In vitro Activity of Moxifloxacin against Local Bacterial Isolates

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Abstract

***Introduction**: The emergence of resistance to common antimicrobials in bacteria has been increasingly reported in various countries. Empirical antimicrobial therapy of various infections would therefore need to be reviewed. The introduction of new fluoroquinolones has created an interest in the use of these as possible agents in the empirical treatment of respiratory tract infections. **Materials and Methods**: The minimum inhibitory concentration (MIC) of the new fluoroquinolone, moxifloxacin, against 400 clinical bacterial isolates was determined by the E-test method. **Results**: All* **Streptococcus pneumoniae** *isolates (penicillin sensitive or resistant) were susceptible to moxifloxacin. Similarly, both β-lactamase and non β-lactamase producing* **Haemophilus influenzae** *and* **Moraxella catarrhalis** *isolates were susceptible to moxifloxacin. As for* **Enterobacteriaceae**, *88.6% of the isolates tested were susceptible to moxifloxacin with MIC <8 mg/L, but resistance was noted for some of* **Proteus mirabilis, Klebsiella** *spp. and* **Escherichia coli**. *Enterococci and* **Acinetobacter baumannii** *were resistant to moxifloxacin, whilst the anaerobes tested were susceptible to moxifloxacin. **Conclusion**: Moxifloxacin has good* **in vitro** *activity against common organisms associated with community and nosocomial infections, with the exception of enterococci, methicillin-resistant* **Staphylococcus aureus** *and ciprofloxacin-resistant gram-negative bacteria. There was good anti-anaerobic activity against* **Bacteroides fragilis** *and* **Clostridium** *spp. Results of this study are consistent with other similar published* **in vitro** *studies.*

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***Key words: Fluoroquinolone, Respiratory tract infection,* Streptococcus pneumoniae**

Introduction

The introduction of newer generation fluoroquinolones has generated great interest, especially in this era of increasing antimicrobial resistance. Among gram-positive resistant bacteria, the most important are methicillin-resistant *Staphylococcus aureus* (MRSA), β-lactam resistant and multidrug-resistant *Streptococcus pneumoniae*, and vancomycin-resistant enterococci. Important gram-negative resistant bacteria include extended-spectrum β-lactamase producing *Klebsiella pneumoniae* and *Escherichia coli*, multidrug-resistant *Acinetobacter baumannii* and *Stenotrophomonas maltophilia.*

Amongst the community-acquired pathogens, drug-resistant *S. pneumoniae* has become increasingly prevalent throughout the Asia Pacific region over the past few years.[1] As resistance rates to standard β-lactams and macrolides increase in some areas, empirical antimicrobial choices for the therapy of respiratory tract infections should be reviewed.

Fluoroquinolones, e.g. ciprofloxacin, have become one of the common alternatives in the treatment of infectious diseases because of their wide antibacterial spectrum and good oral bioavailability. The recent availability of the newer generation of fluoroquinolones has helped to make yet another class of compounds available for use in the treatment of penicillin-resistant *S. pneumoniae*. These include levofloxacin (Cravit®), gatifloxacin (Tequin®) and moxifloxacin (Avelox®) in Singapore. All quinolones act by inhibiting the activities of DNA gyrase, an essential adenosine triphosphate-hydrolyzing topoisomerase, which in turn inhibits bacterial DNA replication and transcription, events that culminate in rapid cell death. Moxifloxacin is a new 8-methoxyquinolone. Chemical modifications to the core molecule has resulted in moxifloxacin possessing the following features: longer elimination half-life and thus a better dosing profile, a broader spectrum of activity against gram-positive (including resistant staphylococci), as well as gram-negative pathogens, atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp.) and anaerobes.[2]

We report an *in vitro* study on the activity of moxifloxacin against local commonly isolated bacterial pathogens.

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Materials and Methods

Collection of Clinical Strains

Four hundred clinical isolates of bacteria commonly associated with community-acquired and nosocomial infections were obtained from the microbiology laboratories of both Singapore General Hospital and KK Women's and Children's Hospital between November 1999 and June 2000. These were collected from in-patients of these two hospitals and first isolates were used to avoid duplication of strains. A breakdown of the strains showed: 40 isolates of *S. pneumoniae,* 40 *Haemophilus influenzae,* 40 *Moraxella catarrhalis,* 20 methicillin-sensitive *Staphylococcus aureus* (MSSA), 20 MRSA, 20 *S. pyogenes,* 20 *Enterococcus* spp., 20 *Serratia* spp., 20 *Enterobacter* spp., 20 *Citrobacter* spp., 20 indole positive *Proteus* spp., 20 *Proteus mirabilis,* 20 *Klebsiella* spp., 20 *Escherichia coli,* 20 *Acinetobacter baumannii,* 20 *Clostridium* spp., and 20 *Bacteroides fragilis.*

