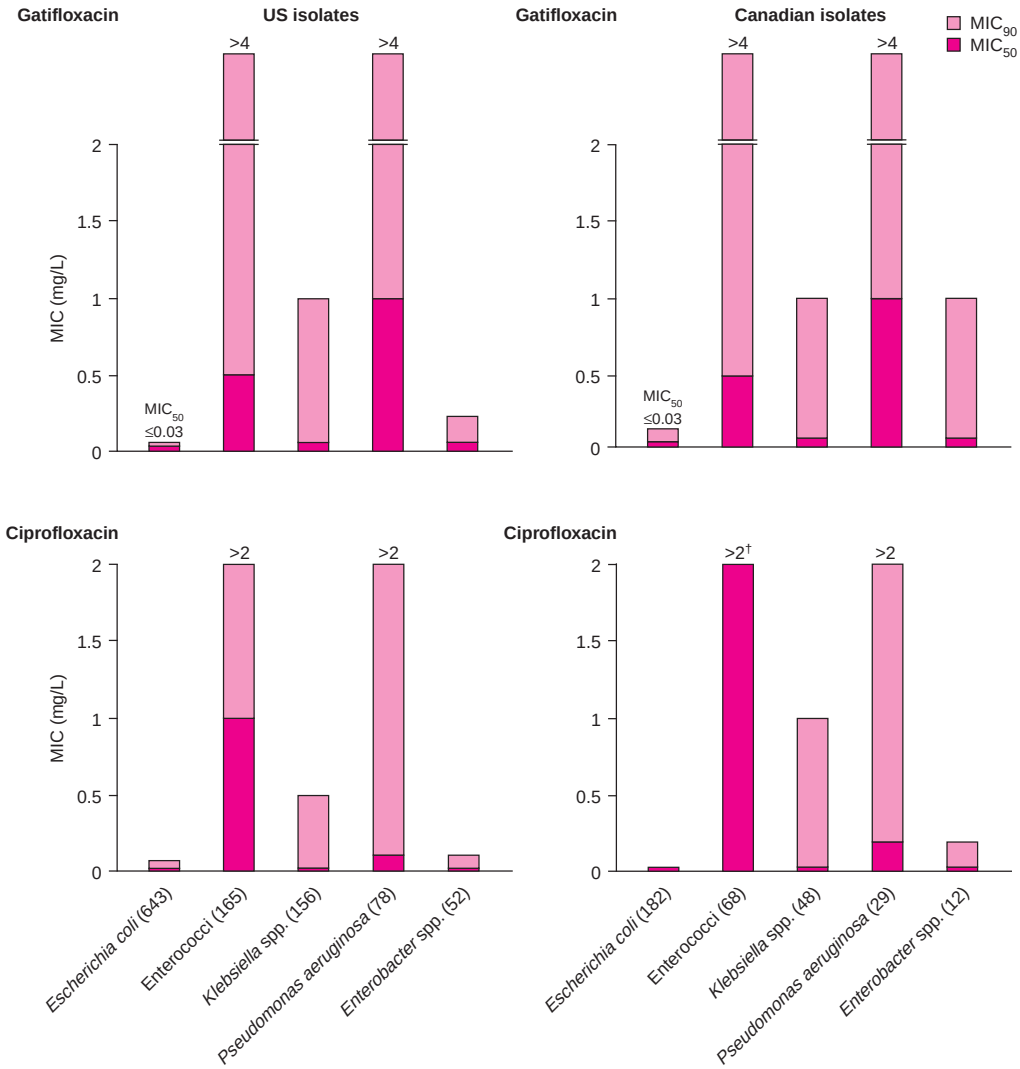


Fig. 1. *In vitro* activity of gatifloxacin and ciprofloxacin against Gram-negative and Gram-positive pathogens causing urinary tract infections in hospitals in North America.[7] **MIC_{50}**; **MIC_{90}** = minimum concentrations required to inhibit 50 and 90% of strains. Where these values are off the scale they are shown above the relevant bar. Where MIC50 and MIC90 values are the same, they are represented by a dark shaded bar. † MIC_{50} 2 mg/L; MIC_{90} >2 mg/L.

