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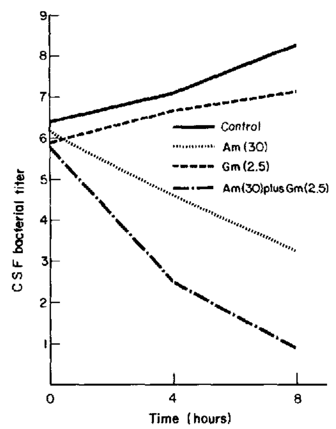
Synergy Between Ampicillin and Gentamicin in Experimental Meningitis Due to Group B Streptococci



Legend. In vivo killing kinetics in experimental meningitis due to group B streptococci type III in rabbits. Data are the mean log cfu of group B streptococci/ml of cerebrospinal fluid (CSF). Uniformly fatal meningitis (when untreated) was induced in 96 New Zealand white rabbits by intracisternal inoculation of 10^6 cfu of group B streptococci type III. Continuous iv infusion (for 8 hr) of antibiotic(s) was begun 16 hr later at the following dosages: ampicillin (Am; 30 or 15 [data not shown] mg/kg of animal body weight per hr), gentamicin (Gm; 2.5 or 1.25 [data not shown] mg/kg per hr), and ampicillin (30 or 15 [data not shown] mg/kg per hr) plus gentamicin (2.5 or 1.25 [data not shown] mg/kg per hr). Samples of serum and CSF were obtained after 0, 4, and 8 hr of therapy for determination of quantitative concentrations of bacteria and antibiotics. Control rabbits received no antibiotic therapy.

Summary

Several studies have shown that a combination of penicillin (usually ampicillin) and an aminoglycoside is more rapidly bactericidal than either agent alone in quantitative "time-kill" experiments in vitro [1] or in experimental bacteremia due to group B streptococci in mice after ip inoculation [2]. We compared the in vivo bactericidal activity of ampicillin and gentamicin in combination with that of either agent alone in experimental meningitis due to group B streptococci in rabbits. The mean percentage of penetration ([concentration in CSF/concentration in serum] × 100) of each drug was highly reproducible and was 13% for ampicillin and 21% for gentamicin. The mean concentrations of ampicillin in the CSF (2.7–3.6 μg/ml) uniformly exceeded the MBC (0.5 μg/ml) for the test strain, but the mean concentrations of gentamicin in the CSF (1.5–3.4 μg/ml) never achieved levels equivalent to the MBC (16 μg/ml). The concentration of group B streptococci in the CSF increased in all untreated (control) animals (mean ± SD increase in bacterial titers, 1.8 ± 0.3 log cfu/ml of CSF in 8 hr); all of these animals died within 48 hr. Gentamicin alone, at either 1.25 or 2.5 mg/kg per hr, failed to influence the course of the disease (all 25 animals died after 48 hr). Ampicillin alone (15 or 30 mg/kg per hr) produced a gradual decline in bacterial titers in the CSF of 2.1–2.7 log after 8 hr of therapy, and sterile CSF was obtained from two of 14 animals after 8 hr (12 of 14 animals died after 48 hr). All combinations of ampicillin and gentamicin were significantly more rapidly bactericidal in this model than was the appropriate dose of the most active agent (ampicillin) alone ($P < 0.01$ by Student's t-test). The best results were obtained with the two drugs in combination at the higher dosage (mean decrease in bacterial titers, 4.96 log after 8 hr; $P = 0.0002$ compared with ampicillin alone). Ten of 15 animals had sterile CSF after 8 hr; five died after 48 hr. The results could not be ascribed to differences of the initial bacterial titers in CSF in the study groups before therapy. In this in vivo model of meningitis due to group B streptococci, ampicillin and gentamicin in combination demonstrated a synergistic effect, even at the antibiotic concentrations used.

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