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In vitro activity of moxifloxacin against common clinical bacterial isolates in Taiwan

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The *in vitro* antimicrobial activities of moxifloxacin were compared with 7 other antimicrobial agents. A total of 707 isolates of 11 common pathogenic bacteria were collected from the National Taiwan University Hospital; antimicrobial activities against these isolates were evaluated by minimum inhibitory concentration using an agar-dilution method. Most common pathogenic bacteria were susceptible to moxifloxacin, including methicillin-susceptible and -resistant *Staphylococcus aureus*, methicillin-susceptible and -resistant *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Enterococcus faecalis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. For many of these bacterial species, moxifloxacin was the most active antimicrobial agent compared with the third- and fourth- generation cephalosporins, carbapenems, monobactam, and other quinolones. Some strains of methicillin-resistant *S. aureus* and methicillin-resistant *S. epidermidis* demonstrated very low levels of minimum inhibitory concentration for moxifloxacin, suggesting the potential application of the drug to treat some drug-resistant gram-positive bacterial infections. Moxifloxacin was less active against *P. aeruginosa*, but was more active against *S. maltophilia* when compared with other fluoroquinolones. In conclusion, moxifloxacin exhibits an increased potency against gram-positive bacteria as compared with other tested antimicrobial agents, while preserving excellent activity against gram-negative bacteria. The drug appears to be a promising agent expressing activity against a wide variety of bacteria in Taiwan.

Key words: Antimicrobial activity, fluoroquinolones, minimum inhibitory concentration, moxifloxacin

Moxifloxacin is a recently developed 8-methoxy-fluoroquinolone that has a broader antibacterial spectrum than other previously developed quinolones [1]. In addition to an activity against gram-negative organisms equivalent to other fluoroquinolones, moxifloxacin has prominent bactericidal effects against gram-positive organisms, atypical pathogens, and anaerobes [2-4].

The *in vitro* and *in vivo* antimicrobial activity of moxifloxacin has already been extensively studied in many Western countries and has shown excellent activity against most clinically important pathogens [2-6]. In areas such as Taiwan where quinolones are widely used and the prevalence of quinolone-resistant bacteria is high, the activity of this new 8-methoxyfluoroquinolone has not yet been evaluated. Previous studies have showed that cross-antimicrobial-resistance to some of the newly developed antimicrobial agents, such as macrolides and fluoroquinolones, may exist even before the commercial launch of the drugs, particularly in geographical areas exhibiting a high prevalence of antimicrobial-resistance [7,8]. This study aimed to evaluate the *in vitro* antimicrobial activity of moxifloxacin, in comparison with 7 other broad-spectrum antimicrobial agents, against 11 relatively common pathogenic bacteria isolated from patients in Taiwan.

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Materials and Methods

Bacterial isolates

A total of 707 isolates of 11 common pathogenic bacteria collected at the National Taiwan University Hospital during 1998 and 1999 were used in this study. The tested bacteria included *Staphylococcus aureus* (118 isolates), *Staphylococcus epidermidis* (118), *Enterococcus faecalis* (51), *Streptococcus pneumoniae* (42), *Escherichia coli* (60), *Klebsiella pneumoniae* (60), *Enterobacter cloacae* (60), *Pseudomonas aeruginosa* (60), *Acinetobacter baumannii* (57), *Burkholderia cepacia* (21), and *Stenotrophomonas maltophilia* (60).

The bacteria were isolated from various clinical specimens and were selected randomly. The specimens were collected from both outpatients and inpatients from various departments and wards of the hospital. Duplicated isolate from the same patient or replicated strains from a single outbreak were not included.

Antimicrobial agents

Moxifloxacin and 7 other antimicrobial agents were supplied by individual pharmaceutical companies in the form of standard reference powders for laboratory use. Moxifloxacin and ciprofloxacin were obtained from Farbenfabriken Bayer GmbH (Leverkusen, Germany), meropenem from Sumitomo Pharmaceuticals (Osaka, Japan), cefepime and aztreonam from Bristol-Myers Squibb (Syracuse, NY, US), imipenem from Merck Sharp and Dohme (Rahway, NJ, US), flomoxef from Shionogi Pharmaceuticals (Osaka, Japan), trovafloxacin from Pfizer (Groton, CT, US), and ceftazidime from Glaxo-Wellcome (Greenford, UK).