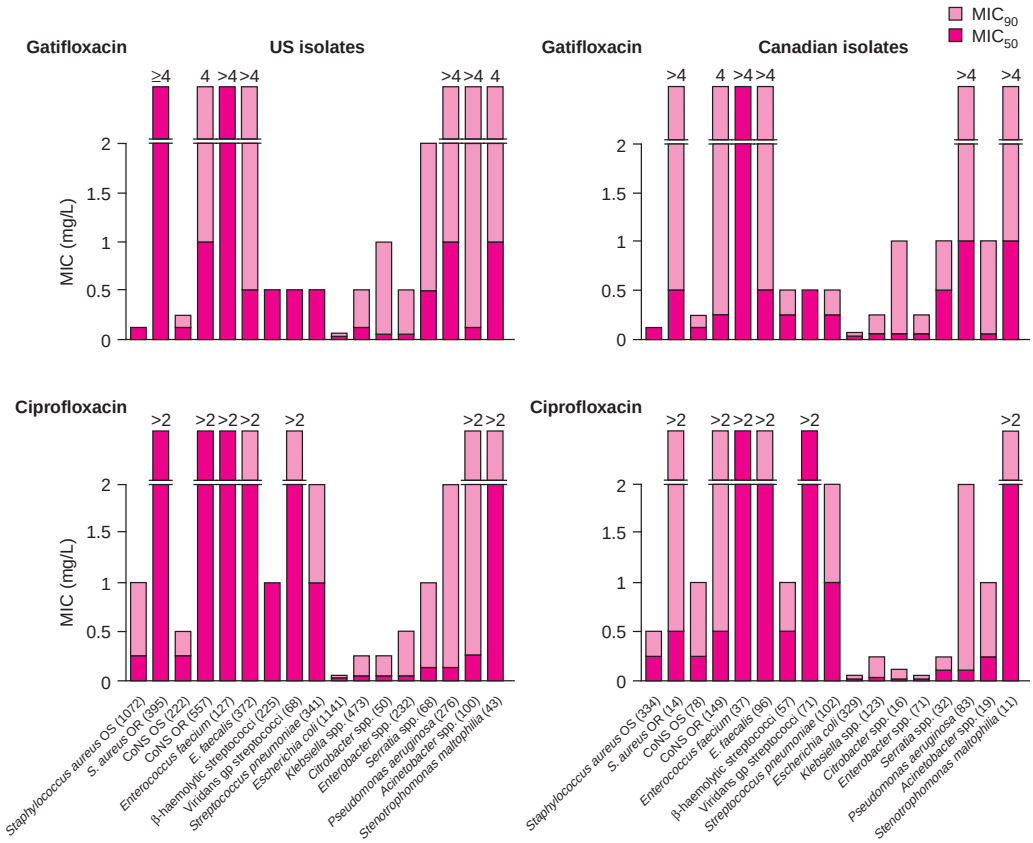


Fig. 2. *In vitro* activity of gatifloxacin and ciprofloxacin against Gram-negative and Gram-positive pathogens causing nosocomial and community-acquired bloodstream infections in North America.[8,9] CoNS = coagulase-negative *Staphylococcus aureus*; **MIC_{50}**; **MIC_{90}** = minimum concentrations required to inhibit 50 and 90% of strains; **OR** = oxacillin-resistant; **OS** = oxacillin-sensitive. Where these values are off the scale they are shown above the relevant bar. Where MIC_{50} and MIC_{90} values are the same, they are represented by a dark shaded bar.

phomonas maltophilia (MIC_{90} 4 mg/L for each of these quinolones).[6] In another study, gatifloxacin showed activity similar to that of sparfloxacin or trovafloxacin against *S. maltophilia* (MIC_{50} values were 0.5 to 1 mg/L) and *Burkholderia* spp. (MIC_{50} 1 to 2 mg/L).[12] The activity of gatifloxacin against *S. maltophilia* was greater than that of ciprofloxacin, levofloxacin or ofloxacin in this latter study (MIC_{50} values were ≥2 mg/L).[12]

- A cross-resistance study showed that gatifloxacin had better activity than ciprofloxacin against *S. maltophilia*, but ciprofloxacin was more active than gatifloxacin against *P. aeruginosa*.[13] The activity of gatifloxacin against *Burkholderia* spp. from patients with cystic fibrosis was similar to that of grepafloxacin, moxifloxacin, trovafloxacin, levofloxacin and ciprofloxacin.[14]

- *Legionella* spp. (n = 181) were highly susceptible to gatifloxacin, with MIC_{90}s ranging from 0.016 to 0.03 mg/L.[15] *Chlamydia pneumoniae* (n = 25; MIC_{90} 0.125 mg/L)[16] and *Mycoplasma pneumoniae* (n = 41; MIC_{90} 0.06 mg/L)[17] were also susceptible to the drug.

• 100% of *Ureaplasma urealyticum* (n = 56) and *M. hominis* (n = 57) strains were inhibited by gatifloxacin at concentrations of 1 and 0.25 mg/L, respectively.[18]

Gram-Positive Bacteria

• Gatifloxacin was consistently more active (generally 2- to 4-fold) than ciprofloxacin against staphylococci (MIC_{90} 0.13 to 0.5 *vs* 0.5 to 1 mg/L, excluding MRSA), streptococci (MIC_{90} 0.25 to 1 *vs* 1 to 4 mg/L) and enterococci (MIC_{90} 2 to 4 *vs* 4 to 16 mg/L) in a study conducted in Europe.[6] In general, gatifloxacin was 2-fold less active than clinafloxacin, trovafloxacin and moxifloxacin against these strains.[6]

