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# Gentamicin Penetration into Cerebrospinal Fluid in Experimental *Haemophilus influenzae* Meningitis

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**We studied the effect of meningitis and the method of parenteral gentamicin administration (intramusclar injection, a 30-min intravenous infusion, or intravenous bolus administration) on achievable concentrations of drug in cerebrospinal fluid (CSF). In normal animals, only intravenous bolus administration of 2 to 8 mg/kg produced a gentamicin concentration of >0.1 μg/ml in CSF in some animals. All CSF samples contained less than the limit of detection (0.1 μg/ml) after the intramuscular administration of 6 mg/kg. In animals with meningitis, gentamicin penetration into cisternal CSF was increased significantly after a bolus administration of 6 mg/kg (mean, 0.197 ± 0.063 μg/ml in normal animals versus 1.68 ± 0.38 μg/ml in animals with meningitis; $P < 0.01$). In meningitic animals that received 6 mg/kg as an intravenous bolus, lumbar CSF had the highest maximum concentration (4.25 ± 1.08 μg/ml), in comparison with ventricular CSF (3.10 ± 0.66 μg/ml). The gentamicin concentration in cisternal CSF decreased more slowly than it did in serum (elimination half-life, 238.70 ± 64.56 min in cisternal CSF versus 82.73 ± 2.91 min in serum), yielding a relative increase in the percentage of penetration. We conclude that maximum penetration by gentamicin into CSF occurs after intravenous bolus administration and that the maximum concentration occurs in lumbar CSF.**

Meningitis caused by gram-negative organisms remains a major therapeutic challenge; mortality from this disease ranges from between 12 and 75% (8, 15, 16). Aminoglycosides administered parenterally are often used to treat this disease (11, 14), although these antibiotics may penetrate the blood-brain barrier poorly. A favorable outcome in patients with meningitis infected with members of the family *Enterobacteriaceae* treated with aminoglycosides has been related to concomitant therapy with another effective antimicrobial agent, usually a beta-lactam (5, 16).

Data on the penetration of gentamicin into cerebrospinal fluid (CSF) in humans following parenteral administration are fragmentary. Gentamicin concentrations in lumber CSF were measured by an radioenzymatic assay on four occasions in three neonates with gram-negative bacillary meningitis following a 2.5-mg/kg dose of gentamicin administered as an infusion over 30 min (5). Gentamicin was detectable (>1.0 μg/ml) in one of four CSF specimens. By a similar assay technique, no gentamicin could be detected in ventricular CSF of four hydrocephalic patients with ventriculitis following an intravenous infusion of undefined duration (20). Moellering and Fischer (17) measured gentamicin concentrations in lumbar CSF by using a microbiological assay in a 17-month-old child with meningitis. CSF concentrations of 0.5 and 0.3 μg/ml were observed 4 and 5 h, respectively, following an intramuscular dose of 2 mg/kg.

In contrast to these results that indicated that aminoglycoside penetrated poorly, Eichenwald (7) found that kanamycin penetrated well into CSF during treatment of infants with meningitis. Additionally, McCracken et al. (16), using a microbiological assay, found a mean gentamicin concentration of 1.6 μg/ml (range, 0.3 to 3.7 μg/ml) in lumbar CSF in 43 infants with gram-negative enteric meningitis, following intramuscular gentamicin administration (2.5 mg/kg per dose). Because of the various routes, infusion durations, and causes of meningitis, the degree of penetration of aminoglycosides into CSF is unclear. Since aminoglycosides are administered with beta-lactams for gram-negative bacillary meningitis before antibiotic susceptibility is known, and since there is often synergism between these two antibiotics with *Enterobacteriaceae*, we sought to optimize the penetration of gentamicin into CSF.

We have previously described (22) experimental *Haemophilus influenzae* meningitis in nonhuman primates. The sequence of events leading to meningitis is believed to mimic that which occurs in humans. Atraumatic intranasal inoculation is followed by bacteremia and meningitis (22). Choroid plexitis, ventricular infection, and other histopathological features of meningitis in infant monkeys (6) are also present in human infants with meningitis caused by enteric gram-negative bacilli (1, 2, 9, 12, 21).

