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Comparative Activity of Mezlocillin, Penicillin, Ampicillin, Carbenicillin, and Ticarcillin Against Gram-Positive Bacteria and *Haemophilus influenzae*

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The in vitro activity of mezlocillin was compared to penicillin G, ampicillin, carbenicillin, and ticarcillin in tests with 195 gram-positive bacteria and 20 *Haemophilus influenzae*. Against gram-positive isolates excluding enterococci, penicillin was the most active drug, followed by ampicillin, mezlocillin, carbenicillin, and ticarcillin. Ampicillin was the most active of the five drugs against enterococci, whereas mezlocillin was the most active drug against 14 strains of ampicillin-susceptible *H. influenzae*.

Mezlocillin is a semisynthetic penicillin with a broad spectrum of antibacterial activity that includes *Pseudomonas* spp. (1, 3, 5, 12). Previous reports indicate that mezlocillin, unlike other anti-*Pseudomonas* penicillins, retains a high degree of potency against gram-positive organisms and *Haemophilus influenzae* (5, 6, 10-12). However, most of those studies focused primarily upon groups A and D streptococci and staphylococci, and many did not simultaneously evaluate other penicillins. Therefore, this investigation was designed to evaluate the in vitro activity of mezlocillin against a large number of various gram-positive organisms and *H. influenzae* in comparison with penicillin G, ampicillin, and two anti-*Pseudomonas* penicillins, carbenicillin and ticarcillin.

Working solutions were prepared in distilled water from the laboratory powders of disodium ticarcillin, disodium carbenicillin (Beecham Laboratories), potassium penicillin G, ampicillin trihydrate (Bristol Laboratories), and mezlocillin sodium monohydrate (Miles Pharmaceuticals). Each solution was prepared on the day of use. Staphylococci, groups A, B, and D streptococci, *Streptococcus pneumoniae*, and *H. influenzae* were clinical isolates. Other streptococci were either clinical isolates or components of the normal flora recovered on throat or dental plaque cultures. Streptococci were grouped and identified to species level by methods described previously (4, 7). Staphylococci were considered to be (i) penicillin susceptible if zones in disk diffusion tests (2) were $\geq$29 mm, (ii) penicillin resistant if zones were $\leq$20 mm, or (iii) methicillin resistant if they were capable of growing on agar containing 25 μg of this drug per ml at 32°C. Strains of *H. influenzae* producing beta-lactamase (9) were designated ampicillin resistant.

Serial twofold dilutions (final volume, 3 ml) were performed in Mueller-Hinton (enterococci and staphylococci), Todd-Hewitt (other streptococci), and Levinthal (*H. influenzae*) broths. An inoculum of 1×10^6 to 3×10^6 colony-forming units per ml (*H. influenzae*) or 3×10^5 to 5×10^5 colony-forming units per ml (all other organisms) was employed. Tests were incubated for 18 to 24 h at 35°C in air (enterococci and staphylococci) or in 10% CO_2 in air (all other organisms). The minimal inhibitory concentration was defined as the lowest concentration of drug preventing macroscopically detectable growth after incubation. Subcultures (0.01 ml) to drug-free media (blood or chocolate agar) were made from all clear tubes. The minimal bactericidal concentration was defined as the lowest concentration of drug in which at least 99.9% of the inoculum had been killed (8). Tests of all drugs against each strain were performed simultaneously by employing the same inoculum for each test. Tests on control strains were performed daily to monitor the reproducibility of the assays.

The comparative in vitro activities of mezlocillin, penicillin G, ampicillin, carbenicillin, and ticarcillin were determined in tests with 40 staphylococci, 155 streptococci, and 20 *H. influenzae* (Table 1). Against 135 non-enterococcal streptococci, penicillin G was the single most active drug. Minimal inhibitory concentrations of penicillin G were 2- to 4-fold lower than those of ampicillin, 4- to 8-fold lower than those of mezlocillin, and 32- to 64-fold lower than those of either carbenicillin or ticarcillin. Among the three anti-*Pseudomonas* penicillins, mezlocillin was clearly the most active. Against 20 entero-

TABLE 1. *Comparative activities of mezlocillin, penicillin G, ampicillin, carbenicillin, and ticarcillin*