Antimicrobial susceptibility testing

The minimum inhibitory concentration (MIC) corresponding to each antimicrobial agent for the tested bacterial isolates was determined by an agar-dilution method as described by the National Committee for Clinical Laboratory Standards [9]. Inocula of 10^4 colony-forming units of aerobic bacteria were inoculated onto the Mueller-Hinton agar plates (Becton-Dickinson, Cockeysville, MD, US) containing a series of 2-fold dilutions of tested antimicrobial agents using the Steers' replicator. Five percent of sheep blood was added to the agar when *S. pneumoniae* was tested. Following the inoculation of agar plates with bacteria and antimicrobial agent, the agar plates were incubated at 35°C in 5% CO_2 for 18 to 20 h. The MIC level was read as the lowest concentration of the antimicrobial agent that completely inhibited the growth of bacteria on the agar plate. Proposed MIC breakpoints for moxifloxacin and trovafloxacin that indicate susceptibility and resistance were defined as ≤1 and ≥4 μg/mL, respectively [1,10,11]. The concentration of antimicrobial agents tested for all bacteria ranged from 0.03 to 256 μg/mL. *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619 were used as controls.

Results

The MIC levels corresponding to moxifloxacin and the comparative drugs against the tested gram-positive bacteria are shown in Table 1. Methicillin-sensitive *S. aureus* (MSSA) demonstrated good susceptibility to all tested agents except ceftazidime. Moxifloxacin, trovafloxacin, and carbapenem (imipenem and meropenem) exhibited a more pronounced efficacy against MSSA than ciprofloxacin and other cephalosporins. Both the MIC_{50} and MIC_{90} for moxifloxacin and trovafloxacin were 8-fold lower than ciprofloxacin and substantially lower than the cephalosporins. The MIC levels corresponding to moxifloxacin and trovafloxacin for the tested strains were all ≤1 μg/mL. Although most of the tested antimicrobial agents, which included ciprofloxacin and carbapenem, revealed poor activity against methicillin-resistant *S. aureus* (MRSA), some strains of MRSA were susceptible to moxifloxacin and trovafloxacin. The MIC_{50} and MIC_{90} levels corresponding to the activity of moxifloxacin against MRSA were 1 and 2 μg/mL, respectively.

Results for *S. epidermidis* were similar to *S. aureus*, although the MIC levels were generally higher for *S. epidermidis*. Methicillin-sensitive *S. epidermidis* (MSSE) demonstrated relatively good susceptibility to all tested agents except ceftazidime. Moxifloxacin and trovafloxacin were as active as ciprofloxacin and other agents. Both the MIC_{50} and MIC_{90} for moxifloxacin and trovafloxacin were 2- to 4-fold lower than for ciprofloxacin and carbapenam, and 16- to 32-fold lower than the third- and fourth-generation cephalosporins. All of the tested antimicrobial agents demonstrated relatively high MIC levels against methicillin-resistant *S. epidermidis* (MRSE), although there were some strains of *S. epidermidis* that revealed low MIC levels for both moxifloxacin and trovafloxacin (MIC ≤0.03 μg/mL).

The susceptibilities of *S. pneumoniae* to fluoroquinolones were not as impressive as methicillin-sensitive staphylococci, although moxifloxacin and trovafloxacin were the most effective antimicrobial agents compared with any other antimicrobial agents. Some strains of *S. pneumoniae* were highly resistant to ciprofloxacin and flomoxef (MIC ≤256 μg/mL) but susceptible to moxifloxacin and trovafloxacin (MIC ≤1 μg/mL).