• Gatifloxacin showed good activity against oxacillin-susceptible strains of both *S. aureus* [n = 1072] (MIC_{90} 0.12 mg/L) and coagulase-negative staphylococci [222] (MIC_{90} 0.25 mg/L) isolated from patients with bloodstream infections in the US, Canada (fig. 2) and Latin America as part of the SENTRY program.[9] Oxacillin-resistant strains of *S. aureus* or coagulase-negative staphylococci were resistant to gatifloxacin; MIC_{90} values were ≥4 mg/L.[9]

• Most studies documented a gatifloxacin MIC_{90} of 0.5 mg/L against *Streptococcus pneumoniae*.[6,9,19-24] Gatifloxacin showed good activity against penicillin-susceptible and -nonsusceptible clinical isolates of *S. pneumoniae*, viridans group streptococci and β-haemolytic streptococci (MIC_{90} 0.5 mg/L) [fig. 2].[9,20,22] 1097 respiratory tract *S. pneumoniae* isolates from patients in US and Canadian SENTRY program sites were susceptible to gatifloxacin (modal MIC 0.5 mg/L).[21] The incidence of high-level resistance to all tested fluoroquinolones, including gatifloxacin, was low in *S. pneumoniae* isolates from the US (0.3% of 890 isolates) and no resistant strains were evident in any of the 210 isolates from Canadian patients.[21]

• The activity of gatifloxacin against *S. pneumoniae* was similar to that of trovafloxacin or sparfloxacin.[22] Its activity was not affected by the susceptibility of pneumococci to penicillin; the MIC_{90} value of gatifloxacin was 0.5 mg/L (compared with 2 mg/L for ciprofloxacin) against 71 penicillin-sensitive, 81 penicillin-intermediate and 55 penicillin-resistant pneumococcal strains.[23]

• MIC_{90} values of gatifloxacin and ciprofloxacin were >4.0 and >2.0 mg/L, respectively, for enterococci isolated from patients with urinary tract infections in North America (fig. 1); MIC_{50} values of gatifloxacin and ciprofloxacin against enterococci were 0.5 and 1 or 2 mg/L, respectively (fig. 1).[7] *Enterococcus faecalis* (n = 372 strains) and *E. faecium* (127 strains) isolated from patients with bloodstream infections in the USA, Canada and Latin America were resistant to gatifloxacin (fig. 2). In another SENTRY program study, the gatifloxacin MIC_{90} was >4 mg/L for enterococcal bloodstream infection isolates from patients in the US and Canada.[24]

• Gatifloxacin was active against most ciprofloxacin-resistant (MIC ≥4 mg/L) isolates of Gram-positive cocci,[25,26] including *S. aureus*, *S. pneumoniae* and other streptococci.[13] Gatifloxacin showed greater activity than trovafloxacin and sparfloxacin against 1676 Gram-positive cocci which were resistant to ciprofloxacin (MIC ≥4 mg/L).[26]

• Against 1566 ciprofloxacin-resistant Gram-positive cocci [*E. faecalis* (n = 268), *E. faecium* (174), *S. aureus* (740), *S. epidermidis* (114) and coagulase-negative staphylococci (270)], median MIC_{50} values (for all species) of gatifloxacin, trovafloxacin and sparfloxacin were 4, 4, and >2 mg/L, respectively.[25] Coagulase-negative staphylococci were more susceptible to gatifloxacin than trovafloxacin, whereas trovafloxacin showed slightly greater activity than gatifloxacin against enterococci and *S. aureus*.[25] Two percent of *S. epidermidis*, 9% of coagulase-negative staphylococci, 14% of *S. haemolyticus* and 45% of *Corynebacterium* spp. were resistant to gatifloxacin (assuming ≥8 mg/L = resistant), compared with resistance rates of ≥50% for the other 2 agents. For *E. faecalis/faecium* and *Enterococcus* spp., resistance rates to all 3 agents were >80%.[26]

• When tested by agar dilution against 9 species of mycobacteria (n = 177 strains), gatifloxacin was

