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Cerebrospinal Fluid Penetration of Amikacin

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Adult volunteers underwent a single lumbar puncture 1 to 8.5 h after one 7.5-mg/kg intramuscular amikacin injection. Eighteen showed no detectable drug in cerebrospinal fluid; six had concentrations <0.5 μg/ml.

Gram-negative bacillary meningitis in adults occurs most often in patients with underlying chronic disease, central nervous system trauma, or following neurosurgery (8). Gram-negative bacilli caused 4.2% of all bacterial meningitis and 69% of postneurosurgical meningitis at one hospial center (8). Reported mortality has ranged from 30 to 70% (10).

The antibiotic selected for initial therapy of this condition should be highly active against *Pseudomonas aeruginosa* and members of the *Klebsiella-Enterobacter-Serratia* tribe because of the frequency of these organisms as etiological agents (4). Because of its broad spectrum of antibacterial activity, gentamicin has been evaluated in an experimental model of gram-negative bacillary meningitis and in humans. With intact meninges, the passage of gentamicin into cerebrospinal fluid (CSF) after parenteral administration is minimal (6, 7, 10, 11). The penetration of gentamicin into CSF is also poor when meningeal inflammation is present (6, 11). The intralumbar route of administration of gentamicin is known to produce insignificant drug concentrations in ventricular CSF (7).

As ventriculitis is often present in patients with gram-negative bacillary meningitis, optimal use of gentamicin in treatment may necessitate intraventricular administration (7), thus further complicating treatment.

Amikacin, a derivative of kanamycin, has a broad range of activity against gram-negative bacilli, including many resistant to gentamicin (9). As amikacin could be valuable in the therapy of gram-negative bacillary meningitis in adults, particularly if it could be shown to readily enter the CSF, we undertook to study its CSF penetration in adult volunteers.

Patient selection and drug administration. Twenty-four adult patients scheduled to undergo lumbar puncture to prove or exclude the diagnosis of neurosyphilis or for myelography in the diagnosis of lumbar disk protrusion were enrolled in the trial. Informed consent was obtained in each case. All patients had normal renal and auditory function as determined by history, physical examination, urinalysis, and measurement of serum creatinine. Each subject received a single intramuscular dose of 7.5 mg of amikacin per kg between 1 and 8.5 h before lumbar puncture. Serum was obtained both before administration of amikacin and at the time of lumbar puncture. Serum and CSF specimens were stored at −70°C prior to assay.

Laboratory methods. Antibiotic concentrations were determined by an agar-well diffusion technique (1). Each well was filled with 50 μl of the fluid to be assayed; determinations were performed in triplicate. *Bacillus subtilis* was the assay organism. Three parallel series of standards were prepared: amikacin in concentrations of 30, 20, 10, 4, 2, 1, 0.5, and 0.25 μg/ml was dissolved in pooled normal human CSF, pooled normal human serum, and phosphate buffer, pH 7.0. The pH of each amikacin standard was measured after addition of the drug to pooled human CSF or pooled human serum. This procedure was employed because pH shifts due to loss of volatile acid (i.e., CO_2) from a fluid with limited buffer capacity such as CSF may significantly influence the in vitro activity of aminoglycoside agents (3). The pH of CSF standards ranged from 8.7 to 9.0; that of serum standards ranged from 7.8 to 8.2. There was no relation of pH to the drug concentration in individual standards; furthermore, there was a linear relationship between the drug concentration and the size of the zone of inhibition produced by CSF standards in the range of 0.5 to 10 μg/ml and for serum standards from 0.5 to 30 μg/ml (Fig. 1). This suggests that small pH variations within the observed ranges did not significantly alter the in vitro activity of amikacin. The pH of individual standards after addition of amikacin to phosphate buffer (pH 7.0) were not deter-

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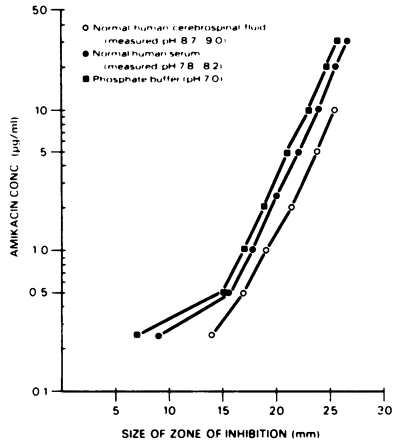

FIG. 1. *Effect of diluting fluid and pH on the zones of inhibition produced by amikacin standards.*

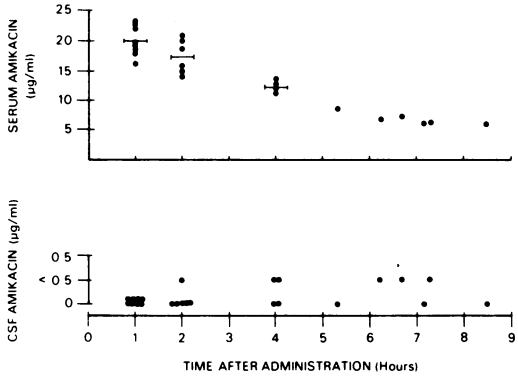

FIG. 2. *Serum and CSF amikacin concentrations after a single 7.5-mg/kg intramuscular dose. Each dot represents a single determination;* (⊢⊣) *represents mean concentration.*

mined; again, the semilogarithmic plot of drug concentration to zone size was linear in the range from 0.5 to 30 µg/ml.

Antibiotic levels. The pH values of serum and CSF test specimens at the time of determination of antibiotic concentrations were in the same ranges, respectively, as those of the serum and CSF standards. Accordingly, serum concentrations were determined from the serum standard curve, and CSF concentrations were determined from the CSF standard curve. No antibiotic activity was found in any of the serum specimens obtained prior to administration of the antibiotic. Figure 2 illustrates the simultaneous serum and CSF concentrations of amikacin at varying times after injection. Mean serum concentrations at 1, 2, and 4 h after administration of drug were 19.7, 17.2, and 12.0 µg/ml, respectively. Eighteen patients had no detectable antibiotic activity in their CSF at intervals ranging from 1 to 8.5 h after injection. Six patients barely had antibiotic activity in CSF (below the range of accuracy of the assay, i.e., <0.5 µg/ml). Five of these patients had their CSF sampled 4 h or longer after injection of amikacin.

The poor penetration of amikacin through intact meninges could have been suspected from the similar characteristics of its parent compound, kanamycin (2). Other pharmacological properties of the agents such as volume of distribution, serum half-life, and renal clearance are identical (5). It is certainly possible that under different circumstances higher CSF concentrations of amikacin may occur after parenteral administration. It will be important to extend the present observations to the measurement of CSF amikacin concentrations in patients receiving repeated parenteral doses of the agent, especially patients with meningeal inflammation.

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