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IN VITRO ACTIVITY OF CEFDITOREN AGAINST A SPECIAL COLLECTION OF CLINICAL ISOLATES OF *STREPTOCOCCUS PNEUMONIAE* FROM HUNGARY*

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Cefditoren is the active form of cefditoren pivoxil, a new, broad-spectrum oral cephalosporin with strong *in vitro* activity against penicillin-susceptible and resistant *Streptococcus pneumoniae*. In this study, the minimum inhibitory concentrations (MICs) of cefditoren were determined for a special selection of *S. pneumoniae* isolates known to be susceptible, moderately susceptible or fully resistant to penicillin; these isolates originated from the lower respiratory tract of adults with pneumonia or the upper respiratory tract of children with or without symptoms of infection. Some of this latter group of isolates exhibited extremely high MICs to penicillin (≥32 mg/l), whereas the MICs of cefditoren did not exceed 2 mg/l. The MIC50 and MIC90 of cefditoren proved to be 0.25 and 1.0 mg/l, respectively, with a range of MICs ≤0.015–2.0 mg/l for all the tested *S. pneumoniae* isolates. Its good activity suggests that cefditoren is expected to be a potent drug in infections caused by penicillin-resistant and multidrug-resistant *S. pneumoniae*.

Keywords: *S. pneumoniae*, penicillin resistance, cefditoren susceptibility

Introduction

Penicillin-non-insensitive *S. pneumoniae* isolates that are also resistant to other antimicrobial agents, such as macrolides and fluoroquinolones, are currently being reported with increasing frequency worldwide [1–3]. The European countries with a particularly high incidence of resistance are Spain and Hungary, both of which reported resistance rates of >40% as early as the mid-1980s [4–6]. Highly

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penicillin-resistant isolates have become a challenge in the treatment of community-acquired pneumonia, sinusitis and acute otitis media and also in the treatment of meningitis, where penicillin treatment is contraindicated for isolates with intermediate or high-level resistance too. The nasopharyngeal carriage of *S. pneumoniae* in children from day-care centres has been shown to be an important epidemiologic risk factor [7]. Another well-recognized risk factor is the irrational and excessive global usage of antibiotics, and especially oral penicillins prescribed to children, that may select the intermediate and highly-resistant strains. The aims of this study were to investigate the *in vitro* activity of a new oral cephem, cefditoren pivoxil, against *S. pneumoniae* isolates obtained from adult patients during a phase III study in Hungary, where community-acquired pneumonia was treated orally with cefditoren-pivoxil. As no highly-resistant *S. pneumoniae* strains were isolated during this study, a special collection of *S. pneumoniae* isolates originating from Hungary were also investigated; these included mostly upper respiratory tract isolates obtained from children, some of which had extremely high MICs (16–64 mg/l) for penicillin.

Materials and methods

During a phase III pneumonia study, carried out in 1996–1997, 25 *S. pneumoniae* strains were isolated, 22 from sputum and 3 from blood cultures. No duplicate isolates from any patient were included. As very few penicillin resistant *S. pneumoniae* strains were found during this clinical study, another special collection of 103 *S. pneumoniae* isolates from earlier studies were also used. The latter collection comprised 25 strains, which were susceptible, 23 which were intermediate resistant and 55 which were highly resistant to penicillin. Most of these isolates were obtained, during years 1993–1995, from the upper respiratory tract including middle ear and sinus effusion of children under the age of 2 years. Only a few isolates (10) belonging to the susceptible group originated from invasive infections (pneumonia with or without bacteraemia). All these *S. pneumoniae* isolates were identified by conventional methods (characteristic colonies on blood agar, optochin susceptibility, bile solubility) and maintained at –70 °C until used in this study. *S. pneumoniae* ATCC 49619 was applied as a reference strain during the MIC determinations. The agar dilution method was used according to the recommendations of NCCLS for the determination of MICs of cefditoren and penicillin in the case of all isolates [8]. Muller-Hinton agar with 5% blood was

supplemented with the appropriate concentrations of penicillin G (Biogal, Hungary) and cefditoren (Tedec-Meiji Farma S.A., Spain.). The concentrations of antibiotics ranged from 0.015 mg/l to 32 for cefditoren and from 0.03 mg/l to 64 for penicillin.