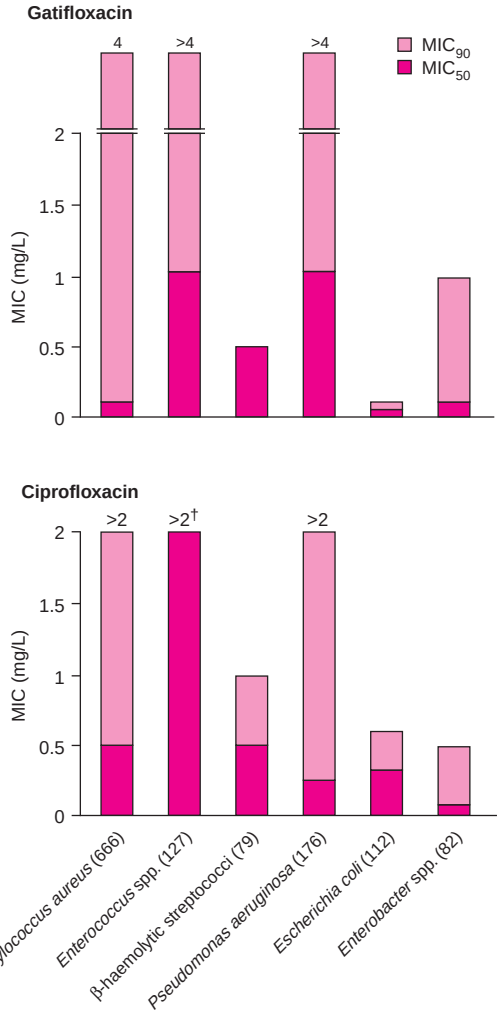


Fig. 3. *In vitro* activity of gatifloxacin and ciprofloxacin against Gram-negative and Gram-positive pathogens isolated from patients with skin and soft tissue infections in North America.[10] **MIC_{50}**; **MIC_{90}** = minimum concentrations required to inhibit 50 and 90% of strains. Where these values are off the scale they are shown above the relevant bar. Where MIC_{50} and MIC_{90} values are the same, they are represented by a dark shaded bar. † MIC_{50} = 2 mg/L.

generally more active than sparfloxacin, with MIC_{90}s <2 mg/L for *Mycobacterium tuberculosis*, *M. kansasii*, *M. marinum* and *M. fortuitum*. Gatifloxacin 1 and 10 mg/L, respectively, inhibited the growth of *M. tuberculosis* and *M. intracellulare* phagocytosed into murine macrophages.[27]

Anaerobes

- Gatifloxacin was 4- to 16-fold more active than ciprofloxacin against anaerobes, including *Clostridium* and *Bacteroides* spp. (MIC_{90} 0.25 to 2 *vs* 1 to 32 mg/L.[6] It was one of the most active compounds tested against *Bacteroides* spp. [MIC_{90} 1 to 2 mg/L (breakpoint)].[6]

- The activity of gatifloxacin was greater than that of ciprofloxacin against *Bacteroides* spp., *Prevotella* spp., *Fusobacterium* spp. and *Clostridium* spp. in another study.[28] Gatifloxacin MIC_{90} values against *Bacteroides* spp., *Prevotella* spp., *Fusobacterium* spp. *Bilophila wadsworthia*, *Clostridium* spp., and *Peptostreptococcus* spp. were 2, 2, 8, 0.5, 1 and 0.25 mg/L, respectively.[28]

- Peptostreptococci and most *Prevotella* and *Fusobacterium* spp. were inhibited by gatifloxacin at ≤1 mg/L in a US study.[29] However, higher MIC_{90} values (≤25 mg/L) were noted for gatifloxacin and other fluoroquinolones in some Japanese anaerobic strains.[30]

Bactericidal Activity

- Minimum bactericidal concentrations (MBCs) of gatifloxacin were equal to, or within 1 to 2 dilutions of, MIC values against *S. aureus*, *E. coli* and *P. aeruginosa*.[31,32] In time-kill assays, gatifloxacin at 1 or 2 × MIC killed >99% of *E. coli*, *P. aeruginosa* and *S. aureus* within 1 to 2 hours.[32] At 2 × MIC, gatifloxacin was bactericidal (99.9% killing) for 4 penicillin-susceptible, 4 penicillin-intermediate and 4 penicillin-resistant strains of pneumococci after 12 and 24 hours.[23]

- In *in vitro* pharmacokinetic models simulating human kinetics following oral administration, gatifloxacin showed extensive killing (≥3 to 4 $\log_{10}$) of *E. coli*, *S. aureus* (at 200mg once daily),[33] and *S. pneumoniae* (at 400 mg once daily)[34] within 2 to 6 hours. The 400mg once daily dosage was sufficient to kill ≥99.9% of an inoculum of several species with MICs of ≤0.5 mg/L.[35]

Postantibiotic Effects

- At 10 × MIC, gatifloxacin showed postantibiotic effects of 0.5 to 4.8 hours against penicillin-susceptible, -intermediate and -resistant *S. pneu-*

moniae, methicillin-susceptible and -resistant *S. aureus* (including ciprofloxacin-resistant strains), *E. faecalis*, *E. coli* and *P. aeruginosa*. More prolonged postantibiotic subMIC effects were also demonstrated at 0.2 to 0.4 × MIC against these strains (1 to ≥9.6 hours).[36]

In Vivo Activity in Animals

- In experimental lung infections in animals, gatiloxacin (1 to 30 mg/kg/day orally or 25 mg/kg/day subcutaneously) markedly reduced the number of *M. pneumoniae*,[17] *P. aeruginosa*[37] or *S. pneumoniae* (including a penicillin-resistant strain)[38] in the lung. At a dosage of 2 mg/kg/day, gatifloxacin completely cleared the lungs of penicillin-resistant pneumococci in 5 of 10 mice. Ten-fold higher dosages of sparfloxacin, trovafloxacin and moxifloxacin were required to achieve similar pathogen clearance and ciprofloxacin cleared the lungs in only 3 of 10 animals at a dosage of 50 mg/kg/day.[38]

- Gatifloxacin 2 to 20 mg/kg/day also protected mice from death from experimental *K. pneumoniae*, *P. aeruginosa*[32] or *C. psittaci*[16] pneumonia.