Organism	No. of strains	Drug[a]	MIC[b] (μg/ml) for indicated % of strains		MBC[c] (μg/ml) for indicated % of strains	
			50	90	50	90
Group A streptococci	20	PEN	≤0.015	≤0.015	≤0.015	2.0
		MEZ	0.06	0.12	2.0	4.0
		AMP	≤0.015	0.03	≤0.015	4.0
		CB	0.5	1.0	16.0	>16.0
		TC	0.5	1.0	>16.0	>16.0
Group B streptococci	20	PEN	0.06	0.12	2.0	8.0
		MEZ	0.25	1.0	16.0	>16.0
		AMP	0.12	0.25	16.0	16.0
		CB	2.0	4.0	>16.0	>16.0
		TC	4.0	4.0	>16.0	>16.0
Group C streptococci	10	PEN	≤0.015	≤0.015	1.0	2.0
		MEZ	0.06	0.25	4.0	4.0
		AMP	0.03	0.03	0.12	4.0
		CB	0.5	0.5	>16.0	>16.0
		TC	0.5	1.0	>16.0	>16.0
Group G streptococci	10	PEN	≤0.015	≤0.015	1.0	2.0
		MEZ	0.12	0.25	4.0	8.0
		AMP	0.03	0.03	2.0	4.0
		CB	0.5	0.5	>16.0	>16.0
		TC	0.5	1.0	>16.0	>16.0
Streptococcus milleri	11	PEN	0.03	1.0	4.0	16.0
		MEZ	0.12	1.0	8.0	>16.0
		AMP	0.12	1.0	16.0	>16.0
		CB	1.0	>16.0	>16.0	>16.0
		TC	2.0	>16.0	>16.0	>16.0
Enterococci	20	PEN	4.0	4.0	>16.0	>16.0
		MEZ	2.0	>16.0	>16.0	>16.0
		AMP	1.0	1.0	>16.0	>16.0
		CB	>16.0	>16.0	>16.0	>16.0
		TC	8.0	>16.0	>16.0	>16.0
Streptococcus mitis	10	PEN	0.06	0.25	0.12	2.0
		MEZ	0.12	0.50	0.25	16.0
		AMP	0.06	0.12	0.12	8.0
		CB	2.0	8.0	8.0	>16.0
		TC	2.0	8.0	8.0	>16.0
Streptococcus mutans	20	PEN	0.03	0.03	0.03	2.0
		MEZ	0.06	0.12	0.12	0.25
		AMP	0.06	0.06	0.12	8.0
		CB	1.0	1.0	2.0	>16.0
		TC	1.0	2.0	2.0	>16.0
Streptococcus sanguis	9	PEN	0.06	0.25	0.5	4.0
		MEZ	0.06	1.0	0.5	>16.0
		AMP	0.25	1.0	2.0	16.0
		CB	2.0	4.0	>16.0	>16.0
		TC	2.0	8.0	>16.0	>16.0
Streptococcus pneumoniae	15	PEN	0.03	0.06	0.03	8.0
		MEZ	0.12	0.12	0.12	4.0
		AMP	0.03	0.06	0.06	8.0
		CB	0.5	2.0	0.5	>16.0
		TC	0.5	2.0	1.0	>16.0