Using this model, we sought to optimize the penetration of gentamicin into CSF by testing the hypothesis that a high concentration of drug in serum would facilitate ingress into CSF. To do this, we measured the gentamicin concentration in CSF after intramuscular injection, slow intravenous infusion, or intravenous bolus administration in normal subhuman primates and those with *H. influenzae* meningitis.

## MATERIALS AND METHODS

Gentamicin for parenteral administration and the standardized reference compound were supplied by Charles Hough (Schering Corp., Kenilworth, N.J.). The formulation for parenteral administration contained gentamicin (40 mg/

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ml), sodium bisulfite (3.2 μg/ml), propylaparaben (0.2 mg/ml), methylparaben (1.8 mg/ml), and sodium EDTA (0.1 mg/ml). Parenteral administration consisted of an intravenous infusion (bolus) over 10 s or at a constant rate for 30 min (with an infusion pump [Harvard]) or an intramuscular injection in the anterior thigh. Serum samples for gentamicin quantitation were collected by venipuncture at defined intervals ranging from 5 to 420 min after the conclusion of administration. Blood was obtained from a central venous cannula, separate from the one used for gentamicin administration. CSF samples from the lumbar subarachnoid space, cisterna magna, or lateral cerebral ventricle were collected at intervals ranging from 15 to 420 min following drug administration. In normal animals, cisternal CSF was obtained at 30, 60, 90, 120, 180, and 420 min after the intravenous bolus administration. In animals with meningitis, cisternal CSF was obtained 15, 30, 60, 120, and 180 min after the intravenous bolus infusion. The techniques for CSF collection from infant subhuman primates have been described elsewhere (6). Lumbar puncture and cisterna magna puncture were performed percutaneously. Ventricular CSF was obtained by cerebral cortical puncture after a burr hole craniotomy was performed. A simultaneous serum specimen was obtained with each CSF sample.

Eight healthy infant *Macaca mulatta* monkeys were obtained from the New England Regional Primate Center and housed in individual incubators. The mean age was 16.3 days (range, 2 to 35 days); the mean weight was 509 g (range, 320 to 690 g). Eight *Macaca nemestrina* monkeys delivered by cesarean section were studied at the Seattle Primate Center. The mean age at the time of the study was 18.2 days (range, 14 to 20 days); the mean weight was 684 g (range, 525 to 964 g). Five infant monkeys, four *M. mulatta* and one *M. nemestrina*, were studied prior to the induction of meningitis. Repeat studies were performed with two *M. mulatta* monkeys after the induction of meningitis. To induce meningitis, animals were inoculated intranasally with *H. influenzae* type b strain E-1 that was originally isolated from a patient with meningitis (6). The lumbar CSF from bacteremic animals was examined 2 days after the bacterial density in the blood exceeded $10^3$ CFU/ml. The presence of meningitis was defined as CSF containing the inoculated bacterium at a density of $\geq 10^3$ CFU/ml and ≥100 polymorphonuclear leukocytes per μl (22). All animals were studied 2 to 9 days after meningitis was found to be present.

Twenty-three studies were performed on 10 animals with meningitis (four *M. mulatta* and six *M. nemestrina*). Fourteen studies were performed on five *M. mulatta* without meningitis; two of these animals were studied both prior to and after the development of meningitis. Two *M. mulatta* with meningitis expired during the study, terminating the studies at 45 and 90 min, respectively. A dose of 6 mg of gentamicin per kg was administered, except when the effect of dose was studied.

Gentamicin concentrations in serum and CSF were measured by a radioenzymatic assay (27) with [$^{14}$C]acetyl coenzyme A (New England Nuclear Corp., Boston, Mass.). C. Hough (Schering Corp.) provided standard powder with a potency of 651 μg/mg. In this assay the sensitivity was increased by increasing the specific activity of the [$^{14}$C]acetyl coenzyme A. A linear standard curve at concentrations from 0.1 to 20.0 μg/ml was constructed (27). All assays were performed in duplicate. Values of <0.1 μg/ml are reported as 0; the coefficient of variation of this assay was 9.6% at gentamicin concentrations between 0.1 and 20 μg/ml. The means of duplicate samples are depicted and were used for the calculations.