- In rabbits with experimental cephalosporin-resistant meningitis, gatifloxacin 30 mg/kg/day reduced CSF bacterial titres by 3.2 $\log_{10}$.[39] Gatifloxacin also reduced middle ear bacterial titres in an acute otitis media model of ciprofloxacin-resistant *S. pneumoniae* (at 50 mg/kg/day) or β-lactamase-producing *H. influenzae* (at 3.16 mg/kg/day).[40]

- In a mixed *E. coli/Bacteroides fragilis* granuloma pouch infection, gatifloxacin (80 mg/kg/day orally) markedly reduced titres of both organisms.[30]

Resistance Issues

- At 4 × MIC, the frequency of spontaneous mutants resistant to gatifloxacin ranged from 1.6×10^{-7} for *P. aeruginosa* to $<5.6 \times 10^{-10}$ for *E. coli*. In *S. aureus* and *S. epidermidis* strains, resistance developed more slowly to gatifloxacin than to ciprofloxacin after 8 serial transfers through sublethal concentrations of the drugs. Gatifloxacin MICs rose from 0.05 and 0.1 mg/L to 0.39 and 0.39 mg/L, respectively. Ciprofloxacin MICs increased from 0.2 and 0.2 mg/L to 100 and 3.13 mg/L.[32]

- In a study that evaluated the relative activities of gatifloxacin and ciprofloxacin against genetically defined mutants of *S. aureus*,[41] topoisomerase IV was shown to be the primary target for gatifloxacin. The study also showed that selection of resistant mutants was reduced with gatifloxacin compared with ciprofloxacin, with common *grl*A mutants having a lesser effect on the MIC of gatifloxacin than on the MIC of the latter agent. Selection of these mutants was not observed with gatifloxacin concentrations that were 3 to 6 times lower than concentrations of the drug achieved in serum.[41]

2. Pharmacokinetic Properties

The pharmacokinetics of orally administered gatifloxacin have been investigated in healthy adult volunteers and in patients with hepatic or renal impairment. Most studies have been reported as abstracts.

Absorption

- Mean maximum plasma gatifloxacin concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values were dose-proportional and increased linearly in volunteers who received single oral doses of 100, 200, 400 or 600mg.[42] Similar findings were reported after single intravenous doses of 200 to 800mg.[43] C_{max} and AUC values were 4.21 mg/L and 51.3 mg/L · h in 140 patients who received multiple oral doses of 400mg gatifloxacin; C_{max} and AUC values were 3.79 mg/L and 33.0 mg/L · h after administration of single 400mg oral doses of the drug.[44]

- C_{max} values were 0.87, 1.71, 3.35 and 5.41 mg/L after single oral doses of 100, 200, 400 and 600mg (6 volunteers per group).[42] Time to reach C_{max} (t_{max}) was 1 to 2 hours. Respective AUC values after 100, 200, 400 and 600mg single doses were

7, 14.5, 32.4 and 53.5 mg · h/L.[42] After administration of single 400mg oral doses of gatifloxacin to 202 patients, the t_{max} was 1 hour.[43]

• In 6 volunteers who received multiple doses of oral gatifloxacin (300mg twice daily for 7 days), C_{max} values were 2.77, 3.45 and 3.36 mg/L on days 1, 4 and 7, respectively. Steady-state concentrations of gatifloxacin were achieved within 2 to 3 days.[42] The mean absolute bioavailability of gatifloxacin was 96% after a single oral dose of 400mg.[1]

• In 6 volunteers, the intake of milk or tea with gatifloxacin did not result in significant changes in C_{max} or AUC values versus values in fasted volunteers.[45]

• The intake of a light (or high fat) meal before administration of single oral doses of gatifloxacin 200 to 600mg did not significantly alter the absorption of the drug (compared with that in fasted volunteers) in all[42,46,47] but 1[42] investigation.