Antimicrobial Susceptibility Testing

The minimum inhibitory concentration (MIC) of moxifloxacin for all isolates and the MIC of penicillin for *S. pneumoniae* were measured by the E-test method. Quality controls were conducted weekly using ATCC 25922 *Escherichia coli,* ATCC 27853 *Pseudomonas aeruginosa,* ATCC 25923 *Staphylococcus aureus,* ATCC 49247 *H. influenzae,* ATCC 49619 *S. pneumoniae,* ATCC 10211 *H. influenzae* and ATCC 29213 *Staphylococcus aureus.* The tests were performed on Mueller-Hinton agar supplemented with 5% sheep blood for *S. pneumoniae,* haemophilus test medium (HTM) for *H. influenzae,* Wilkins Chalgren sheep blood agar for the anaerobes and Mueller-Hinton agar for the remaining isolates in accordance with the National Committee for Clinical Laboratory Standards (NCCLS). Results were interpreted in accordance with the criteria set by the NCCLS.[3]

β-lactamase Activity

This was tested for all *H. influenzae* and *M. catarrhalis* using cefinase paper discs (Baltimore Biological Laboratory, BBL).

Results

Respiratory Tract Pathogens (Table I)

Of the 40 *S. pneumoniae* isolates, 22.5% were penicillin-susceptible (PSSP, MIC of ≤0.06 mg/L), 50% penicillin-intermediate (PISP, MIC of 0.12-1.0 mg/L) and 27.5% penicillin-resistant (PRSP, MIC of ≥2.0 mg/L). Studies on the *S. pneumoniae* strains showed that they were susceptible to moxifloxacin, with MIC_{50} of 0.094 mg/L and MIC_{90} of 0.125 mg/L. The moxifloxacin activity was not affected by penicillin susceptibility as shown in Table 1.

The incidence of β-lactamase production was 20% for *H. influenzae* and 97.5% for *M. catarrhalis.* All the 20 strains of *H. influenzae* and 20 strains of *M. catarrhalis* tested were susceptible to moxifloxacin regardless of their β-lactamase activity (Table I).

Other Pathogens (Table II)

All the 20 strains of MSSA tested were susceptible to moxifloxacin (MIC range of 0.032 to 0.064 mg/L) whilst MRSA isolates appeared to be susceptible (MIC range of 1.5 to 2.0 mg/L) (Table II). All *S. pyogenese* tested were susceptible to moxifloxacin but some of the *Enterococcus* spp. were resistant to moxifloxacin (Table II).

When tested against the 140 strains of *Enterobacteriaceae,* 88.6% of the isolates were susceptible to moxifloxacin (MIC <8 mg/L) but resistance was seen in some of *Proteus mirabilis, Klebsiella* spp., *Escherichia coli* (MIC_{90} >32 mg/L) compared to that for *Serratia, Enterobacter, Citrobacter* and indole-positive *Proteus* spp. (Table II).

The anaerobes tested were susceptible to moxifloxacin (Table II).

Discussion

Resistance to a number of commonly used antimicrobials, including penicillins, cephalosporins, macrolides, tetracyclines and co-trimoxazole, is increasing in *S. pneumoniae*.[1] Data on moxifloxacin compiled from published literature clearly indicate that moxifloxacin is highly active with MIC_{90} values against *S. pneumoniae* ranging from 0.06 to 0.25 mg/L, regardless of whether strains are penicillin-susceptible, intermediate or resistant.[4-9]

Our local data for these strains showed comparable data (MIC_{90} = 0.125 mg/L). Furthermore, these reported studies showed that strains collected from hospitalised patients with invasive disease were as susceptible as strains obtained from outpatients suffering from upper or lower respiratory tract infections. Moxifloxacin has been shown to have good activity against both *H. influenzae* and *M. catarrhalis* and is unaffected by the ability to produce β-lactamase. We showed similar results in our local study and our data (MIC_{90} = 0.064 mg/L) are comparable with other published studies which showed MIC_{90} values of 0.03 to 0.06 mg/L for *H. influenzae* and 0.012 to 0.06 mg/L for *M. catarrhalis.*[4,6,7,9,10]

Although the MIC values for MRSA showed these isolates to be susceptible (MIC_{90} of 1.5 mg/L), other studies have shown that moxifloxacin is less active with MIC_{90} from 1 to 8 mg/L.[4,6,9,11]

MacGowan[12] has shown that enterococci are less susceptible to moxifloxacin than streptococci with MIC_{90} values reported to be higher for ciprofloxacin-resistant *E. faecalis* (16 mg/L) and *E. faecium* (≥2 mg/L). We did not test our enterococcal isolates against ciprofloxacin but