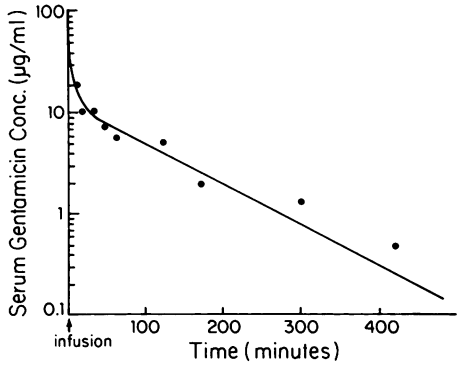


FIG. 1. Gentamicin concentrations in serum in a 0.53-kg *M. mulatta* monkey following a 6-mg/kg intravenous bolus. A biexponential regression line drawn by the least-squares method is indicated. The equation of the regression is $C_t = 37.5^{(-0.32\ min)} + 11.9^{(-0.009\ min)}$, where $C_t$ is the concentration at time $t$. The elimination half-life of the linear disposition phase is 69.3 min.

Least-squares linear regression analysis was used to obtain the slope of the gentamicin concentration in serum (or CSF) versus time curve. The slope of this curve was used to obtain $k_{el}$; the elimination half-life ($t_{1/2}$) was estimated from the relationship $t_{1/2} = (0.693/k_{el})$. Plasma clearance (CL) was estimated from the relationship $CL = k_{el}V$, where $V$ is the volume of distribution calculated by a model-independent method (19). The statistical significance of the differences in gentamicin concentrations or pharmacokinetic parameters was assessed by analysis of variance and the paired Student's $t$ test (3).

## RESULTS

**Elimination of gentamicin from plasma.** A representative curve of the disappearance of drug from serum following an intravenous bolus administration of gentamicin (6 mg/kg of body weight) to an infant *M. mulatta* is illustrated in Fig. 1. The curve is biphasic, suggesting that a two-compartment model best describes gentamicin pharmacokinetics in infant monkeys, similar to the disposition seen in humans (25). In human neonates, a dose increase of 1 mg/kg results in a 1.75-μg/ml increment in the peak concentration in serum (17). We assessed this relationship in two normal infant primates that received separate doses of 2, 4, 6, and 8 mg/kg. When the observed peak was plotted against the dose (data not shown), a linear relationship was observed ($r = 0.95$); a mean increase of 1.65 μg/ml per 1 mg/kg increase in dosage was calculated. These data suggest that infant monkeys distribute gentamicin similarly to human neonates. The mean elimination half-life from serum (calculated from concentrations in serum obtained ≥30 min following an intravenous bolus injection) in two normal infant *M. mulatta* during the dose escalation study was 83.7 ± 38.2 min (range, 38 to 183 min) and was independent of dose.

**Gentamicin concentration in CSF from normal animals.** With an intramuscular administration of 6 mg/kg, the gentamicin concentration in lumbar CSF was <0.1 μg/ml in 23 lumbar CSF samples from five animals obtained between 1 and 6 h after administration.

Gentamicin concentrations in cisternal CSF and the simultaneous concentrations in serum were measured after a

TABLE 1. Gentamicin concentrations in serum and cisternal CSF from normal infant monkeys

| Animal no. | Concn (μg/ml) at the following times (min)[a]: | | | | | | |
|---|---|---|---|---|---|---|---|
| | 30 | 60 | 90 | 120 | 150 | 180 | 420 |
| 1 | | 5.7/0.23 | | | | 2.3/0.21 | 0.5/0.13 |
| 3 | | 6.3/0.14 | | | | 3.2/0.12 | 0.7/0.11 |
| 4 | 9.0/0.12 | 5.1/0.22 | 5.6/0.43 | 3.0/0.12 | 2.5/0.13 | | |
| 5 | | 8.1/0.29 | | | | 3.4/0.14 | 1.8/0.63 |
| 10 | | 6.1/0.15 | | 3.1/0.11 | | 3.2/0.12 | 1.2/0.15 |

