Intraventricular administration of amikacin for complicated Gram-negative meningitis and ventriculitis

TIMOTHY C. WIRT, M.D., ZELL A. MCGEE, M.D., EDWARD H. OLDFIELD, M.D., AND WILLIAM F. MEACHAM, M.D.

Department of Neurosurgery and the Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

Four pediatric neurosurgical patients with Gram-negative meningitis and ventriculitis were treated with parenteral and intraventricular amikacin, a new aminoglycoside. The organisms infecting these patients were resistant to multiple antimicrobial drugs but were sensitive to amikacin. Treatment was continued for 14 days after cerebrospinal fluid cultures became negative. All four patients were cured and have demonstrated no nephrotoxicity, ototoxicity, or evidence of persistent infection on follow-up examination.

KEY WORDS • amikacin • Gram-negative meningitis • intraventricular therapy

In recent years Gram-negative bacteria have been the causative agents of an increasing proportion of cases of meningitis in neurosurgical patients. These bacteria caused 80% of such infections in a recent report. The mortality associated with Gram-negative bacillary meningitis in neurosurgical patients has been about 60%. Therapy via the parenteral route has often been unsuccessful, probably because many of the drugs which were active against Gram-negative bacteria fail to penetrate the blood-brain barrier. Although intralumbar administration of drugs such as the aminoglycosides has been recommended to circumvent this problem, recent studies have documented that aminoglycosides administered via the lumbar intrathecal route do not reliably enter the ventricular system. Therefore the intralumbar route of therapy is not optimal since ventriculitis complicates meningitis in over 70% of cases of Gram-negative meningitis. Rather, parenteral plus intraventricular administration of aminoglycosides, which results in their distribution throughout the intracerebral and extracerebral cerebrospinal fluid (CSF) spaces, is apt to provide optimal therapy.

The recent emergence of Gram-negative organisms resistant to gentamicin, that cause hospital-acquired infections in this and other institutions, has stimulated investigation of alternative antimicrobial agents. Amikacin sulfate, a semisynthetic aminoglycoside related to kanamycin, has a wide range of antimicrobial activity including Pseudomonas and gentamicin-resistant organisms. Amikacin administered by the parenteral and intraventricular route proved successful in the treatment of the four cases of Gram-negative meningitis in pediatric neurosurgical patients reported here.

Clinical Materials and Methods

All pediatric patients with Gram-negative meningitis on the neurosurgical service at Vanderbilt University Hospital who have been treated with parenteral and intraventricular amikacin are included in this study. The sensitivity of infecting organisms to various antimicrobial drugs was determined by the disc-diffusion method of Bauer, et al., the tube-dilution method, or both. Serum and CSF concentrations of amikacin were determined by the zone-inhibition method. In the two patients receiving amikacin by percutaneous intraventricular injections, amikacin concentrations in the CSF were obtained just before the next scheduled dose. In those patients with an Ommaya reservoir or intraventricular catheter, aspirations were obtained at varying intervals after drug administration.

Intraventricular amikacin was given in a concentration of 1 mg/ml. The diluent was saline without preservative. Direct intraventricular instillation was by mild barbotage. In the early phases of this study,
After removal of the shunt he was treated with intravenous chloramphenicol (100 mg/kg/day) and he intraculitis 2 weeks after discharge following planement wound infection and mortal inhibitory concentration of chloramphenicol for the improved clinically. However, positive CSF cultures Persisted even though venous chloramphenicol concentrations were 12.5 mg/ml (the minimum inhibitory concentration of chloramphenicol for the infecting organism was only 3.13 μg/ml). Parenteral and intraventricular administration of amikacin via a percutaneous ventricular puncture was therefore begun. The initial intraventricular dose of 0.2 mg/ml CSF/day was subsequently adjusted to 0.1 mg/ml CSF/day because of rising trough amikacin concentrations in the ventricular CSF. Cultures of multiple CSF specimens were negative after the second day of therapy. Amikacin treatment was administered for 18 days. The VP shunt was replaced and there has been no clinical evidence of infection during 10 months of outpatient observation.

**Case 3**

This 1-year-old baby boy developed recurrent meningitis associated with lumbosacral dermal sinus. After initial therapy of the meningitis with chloramphenicol, excision of the sinus was performed. The initial postoperative course was complicated by meningitis and ventriculitis caused by *Escherichia coli* which was sensitive to chloramphenicol. Therapy with intravenous chloramphenicol (80 mg/kg/day) was administered for 15 days. The organism became resistant to chloramphenicol and CSF cultures remained positive. The organism was found to be susceptible to amikacin, and therapy was begun with this drug via the parenteral and intraventricular routes. Intraventricular therapy was facilitated by placement of an Ommaya reservoir. Cultures remained negative after 1 day of amikacin instillation. No complications ensued. The Ommaya reservoir and catheter were removed 5 months after termination of therapy. There has been normal growth and development during the 22 months of follow-up review, and tests of intelligence and audiometric function have been normal.