Distribution

• Serum protein binding of gatifloxacin was 20% and concentrations of the drug in saliva were about 80% of those in the serum in volunteers who received single 100, 200, 400 or 600mg doses of the drug.[42]

• Gatifloxacin penetrated lung, bone and skin tissue of 32 volunteers who received a single oral 400mg dose; mean gatifloxacin tissue : plasma concentrations of >1 were recorded 2 to 24 hours after administration.[48]

• Similarly, gatifloxacin penetrated genital tissues in women with benign gynaecological tumours who received a single 100 (n = 3) or 150mg (n = 2) oral dose of the drug.[49] Gatifloxacin distributed into the prostatic and seminal fluid of 10 male volunteers who received a single oral 400mg dose; mean concentrations achieved in prostatic fluid (2.10 mg/L) and seminal fluid (1.87 mg/L) were similar to the mean plasma concentration of the drug (1.92 mg/L).[50]

• Gatifloxacin distributes into the CNS. During multiple-dose administration of oral gatifloxacin (150 or 200mg twice daily), the cerebrospinal fluid : serum concentration ratio was 0.36 (range 0.21 to 0.45).[44]

Elimination

• Gatifloxacin undergoes negligible metabolism. Up to 72 hours after a single oral dose of 400mg, 83.2% of the total dose was eliminated unchanged in the urine; cumulative faecal recovery of the drug over this period was 5.7% of the dose.[42] Renal clearance of gatifloxacin was 9.48[51] to 10.4 L/h[42] after a single oral dose of 400mg.

• Steady-state urinary concentrations of gatifloxacin (220 to 290 mg/L) were reached within 2 to 3 days in 6 volunteers who received 300mg twice daily for 7 days.[42] Within 72 hours after the last dose, 78.8% of the drug was eliminated unchanged in the urine.[42]

• The mean plasma elimination half-life ($t_{½\beta}$) of gatifloxacin was 7 to 8 hours after single doses of 100, 200, 400 and 600mg (6 volunteers per group).[42] In 6 volunteers who received gatifloxacin 300mg twice daily for 7 days, $t_{½\beta}$ values were 5.4, 7.0 and 5.7 hours on days 1, 4 and 7, respectively.[42]

Effects of Renal and Hepatic Impairment

• Gatifloxacin AUC and $t_{½\beta}$ values were higher in patients with impaired renal function (including elderly patients[52]) than in healthy volunteers.[53] After administration of single oral 100mg doses of gatifloxacin to patients with creatinine clearances of >3.6 to <5.4 L/h (n = 6), >1.8 to <3.6 L/h (n = 5) or >0.6 to <1.8 L/h (n = 7), AUC values were 13.2, 20.6 and 47.9 mg · h/L and $t_{½}$ values were 8.9, 16.5 and 29.6 hours, respectively.

• In 8 patients with Child-Pugh Classification B or C hepatic impairment who received a single oral 400mg dose of gatifloxacin, C_{max} and AUC values were, respectively, 32 and 23% higher than in healthy volunteers.[54]

Drug Interactions

• Oral ferrous sulphate 160mg reduced the absorption of a concomitant 200mg dose of gatifloxacin;[45] gatifloxacin C_{max} decreased from 2.06 to 0.98 mg/L and AUC decreased from 13.7 to 9.9 mg · h/L.

• No clinically significant interactions were observed between gatifloxacin and digoxin,[55] warfarin,[56] glyburide,[57] cimetidine,[44] or midazolam[58] in volunteers.

• Oral gatifloxacin 400mg twice daily had no significant effect on the pharmacokinetics of concomitantly administered oral theophylline 400mg twice daily in 4 of 5 volunteers.[59] In the fifth volunteer, theophylline C_{max} and AUC values increased and theophylline clearance decreased (values and statistical significance not reported) on day 5 of gatifloxacin administration.[59] Oral gatifloxacin 400mg daily did not significantly alter the pharmacokinetics of coadministered oral theophylline 300mg twice daily in another trial.[60]

• The order of potency of inhibitory effects of various quinolone antibacterial agents on human hepatic microsomes *in vitro* was as follows: enoxacin > ciprofloxacin > sparfloxacin > fleroxacin > levofloxacin > gatifloxacin (inhibition constant values not reported).[61]

3. Therapeutic Trials

Numerous trials of oral gatifloxacin, administered once daily, have been conducted in the US, South America, Canada, South Africa, Australia and Japan.

Most trials were randomised, multicentre, double-blind and comparative in design. All clinical trials of gatifloxacin are currently reported as abstracts; thus, only limited methodological details, including definitions of clinical and bacteriological efficacy, and results are available at present.