[a] All animals received 6 mg/kg as an intravenous bolus. Ratios of concentrations in serum to those in CSF were measured radioenzymatically. Four animals were *M. mulatta*, while one was *M. nemestrina*.

bolus administration (Table 1). Following the intravenous bolus administration, gentamicin was not detected (<0.1 μg/ml) in any of eight samples derived from two normal *M. mulatta* monkeys who received a bolus dose of 2 mg/kg. In the remaining three normal animals, the mean concentrations in cisternal CSF (60 min after administration) were 0.02 μg/ml (range, 0.0 to 0.1 μg/ml), 0.32 μg/ml (range, 0.1 to 0.8 μg/ml), 0.37 μg/ml (range, 0.1 to 2.09 μg/ml), and 0.43 μg/ml (range, 0.0 to 2.26 μg/ml) after intravenous bolus doses of 2, 4, 6, and 8 mg/kg, respectively. The mean lumbar concentration (0.37 ± 0.15 μg/ml) was slightly but significantly higher than the mean cisternal concentration (0.11 ± 0.06 μg/ml; $P < 0.05$ by Student's paired $t$ test) after a dose of 6 mg/kg. The gentamicin concentration in ventricular CSF was measured 10 times between 15 and 420 min after intravenous bolus administration in three animals. The concentration ranged from <0.10 to 2.00 μg/ml (mean concentration, 0.12 μg/ml; values for 4 of 10 monkeys were <0.20 μg/ml).

**Effect of meningitis on gentamicin pharmacokinetics.** Although the apparent volume of distribution was slightly smaller in animals with meningitis (512.27 ± 64.24 ml/kg), the value was not statistically different ($P > 0.05$) than that in normal animals (772.81 ± 119.78 mg/kg). There was no significant difference ($P > 0.05$) in the pharmacokinetic parameters in plasma (elimination half-life or plasma clearance) between infected (82.73 ± 29.91 min and 4.32 ± 0.65 ml/min per kg, respectively) and normal (96.3 ± 39.2 min and 5.65 ± 2.41 ml/min per kg, respectively) animals.

**Effect of duration of infusion on CSF penetration in animals with meningitis.** Because of the data obtained with normal animals, in which gentamicin penetration into CSF occurred only with the intravenous bolus administration, we compared the concentration in cisternal CSF of meningitic animals after a 30-min intravenous infusion and as an intravenous bolus; both were administered as a 6-mg/kg dose (Table 2). The maximum observed concentration in serum after the bolus administration was at 15 min (13.4 ± 2.6 μg/ml). In contrast, the maximum gentamicin concentration in serum occurred 60 min after the start of a 30-min infusion, 30 min after the infusion had concluded; the mean value was 9.9 μg/ml. With the bolus administration, a higher mean gentamicin concentration was achieved in cisternal CSF (2.8 μg/ml in comparison with a mean of 0.45 μg/ml with a 30-min infusion). In addition, there was greater variability in the gentamicin concentration in cisternal CSF with administration by a 30-min intravenous infusion.

**Gentamicin concentration in CSF from various sites during meningitis.** To compare the gentamicin concentrations in various CSF sites, we obtained lumbar and cisternal CSF specimens within minutes of each other at various times following an intravenous bolus administration of 6 mg of gentamicin per kg to six animals. CSF was not obtainable from all sites at each time point. Only averages of values of ≥0.10 μg/ml were obtained (Table 3). Concentrations in lumbar and cisternal CSF were nearly identical in three comparisons. Overall, however, the gentamicin concentration in the lumbar subarachnoid space was higher. The maximum concentration occurred 1 h after administration and was in the lumbar CSF (Table 3). The apparent elimination half-life of gentamicin was shortest in ventricular CSF (mean, 25.6 min) and longest in cisternal CSF (mean, 58.2 min). The average value in lumbar CSF was intermediate (35.2 min).

