

Moxifloxacin in the treatment of skin and skin structure infections

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Abstract: Moxifloxacin is a recent addition to the fluoroquinolone class, differing from ciprofloxacin and other older agents in having much better in vitro activity against Gram-positive aerobes while retaining potent activity against Gram-negative aerobes. It is also active against the pathogens of human and animal bite wounds and those species of atypical mycobacteria associated with dermatologic infections. Its activity against anaerobes is quite variable. Moxifloxacin penetrates well into inflammatory blister fluid and muscle and subcutaneous adipose tissues. Moxifloxacin should thus be a reasonable option for the treatment of skin and skin structure infections (SSSIs). In 3 randomized controlled trials (RCTs), oral moxifloxacin was as effective as cephalexin in the treatment of uncomplicated SSSIs in adults while in 2 RCTs, intravenous/oral moxifloxacin was as effective as intravenous/oral β -lactam/ β -lactamase inhibitor therapy in the treatment of complicated SSSIs in adults. Moxifloxacin does not inhibit cytochrome P450 enzymes and thus interact with warfarin or methylxanthines. However, multivalent cations can reduce its oral bioavailability substantially. Dosage adjustment is not required in the presence of renal or hepatic impairment. The clinical relevance of its electrophysiologic effects (QT_c prolongation) remains unresolved.

Keywords: moxifloxacin, skin infections, fluoroquinolones, skin ulcers, cellulitis

Introduction

Moxifloxacin is one of most-recently marketed of the fluoroquinolone (hereafter called quinolone) antimicrobials (Avelox[®], Bayer, Leverkusen, Germany). Of this group (gatifloxacin, gemifloxacin, moxifloxacin), only moxifloxacin has regulatory approval for use in skin and skin structure infections (SSSIs) (Anonymous 2005). Until recently, this approval was limited to uncomplicated SSSIs in adults caused by *Staphylococcus aureus* or *Streptococcus pyogenes* (Anonymous 2005). In June of 2005, it also received approval for use in complicated SSSIs caused by methicillin-susceptible *S. aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* (Anonymous 2005). Complicated SSSIs are defined as those which involve deeper layers such as fascia or muscle, require significant surgical interventions, or arise in the presence of significant comorbidities such as diabetes or HIV infection (Raghavan and Linden 2004). The purpose of this paper is to review the in vitro antimicrobial activity, pharmacokinetics, clinical and bacteriological efficacy, safety, tolerability, and drug–drug interaction potential of moxifloxacin, concentrating on its potential role in the treatment of complicated (and uncomplicated) SSSIs.

Mechanisms of action and resistance

Moxifloxacin acts by the same mechanism as other quinolones: inhibition of bacterial DNA gyrase (a Type II topoisomerase composed of two *gyr A* and two *gyr B* subunits) and topoisomerase IV (a heterotetramer made up of two *par C* and two *par E* subunits) (Ruiz 2003; Mitscher 2005). Topoisomerase IV is felt to be the preferred target, especially in Gram-positive aerobes (Ince et al 2003). Resistance is mediated in all

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quinolones by either changes in the target site (DNA gyrase and/or topoisomerase IV) or changes that alter intracellular drug accumulation (ie, enhanced efflux).

In vitro antimicrobial activity

Unlike earlier quinolones like ciprofloxacin, moxifloxacin has significant activity against Gram-positive aerobes, including potential dermatologic pathogens such as *S. aureus*, coagulase-negative staphylococci, and groups A/B/C/F/G streptococci (Table 1) (Dalhoff et al 1996; Bauernfeind 1997; Fass 1997; Goldstein et al 1997, 2000; Woodcock et al 1997; Barry et al 1999; Malathum et al 1999; von Eiff et al 1999; Blondeau et al 2000; Fung-Tomc et al 2000; Hardy et al 2000; Hoogkamp-Korstanje et al 2000; Milatovic et al 2000; Amabile-Cuevas et al 2001; Blondeau 2002; Speciale et al 2002; Bowker et al 2003; Hsueh et al 2003; Noviello et al 2003; Edmiston et al 2004, 2005; Jacobs et al 2004; Patel et al 2004; Wenzler et al 2004; Bogdanovich et al 2005; Stratchounski et al 2005). Methicillin-resistant strains of staphylococci are much less susceptible and enterococci are only moderately susceptible to moxifloxacin. Moxifloxacin still retains significant activity against Gram-negative aerobes with the exception of variable activity

against *Pseudomonas aeruginosa*, other pseudomonads, and *Stenotrophomonas maltophilia* (Table 1). Among anaerobes, moxifloxacin is quite active against the majority of pathogens of animal and human bite wounds. Activity against *Bacteroides*, *Fusobacterium*, and *Prevotella* species is variable (Table 2) (Dalhoff et al 1996; Aldridge and Ashcraft 1997; Bauernfeind 1997; Fass 1997; Goldstein et al 1997; MacGowen et al 1997; Woodcock et al 1997; Edlund et al 1998; Betriu et al 1999; Ackermann et al 2000; Fung-Tomc et al 2000; Goldstein et al 2000, 2002, 2006; Hoogkamp-Korstanje et al 2000; Milatovic et al 2000; Schaumann et al 2000; Hoellman et al 2001; Snyderman et al 2002; Speciale et al 2002; Ednie et al 2003; Hedberg et al 2003; Edmiston et al 2004, 2005; Peric et al 2004; Sillerstrom et al 2004; Lion et al 2006).

Moxifloxacin has significant activity against many strains of atypical mycobacteria, microorganisms of significance in dermatological infections. For example, the following minimum inhibitory concentrations of 90% of isolates (MIC₉₀) values (in mg/L) have been reported for a) *Mycobacterium marinum*, b) *M. fortuitum*, c) *M. chelonae*, d) *M. abscessus*, e) *M. kansasii*, and f) *M. goodii*: a) 8.0 (43 isolates) (Braback et al 2002), 1.0 (53 isolates) (Aubry et al 2000); b) 16.0 (69 isolates) (Yang et al 2003), 1.0 (7

Table 1 In vitro activity of moxifloxacin against potential Gram-positive and Gram-negative aerobic pathogens in SSSIs

Organism	Isolates (n)	Range of MIC ₉₀ s (mg/L)	References
<i>Staphylococcus aureus</i>	1427	0.03->4.0	(1-6)
methicillin-sensitive	1221	0.06-4.0	(7-21, 27)
methicillin-resistant	1036	2-16	(2, 7-12, 14-21)
<i>S. epidermidis</i>	183	0.06-4.0	(3, 5, 18, 20)
methicillin-sensitive	424	0.06-2.0	(9-12, 15-17, 19, 22)
methicillin-resistant	641	0.12->8.0	(9-12, 14-17, 19, 27)
Group A streptococci	1882	0.12-0.50	(2, 6-9, 11, 13, 15, 18-20, 23-25)
Group B streptococci	139	0.12-0.50	(6, 9, 11, 15, 18, 19, 23)
<i>Enterococcus faecalis</i>	438	0.25-16	(2, 6, 9, 11, 13-15, 18-23, 27)
<i>E. faecium</i>	263	2->32	(6, 9, 11, 13-15, 18, 20, 23, 27)
<i>Escherichia coli</i>	795	0.015-1.0	(2, 13-16, 18, 19, 22, 26, 27)
<i>Klebsiella pneumoniae</i>	619	0.031-1.0	(2, 14-16, 18, 19, 27)
<i>Citrobacter freundii</i>	290	1-4	(11, 14-16, 18, 19, 22, 27)
<i>Morganella morganii</i>	248	0.13-16	(11, 14-16, 18-20)
<i>Proteus mirabilis</i>	530	0.25-16	(2, 11, 14-16, 18-22, 27)
<i>Enterobacter cloacae</i>	541	0.06-2	(11, 14-16, 18, 19, 27)
<i>E. aerogenes</i>	325	0.5->16	(11, 14-16, 18, 19, 27)
<i>Pseudomonas aeruginosa</i>	2376	4-64	(2, 11, 13, 15, 16, 18-22, 27)
<i>P. vulgaris</i>	141	0.25-1	(11, 15, 16, 18, 20, 22)
<i>Acinetobacter calcoaceticus</i>	60	0.06-1	(2, 11, 22)

Abbreviations: MIC₉₀, minimum inhibitory concentration for 90% of isolates.

Note: For entries with multiple studies, data are the range. To be included, studies had to have a minimum of 10 isolates of the microorganism-of-interest, use a National Committee for Clinical Laboratory Standards - approved methodology, and an inoculum of 10⁴-10⁶ organisms.

References: 1, Stratchounski et al 2005; 2, Blondeau et al 2000; 3, Jacobs et al 2004; 4, Goldstein et al 2000; 5, Goldstein et al 1997; 6, Malathum et al 1999; 7, Bowker et al 2003; 8, Noviello et al 2003; 9, Speciale et al 2002; 10, von Eiff et al 1999; 11, Bauernfeind 1997; 12, Patel et al 2004; 13, Wenzler et al 2004; 14, Edmiston et al 2004; 15, Fung-Tomc et al 2000; 16, Milatovic et al 2000; 17, Hardy et al 2000; 18, Barry et al 1999; 19, Fass 1997; 20, Woodcock et al 1997; 21, Bogdanovich et al 2005; 22, Dalhoff et al 1996; 23, Hoogkamp-Korstanje et al 2000; 24, Hsueh et al 2003; 25, Amabile-Cuevas et al 2001; 26, Blondeau 2002; 27, Edmiston et al 2005.