Results

Altogether 128 *S. pneumoniae* isolates were investigated. Thirty-five originated from community-acquired invasive pneumonia: 30 were isolated from sputum samples and 5 from blood cultures. All these isolates were susceptible (31) or intermediate resistant (4 isolates) to penicillin, with an MIC range between ≤0.03 and 0.25 mg/l. The corresponding MIC50 and MIC90 values of cefditoren were one step lower, with an MIC range of ≤0.015–0.25 mg/l (Table I). The other 93 isolates, which were obtained from the upper respiratory tract of young children (under 2 years of age), were much more resistant to penicillin. The MIC range for penicillin was between ≤0.03 and ≥64 mg/l, but much lower MIC values were measured for cefditoren, with an MIC range between ≤0.015 and 2.0 mg/l. The highest MIC observed for cefditoren was 2 mg/l, in the case of two isolates with MICs of 64 and 32 mg/l for penicillin. Table II shows the MIC50 and MIC90 values of cefditoren for the isolates belonging in the three categories according to their penicillin MIC values. Even in the group of isolates that exhibited a high level of resistance to penicillin, the MIC50 and MIC90 values of cefditoren were 0.5 and 1.0 mg/l, respectively.

Table I

MICs of penicillin and cefditoren for *S. pneumoniae* isolates obtained from adult patients with pneumonia and children with upper respiratory tract infections

Origin of isolates	MICs (mg/l)		
	MIC50	MIC90	MIC range
Pneumonia (35)			
Penicillin	≤0.03	0.06	≤0.03–0.25
Cefditoren	≤0.015	0.03	≤0.015–0.25
Upper respiratory tract infections (93)			
Penicillin	0.5	4.0	≤0.03–≥64
Cefditoren	0.25	1.0	≤0.015–2.0

Table II

MIC values of cefditoren for *S. pneumoniae* isolates (n = 128) considered to be susceptible, intermediate resistant or resistant to penicillin

	Penicillin		
	Susceptible (MIC ≤0.06 mg/l) (n = 46)	Intermediate (MIC 0.12–1 mg/l) (n = 27)	Resistant (MIC ≥2 mg/l) (n = 55)
Penicillin MIC50	≤0.03	0.5	8.0
Penicillin MIC90	≤0.03	1.0	16.0
Cefditoren MIC50	≤0.015	0.12	0.5
Cefditoren MIC90	0.03	0.25	1.0

The MIC values of cefditoren and penicillin were correlated. The correlation index was found to be $R^2 = 0.6888$ for the isolates that were susceptible or intermediate resistant to penicillin. The penicillin MIC values in the fully resistant range showed less correlation with cefditoren MIC values ($R^2 = 0.3865$).

Discussion

Cefditoren is a new oral cephalosporin, in pivaloyloxymethyl ester form, with improved activity against staphylococci, streptococci, *Haemophilus influenzae, Nesseria gonorrhoeae* and some members of the Enterobacteriaceae family [9]. The MICs of cefditoren against penicillin-susceptible, intermediate resistant and penicillin-resistant pneumococci have been shown to be the lowest among all oral beta-lactams [9–11]. Despite the fact that cefditoren, like other beta-lactams, is also showing an increase in MIC for most *S. pneumoniae* isolates that are highly resistant to penicillin, time-kill studies confirm the superior anti-pneumococcal activity of cefditoren relative to cefuroxime or cefpodoxime [9]. In our study on a specially selected collection involving altogether 27 moderately and 55 highly penicillin-resistant isolates, the MIC50 and MIC90 of cefditoren were found 4 times lower than that of penicillin for the group of isolates being intermediately resistant to penicillin. The difference was even more marked for the isolates with high level of resistance to penicillin: the MIC50 and MIC90 for cefditoren were 16 times lower than those for penicillin. Such differences in MICs exceed those normally found between penicillin and ceftriaxone or cefotaxime [9]. The highest MIC of cefditoren was 2 mg/l for two isolates, which is lower than the peak achievable serum concentration of cefditoren (2.3–3.4 mg/l) when a normal dosing regi-

men is used [9]. This level is equal to the resistance breakpoint of cephalosporins for *S. pneumoniae*. A good correlation was observed between the MICs of penicillin and cefditoren for the isolates that were sensitive and intermediate resistant to penicillin. However, no correlation was observed for the penicillin-resistant isolates. Cefditoren proved more active than penicillin against the highly penicillin-resistant isolates.

