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Comparative in-vitro activity of moxifloxacin, penicillin, ceftriaxone and ciprofloxacin against pneumococci isolated from meningitis

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Minimum inhibitory concentrations of penicillin, ceftriaxone, ciprofloxacin, and moxifloxacin (BAY 12-8039), a new 8-methoxyquinolone, were determined for 60 cerebrospinal fluid isolates of *Streptococcus pneumoniae* collected during January 1997–April 1998 at Italian medical centres. Three reference isolates with predetermined MIC values (two penicillin- and multidrug-resistant isolates, one uniformly susceptible to all antibiotics) were also tested with the same antibiotics. The MIC_{90} of penicillin was ≤0.03 mg/L (range ≤0.03–2 mg/L), of ceftriaxone 0.06 mg/L (range ≤0.03–0.5 mg/L), of ciprofloxacin 2 mg/L (range 0.5–8 mg/L) and of moxifloxacin 0.06 mg/L (range 0.03–0.12 mg/L). Moxifloxacin was effective against all the penicillin-resistant isolates tested, with an MIC of 0.06 mg/L. Moxifloxacin was 32-fold more active than ciprofloxacin and was not affected by penicillin and cephalosporin resistance. These results indicate that moxifloxacin could be useful for the treatment of both penicillin-sensitive and -resistant *S. pneumoniae* meningitis.

Introduction

Streptococcus pneumoniae is a notable cause of morbidity and mortality worldwide, being the leading cause of bacterial pneumonia as well as being an important cause of otitis media and meningitis. Over the past decade, there has been a dramatic increase in the prevalence of *S. pneumoniae* isolates resistant to penicillin and other antimicrobial agents,[1,2] making pneumococcal meningitis exceptionally difficult to treat. Furthermore, clinicians have very few treatment options for patient with allergy to β-lactams. For these reasons, there is an urgent need for antimicrobial agents with a different mechanism of action from β-lactams, which can be used for therapy of meningitis caused by resistant isolates or in atopic patients. Thus, a new quinolone antimicrobial agent which has potent activity against Gram-positive organisms and favourable pharmacokinetics in terms of long half-life and good cerebrospinal fluid (CSF) penetration would represent a significant therapeutic advance. One such novel fluoroquinolone is moxifloxacin (BAY 12-8039), an 8-methoxiquinolone with enhanced activity against Gram-positive bacteria.[3,4] The aim of this study was to examine the activity of moxifloxacin in comparison with penicillin G, ceftriaxone and ciprofloxacin against 60 pneumococcal isolates from patients with meningitis.

Materials and methods

Sixty *S. pneumoniae* isolates from CSF of patients with meningitis were kindly provided by Dr Annalisa Pantosti, Istituto Superiore di Sanità, Rome, Italy. The isolates were from a variety of Italian medical centres, mainly from northern regions of the country, and included three penicillin-resistant isolates. They were collected during January 1997–April 1998. Antimicrobial agents were supplied as powders of known potency, as follows: moxifloxacin and ciprofloxacin from Bayer (Leverkusen, Germany); penicillin from Sigma Chemical Co. (St Louis, MO, USA); ceftriaxone from Roche Laboratories (Nutley, NJ, USA).

MICs were determined in duplicate by the agar dilution method recommended by the National Committee for

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Clinical Laboratory Standards, with Mueller–Hinton agar (Difco Laboratories, Detroit, MI, USA) supplemented with 5% sheep blood.[5] Suspensions with a turbidity equivalent to that of a 0.5 McFarland standard were prepared by suspending growth from blood agar plates in 2 mL of Todd–Hewitt broth (Oxoid–Unipath Ltd., Basingstoke, UK). Suspensions were further diluted 1:10 to obtain a final inoculum of 10^4 cfu per spot. Plates were inoculated with a multipoint inoculator (Denley, UK) and incubated overnight in air at 37°C. Three reference isolates, kindly provided by Professor Alexander Tomasz, The Rockefeller University, New York, USA, with predetermined MIC values (two penicillin- and multidrug-resistant isolates, one uniformly susceptible to all antibiotics) were included in each run.[2] The MIC was defined as the lowest drug concentration that inhibited growth after 20 h of incubation.[5]

Results

The results of susceptibility testing are shown in the Table as the cumulative percentage inhibited. The MIC_{90}s of the antibiotics tested were as follows: penicillin G ≤0.03 mg/L, with a range of ≤0.03–2 mg/L; ceftriaxone 0.06 mg/L, range ≤0.03–0.5 mg/L; ciprofloxacin 2 mg/L, range 0.5–8 mg/L; moxifloxacin 0.06 mg/L, range ≤0.03–0.5 mg/L. Three isolates were penicillin-resistant (one highly resistant, two intermediate). The only isolate highly resistant to penicillin was also intermediate to ceftriaxone. As expected, the majority of pneumococci were resistant to ciprofloxacin (two highly resistant and 47 intermediate), and moxifloxacin was uniformly active against all isolates tested, being 32-fold more active than ciprofloxacin.

Discussion

With the significant decline in cases of meningitis caused by *Haemophilus influenzae* type b as a result of effective polysaccharide–protein conjugate vaccines, *S. pneumoniae* is now the most common cause of meningitis in children.[6] The past 20 years have witnessed a dramatic worldwide increase in the incidence of pneumococcal isolates that are resistant to penicillin and other antimicrobial agents.[1,2] Although non-meningitic infections caused by penicillin-resistant pneumococci may be treated with high doses of penicillin or other β-lactams, clinical failure of penicillin in treatment of meningitis caused by isolates with intermediate resistance to penicillin approaches 80%, and no cases of meningitis caused by isolates fully resistant to penicillin have responded to penicillin therapy.[7] The potency of third generation cephalosporins is also diminished as pneumococci develop reduced penicillin susceptibility,[8] and few therapeutic options are left for patients with allergy to β-lactams. Therefore, attention is being focused on the activity of new antimicrobials that can be used for atopic patients, and for therapy of meningitis caused by penicillin-resistant pneumococci. Quinolones are bactericidal, and are less hydrophilic than β-lactam and carbapenem antibiotics and therefore rapidly enter the subarachnoid space.[9] Although older compounds of this class were insufficiently active, new generation quinolones show good activity against Gram-positive bacteria including *S. pneumoniae*, and appear promising for the treatment of bacterial meningitis.[9] Moxifloxacin is an 8-methoxyquinolone with a broad antibacterial spectrum which includes high activity against Gram-positive cocci. Its entry into the subarachnoid space compared well with the CSF penetration of other quinolones in the rabbit model of meningitis, and the CSF concentration is less influenced by the state of the blood–CSF barrier.[4] Moreover, the CSF to serum ratio of this compound is not reduced by the co-administration of dexamethasone.[4] In our study moxifloxacin was 32-fold more active than ciprofloxacin, and was not affected by penicillin and cephalosporin resistance. These results indicate that moxifloxacin could be useful for the treatment of meningitis caused by both penicillin-sensitive and -resistant *S. pneumoniae*, and would be a valid therapeutic option for patients allergic to β-lactams, should it prove to be as potent *in vivo*.

Table. Susceptibility of 60 pneumococci isolated from CSF to moxifloxacin, penicillin G, ciprofloxacin and ceftriaxone

	Cumulative % of strains inhibited at MIC (mg/L) of:								
Antimicrobial agent	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8
Penicillin G	92	93	95	98	98	98	100		
Ceftriaxone	83	90	98	98	100				
Ciprofloxacin					10	47	97	98	100
Moxifloxacin	83	90	100						

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