Table 2 In vitro activity of moxifloxacin against potential bite wound pathogens and Gram-positive and Gram-negative anaerobic pathogens in SSSIs

Organism	Isolates (n)	Range of MIC ₉₀ s (mg/L)	References
<i>Pasturella canis</i>	53	0.015–0.063	(1, 12, 25)
<i>P. multocida</i> subsp. <i>multocida</i>	217	0.015–0.06	(1, 2, 12, 25)
<i>P. multocida</i> subsp. <i>septicum</i>	104	0.016–0.03	(1, 2, 12, 25)
<i>P. stomatis</i>	48	≤0.015–0.125	(1, 12, 25)
<i>Ef-4b</i>	38	0.06–0.25	(1, 2)
<i>Eikenella corrodens</i>	40	0.06–0.125	(1, 2)
<i>Peptostreptococci</i>	376	0.25–2	(1, 6, 7, 9, 13–18)
<i>Clostridium perfringens</i>	312	0.25–4	(5–9, 13–18, 26, 27)
<i>C. difficile</i>	344	1–4	(4, 6, 7, 9, 11, 13–17)
<i>Bacteroides fragilis</i>	2132	0.25–8	(3–6, 8–10, 13–24, 26, 27)
<i>B. vulgatus</i>	357	1–≥32	(5, 14–16, 18–22, 24, 26, 27)
<i>B. ovatus</i>	407	2–32	(5, 15, 16, 18–22, 24, 26, 27)
<i>B. thetaiotaomicron</i>	735	1–32	(5, 6, 8, 14–16, 18–24, 26, 27)
<i>B. distasonis</i>	199	0.5–8	(5, 14–16, 18, 24, 26, 27)
<i>Fusobacterium</i> sp.	307	0.12–>8	(1, 5, 6, 8, 14–19, 22, 26, 27)
<i>F. nucleatum</i>	129	0.125–>8	(1, 2, 5, 13–16, 26, 27)
<i>Prevotella</i> sp.	130	0.5–4	(1, 5, 7, 19, 22, 26, 27)

Abbreviations: MIC₉₀ = minimum inhibitory concentration for 90% of isolates.

Notes: For entries with multiple studies, data are the range. To be included, studies had to have a minimum of 10 isolates of the microorganism-of-interest, use a National Committee for Clinical Laboratory Standards – approved methodology, and an inoculum of 10⁴–10⁶ organisms.

References: 1, Goldstein et al 2000; 2, Goldstein et al 1997; 3, Speciale et al 2002; 4, Bauernfeind 1997; 5, Edmiston et al 2004; 6, Fung-Tomc et al 2000; 7, Milatovic et al 2000; 8, Fass 1997; 9, Woodcock et al 1997; 10, Dalhoff et al 1996; 11, Hoogkamp-Korstanje et al 2000; 12, Goldstein et al 2002; 13, Sillerstrom et al 2004; 14, Peric et al 2004; 15, Ednie et al 2003; 16, Hoellman et al 2001; 17, Edlund et al 1998; 18, Aldridge and Ashcraft 1997; 19, Schaumann et al 2000; 20, MacGowan et al 1997; 21, Snyderman et al 2002; 22, Ackermann et al 2000; 23, Betriu et al 1999; 24, Hedberg et al 2003; 25, Lion et al 2006; 26, Goldstein et al 2005; 27, Edmiston et al 2005.

isolates) (Gillespie and Billington 1999), 0.5 (16 isolates) (Rodriguez Diaz et al 2003); c) 8.0 (39 isolates) (Yang et al 2003), 16.0 (4 isolates) (Rodriguez Diaz et al 2003); d) 16.0 (92 isolates) (Yang et al 2003); e) 0.06 (16 isolates) (Gillespie and Billington 1999), 0.06 (148 isolates) (Alcaide et al 2004), 2.0 (8 isolates) (Rodriguez Diaz et al 2003); f) 0.5 (23 isolates) (Rodriguez Diaz et al 2003).

Important microorganisms in the context of skin and skin structure infections related to foreign devices are the coagulase-negative staphylococci (CNS), especially those strains able to produce biofilm (an extracellular glycocalyx material also called “slime”). Moxifloxacin’s activity has been evaluated in vitro against 19 biofilm-producing (MIC₉₀ = 2 mg/L) and 22 biofilm-nonproducing (MIC₉₀ = 0.25 mg/L) strains of CNS. SubMIC concentrations of moxifloxacin did not modify biofilm production. It had poor activity against stationary phase microorganisms but had some activity against microorganisms in the biofilm. However, high drug concentrations were necessary for this activity (50- and 100-fold MIC concentrations produced mean 1.10 and 1.69 log reductions in bacterial counts, respectively) (Perez-Giraldo et al 2004). In these regards, moxifloxacin unfortunately behaved like many other antimicrobials evaluated previously.

In another study with potential application to foreign device-related infections, an in vitro study was performed evaluating the bactericidal activity of moxifloxacin monotherapy and combination moxifloxacin plus vancomycin/teicoplanin therapy in 9 *S. aureus* isolates (1 being methicillin- and quinolone-sensitive and 8 being resistant to both). These isolates came from patients unresponsive to glycopeptide therapy or relapsing after completion of glycopeptide therapy despite device removal. Moxifloxacin MICs were 0.125 mg/L (in the 1 methicillin-sensitive isolate) and 2.0 mg/L (in all of the methicillin-resistant isolates). All isolates were tolerant to vancomycin, teicoplanin, and moxifloxacin at medium concentrations 2 X MIC. However, moxifloxacin plus glycopeptide combination therapy was bactericidal at the glycopeptide MIC and 0.5 X MIC of moxifloxacin (Tarasi et al 2003). Thus, combination therapy may be worthwhile considering in difficult-to-treat patients.

Characteristic of quinolones, moxifloxacin has concentration-dependent bactericidal activity (Dalhoff et al 1996). This has been shown with methicillin-sensitive and -resistant *S. aureus* and coagulase-negative staphylococci (Lister 2001, Speciale et al 2002; Noviello et al 2003; Bogdanovich et al 2005), *S. pyogenes* (Esposito et al 2000;

Odenholt et al 2002; Speciale et al 2002; Noviello et al 2003), *Enterococcus faecalis* (Speciale et al 2002), and a variety of anaerobes (Credito et al 2003). Bactericidal activity using serum bactericidal titer technology has been demonstrated for *S. aureus*, *S. epidermidis*, *S. pyogenes*, *E. coli*, and *Klebsiella pneumoniae* (Lemmen et al 2003; Dan et al 2004). Also, bactericidal activity using synovial fluid bactericidal titer technology has been demonstrated for *S. aureus*, *S. pyogenes*, and *K. pneumoniae* (Dan et al 2004). Activity against *S. pyogenes* is independent of the presence/absence of macrolide resistance determinants (Critchley et al 2002).

Two recent studies have evaluated the activity of moxifloxacin in in vitro pharmacokinetic/pharmacodynamic models (IVP/PM) of mixed aerobic-anaerobic infection. Hermsen and colleagues (2005) demonstrated bactericidal activity against *Escherichia coli* and *Bacteroides fragilis* in a study using a limited number of isolates of both microorganisms. Using different strains of the same microorganisms, Schaumann and colleagues (2005) demonstrated that the presence of *B. fragilis* did not affect the activity of moxifloxacin against *E. coli* but the presence of *E. coli* reduced the activity against *B. fragilis* significantly.

Another recent study evaluated the pharmacodynamics of moxifloxacin against anaerobes in an IVP/PM. *B. fragilis*, *Clostridium perfringens*, and Gram-positive anaerobic cocci (GPAC) were studied. Dose-ranging using area under the concentration-time curve/minimum inhibitory concentration (AUC/MIC) ratios of 6.7 to 890 (for the reference aerobe *E. coli*) and 9 to 216 (for the anaerobes) revealed differing AUC/MIC antibacterial effect patterns for anaerobes versus the aerobe. For *E. coli*, the AUC/MIC ratios for 50%/90% effect were 34/59 while the corresponding values for *B. fragilis*, *C. perfringens*, and GPAC were 11/26, 9/16, and 7/17, respectively. At similar AUC/MIC ratio values, the activity against anaerobes was less than that against the aerobe. Using Monte Carlo simulations of human pharmacokinetic data and a target anaerobic AUC/MIC ratio value of 7.5, over 90% achievement of this target was possible at MICs < 2 mg/L. The clinical implications of this "pharmacokinetic breakpoint" of 2 mg/L for anaerobes deserves further study (Noel et al 2005).

Despite 10- to 20-fold accumulation of drug intracellularly (vida infra), the bactericidal effect of moxifloxacin intracellularly develops slowly, with only a 1.51 log reduction in post-phagocytosis *S. aureus* inoculum within 24 h (Seral et al 2003). This may be explainable, in part, by the deleterious effect of acid pH on activity. For

example, at pH 5 (mimicking phagolysosome pH), moxifloxacin activity falls at least 4-fold compared with physiologic pH (Seral et al 2003). However, over a pH range of 6 to 8, moxifloxacin activity is unaffected for *S. aureus* and *S. pyogenes* (Dalhoff et al 2005).