Studies Conducted in the USA and Canada

Acute Exacerbations of Chronic Bronchitis

• Analysis of data from a subset of North American patients who had participated in a randomised, double-blind, multinational trial showed that gatifloxacin produced a significantly higher clinical cure rate than cefuroxime axetil in outpatients with acute exacerbations of chronic bronchitis (AECB) [88% had type I exacerbation].[62] Clinical cure was achieved in 76 (89%) of 85 patients who received gatifloxacin 400 mg/day and in 62 (77%) of 81 recipients of cefuroxime axetil 250mg twice daily (p = 0.01) [fig. 4]; treatment was administered for 7 to 10 days. Of the entire study population (number not reported), clinical cure was achieved in 86% of gatifloxacin and 83% of cefuroxime axetil recipients.[51]

• Microbiological eradication rates in patients with documented *S. pneumoniae* infections were 100% (7 of 7 evaluable patients) and 38% (3 of 8 patients) for gatifloxacin and cefuroxime axetil, respectively.[62]

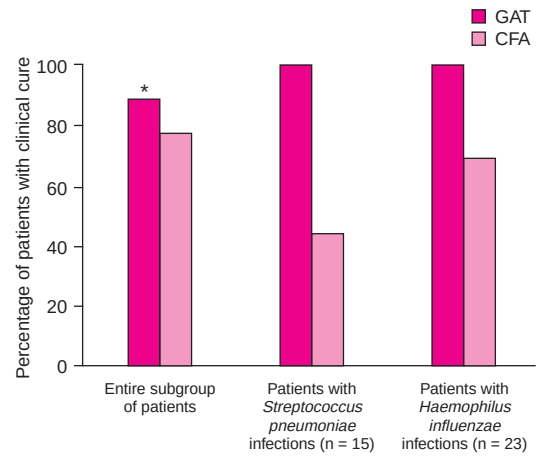


Fig. 4. Clinical cure rates with gatifloxacin (GAT) or cefuroxime axetil (CFA) in a subgroup of patients with acute exacerbations of chronic bronchitis in a randomised, double-blind, multicentre trial.[62] Patients received either oral gatifloxacin 400 mg/day (evaluable n = 85) or cefuroxime axetil 250mg twice daily (n = 81) for 7 to 10 days. *p = 0.01 *vs* cefuroxime axetil group.

• A noncomparative trial showed that gatifloxacin 400 mg/day for 10 days produced a satisfactory clinical response in 88% of 162 evaluable patients with AECB (clinical cure = 71%; clinical improvement = 17%).[63] Analysis of microbiological responses by pathogen showed complete eradication of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* and *S. aureus* and 90% eradication of *H. parainfluenzae*.

Community-Acquired Pneumonia

• Gatifloxacin 400 mg/day for 7 to 14 days showed clinical and bacteriological efficacy similar to that of clarithromycin 500mg twice daily for 7 to 14 days in patients with mild, moderate or severe community-acquired pneumonia in a randomised, double-blind trial.[64] Clinical cure was achieved in 95% of 191 gatifloxacin recipients and in 93% of 190 clarithromycin recipients; bacterial eradication rates for the 2 treatment groups were 98 and 93%, respectively.[51]

• The efficacy of 7 to 14 days of treatment with intravenous switched to oral gatifloxacin 400 mg/day was similar to that of intravenous ceftriaxone 1 to 2g/day with or without erythromycin (dosage not reported) switched to oral clarithromycin 500mg twice daily in patients with community-acquired pneumonia requiring hospitalisation.[65] Clinical cure rates for 205 evaluable patients were 97% for the gatifloxacin group and 91% for the comparator group.

Atypical Pneumonia

• Clinical cure was reported in 27 (90%) of 30 evaluable patients with pneumonia (caused by atypical pathogens, including *M. pneumoniae*, *L. pneumophila* and *C. pneumoniae*) treated with gatifloxacin 400 mg/day for 14 days in a noncomparative trial.[66]

Acute Maxillary Sinusitis

• A 10-day course of gatifloxacin 400 mg/day was as effective as 14 days' treatment with clarithromycin 500 mg twice daily in patients with acute maxillary sinusitis.[67] Clinical success, defined as the resolution or improvement of various symptoms including sinus pain and tenderness, was achieved in 93 and 90% of gatifloxacin and clarithromycin recipients, respectively, 7 to 14 days after treatment.[51]

Urinary Tract Infection

• In a trial that enrolled 1323 women with uncomplicated urinary tract infections who received a single dose of gatifloxacin 400mg, or gatifloxacin 200 mg/day or ciprofloxacin 100mg twice daily (each given for 3 days), respective clinical cure rates were 93, 95 and 93% and bacterial eradication rates were 90, 95 and 89%.[68]

• Pooled analysis of data from 2 double-blind trials that included 730 patients with complicated urinary tract infections (104 had pyelonephritis) showed that positive clinical responses occurred in 93% of patients treated with gatifloxacin 400 mg/day and in 91% of those treated with ciprofloxacin 500mg twice daily (each given for 7 to 10 days).[51,69] Respective bacterial eradication rates were 88 and 83% for the gatifloxacin and ciprofloxacin groups; a higher rate of eradication (statistical significance not reported) of Gram-positive organisms occurred in recipients of gatifloxacin than in the comparator group [32 (97%) of 33 and 26 (79%) of 33].

