NOTES

Comparative In Vivo Activities of Cefsulodin, Sulbenicillin, and Gentamicin Against *Pseudomonas aeruginosa*

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The in vivo activities of cefsulodin, sulbenicillin, and gentamicin were compared in mice infected intraperitoneally with *Pseudomonas aeruginosa*. In mice infected with sulbenicillin- and gentamicin-susceptible strains, cefsulodin was about 12 to 60 times more active than sulbenicillin and had an activity similar to gentamicin. In mice, the activity of cefsulodin was independent whether the strains were resistant to gentamicin or not, but it was considerably affected by resistance of the strains to sulbenicillin.

Cefsulodin [3-(4-carbamoyl-1-pyridiniummethyl)-7 β -(D- α -sulphophenylacetamido)-ceph-3-em-4-carboxylate monosodium salt, previously named SCE-129] has a marked in vitro antibacterial activity against clinical isolates of *Pseudomonas aeruginosa*, including gentamicin-resistant strains. The activity of cefsulodin against sulbenicillin- and carbenicillin-resistant strains of *P. aeruginosa*, however, is inferior to that against susceptible strains (12). Furthermore, it has been reported by Tsuchiya et al. (13) that the activity of cefsulodin is greater in vivo than in vitro.

In the present study, the protective activity of cefsulodin in mice infected intraperitoneally with *P. aeruginosa* was compared to those of sulbenicillin and gentamicin.

Cefsulodin was prepared at Takeda Chemical Industries, Ltd. Sulbenicillin (Lilacillin, Takeda), α -sulfobenzylpenicillin, was obtained from a commercial source. Gentamicin (Gentacin Injectable) was purchased from Shionogi Pharmaceutical Co. Three (N18, NC-5, U31) of the four sulbenicillin- and gentamicin-susceptible strains of *P. aeruginosa* were provided by Y. J. Honma, Institute of Medical Science, University of Tokyo, and the remaining one (SP) was available as a laboratory standard strain. One (TN 1362 = KB 333) of the three gentamicin-resistant strains of *P. aeruginosa* was supplied by M. Koike, Kyushu University, and the other two (TN 1351 = Ju 200; TN 1352 = Ju 376) by N. Kozakai, Juntendo Medical School. The three sulbenicillin-resistant strains (GN 3341, GN 3345, GN 3416) of *P. aeruginosa* were supplied by S. Mitsuhashi, Gunma University. The laboratory strains and clinical isolates were main-

tained in Dorset egg medium (Nissui) and on Trypticase soy agar (BBL), cultivated at 37°C overnight in King A broth, and suspended in 5% mucin (Laboratories Division of Wilson Pharmaceutical and Chemical Corp.). Four-week-old male SLC-ICR mice weighing 19 to 23 g were infected intraperitoneally with 0.5 ml of the bacterial suspension in 5% mucin. The challenge dose of each infection was about 100 times the number of organisms required to kill 50% of the challenge-control mice. Groups of five mice for each dosage level were treated subcutaneously with 0.2 ml of antibiotic solution at 0, 2, and 4 h after infection. All experiments were repeated four to five times. The 50% effective dose (in milligrams per kilogram) was calculated by the probit method from the survival rate of the animals recorded on day 5 after infection (5). Minimum inhibitory concentrations were determined by the agar dilution method (12).

In mice infected intraperitoneally with sulbenicillin- and gentamicin-susceptible strains of *P. aeruginosa*, the protective activity of cefsulodin was similar to that of gentamicin. *P. aeruginosa* N18 was highly susceptible to sulbenicillin as well as to cefsulodin in vitro, but in mice infected with this organism cefsulodin was about 12 times more potent than sulbenicillin. The in vitro activity of cefsulodin against *P. aeruginosa* SP, NC-5, and U31 was 8, 16, and 4 times that of sulbenicillin, respectively, but in mice infected with these strains cefsulodin showed 60, 40, and 18 times more activity than sulbenicillin. Similar observations were made in a comparative experiment of the protective activity of cefsulodin and carbenicillin in mice infected with *P. aeruginosa* (13) (Table 1). In mice infected with gentamicin-

TABLE 1. *Protective effects of cefsulodin, sulbenicillin, and gentamicin in mice infected with P. aeruginosa*^a