The presence of 10%, 30%, and 50% albumin and human serum had no significant effect on the in vitro activity of moxifloxacin (Woodcock et al 1997; Rubinstein et al 2000). The presence of dead bacteria, sterile pus under aerobic conditions, sterile pus under anaerobic conditions, and anaerobic conditions alone had no significant effect on the in vitro activity of moxifloxacin against methicillin-sensitive and -resistant staphylococci, *S. pyogenes*, and *E. coli* (Boswell et al 1997; Rubinstein et al 2000; Wright et al 2002; Noel et al 2005). Anaerobic conditions also do not alter the AUC/MIC ratios for 50% and 90% of effect for *E. coli* and moxifloxacin (Noel et al 2005). Mixed effects have been noted when testing for an inoculum effect (Boswell et al 1997; Woodcock et al 1997).

Moxifloxacin has been evaluated in two mouse models relevant to skin and skin structure infections (systemic infection induced by intraperitoneal inoculation and cellulitis induced by subcutaneous (SC) inoculation). In the systemic infection model using 2 strains of methicillin-sensitive *S. aureus* (both having a moxifloxacin MIC of 0.06 mg/L), the ED₅₀ and ED₉₀ values for SC dosed drug were 0.6 mg/kg, 1.0 mg/kg and 1.7 mg/kg, 2.3 mg/kg, respectively, while corresponding ED values for orally dosed drug were 3.2 mg/kg (for both) and 9.6 mg/kg (for both) (Patel et al 2004). The term ED_{50/90} refers to the doses effective in producing survival rates of 50% and 90%, respectively. In the mouse cellulitis model, one methicillin-sensitive strain (MIC 0.03 mg/L) and two methicillin-resistant strains (MICs 1 mg/L and 4 mg/L) of *S. aureus* were used. For the methicillin-sensitive strain, 2.5 mg/kg and 5 mg/kg SC doses of moxifloxacin were administered 1 h, 4 h, 24 h, and 27 h post-inoculation while for the methicillin-resistant strains, 25 mg/kg and 50 mg/kg SC doses were administered 1 h, 3 h, and 5 h post-inoculation. With the methicillin-sensitive strain, moxifloxacin proved to be bacteriostatic (even 5 mg/kg doses led to a <2 log colony forming unit (CFU) reduction/lesion). With one methicillin-resistant strain, there was a marginal fall in CFU/lesion while with the other, it had no effect (CFU increased) (Patel et al 2004).

Two recent studies have evaluated the activity of moxifloxacin in animal models of osteomyelitis (bone infection). Bone infection can occur as a result of hematogenous seeding or contiguous spread from an area

of soft tissue infection. One study compared moxifloxacin and vancomycin in the treatment of bone infections due to methicillin-sensitive *S. aureus* in rats. Moxifloxacin (10 mg/kg) and vancomycin (15 mg/kg) were both dosed twice daily by the intraperitoneal route. Moxifloxacin was significantly more effective in reducing bacterial colony counts in femoral bone than were placebo and vancomycin (both $p < 0.001$; placebo vs vancomycin, $p = 0.53$). However, no treatment sterilized the infected bone, probably due to the presence of foreign material (ie, the hollow needle maintained in the cavity) (Kalteis et al 2006a). The second study extended the findings of the first to include bacterial counts in infected capsular soft tissue and biofilm adherent to the implanted needle. Moxifloxacin was significantly superior to vancomycin and placebo in reducing bacterial counts in capsular soft tissue (both $p < 0.001$; placebo vs vancomycin, $p = 0.09$) and biofilm ($p = 0.009$ and $p < 0.001$, respectively; placebo vs vancomycin, $p = 0.20$) (Kalteis et al 2006b). Further investigation of moxifloxacin in osteomyelitis appears warranted.

Another atypical mycobacterial infection with dermatological manifestations is leprosy (due to *M. leprae*). The classic test for evaluating the activity of antimicrobials against this microorganism is the mouse footpad model wherein the microorganism is injected into the footpad. In this model, where all drugs were administered orally, moxifloxacin proved superior to the quinolone used most frequently to date in combination regimens for leprosy, ofloxacin (percentages killed of 92.1% vs 60.2%, respectively; $p < 0.05$). In addition, the combination of minocycline plus moxifloxacin was superior to that of minocycline plus ofloxacin (percentages killed of 93.7% vs 74.9%, respectively; $p < 0.05$). Moxifloxacin was equipotent with rifampin, one of the key anti-leprosy drugs (percentage killed by both drugs was 92.1%, $p = \text{NS}$). The most potent combination tested was rifapentine (a rifamycin) plus minocycline plus moxifloxacin which produced a 99.9% killing rate (Ji and Grosset 2000). Moxifloxacin is an important agent to evaluate in vivo in human leprosy.

Performing large-scale surveillance of antimicrobial susceptibility can assist in deciding upon the selection of empiric antimicrobial therapy. In one such study, performed between 1994 and 2001, 12 US hospitals collected 4434 *Bacteroides* isolates for susceptibility testing. The overall moxifloxacin resistance rate rose from 30% to 43% ($p < 0.001$) from 1998 to 2001 (2001 MIC₉₀ = 16 mg/L). Increased moxifloxacin resistance over time was noted in

all species, all infection sites, and in 11 of 12 hospitals. For blood isolates, the resistance rate rose from 38% in 1998 to 52% in 2001. Resistance rates were especially high in the species *ovatus*, *uniformis*, and *vulgatus*. The largest increase in resistance occurred with the species *distasonis* (22% in 1999 to 37% in 2001). Of all infection sites, decubitus ulcer isolates had the highest resistance rates. On multivariate analysis, the association between the year of microorganism isolation and increased resistance rates remained significant after adjusting for hospital, species, and infection site (adjusted odds ratio=1.33, $p < 0.001$) (Golan et al 2003).

In the LIBRA surveillance study in the US in 1999, 324 laboratories participated in an examination of resistance rates in *S. pyogenes* isolates. Isolates came from the respiratory tract ($n = 2039$), skin and skin structure ($n = 405$) and blood ($n = 148$). The modal moxifloxacin MIC was 0.12 mg/L and the MIC₉₀ was 0.25 mg/L. One hundred percent of isolates were susceptible (based on a resistance breakpoint of ≥ 4 mg/L) (Critchley et al 2002).

In 2003, 37 laboratories in 19 countries participated in a survey of resistance rates among *B. fragilis* group isolates. Among the 1284 isolates (the majority coming from abdominal infections and wounds), 9% were resistant to moxifloxacin (breakpoint = 8 mg/L) (range 0%–22%). Moxifloxacin resistance was commonest in Mediterranean Europe (15%) and the UK (22%). In the various infection types, the rates of intermediate (decreased susceptibility) plus resistant isolates were as follows: abdominal infections (5%), wounds (13%), abscesses (4%), blood (11%), and external ulcers/skin infections (16%) (Hedberg et al 2003).

In 2005, results of a six-year (1997–2002) surveillance study of moxifloxacin susceptibility among *B. fragilis* group organisms at a single hospital in Spain were published. Resistance rates to moxifloxacin rose from 6% (1997) to 16.5% (2002), using an MIC breakpoint of 8 mg/L ($p < 0.005$ for trend). Examining resistance rates by species, these rates rose over six years from 1.5% to 12% (*B. fragilis*), 10.3% to 25% (*B. thetaiotaomicron*), and 15.4% to 36.8% (*B. uniformis*) (Betriu et al 2005).

Results of the SENTRY Antimicrobial Surveillance Program (1997–2004) have revealed the emergence in North America and Europe of quinolone resistance among β -hemolytic streptococci (groups A, B, C, G). Although rates are low at present (0.51% and 0.14% in North America and Europe, respectively), further dissemination and expansion of resistance determinants is likely (Biedenbach et al 2006).

Pharmacokinetics

Moxifloxacin is well-absorbed after oral administration, with absolute oral bioavailabilities of 92% (mean) (range 77%–120%) and $86.2 \pm 1.11\%$ (mean \pm standard deviation [SD]) being noted in 2 healthy-volunteer studies (Ballow et al 1999; Stass and Kubitzka 1999). Oral administration in the fed state (high fat breakfast) had nonsignificant effects on moxifloxacin peak plasma concentration (C_{\max}) and area under the plasma concentration-versus-time curve (AUC) but did prolong the median time to C_{\max} (T_{\max}) from 1 to 2.5 hours (not clinically significant) (Lettieri et al 2001). Milk (240–300 mL) and yogurt (250–300 mL) coadministration did not significantly alter moxifloxacin bioavailability (Guay 2005) nor did enteral feeding coadministration (Burkhardt et al 2005). Minor accumulation occurs during multiple dosing and its pharmacokinetics are linear and dose-proportional (Stass et al 1998, 2001; Sullivan et al 1999).