All cephalosporins, which included the fourth-generation cephalosporin cefepime, exhibited poor activities against *E. faecalis*. Although some isolates of *E. faecalis* were fairly susceptible to fluoroquinolones, most of them exhibited a relatively high MIC level (MIC_{50} = 4 μg/mL). Less than half of the bacterial strains used in this study were susceptible to fluoroquinolones; the MIC_{90} levels corresponding to trovafloxacin, ciprofloxacin, and moxifloxacin were 16, 64, and 128 μg/mL, respectively. *E. faecalis* was resistant to all carbapenems and cephalosporins.

Table 1. Comparative *in vitro* activity of moxifloxacin and other antimicrobial agents against gram-positive bacteria

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/mL)			Susceptible rate (%)
		Range	MIC_{50}	MIC_{90}	
Methicillin-susceptible *Staphylococcus aureus* (58)	Moxifloxacin[a]	≤0.03-1	≤0.03	0.06	100
	Trovafloxacin[a]	≤0.03-1	≤0.03	0.06	100
	Ciprofloxacin[a]	0.125-2	0.25	0.5	98.3
	Ceftazidime[b]	1-16	4	8	96.6
	Cefepime[b]	0.5-4	1	2	100
	Flomoxef[b]	0.25-4	0.5	1	100
	Imipenem[c]	≤0.03-0.06	≤0.03	0.06	100
	Meropenem[c]	≤0.03-0.25	0.06	0.125	100
Methicillin-resistant *Staphylococcus aureus* (60)	Moxifloxacin[a]	≤0.03-4	1	2	76.6
	Trovafloxacin[a]	≤0.03-2	1	2	76.6
	Ciprofloxacin[a]	0.25-32	8	16	13.3
	Ceftazidime	16-≥256	≥256	≥256	–
	Cefepime	4-≥256	≥256	≥256	–
	Flomoxef	4-≥256	64	128	–
	Imipenem	0.25-32	8	32	–
	Meropenem	0.25-32	16	32	–
Methicillin-susceptible *Staphylococcus epidermidis* (58)	Moxifloxacin[a]	≤0.03-16	0.06	0.125	94.8
	Trovafloxacin[a]	≤0.03-16	0.06	0.25	94.8
	Ciprofloxacin[a]	0.125-32	0.25	1	94.8
	Ceftazidime[b]	2-≥256	4	32	72.4
	Cefepime[b]	0.25-16	1	4	94.8
	Flomoxef[b]	0.25-16	1	4	89.7
	Imipenem[c]	≤0.03-1	0.06	0.5	100
	Meropenem[c]	≤0.03-4	0.25	1	100
Methicillin-resistant *Staphylococcus epidermidis* (60)	Moxifloxacin[a]	≤0.03-16	0.5	8	60.0
	Trovafloxacin[a]	≤0.03-128	0.5	16	51.6
	Ciprofloxacin[a]	0.125-≥256	1	128	31.6
	Ceftazidime	4-≥256	16	128	–
	Cefepime	1-≥256	8	128	–
	Flomoxef	1-64	4	32	–
	mipenem	0.125-64	2	32	–
	Meropenem	0.25-128	4	64	–
Streptococcus pneumoniae (42)	Moxifloxacin[a]	≤0.03-128	0.25	4	88.1
	Trovafloxacin[a]	≤0.03-32	0.125	0.5	92.9
	Ciprofloxacin	0.06-≥256	2	128	–
	Ceftazidime	≤0.03-128	4	16	–
	Cefepime[d]	≤0.03-16	1	2	45.5
	Flomoxef[d]	≤0.03-≥25	2	32	35.7
	Imipenem[e]	≤0.03-1	0.125	0.5	61.9
	Meropenem[f]	≤0.03-4	0.25	1	73.8
Enterococcus faecalis (51)	Moxifloxacin[a]	0.125-≥256	4	128	45.0
	Trovafloxacin[a]	0.125-128	4	16	49.0
	Ciprofloxacin[a]	0.5-64	4	64	41.2
	Ceftazidime	16-≥256	≥256	≥256	–
	Cefepime	8-≥256	128	≥256	–
	Flomoxef	32-≥256	128	≥256	–
	Imipenem	0.5-16	1	2	–
	Meropenem	1-16	4	8	–

Abbreviation: MIC = minimum inhibitory concentration

The MIC breakpoints for susceptible isolates were [a]≤1 μg/mL; [b]≤8 μg/mL; [c]≤4 μg/mL; [d]≤0.5 μg/mL; [e]≤0.12 μg/mL; and [f]≤0.25 μg/mL.