**Case 4**

This 3-year-old girl underwent suboccipital cranieotomy and excision of a medulloblastoma. This procedure was followed by temperatures of 103° F, and lumbar and ventricular CSF cultures were positive for *Acinetobacter calcoaceticus* (var. Lwoffii) which was resistant to chloramphenicol. Therapy was instituted with parenteral and intraventricular amikacin (administered via an external ventriculostomy through a previously placed occipital burr opening). The initial intraventricular amikacin dose was 0.26 mg/ml CSF/day divided into two 12-hour doses. Because of undesirably high levels of the drug in both the ventricular and lumbar CSF, the dose was lowered to 0.1 mg/ml CSF/day given in one 24-hourly dose. After each intraventricular dose, the shunt was clamped for 2 hours then unclamped until the next dose was administered (Fig. 1). Cultures of CSF were negative on the third day of therapy and remained so for the following 14 days of therapy and in multiple post-therapy specimens. Irradiation and chemotherapy were administered and the patient was subsequently discharged. An audiogram, performed

---

**Case Reports**

**Case 1**

This neonatal boy developed a CSF leak at the site of a myelomeningocele repair 17 days postoperatively. Although he was receiving prophylactic amoxicillin and gentamicin, a febrile course ensued and the ventricular CSF grew *Serratia marcescens*, which was resistant to all commercially available antimicrobial drugs tested except amikacin. Amikacin therapy was initiated via the intraventricular route and by direct ventricular puncture through the anterior fontanel. The dose of intraventricular amikacin was initially 0.3 mg/ml of estimated CSF volume every 24 hours but later was adjusted to 0.1 mg/ml CSF/day after accumulation of amikacin was noted in the CSF. Ventricular CSF cultures became negative on the 10th day of treatment. The patient received a total of 24 days of therapy. Multiple specimens of ventricular CSF taken after cessation of therapy resulted in no growth on culture for bacteria. Communicating hydrocephalus ensued and a ventriculoperitoneal (VP) shunt was placed. No further problems have been encountered at 1 year of follow-up review. Special audiometric testing showed no hearing defects, even though CSF levels of amikacin as high as 146 μg/ml were documented.

**Case 2**

This 2½-month-old baby boy was admitted with a wound infection and *Klebsiella pneumoniae* ventriculitis 2 weeks after discharge following planelment of a VP shunt for communicating hydrocephalus. After removal of the shunt he was treated with intravenous chloramphenicol (100 mg/kg/day) and he improved clinically. However, positive CSF cultures persisted even though ventricular CSF chloramphenicol concentrations were 12.5 mg/ml (the minimum inhibitory concentration of chloramphenicol for the infecting organism was only 3.13 μg/ml). Parenteral

---

**Case Reports**

**Case 1**

This neonatal boy developed a CSF leak at the site of a myelomeningocele repair 17 days postoperatively. Although he was receiving prophylactic amoxicillin and gentamicin, a febrile course ensued and the ventricular CSF grew *Serratia marcescens*, which was resistant to all commercially available antimicrobial drugs tested except amikacin. Amikacin therapy was initiated via the intraventricular route and by direct ventricular puncture through the anterior fontanel. The dose of intraventricular amikacin was initially 0.3 mg/ml of estimated CSF volume every 24 hours but later was adjusted to 0.1 mg/ml CSF/day after accumulation of amikacin was noted in the CSF. Ventricular CSF cultures became negative on the 10th day of treatment. The patient received a total of 24 days of therapy. Multiple specimens of ventricular CSF taken after cessation of therapy resulted in no growth on culture for bacteria. Communicating hydrocephalus ensued and a ventriculoperitoneal (VP) shunt was placed. No further problems have been encountered at 1 year of follow-up review. Special audiometric testing showed no hearing defects, even though CSF levels of amikacin as high as 146 μg/ml were documented.

**Case 2**

This 2½-month-old baby boy was admitted with a wound infection and *Klebsiella pneumoniae* ventriculitis 2 weeks after discharge following planelment of a VP shunt for communicating hydrocephalus. After removal of the shunt he was treated with intravenous chloramphenicol (100 mg/kg/day) and he improved clinically. However, positive CSF cultures persisted even though ventricular CSF chloramphenicol concentrations were 12.5 mg/ml (the minimum inhibitory concentration of chloramphenicol for the infecting organism was only 3.13 μg/ml). Parenteral
Intraventricular therapy of Gram-negative meningitis

![Graph showing pharmacodynamics of amikacin](image)

**Fig. 1. Case 4. Pharmacodynamics of amikacin in ventricular (V) and lumbar (L) cerebrospinal fluid (CSF) following intraventricular administration on three occasions during therapy.** Note that therapeutic concentrations of amikacin were achieved in the lumbar CSF in association with clamping of the ventricular drain. In all of the curves, the CSF concentrations never fall below the minimum inhibitory and bacteriocidal concentrations for the organism (*hatched area* and *asterisk*), which was 0.78 μg/ml.