Mean \pm SD plasma protein binding values of moxifloxacin were $48\% \pm 2.5\%$ (Stass et al 1998) and $39.4\% \pm 2.4\%$ (Stass and Kubitzka 1999). Plasma protein binding of the M1 sulfocompound metabolite was $89.5\% \pm 0.9\%$ and that of the M2 glucuronide metabolite was $4.8\% \pm 4.1\%$ (Stass and Kubitzka 1999). Penetration of moxifloxacin into body compartments relevant to skin and skin structure infections has been the subject of several studies. In one healthy volunteer study, the pharmacokinetics of moxifloxacin in plasma and inflammatory blister fluid (induced by cantharides plasters) were evaluated after single 400 mg oral and intravenous doses. The mean \pm SD (range) penetration of moxifloxacin into inflammatory blister fluid after oral and intravenous dosing were $83.5\% \pm 14.9\%$ (61%–103%) and $93.7\% \pm 8.3\%$ (81%–104%), respectively, as measured by $AUC_{0-\infty}$ (Wise et al 1999). In another study, the serum and synovial fluid concentrations of moxifloxacin after the last of three once-daily oral moxifloxacin 400 mg doses were assessed in 20 patients undergoing knee arthroscopy (mean age of 71.2 years). At 2 h, 6 h, 12 h, and 24 h after the last dose, the mean \pm SD serum/synovial fluid concentrations were $2.42 \pm 0.4/2.76 \pm 0.24$ mg/L, $3.46 \pm 0.78/3.42 \pm 0.51$ mg/L, $1.74 \pm 0.26/1.61 \pm 0.5$ mg/L, and $1.5 \pm 0.21/1.23 \pm 0.14$ mg/L, respectively (Dan et al 2004).

In yet another healthy volunteer study, the penetration of moxifloxacin into the interstitial fluid compartments of muscle and SC adipose fat tissue and inflammatory blister fluid were evaluated after single 400 mg oral and intravenous doses. Mean \pm SD penetration into muscle interstitial fluid was $55\% \pm 12\%$ (using $AUC_{\text{muscle}}/AUC_{\text{total plasma}}$ data) and

$86\% \pm 17\%$ (using $AUC_{\text{muscle}}/AUC_{\text{free plasma data}}$ data). Corresponding SC adipose fat interstitial fluid penetration was $38\% \pm 9\%$ and $81\% \pm 19\%$. These results suggest a virtually total equilibration between these two body compartments and free (unbound) drug in plasma. The concentration over time profiles in these two compartments were virtually superimposable. Mean \pm SD penetration into inflammatory blister fluid (BF) was $64\% \pm 21\%$ (using $AUC_{\text{BF}}/AUC_{\text{total plasma}}$ data) (Muller et al 1999).

The penetration of moxifloxacin into healthy and inflamed SC adipose fat tissues was assessed in 11 patients with skin and skin structure infections (n=5 had diabetes and peripheral occlusive arterial disease (POAD), n=6 did not). A single 400 mg IV dose of moxifloxacin was administered over one hour. In the aggregate analysis (n=11), drug concentrations in healthy and inflamed tissues were consistently below total plasma concentrations and approximately equal to free plasma concentrations. Moxifloxacin total plasma concentration over time profiles were similar in patients with and without diabetes/POAD. Penetration into tissue did not statistically differ in the two groups. In patients with diabetes/POAD, the concentrations in healthy tissue exceeded those in inflamed tissue. Only the healthy tissue concentrations were similar to the free concentrations in plasma (the inflamed tissue concentrations were about 1/2 of the free concentrations in plasma). In the patients without diabetes, exactly the opposite findings were noted. Thus, the mean \pm SD AUC_{0-8h} for inflamed tissue/ $AUC_{0-\infty}$ for free drug in plasma was 0.5 ± 0.4 in patients with diabetes/POAD and 1.2 ± 0.8 in the other group. Mean \pm SD inflamed tissue C_{\max} values were 0.8 ± 0.5 mg/L in patients with diabetes/POAD and 2.3 ± 1.2 mg/L in the other group. The reduced concentrations in inflamed tissues in patients with versus without diabetes/POAD was perhaps due to the vascular compromise associated with POAD. None of these differences between patients with/without diabetes/POAD were significant due to small sample sizes and large interpatient variability. In all cases, tissue and plasma drug concentrations exceeded the MICs of most dermatologic pathogens, suggesting a role for moxifloxacin in the treatment of skin and skin structure infections (Joukhadar et al 2003).

Thirty patients undergoing total knee arthroplasty participated in a study investigating the penetration of moxifloxacin into bone. Ten patients received oral moxifloxacin 2 h (range 1.5–2.5 h) preoperatively and mean plasma, cancellous bone, and cortical bone drug concentrations were 3.45 mg/L, 1.89 mg/kg, and 1.43 mg/

kg, respectively. In the ten patients receiving moxifloxacin 4 h (range 3.5–4.5 h) preoperatively, corresponding mean drug concentrations were 3.73 mg/L, 1.81 mg/kg, and 1.56 mg/kg. In the ten patients receiving the drug 14 h and 2 h (range 1.5–2.5 h) preoperatively, corresponding drug concentrations were 6.26 mg/L, 2.97 mg/kg, and 2.54 mg/kg (Malincarne et al 2006).

As with other quinolones, moxifloxacin penetrates well into polymorphonuclear leukocytes (mean \pm SD internal concentration = 54 ± 0.5 mg/L with an external medium concentration of 4.5 mg/L) (Mandell and Coleman 2001). Moxifloxacin also penetrates well into macrophages (with an external concentration of 4 mg/L, the mean internal–external concentration ratio = 13.4 (in cells infected with *S. aureus*) and 11.4 (in non-infected cells), $p=0.02$) (Seral et al 2003).

Moxifloxacin elimination occurs via a combination of hepatic metabolism, biliary secretion, renal excretion, and perhaps, transintestinal secretion. It is metabolized to 2 inactive metabolites, M1 (N-sulfate) and M2 (acylglucuronide) (Stass et al 2004). Renal clearance (CL_R) of the parent compound involves glomerular filtration and partial renal tubular reabsorption (Stass et al 1998; Stass and Kubitzka 1999). Fecal drug concentrations upon multiple oral dosing are quite high, a result of nonabsorption, biliary secretion, and, possibly, transintestinal secretion (mean \pm SD days 2, 4, and 7 values during 400 mg daily oral dosing were 87.3 ± 2.4 mcg/g, 303.3 ± 1.8 mcg/g, and 573.3 ± 1.9 mcg/g, respectively) (Burkhardt et al 2002). Mass balance studies using oral drug have demonstrated that (mean \pm SD) 44.8% \pm 3.4%, 37.9% \pm 3.6%, and 13.6% \pm 2.8% of the dose is eliminated as moxifloxacin (19.4% \pm 1.2% in urine and 25.4% \pm 3.1% in feces), M1 metabolite (2.5% \pm 0.6% in urine and 35.5% \pm 3.2% in feces) and M2 metabolite (13.6% \pm 2.8% in urine and none in feces), respectively (Stass and Kubitzka 1999). Thus, the urinary and fecal routes account for 35.4% \pm 1.8% and 60.9% \pm 5.1% of the dose, respectively (Stass and Kubitzka 1999). The M1 metabolite is a high clearance compound eliminated mainly via hepatic metabolism and biliary secretion into the feces. Renal secretion occurs via a net active tubular secretion process (Stass and Kubitzka 1999). The M2 metabolite is the main metabolite seen in plasma, undergoing some presystemic clearance via glucuronidation and excretion by the kidneys by active tubular secretion. Biliary/fecal elimination is negligible (Stass and Kubitzka 1999). A summary of the pharmacokinetic parameters for moxifloxacin in healthy volunteers is provided in Table 3

(Stass et al 1998, 2001, 2002, 2004; Ballow et al 1999; Stass and Kubitzka 1999; Sullivan et al 1999, 2001; Wise et al 1999; Lubasch et al 2000; Lettieri et al 2001; Burkhardt et al 2002).

When pharmacokinetic parameters are weight-normalized, there are no significant age- or gender-based effects on moxifloxacin pharmacokinetics (Sullivan et al 2001; Pea et al 2006). Thirty-two individuals participated in a single 400 mg oral dose study of the effects of renal impairment on the pharmacokinetics of moxifloxacin and its M1 and M2 metabolites. With moxifloxacin, there was no significant relationship of AUC with creatinine clearance (CrCl) ($p=0.59$). However, C_{max} did fall as CrCl fell ($p=0.03$). Significant correlations existed between moxifloxacin C_{max} ($r=0.438$, $p=0.012$), fractional renal excretion (F_e) ($r=0.613$, $p=0.0002$) and CL_R ($r=0.6405$, $p=0.0001$) and CrCl. The M1 metabolite was little affected by changes in renal function although significant correlations existed between M1 metabolite F_e ($r=0.620$, $p=0.0002$) and CL_R ($r=0.703$, $p<0.0001$) and CrCl. For the M2 metabolite, AUC rose as CrCl fell ($p=0.0167$) while C_{max} did not change ($p=0.3042$). Significant correlations existed between M2 metabolite AUC ($r=-0.565$, $p=0.0011$), CL_R ($r=0.736$, $p<0.0001$) and F_e ($r=0.514$, $p=0.0026$) and CrCl (Stass et al 2002).