To compare gentamicin concentrations in cisternal CSF from animals with and without meningitis, we obtained serum and CSF specimens from two *M. mulatta* monkeys before intranasal inoculation with *H. influenzae* and after meningitis occurred. The gentamicin dose (6 mg/kg), administration technique (bolus), and sampling times were identical during each study (Table 4). Gentamicin concentrations in cisternal CSF averaged 0.214 and 0.952 μg/ml during the sampling period in healthy and meningitic animals, respectively. This difference was significant at $P < 0.02$ by Student's paired $t$ test.

The penetration of gentamicin (with the concentration in CSF expressed as a percentage of the concentration in

TABLE 2. Effect of infusion duration on gentamicin concentrations in cisternal CSF from six infant *M. nemestrina* with *H. influenzae* meningitis

| Time (min) after administration | Gentamicin concn (μg/ml) in the following samples with the indicated infusion durations[a]: | | | |
|---|---|---|---|---|
| | Serum | | Cisternal CSF | |
| | 30 min | Bolus | 30 min | Bolus |
| 15 | 5.8 ± 1.5 | 13.4 ± 2.6 | 0.12 ± 0.24 | 0.50 ± 0.24 |
| 30 | 8.6 ± 1.8 | 11.8 ± 2.0 | 0.23 ± 0.20 | 1.20 ± 0.41 |
| 60 | 9.9 ± 1.8 | 8.8 ± 1.4 | 0.26 ± 0.16 | 2.85 ± 0.34 |
| 120 | 6.2 ± 1.6 | 6.0 ± 1.2 | 0.45 ± 0.45 | 2.16 ± 0.26 |
| 180 | 3.6 ± 1.0 | 3.4 ± 0.9 | 0.36 ± 0.22 | 1.95 ± 0.21 |

[a] All animals received a 6-mg/kg dose as a bolus.

TABLE 3. Gentamicin concentration in serum and selected CSF sites during meningitis in six infant monkeys[a]

| Time (min) after administration | Gentimicin concn (μg/ml) in[b]: | | | | |
|---|---|---|---|---|---|
| | Serum | CSF[c] | | | |
| | | No. | Cisternal | Lumbar | Ventricular |
| 15 | 12.8 ± 2.4 | 4 | 0.46 ± 0.22 | 0.63 ± 0.15 | 0.42 ± 0.13 |
| 30 | 11.6 ± 1.8 | 5 | 1.20 ± 0.42 | 2.10 ± 0.22 | 1.88 ± 0.11 |
| 60 | 8.2 ± 1.0 | 5 | 2.64 ± 0.86 | 4.25 ± 1.08 | 2.10 ± 0.66 |
| 120 | 5.8 ± 0.8 | 4 | 2.08 ± 0.85 | 3.86 ± 0.86 | 2.08 ± 0.58 |
| 180 | 3.2 ± 0.8 | 5 | 2.02 ± 0.34 | 3.22 ± 0.66 | 1.69 ± 0.22 |

[a] Three infants were *M. mulatta* and three were *M. nemestrina*; data from these monkeys are included in Table 2.
[b] The mean gentamicin concentration ± the standard deviation is depicted. All animals received a 6-mg/kg dose as a bolus.
[c] CSF samples were not obtained from all six infants at each time point. No. refers to the number of infants from whom data at that time point were available.

serum) was also greater in animals with meningitis ($P < 0.05$ by Student's paired $t$ test). The ratio of the concentration in cisternal CSF to that in serum calculated from data in Table 2 ranged from 0 to 0.67, with a mean of 0.105, and tended to increase with time following drug administration (Fig. 2). The data in Table 4 also reflect this phenomenon. Higher ratios were almost exclusively a function of the declining concentrations in serum with time, while the concentrations in CSF remained relatively constant. The ratio of the concentrations in CSF to that in serum was higher in meningitic animals ($P < 0.01$ by analysis of variance), reflecting the higher concentrations in CSF observed in these animals.