<i>P. aeruginosa</i> strain	Challenge dose (CFU/animal)	Antibiotic ^b	ED ₅₀ (mg/kg) ^c	MIC (μg/ml) ^d	
				10 ⁸ CFU/ml	10 ⁶ CFU/ml
N18 (SBPC ^a , GM ^a)	10 ⁶	Cefsulodin	1.93 (1.58–2.36)	3.13	3.13
		SBPC	24.2 (20.1–29.3)	3.13	3.13
		GM	1.85 (1.58–2.18)	1.56	1.56
SP (SBPC ^a , GM ^a)	10 ⁶	Cefsulodin	9.36 (6.99–12.0)	6.25	3.13
		SBPC	564 (453–690)	50	25
		GM	13.1 (11.3–15.0)	3.13	0.78
NC-5 (SBPC ^a , GM ^a)	10 ³	Cefsulodin	15.5 (12.7–19.2)	6.25	6.25
		SBPC	582 (477–726)	200	200
		GM	38.7 (33.9–44.4)	12.5	6.25
U31 (SBPC ^a , GM ^a)	10 ⁶	Cefsulodin	31.3 (23.6–40.1)	6.25	6.25
		SBPC	552 (429–699)	50	50
		GM	33.6 (28.2–40.1)	6.25	1.56
TN 1351 (SBPC ^a , GM ^a)	10 ⁵	Cefsulodin	3.13 (2.65–3.85)	1.56	1.56
		SBPC	105 (86.7–127)	25	12.5
		GM	275 (224–339)	50	25
TN 1352 (SBPC ^a , GM ^a)	10 ⁵	Cefsulodin	6.02 (4.93–6.80)	6.25	3.13
		SBPC	106 (90.1–125)	100	25
		GM	>480	>100	>100
TN 1362 (SBPC ^a , GM ^a)	10 ⁵	Cefsulodin	7.65 (6.21–9.60)	6.25	6.25
		SBPC	143 (116–184)	50	50
		GM	>480	>100	>100
GN 3345 (SBPC ^a , GM ^a)	10 ⁵	Cefsulodin	77.7 (62.4–96.3)	25	12.5
		SBPC	>2,400	>800	>800
		GM	17.7 (15.2–20.6)	3.13	3.13
GN 3341 (SBPC ^a , GM ^a)	10 ⁵	Cefsulodin	96.9 (74.1–126)	100	25
		SBPC	>2,400	>800	>800
		GM	8.82 (6.90–11.1)	3.13	1.56
GN 3416 (SBPC ^a , GM ^a)	10 ⁵	Cefsulodin	137 (108–174)	100	25
		SBPC	>2,400	>800	>800
		GM	18.6 (15.5–22.3)	3.13	3.13

^a Mice were infected intraperitoneally with the appropriate number of colony-forming units (CFU) of the test organism in 0.5 ml of 5% mucin.

^b Antibiotics were administered subcutaneously at 0, 2, and 4 h after infection. SBPC, Sulbenicillin; GM, gentamicin.

^c The 50% effective dose (ED₅₀) was calculated by the probit method. Numbers in parentheses indicate 95% confidence limits.

^d Minimum inhibitory concentrations (MIC) were determined by the agar dilution method in Trypticase soy agar. Inoculum size was one loopful (2-mm diameter) of bacterial suspension.

resistant strains of *P. aeruginosa*, cefsulodin was 16 to 33 times more active than sulbenicillin. The 50% effective dose levels of cefsulodin and sulbenicillin in mice infected with gentamicin-resistant strains were similar to those obtained in mice infected with strains susceptible to sulbenicillin and gentamicin. The activity of cefsulodin in mice infected with sulbenicillin-resistant *P. aeruginosa* was inferior to that in mice infected with sulbenicillin-susceptible strains, but

was similar to that of sulbenicillin in mice infected with sulbenicillin-susceptible strains.

Among gentamicin-resistant strains of *P. aeruginosa*, some are susceptible to amikacin (4), tobramycin (3), sisomicin (16), and netilmicin (8), but many are resistant to these aminoglycoside antibiotics. These aminoglycoside antibiotics also have been considered to result in oto- and nephrotoxicity, as gentamicin does (2, 6, 10). Recently reported semisynthetic penicil-

lins such as ticarcillin (11), BL-P 1654 (15), mezlocillin (1), piperacillin (9), PC 904 (7), and piperacillin (14) are active against *P. aeruginosa* but ineffective against carbenicillin- and sulbenicillin-resistant strains. Cefsulodin had the same activity against both gentamicin-susceptible and gentamicin-resistant strains of *P. aeruginosa* in vivo. In mice, cefsulodin was also active against sulbenicillin- and carbenicillin-resistant strains. These results correlate well with those obtained in the in vitro experiments and suggest that cefsulodin might be a useful chemotherapeutic agent in the treatment of infections due to *P. aeruginosa*.

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