Single and multiple dose pharmacokinetics of moxifloxacin have also been evaluated in end-stage renal disease patients undergoing hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD). Following a single oral 400 mg dose, the AUC's of parent compound in these patients were statistically similar to those found generally in healthy volunteers. However, C_{max} values were reduced by about 45% (HD) and 33% (CAPD) compared with historical healthy control subject data. The systemic exposure to the M1 metabolite rose by 1.4- to 1.5-fold (based on AUC) while that to the M2 metabolite rose 7.5-fold (based on AUC) and 2.5- to 3-fold (based on C_{max}) compared with historical healthy control subject data. The possible consequences of increased metabolite exposure are not known. Multiple once-daily oral dosing of 400 mg for 7 days in these patients produced systemic exposure (AUC) similar to that seen in healthy volunteers. Steady-state C_{max} values in HD patients were approximately 22% lower than those in healthy volunteers while they were comparable for CAPD patients. Dialysis removal of moxifloxacin was low (9% by HD, 3% by CAPD) (Anonymous 2005). Continuous renal replacement therapy (continuous venovenous hemodiafiltration) does not affect

Table 3 Mean \pm SD pharmacokinetic parameters of moxifloxacin in healthy adult volunteers

Reference	n	Regimen	C _{max} (mg/L)	T _{max} (h)	t 1/2 (h)	CL/F (L/h)	CL _R (L/h)	F _e (%)
(1)	11	400 mg PO x 1	2.53 \pm 1.31	1.0 ^a	14.6 \pm 1.18	13.7 \pm 1.16	3.17 \pm 1.12	23.2 \pm 2.7
(2)	12	400 mg PO qd						
		dose 1	3.10 \pm 0.60 ^b	1.67 \pm 0.96	10.6 ^{a,b}	11.6 \pm 2.1	—	—
		dose 7	3.98 \pm 1.10 ^b	1.59 \pm 0.79	14.9 ^{a,b}	10.4 \pm 2.0	—	—
(3)	12	400 mg PO x 1	2.50 \pm 1.29	2.0 ^a	15.6 \pm 1.15	11.6 \pm 1.21	2.58 \pm 1.25	19.3 \pm 2.8
(4)	8	400 mg PO x 1	4.38 \pm 1.4	0.77 ^a	14.9 \pm 1.5	9.2 \pm 1.4	2.3 \pm 1.3	24.2 \pm 1.4
(5)	16	400 mg PO x 1	2.8 (31.7%) ^c	1.0 ^a	11.5 (12.8%) ^c	—	—	—
(6)	8 ^d	200 mg PO x 1	1.31	1.28	13.16	10.61	2.25	19.63
	8 ^e		1.55	0.97	12.42	10.38 ^b	1.84	16.60
	8 ^f		1.92	1.50	11.47	8.05 ^b	1.74	20.55
(7)	8	100 mg PO bid x 5 days						
		day 1	0.63 \pm 1.47	2.0 ^a	9.39 \pm 1.08	13.1 \pm 1.25	2.54 \pm 1.28	15.8 \pm 1.21
		day 5	0.90 \pm 1.28	1.5 ^a	13.7 \pm 1.20	13.8 \pm 1.22	3.32 \pm 1.31	24.0 \pm 1.24
	8	200 mg PO bid x 5 days						
		day 1	1.16 \pm 1.96	1.5 ^a	10.4 \pm 1.26	14.0 \pm 1.33	3.24 \pm 1.36	18.2 \pm 1.24
		day 5	1.96 \pm 1.23	1.3 ^a	15.0 \pm 1.18	13.1 \pm 1.26	3.08 \pm 1.29	23.5 \pm 1.34
	7	400 mg PO qd x 5 days						
		day 1	3.10 \pm 1.34	0.5 ^a	9.6 \pm 1.12	12.9 \pm 1.12	2.33 \pm 1.27	14.7 \pm 1.25
		day 5	3.24 \pm 1.19	1.5 ^a	15.1 \pm 1.05	11.8 \pm 1.22	2.51 \pm 1.14	21.3 \pm 1.19
	7	600 mg PO qd x 10 days						
		day 1	4.21 \pm 1.18	1.0 ^a	9.11 \pm 1.16	11.9 \pm 1.26	3.30 \pm 1.62	23.0 \pm 1.46
		day 10	5.67 \pm 1.19	1.5 ^a	13.7 \pm 1.06	10.0 \pm 1.23	2.41 \pm 1.15	24.2 \pm 1.18
(8)	12	400mg PO x 1	4.34 \pm 1.61	1.02 \pm 0.72	9.15 \pm 1.62	—	30.5 \pm 6.18 ^g	19.9 \pm 4.55
(9)	7	400 mg PO x 1	4.98 \pm 1.01	1.0 \pm 0.91	8.32 \pm 1.70	147.8 ^h	22.3 ^h	15.10 \pm 3.61
		400 mg IV x 1	5.09 \pm 1.11	—	8.17 \pm 1.58	151.5 ^h	23.0 ^h	15.2 \pm 3.40
(10)	10	100 mg PO x 1	1.15	0.86	13.5	—	—	24.4
		100 mg IV x 1	1.34	—	12.7	—	—	25.3
(11)	7 ⁱ	400 mg PO qd						
	3 ^j	x 10 days						
		day 1	3.36 (21.5%) ^c	1.49 (62.2%) ^c	9.30 (12.1%) ^c	—	—	—
		day 10	4.52 (12.2%) ^c	1.24 (48.0%) ^c	11.95 (10.8%) ^c	—	—	—
		400 mg PO x 1	2.53 \pm 1.31	1.0 ^a	14.6 \pm 1.18	13.7 \pm 1.16	3.17 \pm 1.12	23.2 \pm 2.7
(12)	6	50 mg PO x 1	0.29 \pm 1.25	1.75 ^a	11.4 \pm 1.11	12.9 \pm 1.13	2.77 \pm 1.22	20.4 \pm 1.15
	6	100 mg PO x 1	0.59 \pm 1.21	2.0 ^a	12.2 \pm 1.11	11.8 \pm 1.21	2.38 \pm 1.25	18.9 \pm 1.34
	6	200 mg PO x 1	1.16 \pm 1.35	2.50 ^a	14.0 \pm 1.14	13.0 \pm 1.20	2.64 \pm 1.25	19.8 \pm 1.16
	7	400 mg PO x 1	2.50 \pm 1.31	1.5 ^a	13.1 \pm 1.06	14.9 \pm 1.18	3.03 \pm 1.17	20.1 \pm 1.20
	7	600 mg PO x 1	3.19 \pm 1.19	2.5 ^a	12.5 \pm 1.14	15.0 \pm 1.11	2.67 \pm 1.10	17.5 \pm 1.16
	7	800 mg PO x 1	4.73 \pm 1.16	3.0 ^a	12.3 \pm 1.13	13.4 \pm 1.24	2.50 \pm 1.28	18.7 \pm 1.25

Abbreviations: bid, twice daily; C_{max}, peak serum concentration; CL/F, total body clearance; CL_R, renal clearance; F_e, fractional elimination in urine as unchanged parent compound; IV, intravenous; T_{max}, time to C_{max}; t 1/2, terminal disposition half-life; PO, oral; qd, once daily.

Notes: ^aMedian; ^bLinks parameters that are significantly different (p \leq 0.05); ^c% coefficient of variation; ^dYoung males (mean age, 32); ^eOlder males (mean age, 74); ^fOlder females (mean age, 74); ^gmL/min/1.73m²; ^hMean values in mL/min; ⁱMale; ^jFemale.

References: 1, Stass et al 2004; 2, Burkhardt et al 2002; 3, Stass and Kubitzka 1999; 4, Stass et al 2002; 5, Lettieri et al 2001; 6, Sullivan et al 2001; 7, Stass et al 2001; 8, Lubasch et al 2000; 9, Wise et al 1999; 10, Ballow et al 1999; 11, Sullivan et al 1999; 12, Stass et al 1998.

moxifloxacin disposition to a clinically-meaningful extent (Fuhrmann et al 2004).

Clinical efficacy

This section will deal only with the clinical efficacy of moxifloxacin in skin and skin structure infections (SSSIs). Table 4 illustrates the results of moxifloxacin clinical trials in uncomplicated and complicated SSSIs (Leal del Rosal, Fabian, et al 1999; Leal del Rosal, Martinez, et al 1999; Parish et al 2000; Anonymous 2005; Giordano et al 2005). All have been active-controlled in design, with cephalexin as the control in the three uncomplicated SSSI studies, unspecified β -lactam/ β -lactamase-inhibitor combinations in the 2 unpublished complicated SSSI studies, and piperacillin-tazobactam followed by amoxicillin-clavulanate as the control in the one published complicated SSSI study. As may be seen, there were no significant or substantial inter-group differences in clinical or bacteriological efficacy or tolerability.

These results should be interpreted while keeping in mind potential study limitations. In general, these studies did not provide evidence of power analyses conducted to establish proper group sizes. Thus, they were underpowered to avoid type II statistical errors (ie, false negative intergroup differences), especially with respect to subgroup analyses based on comorbidities or individual pathogens. Three of five studies remain unpublished, available only as abstracts or in the product information. The limitations of this should be obvious to the reader. The extensive number and breadth of exclusion criteria generated study populations much different from the "real world" patients who would require treatment. Hence, the generalizability of study results can be questioned. Clinical trials of SSSIs have long been difficult to design in a way that renders them rigorous and reproducible. Although the publication of SSSI study design criteria by the Infectious Diseases Society of America (IDSA) have helped in this regard (Calandra et al 1992), deficient study designs are, unfortunately, still far too frequently seen. The ability of investigators to add anti-anaerobic coverage (eg, metronidazole) for presumed mixed SSSIs makes it impossible to judge whether or not the anaerobic coverage of moxifloxacin is clinically-relevant. Lastly, the definitions of clinical endpoints can vary between SSSI studies, making it difficult to obtain a global perspective of drug efficacy.