The MIC levels corresponding to moxifloxacin and comparative drugs against the tested gram-negative bacteria are shown in Table 2. All the antimicrobial agents tested revealed good activity against isolates of *E. coli* and *K. pneumoniae*, representatives of *Enterobacteriaceae*, although some strains of *K. pneumoniae* showed a pronounced resistance to ceftazidime. The fluoroquinolones were generally less active than the carbapenems and cephalosporins against *Enterobacteriaceae* (Table 2). The MIC_{50} for these antimicrobial agents were similar except the fluoroquinolones, which revealed a MIC_{90} 4- to 32-fold greater than other antimicrobial agents. Overall, 20% to 30% of the isolates were quite resistant to fluoroquinolones such as moxifloxacin. Fluoroquinolones exhibited an activity at least as good as carbapenem and better than the third-generation cephalosporins against *E. cloacae*. The MIC_{50} and MIC_{90} of moxifloxacin against *E. cloacae* were 0.125 and 1 μg/mL, respectively.

For *P. aeruginosa*, the new fluoroquinolones were as active as carbapenam and antipseudomonal cephalosporins. Although all antipseudomonal agents exhibited relatively good activity against *P. aeruginosa*, some of the tested bacterial strains were β-lactam resistant. A few strains of *P. aeruginosa* were resistant to all tested drugs, with moxifloxacin being the least potent agent among the tested antipseudomonal agents. The MIC levels of the activity of moxifloxacin against *P. aeruginosa* were 4- and 8-fold higher than for trovafloxacin and ciprofloxacin.

The fluoroquinolones were generally less active against *A. baumannii* than the carbapenems but more active than the cephalosporins. Among the fluoroquinolones, trovafloxacin exhibited a 2-fold lower MIC than moxifloxacin and 4-fold lower MIC than ciprofloxacin. For *B. cepacia*, meropenem was the most active agent, revealing a relatively high antimicrobial efficacy in more than 90% of the tested strains. Other tested antimicrobial agents, including moxifloxacin, were much less active than meropenem, although moxifloxacin was more potent than ciprofloxacin (susceptibility, 47.6% and 38.1%, respectively). Strains of *S. maltophilia* were susceptible to moxifloxacin, with MIC levels generally lower than 1 μg/mL. The MIC levels for moxifloxacin tested on *S. maltophilia* were 4- to 8-fold lower than ciprofloxacin and trovafloxacin. The β-lactams and carbapenems appeared to be compromised against *S. maltophilia*.

Discussion

This study showed that moxifloxacin expresses a very pronounced antimicrobial activity against a variety of pathogenic bacteria commonly isolated in Taiwan. The potency of moxifloxacin was similar to a number of newly developed fluoroquinolones, including trovafloxacin [6]. Moxifloxacin was generally more active than ciprofloxacin against both gram-positive and gram-negative bacteria except for *P. aeruginosa*, for which the contrary was the case. Results of this study agree with reports from other Western countries [10, 12-17].

In this study, moxifloxacin has revealed an enhanced activity against all gram-positive cocci, including staphylococci and pneumococci, compared with ciprofloxacin. The relative activity of moxifloxacin and trovafloxacin against pneumococci was more pronounced than the third- and fourth-generation cephalosporins and carbapenems. Although the newly developed fluoroquinolones, moxifloxacin, and trovafloxacin demonstrated a more notable *in vitro* activity against methicillin-resistant staphylococci than ciprofloxacin, it is not known whether this greater activity can be maintained for a prolonged period of time. From previous experience with the antimicrobial efficacy of fluoroquinolones other than moxifloxacin and trovafloxacin, the anti-MRSA activity of fluoroquinolones diminished quickly after the drug was clinically launched [18]. It is likely that MRSA isolates will become resistant to moxifloxacin and trovafloxacin once these drugs become widely used in clinical practice. More than half of *E. faecalis* isolates in this study were resistant to ciprofloxacin, and were also moxifloxacin- and trovafloxacin-resistant; this conforms with results from other studies [10,19].

