ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1995, p. 2819–2821 Vol. 39, No. 12
0066-4804/95/$04.00+0

Activities of Oral Antibiotics on *Providencia* Strains Isolated from Institutionalized Elderly Patients with Urinary Tract Infactions

GIUSEPPE CORNAGLIA,[1]* SERGIO FRUGONI,[2] ANNARITA MAZZARIOL,[1] EDDA PIACENTINI,[1] AMELIA BERLUSCONI,[2] AND ROBERTA FONTANA[1]

Istituto di Microbiologia, Università degli Studi di Verona, I-37134 Verona,[1] *and Pio Albergo Trivulzio, I-20146 Milan,*[2] *Italy*

Received 2 August 1995/Returned for modification 30 August 1995/Accepted 28 September 1995

More than 250 *Providencia* strains isolated from the urine of institutionalized elderly patients were tested against cefaclor, cefuroxime, cefetamet, cefpodoxime, ciprofloxacin, and amoxicillin-clavulanic acid. Our results confirm the strong activities of expanded-spectrum oral cephalosporins against *Providencia* isolates, as well as the marked differences in susceptibilities among accurately identified *Providencia* species.

The prevalence of urinary tract infection increases substantially with advancing age, and in institutionalized elderly subjects it increases with functional disability and length of residence (16). Bacteria of the genus *Providencia*, with special reference to *Providencia stuartii*, are among those most frequently isolated from urine specimens from elderly subjects, and they are gaining ground as prominent organisms in bacteriuria among both institutionalized patients (16, 20, 21) and patients receiving home care (7, 8, 20). The ability of this species to persist in the catheterized urinary tract seems to be related to specific adherence characteristics (12, 13).

A distinctive feature of *P. stuartii* strains is that unlike all the other species in the *Proteeae* group, they often present with multiple resistance to disinfectants and antibacterial agents (4, 9, 10, 17, 19). However, susceptibility to expanded-spectrum cephalosporins is usually maintained.

Over the last few years, we have witnessed intense activity in the development of orally absorbable cephalosporins, which are claimed to be superior to earlier drugs owing to their resistance to several β-lactamases (1, 5, 6, 11) and/or their improved ability to overcome the permeability barrier in gram-negative organisms (3).

The objective of the study described here was to determine the in vitro susceptibilities of *Providencia* isolates, accurately identified to the species level, to cefetamet and cefpodoxime, two expanded-spectrum oral cephalosporins. The susceptibilities of the organisms to these two drugs were also compared with those to other antibiotics suitable for oral therapy of urinary tract infections, namely, two older oral cephalosporins (cefaclor and cefuroxime), a fluoroquinolone (ciprofloxacin), and a penicillin combined with a β-lactamase inhibitor (amoxicillin-clavulanic acid).

In our study we examined 255 clinical isolates of the genus *Providencia*. All strains were freshly isolated from the urine of elderly catheterized patients hospitalized at the University Hospital of Verona or at the Pio Albergo Trivulzio Geriatric Hospital, Milan. Only one isolate from a patient was tested to avoid testing multiple copies of the same strain. The great variety of susceptibility profiles obtained in routine susceptibility tests would signify that we isolated many unique strains rather than a few strains colonizing the entire hospital.

Identifications were performed by using a commercial identification system (API 20 E), but because of the difficulty in correctly identifying the various species (2, 9), they were confirmed by additional polyhydric alcohol (adonitol, arabitol, and trehalose) fermentation tests, and all strains were also tested for their phosphatase activities by a novel method (the methyl green-phenolphthalein method). The methyl green-phenolphthalein method is based on the determination of phosphatase activity, as revealed by the green color of the colonies in a medium containing methyl green and a substrate suitable for bacterial phosphatases. When the substrate is phenolphthalein diphosphate, practically all strains of *P. stuartii*, and only these strains, form colored colonies surrounded by a halo of the same color (18). Of the 255 isolates, 202 turned out to be *P. stuartii*, 40 were *Providencia rettgeri*, and 13 were *Providencia alcalifaciens.*

All strains were tested against four oral cephalosporins, namely, cefaclor, cefuroxime, cefetamet, and cefpodoxime, and against two other antibiotics suitable for oral administration, namely, a fluoroquinolone (ciprofloxacin) and a penicillin combined with a β-lactamase inhibitor (amoxicillin-clavulanic acid). The determination was carried out by agar dilution, and the isolates were assigned to different interpretative categories, as suggested by the National Committee for Clinical Laboratory Standards (NCCLS) (14, 15). All drugs were purchased from commercial sources.