A recent case report detailed a case of a patient with an infected cat-bite wound failing therapy with IV cefuroxime, ciprofloxacin, and metronidazole which responded to the

addition of IV moxifloxacin (Draenert et al 2005). Another case report documented successful therapy of a *M. thermoresistibile* infection following knee replacement surgery with long-term therapy using moxifloxacin and doxycycline (Labombardi et al 2005).

A recent review of potential antitubercular drugs included encouraging in vitro, in vivo, (animal) and pilot human clinical data regarding moxifloxacin use in infections due to *M. tuberculosis* (Duncan and Barry 2004). These data, in conjunction with in vitro susceptibility data reviewed earlier in this paper, suggest that moxifloxacin may play an important role in the treatment of SSSIs caused by atypical mycobacteria. Clinical trials in this area are warranted.

Safety

As with other quinolones, moxifloxacin is generally well-tolerated, with the majority of adverse events referable to the gastrointestinal tract (nausea, diarrhea, vomiting, constipation, abdominal pain, vaginitis, taste alteration) or the central nervous system (headache, dizziness) (Anonymous 2005). There were only three adverse events, judged by investigators to be at least possibly drug-related, occurring in at least 2% of over 8600 moxifloxacin-treated patients in the drug development process: nausea (6%), diarrhea (5%), and dizziness (2%) (Anonymous 2005). Premature study discontinuation rates for drug-related adverse events were 2.9% (oral) and 4.6% (IV \rightarrow oral) (Anonymous 2005). Moxifloxacin is not associated with the phototoxicity characteristic of lomefloxacin and sparfloxacin (Man et al 1999) and has only been associated with the "temafloxacin hypersensitivity syndrome" in 1 patient (Nori et al 2004). This patient exhibited toxic epidermal necrolysis and fulminant hepatic failure leading to death. Moxifloxacin is not associated with the hypo or hyperglycemia seen with gatifloxacin therapy (Park-Wyllie et al 2006).

In 2004, a cumulative safety review of oral and intravenous moxifloxacin from the drug development program and postmarketing surveillance studies was published. For the oral agent, the database comprised 30 phase II/III active comparator studies (moxifloxacin n=7368, comparators n=5687), one phase IV study (n=18374), and 4 postmarketing observation studies (n=27756). For the intravenous agent, the database comprised two phase III active comparator studies (moxifloxacin n=550, comparators n=579). With both formulations, the commonest adverse events involved the gastrointestinal tract (for the oral agent, nausea in 7.1% and

Table 4 Clinical efficacy and tolerability of moxifloxacin in skin and skin structure infections (SSSIs)

Reference	Study Design	# evaluable subjects (C/B) ^a	Regimens	Results
Uncomplicated SSSIs				
(1)	MC/R/DB/PG	180/68	Moxi 400 mg PO qd x 7 days	Clinical cure/improvement rates at 7–21 d after the end of therapy were 90% (Moxi) and 91% (Ceph) (p=NS). Clinical response rates were lower in men than women, esp. with Moxi (86% men, 94% women; stats NA). Clinical response rates were highest in ≥65 yo age group (95%, stats NA). Clinical response rates with Ceph were approx. equivalent for spontaneous infections and those occurring with a wound while, for Moxi, rates were higher for infections occurring with a wound (96% vs. 87%, stats NA). Bact. eradication/presumed eradication rates at 7–21 days after the end of therapy were 91% in both groups (stats NA). For <i>S. aureus</i> , eradication rates were 92% (Moxi) and 93% (Ceph) (stats NA) while for <i>Streptococcus</i> species they were 90% (Moxi) and 82% (Ceph) (stats NA). AE profiles for the 2 drugs were similar (stats NA). AEs occurred in 21% of Moxi and 19% of Ceph patients. 9 AEs were serious/life-threatening in 7 patients (1 with Moxi, 6 with Ceph). AEs led to premature study D/C in 13 patients (6 Moxi, 7 Ceph). Majority of AEs were referable to GI tract and skin and frequencies/types were similar in the 2 groups.
		171/57	Ceph 500 mg PO tid x 7 days	
(2)	MC/R/DB/PG	191/100	Moxi 400 mg PO qd x 5–14 days	Clin. cure or improvement occurred in 93% of patients in both groups. Bact. eradication/presumed eradication occurred in 89% (Moxi) and 94% (Ceph) of patients. Eradication rates for <i>S. aureus</i> were 92% (Moxi) and 89% (Ceph). No mention was made of AEs and results of statistical analyses NA.
		194/112	Ceph 500 mg PO tid x 5–14 days ^b	
(3)	MC/R/DB/PG	21/18	Moxi 200 mg PO qd x 5–14 days	Clin. cure or improvement occurred in 95% (Moxi 200), 100% (Moxi 400), and 89% (Ceph) of patients. Corresponding bact. eradication/presumed eradication rates were 72%, 80%, and 80%. Predominant pathogens were <i>S. aureus</i> (37.5%), <i>S. haemolyticus</i> (18.8%), and <i>E. faecalis</i> (10.4%). All treatments were “well-tolteredated” with “similar frequencies of drug-related AEs”. Results of statistical analyses NA.
		22/15	Moxi 400 mg PO qd x 5–14 days	
		26/15	Ceph 500 mg PO tid x 5–14 days	
Complicated SSSIs				
(4)	MC/R/DB/PG (North America)	162/NA	Moxi IV → PO (total of 7–14 days)	Clin. cure or improvement occurred in 77.2% of Moxi and 81.5% of β-lactam comparator recipients (p=NS).
		173/NA	β-lactam/β-lactamase inhibitor IV → PO (total of 7–14 days)	

Note: ^aClinically/bacteriologically; ^bCould add metronidazole 400 mg tid for anaerobic coverage; ^cMethicillin-susceptible strains.

Abbreviations: AE, adverse event; Amox-Clav, amoxicillin-clavulanate; Ceph, cephalixin; CHF, chronic heart failure; DB, double-blind; D/C, discontinuation; GI, gastrointestinal; IV, intravenous; I + D, incision + drainage; MC, multicenter; Moxi, moxifloxacin; NA, not available; NS, non-significant; PG, parallel group; R, randomized; qd, once daily; tid, thrice daily; Pip-Tazo, piperacillin-tazobactam; PMC, pseudomembranous colitis; PO, oral.

Reference key: 1, Parish et al 2000; 2, Leal del Rosal, Fabian, et al 1999; 3, Leal del Rosal, Martinez, et al 1999; 4, Anonymous 2005; 5, Giordano et al 2005.

Table 4 Continued

Reference	Study Design	# evaluable subjects (C/B) ^a	Regimens	Results
Complicated SSSIs				
	MC/R/PG (International)	315/NA	Moxi 400 mg IV → PO qd x 7–21 days	Clin. cure or improvement occurred in 80.6% of Moxi and 84.5% of β-lactam comparator recipients (p=NS).
		317/NA	β-lactam/β-lactamase inhibitor IV → PO (total of 7–21 days)	<u>Pooled results (stats NA)</u> Surgical I + D or debridement occurred in 55% of Moxi and 53% of β-lactam comparator subjects. Success rates varied by diagnosis (61% in infected skin ulcers to 90% in complicated erysipelas). Clin. cure or improvement by pathogen was as follows: <i>S. aureus</i> ^c : Moxi 82.2%, Comparator 87.6% <i>E. coli</i> : Moxi 81.6%, Comparator 84.8% <i>K. pneumoniae</i> : Moxi 91.7%, Comparator 70.0% <i>E. cloacae</i> : Moxi 81.8%, Comparator 57.1%
(5)	MC/R/DB/PG	180/119 187/119	Moxi 400mg IV → PO (total of 7–14 days) Pip-Tazo 3.375 g IV qd → Amox-Clav PO 800 mg bid (total of 7–14 days) minimum duration of IV therapy was 3 days.	Clin. cure rates 10–42 days post-therapy were 79% (Moxi) and 82% (Pip-Tazo → Amox-Clav) (p=NS). Clin. cure rates were similar by infection type in the 2 groups except abscess (79% Moxi vs. 93% Pip-Tazo → Amox-Clav, p=0.04). Univariate followed by multivariate regression analysis identified the no. of surgeries (ie, ≥2) as being an independent risk factor for failure of abscess cure. After adjusting for risk factors for failure of abscess cure, the difference between groups disappeared (odds ratio, 1.05; p=0.12). There were no significant differences between the groups in bacteriologic eradication rates by organism or for monomicrobial or polymicrobial infections. AE rates were comparable in the 2 groups (drug-related AEs in 31% and 30% of Moxi and Pip-Tazo → Amox-Clav patients, respectively; corresponding rates of diarrhea were 5% and 8%, and nausea were 4% and 2%; premature D/C for drug-related AEs in 14 and 17 patients). Drug-related serious AEs with Moxi included weakness, worsening of drug reaction rash, cellulitis exacerbation, PMC, and clinical failure and with Pip-Tazo → Amox-Clav included cardiopulmonary arrest, worsening CHF, allergic reaction, asthenia, worsened skin eruption, allergic reaction, persistent right leg abscess, bloody diarrhea, osteomyelitis, and clinical failure.