It has been reported that moxifloxacin is almost as active an antimicrobial agent as ciprofloxacin against gram-negative bacteria except for *P. aeruginosa* [3,6, 20], although more than 80% of *P. aeruginosa* isolates tested in this study were susceptible to moxifloxacin. In contrast to results of other reports [3,6,14,20,21], the MIC levels for *E. coli* and *K. pneumoniae* for fluoroquinolones were much higher than for other non-quinolone antimicrobials in this study. Nearly one third of the *Enterobacteriaceae* strains tested in this study were resistant to fluoroquinolones, suggesting a high prevalence of quinolone-resistant bacterial strains in Taiwan, as shown in an earlier review [7].

A. baumannii, *B. cepacia*, and *S. maltophilia* have emerged as important causes of morbidity and mortality among hospitalized patients in Taiwan [22-24]. The increasing resistance of these bacterial species has hindered desirable therapeutic management of patients infected with such bacterial agents. Results of this study showed a more substantial activity of moxifloxacin

Table 2. Comparative *in vitro* activity of moxifloxacin and other antimicrobial agents against gram-negative bacteria

Microorganism (no. of isolates)	Antimicrobial agent	MIC (μg/mL)			Susceptible rate (%)
		Range	MIC_{50}	MIC_{90}	
Escherichia coli (60)	Moxifloxacin[a]	≤0.03-16	0.125	8	71.7
	Trovafloxacin[b]	≤0.03-32	0.125	16	71.7
	Ciprofloxacin[b]	≤0.03-64	0.06	16	71.7
	Ceftazidime[b]	≤0.03-32	0.125	2	96.7
	Cefepime[b]	≤0.03-8	≤0.03	0.25	100
	Flomoxef[b]	≤0.03-2	0.06	0.125	100
	Imipenem[c]	≤0.03-1	0.125	0.25	100
	Meropenem[c]	≤0.03-0.5	0.06	0.125	100
Klebsiella pneumoniae (60)	Moxifloxacin[a]	≤0.03-8	0.06	4	80.0
	Trovafloxacin[a]	≤0.03-16	0.06	8	78.3
	Ciprofloxacin[a]	≤0.03-16	≤0.03	4	81.7
	Ceftazidime[b]	0.06-≥256	0.125	128	73.3
	Cefepime[b]	≤0.03-64	≤0.03	4	93.3
	Flomoxef[b]	≤0.03-8	0.06	0.25	100
	Imipenem[c]	0.06-1	0.25	0.5	100
	Meropenem[c]	≤0.03-1	≤0.03	0.25	100
Enterobacter cloacae (60)	Moxifloxacin[a]	≤0.03-8	0.125	1	90.0
	Trovafloxacin[a]	≤0.03-8	0.6	4	90.0
	Ciprofloxacin[a]	≤0.03-8	0.6	0.5	90.0
	Ceftazidime[b]	0.125-≥256	16	128	35.0
	Cefepime[b]	≤0.03-≥256	1	4	96.7
	Flomoxef[b]	0.5-≥256	64	≥256	26.6
	Imipenem[c]	0.125-64	1	4	90.0
	Meropenem[c]	≤0.03-16	0.06	1	95.0
Pseudomonas aeruginosa (60)	Moxifloxacin[a]	0.25-8	1	2	81.7
	Trovafloxacin[a]	0.06-8	0.25	0.5	95.0
	Ciprofloxacin[a]	0.06-4	0.125	0.25	95.0
	Ceftazidime[b]	0.5-≥256	2	16	91.7
	Cefepime[b]	0.5-≥256	2	8	90.0
	Flomoxef[b]	≥256	≥256	≥256	–
	Imipenem[c]	0.5-32	1	4	93.3
	Meropenem[c]	≤0.03-16	0.5	2	96.7
Acinetobacter baumannii (57)	Moxifloxacin[a]	≤0.03-16	≤0.03	16	78.9
	Trovafloxacin[a]	≤0.03-8	≤0.03	8	77.2
	Ciprofloxacin[a]	0.06-64	0.125	32	77.2
	Ceftazidime[b]	1-128	4	128	70.2
	Cefepime[b]	0.5-128	2	128	70.2
	Flomoxef[b]	1-≥256	64	≥256	12.3
	Imipenem[c]	0.06-32	0.125	1	96.5
	Meropenem[c]	0.06-32	0.25	1	96.5
Burkholderia cepacia (21)	Moxifloxacin[a]	0.06-32	2	8	47.6
	Trovafloxacin[a]	0.125-16	1	8	57.1
	Ciprofloxacin[a]	0.125-32	2	16	38.1
	Ceftazidime[b]	1-≥256	4	128	76.2
	Cefepime[b]	1-≥256	8	≥256	61.9
	Flomoxef[b]	4-≥256	128	≥256	23.8
	Imipenem[c]	0.25-32	4	16	52.4
	Meropenem[c]	0.25-16	2	4	92.8
Stenotrophomonas maltophilia (60)	Moxifloxacin[a]	0.06-4	0.5	1	90.0
	Trovafloxacin[a]	≤0.03-16	0.5	4	53.3
	Ciprofloxacin[a]	0.5-32	2	8	38.3
	Ceftazidime[b]	1-≥256	32	128	23.3
	Cefepime[b]	2-128	32	64	25.0
	Flomoxef[b]	16-≥256	≥256	≥256	–
	Imipenem[c]	32-≥256	≥256	≥256	–
	Meropenem[c]	32-≥256	128	≥256	–

