Cerebrospinal Fluid Diffusion of Kanamycin in Newborn Infants

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Cerebrospinal fluid (CSF) diffusion of kanamycin was studied in 35 newborn infants. Five infants had bacterial meningitis and two had viral meningitis. One-half of the infants received an intramuscular injection of 7.5 mg of kanamycin per kg, whereas the other half received 12.5 mg/kg. Serum and CSF specimens were obtained 3 to 6 hr and 11 to 12 hr after injection. No significant difference was observed between serum levels of kanamycin after the 7.5 and 12.5 mg/kg doses at either sampling time. However, at 3 to 6 hr, in those infants without meningitis, there was a significantly higher concentration of kanamycin in the CSF after the larger 12.5 mg/kg dose. CSF levels of kanamycin did not rise to the desirable therapeutic range with either dose. We were unable to draw a definite conclusion regarding the CSF diffusion of kanamycin in bacterial meningitis, but our data suggest that complete confidence in intramuscular kanamycin in the treatment of gram-negative neonatal meningitis may not be justified, even in those cases with a brisk inflammatory response.

Despite scant information in the literature regarding cerebrospinal fluid (CSF) diffusion in the newborn infant, intramuscular kanamycin is recommended and routinely employed in the treatment of neonatal meningitis. In 1958, Tisch et al. (10) reported CSF levels of 11 to 28 µg/ml at 2 to 6 hr after intramuscular injection of kanamycin in a dose of 50 mg/kg to anesthetized dogs. However, Boger and Gavin (2) and Ruiz-Sanchez et al. (7) demonstrated very low levels of kanamycin in the CSF of humans with uninflamed meninges. Despite high peak serum levels after intramuscular administration, only a trace to 0.5 µg of the antibiotic per ml was detected in the CSF. Eichenwald (3) determined kanamycin levels in the serum and CSF of premature and full-term infants with and without meningitis. He found a mean peak serum level of 18 µg/ml 1 hr after the intramuscular injection of 7.5 mg of kanamycin per kg and showed that the serum levels attained were not significantly affected by the age or weight of the infant. In Eichenwald's study, spinal fluid concentration of the antibiotic ranged from 0.1 to 0.2 the peak serum level, and the highest CSF levels occurred 3 to 6 hr after injection. A mean peak CSF concentration of 9 µg/ml was detected in eight infants with bacterial meningitis after an intramuscular dose of 7.5 mg of kanamycin per kg. This level was more than twice that attained in eight infants with uninflamed meninges.

Because the literature contains only these few studies of CSF diffusion of kanamycin and because we were perplexed by several clinical experiences suggesting inadequate eradication of susceptible strains from CSF, we re-examined serum and CSF levels of kanamycin in the neonate.

MATERIALS AND METHODS

To study the CSF diffusion of kanamycin, we obtained serum and CSF samples from 35 infants in the Newborn Nursery and Neonatal Intensive Care Unit at Harbor General Hospital during 1967 to 1969. All of these infants were receiving kanamycin, as well as penicillin or ampicillin, for therapeutic or prophylactic purposes. The group included 19 full-term babies from 1 to 54 days of age and 16 preterm infants from 1 to 53 days old. Among the full-term infants, three had meningeal inflammation as evidenced by an abnormal number of leukocytes in the CSF, but two of these were subsequently shown to have viral meningitis. In the preterm group, four infants had bacterial meningitis.

In approximately one-half of the infants studied, samples were collected after an injection of 7.5 mg of kanamycin per kg, whereas the other half received 12.5 mg/kg. In each case, the kanamycin was given intramuscularly in an undiluted form by using a 1-ml tuberculin syringe. The pediatric preparation of
kanamycin is dispensed in solution by the manufacturer and contains 75 mg of the antibiotic per 2 ml. In addition to kanamycin, all the infants studied received either penicillin or ampicillin intravenously or intramuscularly in another extremity.

Both serum and CSF specimens were obtained at 3 to 6 hr after injection, when peak levels of kanamycin reportedly occur in the spinal fluid, and again at 11 to 12 hr. In certain instances, we were unable to collect a sample at 11 to 12 hr, and so these determinations are fewer in number.

Blood specimens were centrifuged, and the serum was frozen. CSF samples were frozen without further processing. All specimens were shipped in the frozen state to Bristol Laboratories where concentrations of kanamycin were determined by means of an agar plate bioassay technique. Penicillinase was added to inactivate the penicillin or ampicillin in the samples.

RESULTS

Serum. At 3 to 6 hr after an intramuscular injection of 7.5 mg of kanamycin per kg, the mean serum level of kanamycin was 8 μg/ml (standard deviation [SD] ± 5.0; range 2.0–19.0), and at 11 to 12 hr this level had dropped to a mean of 3.6 μg/ml (SD ± 2.5; range 0.9–7.3). After a dose of 12.5 mg/kg, we found a mean serum level of 10 μg/ml (SD ± 6.8; range 1.0–13.0) at 11 to 12 hr.

The difference between the mean serum level attained with a 7.5-mg dose of kanamycin per kg and that reached with a 12.5 mg/kg dose at either 3 to 6 or 11 to 12 hr after intramuscular injection was not statistically significant (Student’s t test). Moreover, we were unable to correlate antibiotic levels with the age or weight of the infants.

