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Analysis of the Interactions Between Piperacillin, Ticarcillin, or Carbenicillin and Aminoglycoside Antibiotics

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Enhanced activity against clinical isolates of *Pseudomonas aeruginosa* was demonstrated with piperacillin, ticarcillin, and carbenicillin in combination with gentamicin, tobramycin, and amikacin.

Piperacillin (T-1220) (PIP) is a new semisynthetic derivative of aminobenzyl-penicillin with a broad spectrum of antimicrobial activity, which particularly is more active than either carbenicillin (CARB) or ticarcillin (TIC) against *Pseudomonas aeruginosa* (3-7). In the study reported here, the in vitro activities of PIP, CARB, and TIC in combination with gentamicin (GM), tobramycin (TM), and amikacin (AM) against 54 isolates of *P. aeruginosa* were compared.

Minimal inhibitory concentrations (MICs) of each penicillin, alone and in combination with each aminoglycoside, were determined by the broth microdilution testing method. Serial twofold dilutions of the penicillins and aminoglycosides were prepared in Mueller-Hinton broth (Difco) and automatically delivered (MIC 2000 Dispenser, Cooke Engineering Co.) in a checkerboard pattern into microtiter trays. The trays were stored at −20°C and were used within 10 days of preparation. Fifty-four recent clinical isolates of *P. aeruginosa* were obtained from the Barnes Hospital Diagnostic Microbiology Laboratory. The test inoculum was prepared with an overnight growth of each isolate, which was adjusted to a turbidity equivalent to one-half a no. 1 McFarland standard. Each microtiter well was inoculated with 1 μl of this suspension (10^5 colony-forming units), and the trays were incubated at 35°C. The MIC of each antibiotic alone and in combination was determined to be the lowest concentration with no visibly detectable growth after 18 to 24 h of incubation.

The fractional inhibitory concentration (FIC) was determined for the antibiotic combinations. The FIC is the ratio of the MIC of each antibiotic in combination to the MIC of each antibiotic alone, expressed as a decimal fraction. The FIC index is the sum of the FICs of each combined antibiotic. The interaction of each antibiotic combination was interpreted as synergistic, additive, or antagonistic when the FIC index was less than, equal to, or more than 1, respectively (1). The activity of the antibiotic interaction was indeterminate when the MIC for one antibiotic was less than the lowest concentration tested.

In Table 1 is summarized the inhibitory activity of PIP, TIC, and CARB against the 54 *P. aeruginosa* isolates. At a concentration of 12.5 μg/ml, 83% of the isolates were inhibited with PIP, compared to 4 and 2% with TIC and CARB, respectively. A concentration of ≥200 μg of CARB or TIC per ml was required to inhibit 14 isolates, 13 of which were inhibited by PIP at a concentration of at least 25 μg/ml.

TABLE 1. *Inhibitory activity of PIP, TIC, and CARB against 54 P. aeruginosa isolates*

Antibiotic	Cumulative % inhibited at MIC (μg/ml) of:				
	12.5	25	50	100	≥200
PIP	83	98			100
TIC	4	41	69	83	100
CARB	2	11	50	75	100

The antimicrobial activities of the penicillin-aminoglycoside combinations are summarized in Table 2. The majority of all antimicrobial combinations were either synergistic or indeterminate. For 188 of the total 193 indeterminate combinations, the MIC of one of the two antibiotics when used alone was equal to or less than the lowest concentration tested. Only three antagonistic combinations were observed: TIC-AM (MIC [μg/ml]: TIC, 50; AM, 3.1), TIC-TM (MIC: TIC, 200; TM, 0.4), and CARB-TM (MIC: CARB, 100; TM, 0.4). Synergy was observed with all aminoglycoside combinations with PIP for these three isolates. Fu and Neu (3) likewise reported that the combination of PIP with GM or AM was either synergistic or indeterminate with all isolates of *Pseudomonas* tested.

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TABLE 2. *Effect of antibiotic combinations against P. aeruginosa isolates*

Antibiotic combinations	No. tested	No. of isolates				Mean FIC index[a]
		Synergy	Additive	Indeterminate	Antagonism	
PIP + AM	54	32	2	20	0	0.63
PIP + GM	54	26	1	27	0	0.64
PIP + TM	54	21	1	32	0	0.64
TIC + AM	54	36	1	16	1	064
TIC + GM	54	33	1	20	0	0.61
TIC + TM	54	21	2	30	1	0.68
CARB + AM	54	42	6	6	0	0.66
CARB + GM	54	24	7	23	0	0.71
CARB + TM	54	30	4	19	1	0.68

[a] Mean FIC index was calculated from the FIC index of each synergistic, additive, and antagonistic combination.

Fourteen isolates were resistant (MIC $\geq$ 200 μg/ml) to CARB or TIC. The combinations of PIP-AM, PIP-GM, and PIP-TM were synergistic for 10, 9, and 6 of the 14 isolates, respectively. In this study only one of the 54 isolates was resistant to any of the aminoglycosides, with MICs of 50 (AM), $\geq$50 (TM), and 0.8 μg/ml (GM), as well as $\geq$200 μg/ml with the three penicillins. Synergy was demonstrated for this isolate with the combinations of PIP-GM, PIP-TM, PIP-AM, TIC-AM, and CARB-AM. All other antibiotic combinations were indeterminate. The mean FIC index (Table 2) was not significantly different (at $P < 0.05$) for the combinations of a penicillin with the three aminoglycosides or for the combinations of an aminoglycoside with the three penicillins, except for GM combined with TIC or CARB (paired τ test, 2).

PIP, alone and in combination with various aminoglycosides, is highly active against isolates of *P. aeruginosa* that are either susceptible or resistant to other semisynthetic penicillins.

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