TABLE 1—*Continued*

Organism	No. of strains	Drug[a]	MIC[b] (μg/ml) for indicated % of strains		MBC[c] (μg/ml) for indicated % of strains	
			50	90	50	90
Streptococcus salivarius	10	PEN	0.06	0.5	2.0	16.0
		MEZ	0.12	2.0	1.0	4.0
		AMP	0.12	0.25	0.5	4.0
		CB	2.0	>16.0	16.0	>16.0
		TC	4.0	16.0	>16.0	>16.0
Staphylococcus aureus (PEN susceptible)	11	PEN	0.06	0.12	8.0	16.0
		MEZ	1.0	2.0	>16.0	>16.0
		AMP	0.12	0.25	16.0	>16.0
		CB	2.0	2.0	>16.0	>16.0
		TC	2.0	4.0	>16.0	>16.0
Staphylococcus aureus (PEN resistant)	5	PEN	16.0	>16.0	>16.0	>16.0
		MEZ	16.0	>16.0	>16.0	>16.0
		AMP	4.0	>16.0	>16.0	>16.0
		CB	8.0	16.0	>16.0	>16.0
		TC	16.0	>16.0	>16.0	>16.0
Staphylococcus aureus (METH resistant)	4	PEN	>16.0	>16.0	>16.0	>16.0
		MEZ	>16.0	>16.0	>16.0	>16.0
		AMP	>16.0	>16.0	>16.0	>16.0
		CB	>16.0	>16.0	>16.0	>16.0
		TC	>16.0	>16.0	>16.0	>16.0
Staphylococcus epidermidis (PEN susceptible)	10	PEN	≤0.015	0.03	1.0	4.0
		MEZ	0.12	0.5	>16.0	>16.0
		AMP	0.03	0.12	2.0	8.0
		CB	0.5	2.0	>16.0	>16.0
		TC	1.0	2.0	>16.0	>16.0
Staphylococcus epidermidis (PEN resistant)	10	PEN	0.5	16.0	>16.0	>16.0
		MEZ	2.0	4.0	>16.0	>16.0
		AMP	1.0	4.0	>16.0	>16.0
		CB	4.0	16.0	>16.0	>16.0
		TC	8.0	>16.0	>16.0	>16.0
Haemophilus influenzae (AMP susceptible)	14	PEN	0.12	1.0	>16.0	>16.0
		MEZ	≤0.015	0.25	0.06	8.0
		AMP	0.06	0.25	0.5	>16.0
		CB	0.12	0.5	>16.0	>16.0
		TC	0.06	0.5	>16.0	>16.0
Haemophilus influenzae (AMP resistant)	6	PEN	>16.0	>16.0	>16.0	>16.0
		MEZ	>16.0	>16.0	>16.0	>16.0
		AMP	>16.0	>16.0	>16.0	>16.0
		CB	>16.0	>16.0	>16.0	>16.0
		TC	>16.0	>16.0	>16.0	>16.0

[a] PEN, Penicillin G; MEZ, mezlocillin; AMP, ampicillin; CB, carbenicillin; TC, ticarcillin.
[b] MIC, Minimal inhibitory concentration.
[c] MBC, Minimal bactericidal concentration.

cocci, ampicillin was the most active drug, followed by penicillin G. One half of the strains were as susceptible to mezlocillin as to penicillin G; the remainder were less susceptible to mezlocillin. The activity of ticarcillin was similar to that of mezlocillin, whereas carbenicillin displayed little activity against these strains (Table 1). In tests with 21 penicillin-susceptible staphylococci, penicillin G was the most active drug. Minimal inhibitory concentrations of penicillin G were 2-fold lower than those of ampicillin, 8- to 16-fold lower than those of mezlocillin, and 32- to 64-fold lower than those of either carbenicillin or ticarcillin. In general, each of the five

drugs was more active against penicillin-susceptible *Staphylococcus epidermidis* than against penicillin-susceptible *Staphylococcus aureus* (Table 1). None of the five drugs was highly active against 19 penicillin or methicillin-resistant staphylococci (Table 1); however, the relative order of activity was similar to that seen with the penicillin-susceptible staphylococci. Mezlocillin was the most active drug against the 14 strains of ampicillin-susceptible *H. influenzae* tested (Table 1). Minimal inhibitory concentrations of mezlocillin were two- to fourfold lower than those of ampicillin and four- to eightfold lower than those of penicillin G, carbenicillin, or ticarcillin. Most ampicillin-resistant *H. influenzae* were not inhibited by any of the drugs at concentrations of less than 16 μg/ml. The relative order of activity of the five drugs was similar when minimal bactericidal concentrations were compared (Table 1).

These results indicate that mezlocillin was clearly the most active of the three anti-*Pseudomonas* penicillins tested. Although mezlocillin was less active than was penicillin G or ampicillin against gram-positive bacteria, it was more active than either of these drugs against *H. influenzae*. This enhanced activity of mezlocillin in comparison with other anti-*Pseudomonas* penicillins may prove to be an advantage in certain clinical settings, especially in those instances of mixed infections caused by both gram-positive and gram-negative bacteria.

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