Intraventricular Levels of Amikacin After Intravenous Administration

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Serum and ventricular fluid pharmacokinetic data for amikacin were evaluated prospectively in 10 hydrocephalic children with suspected ventriculitis. After the fourth or fifth intravenous 7.5-mg/kg dose of amikacin given every 8 h, mean peak serum levels were 24.3 ± 3.2 μg/ml (achieved at 0.5 h) with a calculated half-life of 2.2 ± 1.1 h. Mean peak ventricular fluid levels in five patients with bacterial infection were 6.1 ± 2.0 μg/ml (achieved at 3 h). In the remaining five patients without bacterial ventriculitis, very low levels (≤0.7 μg/ml) of amikacin were detected. Ventricular fluid pleocytosis was directly correlated and glucose levels were inversely correlated with penetration of amikacin. Systemic therapy with amikacin may be the treatment of choice for children with ventriculitis-meningitis caused by bacteria which are highly susceptible to this drug, thereby permitting the avoidance of the potentially hazardous intraventricular route of administration.

Although Staphylococcus epidermidis and Staphylococcus aureus are the major causes of shunt infections in hydrocephalic pediatric patients, gram-negative enteric bacteria such as Escherichia coli and Klebsiella and Proteus species account for 13% of such infections (15). Twenty percent of shunt infections in our hospital were caused by gram-negative bacilli (13). Aminoglycosides are often the drugs of choice for treatment of these infections. Although gentamicin was reported to penetrate the blood-brain barrier of rabbits with experimental meningitis (17) and newborns with meningitis (11), the concentrations of this drug in cerebrospinal fluid (CSF) of children and adults with central nervous system infections were very low (3, 8, 14). This may explain the high percentage of treatment failures associated with systemic aminoglycoside treatment. Recent reports suggest that amikacin administered systemically to patients with meningitis or ventriculitis reaches levels in CSF or ventricular fluid which will inhibit or kill many of the common gram-negative bacteria that cause central nervous system infections (7, 16, 19).

In this report, we present data regarding the pharmacokinetics of amikacin in serum and ventricular fluid after intravenous administration to hydrocephalic children with and without ventriculitis.

MATERIALS AND METHODS

Ten hydrocephalic children aged 1 month to 6 years with suspected ventriculo-peritoneal shunt infections were studied. It is standard neurosurgical management in our institution to remove the shunt from each patient with suspected shunt infection and to place an extraventricular drainage system. After informed consent was obtained from parents, intravenous amikacin in a dose of 7.5 mg/kg every 8 h was started. Each dose was infused over a 20- to 30-min period. After the fourth or fifth dose of amikacin, blood and ventricular fluid samples were obtained at 30 min, and 1, 2, 3, 6 (only blood), and 7 h after infusion. To assure that ventricular fluid samples were from the ventricular system and not from the extraventricular drainage catheter, 1.5 ml of ventricular fluid was aspirated (the dead-space volume of the catheter was 0.8 to 1.0 ml) and discarded; 0.5 ml was then obtained with a fresh syringe for amikacin determination.

Serum and ventricular fluid samples were stored at −70°C until assayed. All specimens from a patient were analyzed at the same time within 10 days of their collection. An amikacin radioimmunoassay kit (Diagnostic Products Corp., Los Angeles, Calif.) was used to determine amikacin levels (10). For determination of infection, ventricular fluid was cultured on sheep blood agar, eosin methylene blue agar, and chocolate agar plates. Identification and semiquantitation of bacterial growth were made by routine bacteriological procedures. Portions from the 30-min samples of ventricular fluid were analyzed for leukocyte count, glucose, and protein level.

RESULTS

Five patients were found to have bacterial ventriculitis (four of them with gram-negative bacilli), and no organism was isolated from the remaining five (Table 1). All patients were treated with systemic amikacin (7.5 mg/kg per
within 3 days showed a patient of quantitative 5 day given every 4 h. The peak carbenicillin venous dose every 8 h.

Serum and carbenicillin 100 mg/kg per day was added to the treatment of patient no. 3 on day 6. Semiquantitative cultures from ventricular fluid showed a 1 to 2 log decline in bacterial counts within 3 to 5 days after initiation of therapy in the four patients with gram-negative ventriculitis. Cultures became sterile in these patients within 5 to 10 days (mean, 7.75 days).

After either the fourth or fifth dose of intravenous amikacin, peak serum levels ranged from 19.5 to 29.0 μg/ml. The mean (±standard deviation) serum half-life was 2.2 ± 1.1 h (range, 1.1 to 4.6 h). The youngest patient (patient no. 4) had the longest half-life. Amikacin serum levels at various times after infusion in the 10 patients studied can be seen in Fig. 1.