CSF. After an intramuscular dose of 7.5 mg of kanamycin per kg, the mean level of kanamycin attained in those infants without meningitis was 1.3 μg/ml (SD ± 0.7) at 3 to 6 hr and 1.0 μg (SD ± 0.5) at 11 to 12 hr (Fig. 1). At 3 to 6 hr, the two infants with viral meningitis showed concentrations below 1.0 μg/ml, but the infant with bacterial meningitis had attained a concentration of 3.9 μg/ml. At 11 to 12 hr, the levels in all three infants were 1.0 and less than 1.0 μg/ml.

After an intramuscular dose of 12.5 mg/kg, the mean CSF concentration of kanamycin attained by the group without meningitis was 2.2 μg/ml (SD ± 1.3) at 3 to 6 hr postinjection and 1.5 μg (SD ± 0.9) at 11 to 12 hr (Fig. 2). All four cases of meningitis were bacterial in origin, and we observed a good inflammatory response in the CSF. The mean CSF level of kanamycin in these patients was 1.6 μg/ml (SD ± 1.0) 3 to 6 hr after injection. Unfortunately, only one level was determined at 11 to 12 hr (0.8 μg/ml).

We could not relate the concentrations measured in the CSF to the age or weight of the infants. However, at 3 to 6 hr after injection in infants without meningitis, we did observe a statistically significant difference (P < 0.01 Student’s t test) between the CSF level of kanamycin attained after a 7.5-mg dose and that reached after a 12.5 mg/kg dose. The mean level with the higher dose was almost twice as high as that with the lower dose. The number of cases of meningitis in either group was too small to allow significant comparison of the CSF level of kanamycin in these infants with that in the infants with normal meninges. We can only point out that in those infants with bacterial meningitis the peak level of
kanamycin in the spinal fluid at 3 to 6 hr, despite the dosage used, remained below the minimal inhibitory concentration for the usual gram-negative bacillary pathogens of the neonate.

**DISCUSSION**

According to some investigators, the species responsible for most gram-negative neonatal infections are susceptible to kanamycin at a concentration of 5.0 \( \mu g/mL \) (3, 6, 12), although other studies demonstrate that a higher concentration is necessary (4, 5, 11). In small infants, adequate serum levels of kanamycin, well within the accepted therapeutic range, can be attained with the usually recommended intramuscular dose of 7.5 mg/kg, given every 12 hr. The mean peak serum level of approximately 18 \( \mu g/mL \) occurs about 1 hr after injection (1, 3, 8). We collected our first serum samples at 3 to 6 hr postinjection, the time of the expected peak levels in the CSF. As a function of the antibiotic dose, a mean serum concentration of 8 to 10 \( \mu g/mL \) is not surprising between 3 and 6 hr after injection. However, a broad scatter of antibiotic concentrations was observed. This wide range can be explained partially by the observation that serum levels of kanamycin decline rapidly during this period of time (1, 3). Indeed, levels measured at 3 hr postinjection have been reported to be as much as five times higher than those measured at 6 hr. Each infant's rate of kanamycin metabolism provides possible explanation for the variability of serum levels encountered between 3 and 6 hr after administration, when the metabolism of the drug is already underway. The injection of kanamycin in an undiluted form may also contribute to the wide range of antibiotic concentrations, despite the use of a small syringe. Since the kanamycin preparation available to the pediatrician contains 75 mg of the antibiotic in 2 mL of solution, the excess or loss of only a few drops of the drug during administration might result in significant differences in the serum level, especially when very small doses must be given.

As noted above, no significant difference was observed, at either sampling time, between serum levels achieved after a 7.5 mg/kg dose and the levels resulting from a 12.5 mg/kg dose. This difference may have occurred prior to our first sampling time, but we have no data to substantiate it.

On the other hand, at 3 to 6 hr after an injection in those infants without meningitis, we did observe a significantly higher concentration of kanamycin in the CSF after the 12.5 mg/kg dose. This difference may justify the use of the larger dose in infants with meningitis.

Regardless of the dose of kanamycin administered, in our experience the CSF levels at either time of sampling did not rise to the desired therapeutic range. As reported by Eichenwald (3), this is not surprising in patients with normal meninges. We could not study enough infants with inflamed meninges to draw a definite conclusion regarding the CSF diffusion of kanamycin in bacterial meningitis. Our data do suggest, however, that complete confidence in the use of intramuscular kanamycin in the treatment of gram-negative neonatal meningitis may not be justified, even in those cases with a brisk inflammatory response.

If we were certain that inflamed meninges allow adequate diffusion of kanamycin into the CSF, we must still recall that many infants do not produce the desired meningeal inflammatory response. This is especially true of small debilitated infants and of many who develop meningitis accompanying sepsis. A repeat lumbar puncture 24 to 48 hr after initiation of therapy should be performed in all cases of neonatal meningitis treated with intramuscular kanamycin, to define the eradication of bacteria.

The use of intrathecal kanamycin, as proposed by Smith (9) and Yow and Yow (13), would constitute a valuable adjunct to the intramuscular administration of this antibiotic, particularly when a repeat spinal tap reveals persistent cellular and biochemical abnormality or bacteria.

If intramuscular therapy alone is to continue, administration of kanamycin in this fashion should be performed with strict attention to detail on the part of nursing personnel. When very small doses are given, the preparation should probably be diluted in the syringe, lest the loss of a few drops during injection contribute to undesirably low levels in the patient.

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**LITERATURE CITED**

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