Uncomplicated Gonococcal Infections

• The efficacy of single doses of gatifloxacin (400 or 600mg) or ofloxacin 400mg in 728 patients with uncomplicated gonococcal infections was investigated in a randomised, double-blind trial.[70] Bacterial eradication rates in men with urethral gonorrhoea were 99, 100 and 100% with gatifloxacin 400mg, gatifloxacin 600mg and ofloxacin 400mg, respectively; in women with endocervical gonorrhoea, bacterial eradication rates were 99, 99 and 100%.

Skin and Soft Tissue Infections

• Gatifloxacin 400 mg/day for 7 to 10 days showed clinical and bacteriological efficacy similar to that of 7 to 10 days' treatment with levofloxacin 500 mg/day in 407 patients with uncomplicated skin and soft tissue infections in a randomised, double-blind trial.[71] Clinical cure rates were, respectively, 91 and 84% for the gatifloxacin and levoflox-

acin treatment groups. The bacterial eradication rate was 92% in both groups, with 93 and 91% of *S. aureus* isolates eradicated in the gatifloxacin and levofloxacin groups.

Studies Conducted in Japan

Pneumonia

• Gatifloxacin 200mg twice daily was as effective as levofloxacin 100mg 3 times daily (each given for 14 days) in patients with various types of pneumonia in a double-blind, comparative trial.[72] Of 200 clinically evaluable patients, 170 presented with bacterial pneumonia, 24 with *Mycoplasma* pneumonia, 4 with *Chlamydia* pneumonia and 2 with a 'mixed type' of pneumonia. Clinical efficacy (not defined) was documented in 98% of 100 gatifloxacin recipients and in 95% of 100 patients treated with levofloxacin.[72]

• Whereas bacterial eradication was achieved in all 39 evaluable gatifloxacin recipients, the eradication rate in the levofloxacin group was 87.5% (21 of 24 patients); persistent bacteria were single strains of *S. pneumoniae*, *S. aureus* and a group B *Streptococcus*.

Chronic Prostatitis

• In patients with chronic bacterial prostatitis, eradication of causative pathogens (including *E. coli*, *E. faecalis*, *S. epidermidis* and *S. agalactiae*) was achieved in 9 patients after treatment with gatifloxacin 200mg twice daily for 2 weeks.[73] However, 2 or 4 weeks after the end of treatment, bacteria were again isolated from 5 of the 9 patients.[73]

Complicated Urinary Tract Infections

• Bacterial eradication was achieved in 89.8, 90.5 and 94.8% of patients with complicated urinary tract infections treated with gatifloxacin 100mg twice daily (n = 40), 150mg twice daily (n = 40) or 200mg twice daily (n = 39).[74] 'Excellent and moderate' clinical responses were documented in 85, 82.5 and 92.3% of patients in the 100, 150 and 200mg treatment groups, respectively.[74]

4. Tolerability

• Oral gatifloxacin 400 mg/day administered for up to 14 days appeared to be well tolerated in patients with respiratory tract, urogenital and skin and soft tissue infections,[62,64,66-69,71,75] and in healthy volunteers.[42]

• No crystalluria was observed in volunteers who received single 400 or 600mg or multiple 300mg doses of gatifloxacin.[42] No abnormal changes in vital signs, blood chemistry, haematology or urinalysis were evident in 6 volunteers who received gatifloxacin 300mg twice daily for 7 days.

• Analysis of pooled data from clinical trials of oral gatifloxacin 400 mg/day (n = 3021) and comparator antibacterial agents (including ciprofloxacin, levofloxacin, ofloxacin, ceftriaxone, cefuroxime axetil, clarithromycin and erythromycin) [n = 2111] showed that the most common adverse events in recipients of gatifloxacin were nausea (8%), diarrhoea (4%), headache (4%) and dizziness (3%);[75] there was no evidence of phototoxicity, crystalluria or tendonitis.

• No skin photosensitivity was observed with oral gatifloxacin 400mg daily in a double-blind, placebo- and positive-controlled trial in 48 healthy volunteers.[76] Skin photosensitivity was determined before and 7 days after the start of treatment with the drug. There were no significant differences in the phototoxic indices [the mean minimal erythemal dose (MED) at different ultraviolet light wavelengths at baseline/mean MED value on day 7 of treatment] of gatifloxacin and placebo recipients. However, statistically significant changes in the MED (within the ultraviolet banding region) [$p < 0.05$ versus placebo] were observed in patients treated with ciprofloxacin 500mg twice daily or lomefloxacin 400mg daily.[76]

5. Gatifloxacin: Current Status

Gatifloxacin is an 8-methoxy fluoroquinolone antibacterial agent that is in late stages of clinical development. It has shown efficacy in the treatment of a large number of adults with respiratory (upper and lower) infections, sinusitis, urogeni-

tal and skin and soft tissue infections. Gatifloxacin appears to be well tolerated and has not been shown to produce phototoxic effects at therapeutic dosages.

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