## DISCUSSION

Aminoglycosides, like other polar drugs, enter the CSF primarily through the ventricular choroid plexus. A smaller fraction enters by transcapillary migration into the extracellular fluid of the brain and then goes into the CSF. The unionized, unbound form of the drug is thought to be the portion which penetrates the blood-CSF barrier. Gentamicin has a $pK_a$ of 8.6, which is outside the physiological pH range of blood of CSF. Thus, the amount of unionized drug is little affected by acid-base status. In patients with meningitis, there is loss of integrity of the blood-CSF barrier and an increased penetration of polar antibodies into CSF. The decreased barrier to aminoglycoside penetration in patients with meningitis appears to be due to the loss of capillary integrity in the choroid plexus (6) and in the meninges (1).

Data on the aminoglycoside penetration into the CSF compartment in humans and animals with meningitis indicate that there is a wide variation in achievable concentrations (4, 5, 10, 11, 23, 24). Since microbiological, immunological, and radioenzymatic assays were used to quantitate the concentrations in serum and CSF, interassay variability may have contributed to the wide variation in results. We used a radioenzymatic assay (27), as it requires small sample volumes and is not affected by the sample matrix (including other antibiotics) and the sensitivity can be increased by using radioactive substrates with high specific activities.

We found a consistent penetration of gentamicin into CSF in normal infant primates, but most values were ≤0.20 μg/ml. Gentamicin concentrations in CSF decreased little over the 8-h sampling interval in normal animals. The site with the slowest rate of gentamicin elimination, the lumbar area, is also thought to be an area of sluggish CSF flow. The gentamicin concentration in CSF increased approximately 5-fold in monkeys with meningitis, while the peak concentration in serum was only slightly greater (1.13-fold) (Table 2).

We found that an intravenous bolus administration produced the highest gentamicin concentrations in CSF. These data confirm the concept that the penetration of gentamicin into CSF is limited by diffusion. With high, although transient, gentamicin concentrations in serum produced by bolus administration, a greater concentration gradient between serum and CSF exists, favoring increased penetration. Our data on the method of aminoglycoside administration does not explain the discrepant data recorded in studies in human patients with meningitis. Chang et al. (5) did not detect gentamicin or kanamycin penetration into CSF following intravenous infusion in 10 infants. Eichenwald (7) found that after intramuscular administration, kanamycin was detectable in the CSF of all infants, whether or not meningitis was present. In infants with meningitis, Eichenwald (7) found concentrations as high as 9 μg/ml (7). Bruckner et al. (4) found that the average CSF (from the lumbar area) level of netilmicin in seven patients with bacterial meningitis was 1.15 μg/ml, while a maximum of 5.0 μg/ml was found in one patient; the average value in 23 samples from nine patients

TABLE 4. Mean gentamicin concentrations in serum and cisternal CSF from two infant monkeys before and after meningitis

| Time (min) after administration | Mean gentamicin concn (μg/ml) in[a]: | | | | | |
|---|---|---|---|---|---|---|
| | Normal monkeys | | | Monkeys with meningitis | | |
| | Serum | CSF | % Penetration | Serum | CSF | % Penetration |
| 15 | 11.7 | 0.201 | 1.7 | 13.3 | 0.411 | 3.0 |
| 30 | 8.2 | 0.196 | 2.4 | 11.5 | 1.103 | 9.6 |
| 45 | 6.4 | 0.198 | 3.1 | NA[b] | 1.206 | NA |
| 60 | 5.7 | 0.204 | 3.6 | 7.8 | 1.274 | 16.2 |
| 120 | 3.0 | 0.185 | 5.0 | 5.3 | 1.353 | 25.5 |
| 420 | 1.1 | 0.304 | 27.6 | 1.1 | 0.362 | 32.9 |

[a] Both *M. mulatta* monkeys received 6 mg/kg as an intravenous bolus.
[b] NA, Serum not available.