The MICs of oral antibiotics for *P. stuartii* and for non-*P. stuartii Providencia* isolates are listed in Table 1, and the percentages of isolates in the different NCCLS interpretative categories are listed in Table 2. The data in Table 3 indicate the incidences of susceptibilities to the other antibiotics tested for all isolates resistant to a given antibiotic.

No difference could be found between the strains isolated at the University Hospital of Verona and those isolated at the Pio Albergo Trivulzio Geriatric Hospital. As far as the non-*P. stuartii* strains of *Providencia* are concerned, no difference between the *P. rettgeri* and the *P. alcalifaciens* strains could be found, and thus, the results for these two species have been pooled throughout the present work.

The present study confirmed the greater activities of expanded spectrum oral cephalosporins against *Providencia* isolates compared with those of older oral β-lactams and, in many

* Corresponding author. Mailing address: Istituto di Microbiologia, Strada Le Grazie, 8, 37134 Verona, Italy. Phone: 0039-45-8098196. Fax: 0039-45-584606. Electronic mail address: giuseppe@borgoroma.univr.it.

TABLE 1. MICs of oral antibiotics for *P. stuartii* and non-*P. stuartii Providencia* isolates

Organism (no. of isolates)	Antibiotic	MIC (μg/ml)		
		Range	50%	90%
P. stuartii (202)	Ciprofloxacin	0.007–>128	4	64
	Amoxicillin-clavulanate	1–>128	128	>128
	Cefaclor	0.5–>128	>128	>128
	Cefuroxime	0.06–>128	32	>128
	Cefetamet	0.03–>128	1	32
	Cefpodoxime	0.007–128	2	32
Non-*P. stuartii Providencia* spp. (53)	Ciprofloxacin	0.007–64	0.030	8
	Amoxicillin-clavulanate	0.125–>128	2	128
	Cefaclor	0.05–>128	4	>128
	Cefuroxime	0.007–>128	0.25	32
	Cefetamet	0.03–64	0.5	16
	Cefpodoxime	0.007–32	0.007	2

instances, those of another oral drug widely used in clinical settings, namely, the fluoroquinolone ciprofloxacin.

Both cefetamet and cefpodoxime generally proved to be more active than the other β-lactams tested. The incidence of susceptible isolates was definitely higher for the newer cephalosporins than for all the other β-lactams tested, apart from the cefuroxime-susceptible non-*P. stuartii* isolates, whose number exceeded that of the isolates susceptible to cefetamet.

The MICs of both cefetamet and cefpodoxime for *P. stuartii* were lower than those of ciprofloxacin, with the difference being quite small and virtually the same for the two drugs. For the non-*P. stuartii* isolates, on the other hand, both the MIC at which 50% of strains are inhibited (MIC_{50}) and the MIC_{90} of cefpodoxime were four times lower than those of ciprofloxacin, but the cefetamet MIC_{50} and MIC_{90} were twice as high as those of the fluoroquinolone. The incidence of susceptible isolates was generally higher for the newer cephalosporins, but once again, the number of ciprofloxacin-susceptible non-*P. stuartii* isolates exceeded that of isolates susceptible to cefetamet.

Besides being active against substantial percentages of isolates, cefetamet and cefpodoxime often proved to be efficacious against isolates resistant to other antibiotics; thus, they not only appear to be suitable for empirical therapy but they also offer an effective advantage over the alternative oral antibiotics. In terms of cost-utility analysis, if one assumes a linear correlation between susceptibility and outcome rate and since efficacy and freedom from adverse effects are the major determinants of a favorable cost-effectiveness ratio, the enhanced first success rate and the relative safety of their therapeutic use make these drugs preferable to other orally administered compounds, despite their higher cost.