Our study, and also earlier publications [9–12], provide evidence that cefditoren is a potent drug against beta-lactam-resistant *S. pneumoniae*, most of which are additionally multidrug-resistant. Cefditoren seems to have the currently highest *in vitro* activity among the oral cephalosporins against penicillin-resistant *S. pneumoniae,* and *Haemophilus influenzae* and *Moraxella catarrhalis* are also covered by its antibacterial spectrum [10, 13]. Since resistant *S. pneumoniae* is most prevalent among upper respiratory tract isolates, this drug is expected to be particularly useful in the therapy of otitis media and sinusitis. Pharmacokinetic and clinical studies [4] have provided supportive evidence that, over its excellent *in vitro* activity, the favourable pharmacological properties of cefditoren contribute to the eradication of the pathogens in middle ear and sinus fluids. Patients with severe invasive infections such as pneumonia and meningitis caused by penicillin-resistant *S. pneumoniae* need a suitable parenteral drug as initial therapy, such as ceftriaxone, cefotaxime or vancomycin.

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References

1. Appelbaum, P. C.: Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin Infect Dis **15,** 77–83 (1992).
2. Klugman, K. P.: Pneumococcal resistance to antibiotics. Clin Microbiol Rev **3,** 171–196 (1990).
3. Tomasz, A.: Antibiotic resistance in *Streptococcus pneumoniae*. Clin Infect Dis **24,** *Suppl. 1,* S85–88 (1997).
4. Fenoll, A., Martin-Bourgon, C., Munoz R., Vicioso, D., Casal, J.: Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. Rev Infect Dis **13,** 56–60 (1991).
5. Linares, J., Pallares, R., Alonso, T. et al.: Trends in antimicrobial resistance of clinical isolates of *Streptococcus pneumoniae* in Bellvitge Hospital Barcelona, Spain (1979–1990). Clin Infect Dis **15,** 99–105 (1992).
6. Marton, A.: Epidemiology of resistant pneumococci in Hungary. Microbial Drug Resistance **1,** 127–130 (1995).

7. Tomasz, A.: The challenge of multiresistant *Streptococcus pneumoniae*: international initiatives in day-care centers and use of molecular epidemiological techniques. Clin Microbiol Infect **5,** *Suppl. 4,* S29–37 (1999).
8. NCCLS Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 4th edition. Approved Standard-M7-A4 (1997).
9. Spangler, S. K., Jacobs, M. R., Appelbaum, P. C.: Time-kill studies on susceptibility of nine penicillin susceptible and resistant pneumococci to cefditoren compared with nine other other beta-lactams. J Antimicrobial Chemother **39,** 141–148 (1997).
10. Canton, R., Linares, J., Martinez-Beltran, J., Tubau, F., Almaraz, F. A., Baquero, F.: Bactericidal activity of cefditoren (ME-1206) on *Streptococcus pneumoniae* and *Streptococcus* of the viridans group. In Proceedings of the Thirty-fourth Interscience Conference on Antimicrobial Agents and Chemotherapy 1994. Abstract E1 p. 28 (1994).
11. Soriano, F., Fernandez-Roblas, R., Coronel, P., Gimeno, M., Ródenas, E., Gracia, M., Granizo, J. J.: *In vitro* activity of cefditoren and 10 other antimicrobials against 877 *S. pneumoniae* strains isolated in Southern European Countries (ARISE Project) 12th European Congress of Clinical Microbiology and Infection Abstract P1367, Clin Microbiol Infect **8,** *Suppl.1*, 320 (2002).
12. Fremaux, A., Sissia, G., Brumpt, I., Geslin, P.: Cefditoren (ME-1206), a new cephalosporin: *in vitro* activity against penicillin susceptible and resistant pneumococci. In: Proceedings of the Eighteenth International Congress of Chemotherapy, Abstract 998, p. 289 (1993).
13. Sugita, R., Deguchi, K., Fujimaki, Y., Harada, S., Shimizu, K., Kimura, S., Watanabe, H., Komatsu, N., Okano, K., Naito, M., Nomura, T., Takona, M., Yoshida, Y., Tanaka, H., Iwai, N., Nakamura, H.: Clinical efficacy in pediatric sinusitis infections of cefditoren pivoxil granule therapy and its *in vitro* antibacterial activity against clinically isolated strains. Jap J Antibiotics **50,** 727–737 (1997).