TABLE I: *IN VITRO* ACTIVITY OF MOXIFLOXACIN AGAINST COMMON RESPIRATORY PATHOGENS

Organism	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Streptococcus pneumoniae (40)	0.094 – 0.25	0.094	0.125
Penicillin-sensitive *S. pneumoniae* (9)	0.094 – 0.19	0.094	0.125
Penicillin-intermediate *S. pneumoniae* (20)	0.094 – 0.25	0.094	0.125
Penicillin-resistant *S. pneumoniae* (11)	0.094 – 0.125	0.094	0.125
Haemophilus influenzae (20)	0.008 – 0.094	0.023	0.064
β-lactamase positive (4)	0.023 – 0.094	0.023	0.047
β-lactamase negative (16)	0.008 – 0.064	0.023	0.047
Moraxella catarrhalis (20)	0.032 – 0.064	0.047	0.064
β-lactamase positive (19)	0.032 – 0.064	0.047	0.064
β-lactamase negative (1)	0.047	–	–

MIC: minimum inhibitory concentration

TABLE II: *IN VITRO* ACTIVITY OF MOXIFLOXACIN AGAINST NON-RESPIRATORY PATHOGENS

Organism	MIC range (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Methicillin-sensitive *Staphylococcus aureus,* MSSA (20)	0.032 – 0.064	0.047	0.064
Methicillin-resistant *S. aureus,* MRSA (20)	1.5 – 2.0	1.5	1.5
Streptococcus pyogenes (20)	0.064 – 0.19	0.125	0.19
Enterococcus spp. (20)	0.19 – >32	0.25	>32
Enterobacteriaceae (140)	0.012 – >32	0.125	>32
Serratia, Enterobacter, Citrobacter and indole positive *Proteus* spp. (80)	0.016 – >32	0.094	6
Proteus mirabilis, Klebsiella spp. and *Escherichia coli* (60)	0.094 – >32	0.19	>32
Acinetobacter baumannii (20)	0.016 – >32	0.094	>32
Bacteroides fragilis and *Clostridium* spp. (40)	0.023 – 1.5	0.125	0.5

MIC: minimum inhibitory concentration

MacGowan's finding is not surprising as cross-resistance amongst the fluoroquinolones is known to exist.

In comparison to ciprofloxacin, the newer fluoroquinolones are designed with improved potency against gram-positive pathogens, especially *S. pneumoniae,* while retaining the favourable activity against gram-negative bacteria associated with ciprofloxacin. In MacGowan's study, generally, MIC_{90} values of ≤0.25 mg/L were noted for *Serratia, Enterobacter, Citrobacter* and indole-positive *Proteus* spp., which show these organisms to be highly susceptible to moxifloxacin.

Dalhoff et al[11] showed that isolates of *Acinetobacter baumannii,* which are less susceptible to ciprofloxacin also tend to be less susceptible to moxifloxacin. This is expected as in general, there is cross resistance between ciprofloxacin and other quinolones against gram-negative bacteria. Our 20 local strains were resistant to both ciprofloxacin and moxifloxacin and had a high moxifloxacin MIC_{90} of >32 mg/L (Table II).

Until the introduction of the newer fluoroquinolones, the most serious deficiency of quinolones was their lack of anaerobic activity. Compared with ciprofloxacin, some of the newer fluoroquinolones (clinafloxacin, gatifloxacin, moxofloxacin) have significantly better *in vitro* activity against *B. fragilis.* Moxifloxacin was shown to give good susceptibility results against a wide range of anaerobes with reported MIC_{90} values of ≤0.25 mg/L for *C. perfringens, Actinomyces* spp., *Eubacterium* spp., gram-positive anaerobic cocci and *Propionibacterium* spp.; 1 to 2 mg/L for *Fusobacterium* spp., *Veillonella parvula* and *Weeksella zoohelicum*; 0.25 to 4 mg/L for *Prevotella* spp. and *B. fragilis;* and 1 to 16 mg/L for other *Bacteroides* spp.[12] Our local data showed a low MIC_{90} of 0.5 mg/L for our 40 strains of *B. fragilis* and *Clostridium* spp. (Table II).

Conclusion

Moxifloxacin has good *in vitro* activity against common organisms associated with community and nosocomial infections, with the exception of enterococci, MRSA and ciprofloxacin-resistant gram-negative bacteria. Results of this study are consistent with other similar published *in vitro* studies.[4-12] It confirmed the clinical therapeutic potential of moxifloxacin in the treatment of community-acquired infections in Singapore, especially those attributed to drug-resistant *S. pneumoniae*. Its

anti-anaerobic activity together with the activity against gram-negative bacteria makes it another useful alternative to our options in antimicrobials for the treatment of nosocomial infections.

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