Abbreviation: MIC = minimum inhibitory concentration
The MIC breakpoints for susceptible isolates were [a]≤1 μg/mL; [b]≤8 μg/mL; and [c]≤4 μg/mL.

against *S. maltophilia* and *A. baumannii* than that reported in other studies [12,13,20,21], although the activity of moxifloxacin appears to be less pronounced against *B. cepacia*. More technically advanced quinolones such as moxifloxacin have been suggested to be the agent of choice for *S. maltophilia* infections [20,21], and the combined therapy of trovafloxacin and antipseudomonal cephalosporins has exhibited a synergistic activity against *S. maltophilia*, and thus could be used to avoid the emergence of antibacterial resistance [25]. The fluoroquinolones were shown to be less active against *A. baumannii* and *B. cepacia*, they should therefore only be used as an alternative regimen when microbiological susceptibilities were clearly documented.

The optimization of the fluoroquinolone structure has led to the development of the new-generation fluoroquinolones over recent decades [1,3,17,21]. Based on the reported *in vitro* activity tests of this drug family, there appears to be little difference in drug efficacy to warrant the choice of any one advanced fluoroquinolones over any other [14,15,20]. Recent problems with toxicity have resulted in the withdrawal of some quinolones from clinical use; trovafloxacin being an example. The future role of moxifloxacin among the remaining agents in this family of drugs will depend on further clinical efficacy evaluation and post-marketing safety profile studies [26].

In conclusion, the newly developed fluoroquinolone, moxifloxacin, demonstrates an increased potency against gram-positive bacteria, while maintaining excellent activity against gram-negative organisms when compared with other members of the fluoroquinolone family and predecessor antimicrobial agents. The *in vitro* activity of moxifloxacin against most clinically isolated pathogens in Taiwan is similar to that reported in Western countries [12-17], even though Taiwan seems to demonstrate a more pronounced rate of ciprofloxacin resistance than many Western countries. Among the suite of broad-spectrum antimicrobial agents that were tested in this study, moxifloxacin is the most promising antimicrobial agent against methicillin-resistant staphylococci, pneumococci, and *S. maltophilia*. Although this study has revealed that the development of microbial resistance to moxifloxacin was less pronounced [3], the appropriate antimicrobial use of the new fluoroquinolones for patient infection control should be encouraged to prevent the emergence of antimicrobial-resistant bacterial strains.

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