Note: ^aClinically/bacteriologically; ^bCould add metronidazole 400 mg tid for anaerobic coverage; ^cMethicillin-susceptible strains.

Abbreviations: AE, adverse event; Amox-Clav, amoxicillin-clavulanate; Ceph, cephalexin; CHF, chronic heart failure; DB, double-blind; D/C, discontinuation; GI, gastrointestinal; IV, intravenous; I + D, incision + drainage; MC, multicenter; Moxi, moxifloxacin; NA, not available; NS, non-significant; PG, parallel group; R, randomized; qd, once daily; tid, thrice daily; Pip-Tazo, piperacillin-tazobactam; PMC, pseudomembranous colitis; PO, oral.

Reference key: 1, Parish et al 2000; 2, Leal del Rosal, Fabian, et al 1999; 3, Leal del Rosal, Martinez, et al 1999; 4, Anonymous 2005; 5, Giordano et al 2005.

diarrhea in 5.2%; for the intravenous agent, nausea in 3.1% and diarrhea in 6.2%). Premature discontinuation rates due to adverse events to moxifloxacin were 2.7% (oral) and 6.0% (intravenous) while mortality rates were 2.7% (oral) and 4% (intravenous). Cardiovascular adverse events, including surrogate markers for arrhythmias such as tachycardia, palpitations, syncope, and hypotension, occurred at rates far below 1%. Blood sugar-related events were practically nonexistent (Ball et al 2004).

In the same year, a similar retrospective review of the phase II/III clinical trial database (32 trials, n=14731 patients (moxifloxacin n=8474, active comparators n=6257)) and postmarketing surveillance studies (n=46130) were reviewed with a focus on adverse events involving glucose metabolism. In the clinical trials, there were 0 and 3 drug-related hypoglycemic adverse events with moxifloxacin and active comparator patients, respectively (latter were 2 cases with levofloxacin and 1 case with trovafloxacin). Drug-related hypoglycemic events occurred in 7 moxifloxacin and 1 active comparator patients. No evidence was found supporting the presence of drug–drug interactions with oral antidiabetic drugs. In the postmarketing studies, no cases of drug-related hypoglycemia were noted. This same paper described results of *in vivo* (rat) studies utilizing single 30 mg/kg and 100 mg/kg oral doses of moxifloxacin, gatifloxacin, and levofloxacin (positive control was glibenclamide 10 mg/kg). Blood was sampled predosing and at 0.5 h and 1.5 h postdosing. In fasted rates, glibenclamide had the expected effect (blood glucose fell a mean of 24% at 1.5 h postdose which was preceded by a rise in serum insulin). Blood glucose was not significantly affected by either moxifloxacin or levofloxacin but fell means of 8% and 18% with 30 mg/kg and 100 mg/kg doses of gatifloxacin, respectively. No significant effects on serum insulin were noted with any quinolone. In fed rats, glibenclamide increased serum insulin and reduced blood glucose approximately 40% at 1.5 h postdosing. Again, moxifloxacin and levofloxacin had no significant effect on blood glucose or serum insulin. Gatifloxacin 30 mg/kg and 100 mg/kg reduced blood glucose by means of 17% and 26%, respectively. This was preceded by a reduction in serum insulin (only significant at 0.5 h with 100 mg/kg dose). Thus, the gatifloxacin effect was felt to be insulin-independent (Gavin et al 2004).

Results of the last of the large retrospective database reviews for safety purposes were published in 2005 and focused on the safety of oral moxifloxacin in the clinical trial database as a function of aging. The database involved

27 phase II/III clinical trials analyzed by age grouping (<65, 65–74, ≥75 years old) and treatment (moxifloxacin and active comparators). Valid data were available from 12231 subjects (moxifloxacin n=6270, active comparators n=5961; comparators were primarily clarithromycin and cefuroxime axetil). The subject distribution by age was as follows: n=9671 were <65, n=1631 were 65–74, and n=924 were ≥75 years old. The distribution of drug-related adverse events comparing moxifloxacin with active comparators was not affected by increasing age (p=0.43) nor were premature discontinuations due to adverse events (p=0.552). The number of deaths were also similar (moxifloxacin n=17, active comparator n=19). No arrhythmias due to QT_c interval prolongation were noted in the entire population. The differences in adverse event profiles across the 3 age groups were not significant for moxifloxacin (p=0.599) with 1 exception. For drug-related adverse events with moxifloxacin, the profiles did differ across the 3 age groups (p=0.001) but, unexpectedly most rates increased as age fell (eg, nausea, vomiting, dyspepsia, and vaginal moniliasis rates rose as age fell but insomnia rates rose as age rose). There were no clinically-significant differences between the treatments in the prevalence of serious drug-related events (≤1%) and these were not related to age. In 787 patients who had pre and 3 day-post 12-lead electrocardiograms (n=651 were <65, n=136 were ≥65 years old), the mean ± SD QT_c interval prolongation was 7 ± 25 msec in the <65 group and 2 ± 28 msec in the ≥65 group (p=0.055, trend) (Andriole et al 2005).

Pharmacokinetic drug–drug interactions

Based on the significant role of metabolism in the elimination of moxifloxacin, a study was conducted to evaluate the effect of concurrent use of a potent cytochrome P450 isozyme 3A4 inhibitor (itraconazole) on moxifloxacin pharmacokinetics. Nine days of itraconazole 200 mg orally daily had no significant effect on the single-dose kinetics of oral moxifloxacin 400 mg (administered on day 7 of the 9-day itraconazole regimen). Moxifloxacin also had no significant effect on itraconazole kinetics (Stass et al 2004). Moxifloxacin 400 mg orally daily had no significant effect on theophylline total body clearance and terminal disposition half-life in 2 studies (Guay 2005). Moxifloxacin 400 mg orally once daily had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin in healthy volunteers (Guay 2005). However, case reports have documented moxifloxacin-associated increases in INR

(international normalized ratio of prothrombin time) in warfarin recipients (Elbe and Chang 2005; Guay 2005). Pending additional information, patients receiving long-term warfarin therapy in whom moxifloxacin is to be used should be monitored for changes in INR. Moxifloxacin does not significantly affect low-dose oral contraceptive or digoxin pharmacokinetics (Guay 2005). Unlike the case with ciprofloxacin, norfloxacin, levofloxacin, and gatifloxacin, probenecid does not significantly alter the systemic pharmacokinetics of moxifloxacin (Guay 2005).

Like all quinolones, moxifloxacin is susceptible to interactions with multivalent cations, wherein the reductions in bioavailability may be clinically-relevant and lead to a loss of therapeutic benefit. For example, calcium carbonate or calcium lactate-gluconate given immediately before and 12 h and 24 h after single-dose moxifloxacin resulted in a mean 15% reduction in C_{max} ($p \leq 0.05$) and a mean 2% reduction in AUC ($p = NS$) (Guay 2005). Simultaneous administration of single-dose ferrous sulfate lead to mean reductions of 59 and 39% in single-dose moxifloxacin C_{max} and AUC, respectively (both, $p \leq 0.05$) (Guay 2005). Single-dose magnesium-aluminum antacid administered simultaneously with single-dose moxifloxacin resulted in mean 61% and 59% reductions in C_{max} and AUC, respectively (both, $p \leq 0.05$). When the antacid administration was delayed until 2 h after moxifloxacin administration, the mean 7% reduction in C_{max} was non-significant but the mean 26% reduction in AUC was significant ($p \leq 0.05$). Even administering the antacid 4 h before moxifloxacin administration still resulted in a significant reduction in quinolone AUC (mean 23%, $p \leq 0.05$) although the mean 1% fall in C_{max} was not (Guay 2005). Sucralfate administered simultaneously with and then 5 h, 10 h, 15 h, and 24 h following single-dose moxifloxacin administration resulted in mean 71% and 60% reductions in quinolone C_{max} and AUC, respectively (both, $p \leq 0.05$) (Guay 2005). Ranitidine, a histamine-2 receptor antagonist, does not interact with moxifloxacin (2 studies) and can be recommended as a noninteracting antiulcer therapy alternative to sucralfate and antacids (Guay 2005).

Pharmacodynamic drug–drug interactions

The only potentially clinically-relevant pharmacodynamic drug–drug interaction with moxifloxacin involves additive electrophysiological effects with other drugs that can also prolong the QT_c interval on the electrocardiogram (Table 5) (Guay 2005). Drugs which prolong cardiac repolarization

Table 5 Drugs prolonging the QT_c interval that may potentially interact pharmacodynamically with moxifloxacin. Modified from Guay 2005

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- Amiodarone (rare)
 - Bepridil
 - β -blockers (rare)
 - Chloroquine
 - Dofetilide
 - Disopyramide
 - Encainide
 - Flecainide
 - Halofantrine
 - Ibutilide
 - Lidocaine (rare)
 - Lidoflazine
 - Macrolides (erythromycin, clarithromycin, spiramycin)
 - Mexiletine (rare)
 - Pentamidine
 - Phenothiazines
 - Procainamide
 - Quinidine
 - Sotalol
 - Tricyclic antidepressants
-

may, on rare occasions, be associated with the development of polymorphous ventricular tachycardia (“torsades de pointes”) which, in turn, may degenerate into ventricular fibrillation. Quinolones cause a drug-specific, dose-dependent prolongation of QT_c interval by inhibiting outward potassium currents in myocytes. In numerous in vitro models examining the mechanism(s) underlying this arrhythmogenic effect, sparfloxacin has been more potent than moxifloxacin (= grepafloxacin) which, in turn, has been more potent than the other tested quinolones (Guay 2005). In in vivo (animal) models, sparfloxacin again was most potent followed by the trio of moxifloxacin–gatifloxacin–grepafloxacin (latter agent has been withdrawn from the market) (Guay 2005). Concentration–response relationships have been demonstrated in both in vitro and in vivo preclinical models (Chen et al 2005).