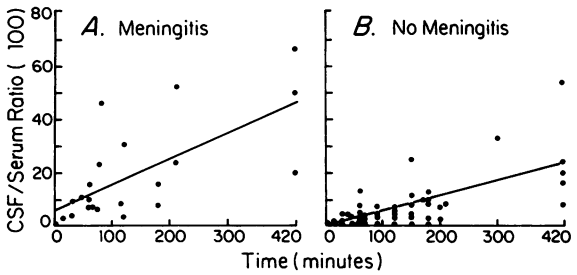


FIG. 2. Ratio of (gentamicin concentrations in CSF to that in serum) × 100 from animals with (A) and without (B) meningitis. Data from the study of six animals (Tables 1 and 2) are pooled. Linear regression lines obtained by the least-squares method are indicated. The equations of the regression lines are as follows: Meningitis $C_t = 6.38 + 0.09$ (min) (A); no meningitis $C_t = -0.1 + 0.06$ (min) (B), where $C_t$ is the concentration at time $t$.

was 1.11 μg/ml. Chang et al. (5) used the more specific radioenzymatic assay, while Eichenwald (7) used a bioassay. The differences in the results may be a reflection of the assay techniques that were used.

Cationic drugs such as gentamicin are thought to be cleared from the CSF primarily by bulk flow (26). We estimated the clearance of gentamicin from CSF in patients with meningitis in this study (Tables 2 and 3) by assuming that the infant monkey CSF volume is 5 ml and that it remains constant over the study and by calculating the excretion rate from the measured concentrations. Clearance is estimated by dividing the CSF excretion rate by the midpoint concentration of the elimination phase observed in a CSF compartment. By doing this, we found that clearance ranged from 9.8 to 26.6 μl/min. These values are 28 to 76% of the rate of CSF formation measured in adult monkeys (13, 28). This suggests the binding of gentamicin to tissue surrounding the CSF compartment or a decrease in CSF flow through arachnoid villi into the superior saggital sinus. Arachnoid villus dysfunction has been found in experimental meningitis in rabbits and is probably responsible for the decreased clearance of gentamicin from CSF.

Bolus intravenous gentamicin administration may achieve therapeutic concentrations in CSF in certain patients. However, if aminoglycosides are to be the sole antibiotics administered, as in the treatment of beta-lactam-resistant gram-negative bacterial meningitis, intrathecal administration ensures concentrations in CSF that are thought to be efficacious.

