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Evaluation of Gentamicin and Penicillin as a Synergistic Combination in Experimental Murine Listeriosis

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The administration of a combination of penicillin and gentamicin to mice given an intraperitoneal challenge of a highly pathogenic strain of *Listeria monocytogenes* resulted in increased survival as compared with groups receiving penicillin alone or gentamicin alone or a control group that received no antibiotic. The median survival of animals that eventually died was also longer than in groups receiving single antibiotics and suggests that additional studies should be carried out to further investigate the possibility of synergism in animal models.

The present study was carried out to evaluate whether treatment with penicillin and gentamicin in combination results in increased survival rates in mice challenged with a lethal dose of *Listeria monocytogenes*. The isolate used was strain 10403, serotype 1, originally identified by M. L. Gray (obtained from Elizabeth Hall, Washington State University, Pullman) and was selected because of its consistently high degree of pathogenicity for the Swiss-Webster mouse. In vitro killing studies were carried out in tryptose phosphate broth by standard methods (1) and demonstrated synergism of the penicillin and gentamicin combination against this organism with concentrations of 0.5 and 2.5 μg/ml, respectively.

(This study was presented in part at the 75th Annual Meeting of the American Society for Microbiology, New York, N.Y., 27 April-2 May, 1975.)

Experimental infection studies used female mice (Swiss-Webster, Spartan Research, Haslett, Mich.) 1 month of age which were segregated into groups of 15 mice each designated as control group, penicillin group, gentamicin group, and a combined treatment group. The animals in experiment 1 received 5×10^6 colony-forming units of *Listeria* intraperitoneally, and in experiment 2 the animals received 5×10^7 colony-forming units. This injection was given 2 h before the initiation of antibiotic treatment which consisted of intramuscular penicillin G (Eli Lilly, Indianapolis, Ind.) at 4.5 mg/kg in 0.025 ml given every 12 h for 7 days; intramuscular gentamicin (Garamycin injectable, Schering Corp., Bloomfield, N.J.) at 3.35 mg/kg in the same volume, dosage, interval, and duration; or the two drugs, at separate sites, all given in the hind legs. The experiments were terminated at 6 weeks, which was 5 weeks after the cessation of antibiotic therapy.

The results of the two experimental infection studies are shown in Table 1. On day 1, the majority of animals manifested clinical signs of illness consisting initially of ruffled fur and respiratory distress, whereas other symptoms manifested less frequently included torticollis, hemiplegia, conjunctivitis, and urethritis. The latter was documented as being listerial in etiology by culture in 16 out of 29 animals studied. The first experiment yielded a survival rate of 80% in the penicillin-plus-gentamicin group, whereas 13% survived in the penicillin group. In addition, the median survival of the animals that died in the combination group was 20 days as compared with 2 days for the other groups. The second experiment demonstrated earlier killing of the animals in the penicillin and gentamicin groups, with one animal surviving in the control group (7%), as opposed to five in the combination group (33%). The median survival of the combination group was 3.5 days as compared with 1 day for the other groups.

The possibility of in vivo synergism is suggested rather than a simple additive effect, because, on the basis of pure survival numbers alone, both experiments 1 and 2 have survival frequencies in the combined treatment groups that exceed the totals for the penicillin and gentamicin groups added together. Penicillin-aminoglycoside synergism has also recently been reported in experimental *Listeria* meningitis in rabbits (W. M. Scheld, D. D. Fletcher, F. N. Fink, and M. A. Sande, Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta,

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TABLE 1. *Survival of mice given antibiotics singly or in combination after an intraperitoneal challenge of L. monocytogenes*

Expt no. (CFU in inoculum)[a]	Treatment group[b]	42-day survivors		Median days of survival of mice that died[c] (range)
		No.	%	
1 (5×10^6)	Untreated	0	0	2 (0–3)
	Pen	2	13	2 (2–4)
	Gent	0	0	2 (2–4)
	Pen + Gent	12	80	20 (13–29)
2 (5×10^7)	Untreated	1	7	1 (0–2)
	Pen	0	0	1 (0–3)
	Gent	0	0	1 (0–1)
	Pen + Gent	5	33	3.5 (1–9)

[a] CFU, Colony-forming units.

[b] Fifteen animals in each group for a total of 60 animals per experiment. Pen, Penicillin G (4.5 mg/kg) intramuscularly every 12 h for 7 days. Gent, 3.35 mg of gentamicin per kg intramuscularly every 12 h for 7 days. Pen + Gent, both drugs given in dosages and duration described above.

[c] Animals living less than 24 h were classified as 0 days of survival.

Ga., Abstr. no. 248, 1978), where the addition of gentamicin to either penicillin or ampicillin alone significantly increased the in vivo bactericidal activity. Successful medical therapy of *Listeria* prosthetic valve endocarditis with a combination of penicillin and tobramycin that showed in vitro synergism has also been described (4), and the suggestion has been made that laboratory studies may help in selecting combinations of antimicrobial agents for treatment. The present investigation supplies additional evidence that the penicillin-aminoglycoside synergism demonstrated previously by in vitro (1–3) methods may be of potential clinical significance and should be investigated further.

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