In one healthy volunteer study, single 400 mg and 800 mg oral doses of moxifloxacin caused mean \pm SD $4.0\% \pm 5.1\%$ and $4.5\% \pm 3.8\%$ QT_c interval prolongation at rest compared with baseline, respectively (both, $p \leq 0.05$). Significant QT_c interval prolongation occurred at all heart rates and across the entire RR interval range (400–1000 msec). There were no gender-dependent differences in results. The correlation of moxifloxacin plasma concentrations and QT interval was significant but weak ($r = 0.35$) (Guay 2005).

Only two comparative studies of the effect of quinolones on QT_c intervals have been published. In the first, single

oral doses of levofloxacin (1000 mg), ciprofloxacin (1500 mg) and moxifloxacin (800 mg) were evaluated in a placebo-controlled, crossover trial in healthy volunteers. Mean QT and QT_c interval prolongation was significantly greater for moxifloxacin compared with placebo for all end points, but it was generally not for the other two quinolones. The proportion of subjects with QT_c interval prolongation of 30 msec. or higher was greater with moxifloxacin (72%–81%) compared with levofloxacin (33%–38%) and ciprofloxacin (34%–40%) (Guay 2005). In the second, 13 healthy volunteers received three 7-day regimens in random order: ciprofloxacin 500 mg twice daily, levofloxacin 500 mg once daily, and moxifloxacin 400 mg once daily. Washout periods between treatments were one week in length. Twelve-lead electrocardiograms were obtained before, 2 h after the first dose, and at the end of each regimen. At the end of 7 days, moxifloxacin prolonged QTc by a mean of 6 msec compared with baseline ($p=0.022$) and a mean of 11 msec from the 2 h baseline value ($p=0.003$). Ciprofloxacin and levofloxacin had no significant effect on QTc. No quinolone had a significant effect on QT dispersion, a parameter felt to be a more selective marker for risk of polymorphous ventricular tachycardia (Tsikouris et al 2006). Further studies of QT dispersion, especially in patients receiving quinolone therapy, with/without concurrent use of other drugs which also prolong QTc, are warranted.

The lack of multiple dose studies and well-done epidemiologic studies do not allow an assessment of the clinical relevance of the above-cited findings. In a recent randomized trial comparing the cardiac safety of IV/oral moxifloxacin and levofloxacin in elderly patients hospitalized for community-acquired pneumonia, the two agents had similar cardiac rhythm safety profiles (Morganroth et al 2005). However, it is prudent to use caution when using moxifloxacin (and other quinolones) in patients already receiving potentially arrhythmogenic drugs (Table 5) (Guay 2005). Similarly, caution is warranted when use is contemplated in patients with abnormal pretreatment QT_c intervals, electrolyte abnormalities (especially hypokalemia, hypomagnesemia, rarely hypocalcemia), starvation/liquid protein fast diets, and prior/current history of coronary artery disease or arrhythmias.

Dosing

Moxifloxacin is available as 400 mg oral tablets and premixed moxifloxacin 400 mg in 250 mL 0.8% sodium chloride IV bags (Anonymous 2005). For SSSIs, the recommended daily dose is 400 mg and the recommended

durations of therapy are 7 days (uncomplicated infections) and 7–21 days (complicated infections). Oral doses of moxifloxacin should be administered at least 4 h before or 8 h after magnesium/aluminum antacids, sucralfate, metal cations (eg, iron), multivitamin + mineral supplements (especially with zinc), and didanosine chewable/buffered tablets or pediatric powder for solution (Anonymous 2005). No dosage adjustment is needed with any level of renal impairment or mild or moderate (Child-Pugh Class A or B) hepatic impairment (Anonymous 2005). In severe (Child-Pugh Class C) hepatic impairment, there are no data to guide the clinician (Anonymous 2005).

Conclusions

Optimal therapy for SSSIs requires careful patient evaluation, including obtaining a thorough medical and social history, performing a meticulous examination of the lesion(s), and examination of Gram-stained smears of lesion exudates. Early empirical antimicrobial therapy is the next step after obtaining culture specimens, with subsequent tailoring of therapy based on culture and sensitivity results. Local measures, including debridement, are important adjuncts to antimicrobial therapy. Selection of empiric therapy for SSSIs depends on a number of factors, including type of infection (uncomplicated vs complicated), location of acquisition (community versus hospital), and local sensitivity patterns for the commonest dermatologic pathogens.

Older quinolones have been demonstrated to be efficacious in the treatment of uncomplicated and complicated SSSIs over the past 20 years (Blondeau 2002; Sable and Murakawa 2003). In addition, more limited data support the efficacy of the newer quinolones in the treatment of uncomplicated SSSIs (gatifloxacin, levofloxacin 500 mg/d, and moxifloxacin) (Leal del Rosal, Fabian, et al 1999; Leal de Rosal, Martinez, et al 1999; Parish et al 2000; Raghavan and Linden 2004). To these data may be added those documenting the efficacy of high-dose levofloxacin (750 mg/d) and moxifloxacin in the treatment of complicated SSSIs (Raghavan and Linden 2004; Anonymous 2005).

What have other reviews recently said regarding the role of quinolones in the treatment of SSSIs? In a recent review of the diagnosis and treatment of facial bite wounds, moxifloxacin was felt to be a reasonable monotherapy for infected human facial bite wounds, especially in patients who are penicillin-allergic. The suggested duration of a prophylactic regimen ranged from 3–5 days (10–14 days if bone was involved). For treatment, if bones or joints were

involved, a duration of 21+ days was recommended (Stefanopoulos and Tarantzopoulou 2005).

In a review of the role of quinolones in the treatment of SSSIs, Blondeau felt that both older and newer quinolones had roles to play. The older ciprofloxacin-type quinolones were recommended only in SSSIs where Gram-negative aerobic bacilli were known pathogens, adding clindamycin or metronidazole in suspected mixed infections. The newer quinolones (including moxifloxacin) were recommended in SSSIs where non-pseudomonal Gram-negative aerobic bacilli were known pathogens, where there was a mixed infection with anaerobes within the quinolone's spectrum of activity, where non-methicillin-resistant *S. aureus* gram-positive aerobes were involved, and where Gram-positive and Gram-negative aerobic pathogens were coexisting (Blondeau 2002).

The first organization-based guidelines for the diagnosis and management of SSSIs were published by IDSA in November 2005 (Stevens et al 2005). Quinolones are mentioned in the context of several general and organism-specific infections. Quinolones are one of many empirical choices in human and animal bite wounds, especially in patients with severe penicillin allergies. Ciprofloxacin, gatifloxacin, and moxifloxacin with/without clindamycin or metronidazole are those specifically mentioned. Again, quinolones are one of many empirical choices in SSSIs in the immunocompromised host. A quinolone (probably ciprofloxacin) plus an extended-spectrum β -lactam is the specific quinolone mentioned. Quinolones are one of several choices for the empiric management of each of three defined types of surgical wound infections. In community-acquired mixed necrotizing fasciitis, one option is a combination of ciprofloxacin plus a β -lactam- β -lactamase inhibitor. In SSSIs due to community-acquired MRSA, the newer quinolone group (including moxifloxacin) is one option (author's comment: based on 20 years of experience with quinolones in infections due to MRSA, the likelihood of the development of resistance to quinolones during such use is quite high. caution is warranted). Lastly, in infected wounds after intestinal or genital tract surgeries, a combination of a quinolone plus one of clindamycin/metronidazole/chloramphenicol/ β -lactam- β -lactamase inhibitor is one option. Quinolones are mentioned in the context of the patient with severe penicillin allergies. In cutaneous anthrax, ciprofloxacin is the drug-of-choice (newer quinolones are also considered likely effective). In erysipeloid, quinolones are options only in patients with severe penicillin allergies. Lastly, among many options,

levofloxacin and ciprofloxacin are considered options for tularemia but only in mild to moderate illness.

Evolving resistance trends, especially amongst staphylococci and enterococci, and sporadic intolerance to conventional β -lactam therapy have led to the need for novel options with proven efficacy and tolerability. Moxifloxacin is comparable in both efficacy and tolerability with conventional agents for SSSIs and is also effective against many organisms resistant to these agents (exception: methicillin-resistant staphylococci). It also possesses activity against atypical mycobacteria associated with SSSIs (moxifloxacin may develop into a first-line therapy for these types of SSSIs but much work remains to be done before this can be recommended). Despite its proven activity against dermatologic pathogens, one could argue that its use be carefully considered and, in general, restricted to serious, life-threatening infections caused by resistant pathogens or those patients with serious intolerances to conventional therapy. In this way, the development and progression of resistance might be blunted and its "lifespan" as an antimicrobial for dermatologic infections prolonged.

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