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## LITERATURE CITED

1. **Adams, R. D., C. S. Kubik, and F. J. Bonner.** 1948. The clinical and pathological aspects of influenzal meningitis. Arch. Pediatr. **63**:354–365, 408–414.
2. **Berman, P. H., and B. Q. Banker.** 1966. Neonatal meningitis. A clinical and pathological study of 29 cases. Pediatrics **38**:6–24.
3. **Brown, M. D., L. Engleman, J. W. Frame, M. A. Hill, R. I. Jenarich, and J. D. Toporek.** 1985. BMDP statistical software, p. 347–358. University of California Press, Berkeley.
4. **Bruckner, O., M. Trautmann, D. Kolodziejczyk, M. Alexander, and H. Collmann.** 1983. Netilmicin in human CSF after parenteral administration in patients with slightly and severely impaired blood CSF barrier. J. Antimicrob. Chemother. **11**:565–571.
5. **Chang, M. J., M. Escobedo, D. C. Anderson, L. Hillman, and R. D. Feigin.** 1975. Kanamycin and gentamicin treatment of neonatal sepsis and meningitis. Pediatrics **56**:695–699.
6. **Daum, R. S., D. W. Scheifele, V. P. Syriopoulou, D. R. Averill, and A. L. Smith.** 1978. Ventricular involvement in experimental *Haemophilus influenzae* meningitis. J. Pediatr. **93**:927–930.
7. **Eichenwald, A.** 1966. Some observations on dosage and toxicity of kanamycin in premature and full-term infants. Ann. N.Y. Acad. Sci. **132**:984–991.
8. **Fosson, A. R., and R. N. Fine.** 1968. Neonatal meningitis: presentation and discussion of 21 cases. Clin. Pediatr. **7**:404–410.
9. **Gilles, F. H., J. L. Jammes, and W. Berenberg.** 1977. Neonatal meningitis. The ventricle as a bacterial reservoir. Arch. Neurol. **34**:560–562.
10. **Goitein, K., J. Michel, and T. Sacks.** 1975. Penetration of parenterally administered gentamicin into the cerebrospinal fluid in experimental meningitis. Chemotherapy **21**:181–188.
11. **Kaiser, A. B., and Z. A. McGee.** 1975. Aminoglycoside therapy of gram-negative bacillary meningitis. N. Engl. J. Med. **293**: 1215–1220.
12. **Lee, E. L., M. J. Robinson, M. L. Thong, T. H. Ong, and K. K. Ng.** 1978. Intraventricular chemotherapy in neonatal meningitis. J. Pediatr. **91**:991–995.
13. **Levin, V. A., T. H. Milhorst, J. D. Fenstermacher, M. K. Hammock, and D. P. Roll.** 1971. Physiological studies on the development of obstructive hydrocephalus in the monkey. Neurology **21**:238–246.
14. **McCracken, G. H., and H. F. Eichenwald.** 1978. Antimicrobial therapy in infants and children. II. Therapy of infectious conditions. J. Pediatr. **93**:357–377.
15. **McCracken, G. H., and S. G. Mize.** 1976. A controlled study of intrathecal antibiotic therapy in gram negative enteric meningitis of infancy. Report of the Neonatal Cooperative Study Group. J. Pediatr. **89**:66–72.
16. **McCracken, G. H., S. G. Mize, and N. Threlkeld.** 1980. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Lancet **i**:787–791.
17. **Moellering, R. C., and E. G. Fischer.** 1972. Relationship of intraventricular gentamicin levels to cure of meningitis. J. Pediatr. **81**:534–537.
18. **Paisley, J. W., A. L. Smith, and D. H. Smith.** 1973. Gentamicin in newborn infants. Comparison of intramuscular and intravenous administration. Am. J. Dis. Child. **126**:473–477.
19. **Perrier, D., and Mayersohn, M.** 1982. Noncompartmental determination of the steady-state volume of distribution for any mode of administration. J. Pharm. Sci. **71**:372–373.
20. **Pickering, L. K., C. D. Ericsson, G. Ruiz-Palacios, J. Blevins, and M. E. Miner.** 1978. Intraventricular and parenteral gentamicin therapy for ventriculitis in children. Am. J. Dis. Child. **132**:480–483.
21. **Salmon, J. H.** 1972. Ventriculitis complicating meningitis. Am. J. Dis. Child. **124**:35–40.
22. **Scheifele, D. W., R. S. Daum, V. P. Syriopoulou, D. R. Averill, and A. L. Smith.** 1980. *Haemophilus influenzae* bacteremia and meningitis in infant primates. J. Lab. Clin. Med. **95**:450–462.
23. **Scheld, W. M., R. S. Brown, and M. A. Sande.** 1978. Comparison of netilmicin with gentamicin in the therapy of experimental *Escherichia coli* meningitis. Antimicrob. Agents Chemother. **13**: 899–904.
24. **Scheld, W. M., R. G. Dacey, H. R. Winn, J. E. Walsh, J. E. Jane, and M. A. Sande.** 1980. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis. J. Clin.

Invest. **66**:243–253.
25. **Siber, G. R., P. Echeverria, A. L. Smith, J. W. Paisley, and D. H. Smith.** 1975. Pharmacokinetics of gentamicin in children and adults. J. Infect. Dis. **132**:637–651.
26. **Spector, R.** 1975. The transport of gentamicin in the choroid plexus and cerebrospinal fluid. J. Pharmacol. Exp. Ther. **194**: 82–88.
27. **Weber, A., A. L. Smith, and K. E. Opheim.** 1985. Radioenzymatic assays for aminoglycosides with kanamycin 6′-acetyltransferase. J. Clin. Microbiol. **21**:419–424.
28. **Welch, K., and M. Pollay.** 1961. Perfusion of particles through the arachnoid villi of the monkey. Am. J. Physiol. **201**:651–654.