Our data also support previous findings of marked differences in susceptibilities which can be observed among *Providencia* strains when they are accurately identified to the species level (4, 9, 10, 17, 19).

TABLE 2. Susceptibilities of *P. stuartii* and non-*P. stuartii Providencia* isolates to oral antibiotics

Organism (no. of isolates)	Antibiotic	No. (%) of isolates in the following interpretative categories[a]:		
		Susceptible	Intermediate	Resistant
P. stuartii (202)	Ciprofloxacin	67 (33.2)	26 (12.9)	109 (54.0)
	Amoxicillin-clavulanate	8 (4.0)	7 (3.5)	187 (92.6)
	Cefaclor	12 (5.9)	6 (3.0)	184 (91.1)
	Cefuroxime	50 (24.8)	50 (24.8)	102 (50.5)
	Cefetamet	145 (71.8)	21 (10.4)	36 (17.8)
	Cefpodoxime	106 (52.5)	26 (12.9)	70 (34.7)
Non-*P. stuartii Providencia* (53)	Ciprofloxacin	44 (83.0)	0 (0.0)	9 (17.0)
	Amoxicillin-clavulanate	34 (64.2)	0 (0.0)	19 (35.8)
	Cefaclor	29 (54.7)	0 (0.0)	24 (45.3)
	Cefuroxime	43 (81.1)	0 (0.0)	10 (18.9)
	Cefetamet	40 (75.5)	4 (7.5)	9 (17.0)
	Cefpodoxime	49 (92.5)	0 (0.0)	4 (7.5)

[a] NCCLS MIC breakpoints: ciprofloxacin, ≥4 μg/ml for resistant and ≤1 μg/ml for susceptible; amoxicillin-clavulanate 16 and 8 μg/ml, respectively, for resistant and ≤8 and 4 μg/ml, respectively, for susceptible; cefaclor, ≥32 μg/ml for resistant and ≤8 μg/ml for susceptible; cefuroxime, ≥32 μg/ml for resistant and ≤4 μg/ml for susceptible; cefetamet, ≥16 μg/ml for resistant and ≤4 μg/ml for susceptible; cefpodoxime, ≥8 μg/ml for resistant and ≤2 μg/ml for susceptible (14, 15).

TABLE 3. Percentages of susceptibilities to all antibiotics tested in the case of *P. stuartii* and non-*P. stuartii Providencia* isolates which were resistant to a given antibiotic

Organism	Drug to which isolates are resistant (no. of isolates)	% Isolates susceptible to[a]:					
		CIP	AMX	CEC	CXM	CTM	CPX
P. stuartii	Ciprofloxacin (109)		2.8	3.7	29.4	63.3	45.9
	Amoxicillin-clavulanate (187)	31.6		31.6	31.6	31.6	49.2
	Cefaclor (184)	32.6	0		29.3	69.0	48.9
	Cefuroxime (102)	25.5	0	0		52.9	29.4
	Cefetamet (36)	41.7	0	0	11.1		13.9
	Cefpodoxime (70)	21.4	0	0	4.9	42.9	
Non-*P. stuartii Providencia* spp.	Ciprofloxacin (9)		0	0	0	55.6	66.7
	Amoxicillin-clavulanate (19)	47.4		47.4	47.4	47.4	73.7
	Cefaclor (24)	62.5	33.3		58.3	66.6	83.3
	Cefuroxime (10)	10.0	0	0		50.0	60.0
	Cefetamet (9)	66.7	44.4	33.3	55.6		66.7
	Cefpodoxime (4)	0	0	0	0	50.0	

[a] CIP, ciprofloxacin; AMX, amoxicillin-clavulanate; CEC, cefaclor; CXM, cefuroxime; CTM, cefetamet; CPX, cefpodoxime.

We thank Andrea Di Clemente for excellent technical assistance and Anthony Steele for help with the English-language version of this paper.

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