Peak ventricular fluid amikacin levels are shown in Table 1. All five children with bacterial infections had peak ventricular fluid amikacin levels exceeding 4 μg/ml, whereas none of the five children with sterile ventricular fluid had peak ventricular fluid levels greater than 0.7 μg/ml. The concentrations of amikacin in the ventricular fluid at various times after administration of the drug to the five infected patients are shown in Fig. 1. In one patient (patient no. 3), the peak level was achieved 2 h after the end of the drug infusion. In the remaining four patients, the peak was reached 3 h after the end of infusion. In contrast, concentrations in serum peaked 30 min after administration of drug. The peak ventricular concentration ranged from 18.2 to 32.8% of the peak serum levels (V/S) in the five patients with bacterial ventriculitis; in the five patients without infections the ventricular fluid peak was less than 9% of the serum peak.

The correlation between the ventricular fluid protein concentration and the above V/S was poor (r = -0.008). When ventricular fluid glucose levels were compared to the respective V/S amikacin ratio, a strong inverse correlation was found (r = -0.687, with P < 0.05). The best correlation was found between degree of ventricular pleocytosis and the V/S ratio of amikacin (r = 0.722, P < 0.02). Although patients no. 5 and 8 had similar degrees of pleocytosis and comparable levels of protein and glucose in ventricular fluid, both their peak ventricular fluid amikacin levels (5.6 and 0.4 μg/ml, respectively)
and V/S ratios (25.4% versus 1.6%) were very different, suggesting that although pleocytosis is well correlated with amikacin penetration into the ventricular fluid, other variables, including the mechanism(s) which affect glucose levels, appear to influence the concentrations of amikacin in ventricular fluid.

**DISCUSSION**

Previous studies indicated that the minimal inhibitory concentration of amikacin for the majority of strains of *E. coli*, Klebsiella pneumoniae, Proteus (indole positive), and Pseudomonas aeruginosa, the most common gram-negative bacteria causing shunt infections, is less than 4 μg/ml (1, 4, 5). Each of the five patients with bacterial ventriculitis in this study had ventricular fluid levels of amikacin in excess of 4 μg/ml. Although Lambert found a poor correlation between CSF antibiotic concentration and therapeutic outcome in neonatal meningitis (9), most investigators believe that if the level does not exceed the in vitro minimal inhibitory concentration of the infecting agent, sterilization of the CSF will not be achieved. The high overall mortality from gram-negative meningitis-ventriculitis treated with systemic gentamicin (18) is due at least in part to the poor CSF penetration of gentamicin. On the other hand, a higher death rate (42.9%) among infants who received intraventricular and systemic gentamicin was noted as compared to those who received systemic gentamicin alone (12.5%) (12), suggesting that very high levels of gentamicin in the ventricular fluid may be harmful. Recently, Hodges et al. (6) reported neurological and pathological disturbances in rabbits dosed intraventricularly with 0.25 and 0.5 mg of gentamicin per kg, resulting in peak CSF levels of 147.8 and 306 μg/ml. Doses of 0.05 mg/kg with peak CSF levels of 39.6 μg/ml evoked neither neurological or morphological changes.

Howard et al. found that the concentrations of amikacin in CSF of infants with meningitis 1 to 12 h after a 7.5-mg/kg intramuscular dose ranged from 0.8 to 9.2 μg/ml (mean, 4.4 μg/ml) (7). Concentrations in the CSF of adult volunteers without meningitis after one 7.5-mg/kg intramuscular amikacin injection were low (2). In our study, patients with bacterial ventriculitis had peak concentrations of amikacin in the ventricular fluid that averaged 25% of the peak serum levels, whereas patients without active infection had peak levels in ventricular fluid of from <1 to 2.7% of their peak concentrations in serum. There was a significant (P < 0.05) inverse correlation (r = −0.687) between the ventricular fluid glucose levels and amikacin penetration and a stronger direct correlation (r = 0.722, P < 0.02) between the degree of pleocytosis present and the V/S amikacin ratio. In contrast, Trujillo et al. observed no relationship between amikacin penetration and degree of meningeal inflammation in pediatric patients (19), suggesting that pleocytosis is but one variable affecting penetration of this drug into the CSF.

The responses of the four patients with gram-negative ventriculitis to systemic treatment alone was favorable. There was a 10- to 100-fold reduction in bacterial count within 3 to 5 days, with sterilization in 5 to 10 days. Wright et al. recently reported that administration of amikacin intraventricularly resulted in cure of gram-negative bacillary meningitis in six of eight patients (20), although persistence of positive cultures for 4 to 5 days was noted in spite of ventricular fluid levels of >100 μg/ml.

Maintenance of high concentrations of amikacin in ventricular fluid appears to reduce persistence of the infecting organism (up to 10 days in our patients versus up to 5 days in Wright’s patients). In selected cases, intraventricular administration may be essential to eradication of the bacteria. On the other hand, systemic administration of the drug alone may suffice in patients with ventriculitis due to bacteria which are highly susceptible to amikacin (minimal bactericidal concentration, ≤1 μg/ml), especially when ventricular pleocytosis and hypoglycorrhachia are present. This group of patients may be spared the need for invasive neurosurgical procedures as well as the potentially serious consequences of direct intraventricular administration of aminoglycosides.

**LITERATURE CITED**