After the full course of amikacin, was normal. There has been no evidence of recurrent infection in 7 months of follow-up observation.

**Summary of Results**

All patients had culture-proven Gram-negative meningitis and ventriculitis associated with clinical manifestations of infection. The organisms from three of the four patients were either resistant to gentamicin initially or developed resistance to chloramphenicol during therapy. With amikacin therapy there were no treatment failures. No morbidity or mortality attributable to parenteral or intraventricular amikacin therapy was observed. Despite the high concentrations of amikacin achieved for over 2 weeks of therapy in all cases, audiometric testing, which was carried out in three patients, showed no abnormalities. One patient, who had an Ommaya reservoir in place for 5 months, had intelligence tests performed before and after removal of the reservoir and had normal intelligence for his age. Follow-up periods ranged from 7 to 22 months.

A variety of methods were used to administer intraventricular amikacin. Neither the concentrations of amikacin obtained in the ventricular and lumbar CSF nor the response to treatment was affected by the particular means of intraventricular administration of amikacin.

The bacteriological response to therapy, as measured by sterile CSF cultures, was prompt in two patients whose CSF showed no growth after the first intraventricular dose. Sterilization of the CSF did not occur until 10 and 13 days after initiation of therapy in the remaining two cases, yet they were cured by continuing amikacin which was bacteriocidal for the infecting organism.

Although optimal intraventricular doses of amikacin have not been systematically established, we have attempted to give a dose once a day that yields CSF concentrations which, at the end of the interval between doses are at, or slightly above, the concentrations required to kill the infecting organism (minimum bacteriocidal concentration). Adjustment of the initial intraventricular dose was necessary in all
four patients because of accumulation of drug beyond desired trough levels relative to the minimum inhibitory and bacteriocidal concentrations of the organisms involved.

With a 0.1 mg/ml intraventricular dose of amikacin, the intraventricular and lumbar drug levels were relatively consistent from day to day when levels obtained at equal intervals after drug administration were compared. The CSF antibiotic concentration could, therefore, be reliably estimated at varying intervals after drug administration in each patient once a constant daily intraventricular dosage had been employed.

The minimum inhibitory and bacteriocidal concentrations of amikacin for the infecting organisms ranged from 0.78 to 3.13 μg/ml and 0.78 to 6.25 μg/ml, respectively. These concentrations were consistently exceeded by the CSF drug levels for the duration of the 24-hour period between doses, with doses of 1 to 8 mg/24 hrs or 0.1 to 0.3 mg/ml CSF/24 hrs intraventricularly, in addition to the parenteral dose of 7.5 mg/kg/12 hrs.

Discussion

The increasing proportion of hospital-acquired meningitis caused by Gram-negative organisms is exemplified by a recent 15-year retrospective study of hospital-acquired meningitis in neurosurgical patients. Over 80% of cases were caused by Gram-negative enteric organisms, and 58% of the patients died. Fourteen of the 19 Gram-negative infections were due to Klebsiella, Enterobacter, or Serratia. Half the deaths occurred within 1 week of initiation of therapy. The results of therapy were not altered by lumbar intrathecal gentamicin administration as opposed to other modes of therapy.

Optimal aminoglycoside therapy of Gram-negative bacillary ventriculitis may require direct instillation of the antibiotic into the ventricular CSF. Intravenous administration of aminoglycosides alone does not result in therapeutic CSF levels. This has been well documented in previous studies with other aminoglycosides and specifically with amikacin. Lumbar intrathecal therapy is difficult after the first few days of therapy and was contraindicated in two of the four patients in our series because of naturally occurring or surgical defects in the lumbar subarachnoid space. More importantly, antibiotics administered into the lumbar area generally fail to reach the ventricular system. In contrast, antibiotics administered into the ventricles are distributed throughout the intracerebral and extracerebral CSF space.

The previously reported death rate in patients with Gram-negative bacillary meningitis who received parenteral or parenteral plus intralumbar therapy has ranged from 30% to 60%. However, in a recent series, in which all patients received parenteral plus intraventricular therapy, the death rate was only 6%.

Thirteen of the 16 patients had a Rickham reservoir inserted for ease of access to the ventricles. This supports the importance of intraventricular administration of an appropriate antibiotic.

Delay in sterilization of the ventricular CSF despite adequate trough levels of antibiotic for the minimum inhibitory or bacteriocidal concentrations of the organisms was encountered in two of our patients. A similar delay has previously been emphasized with Gram-negative meningitis treated with parenteral therapy alone. This was also noted in the report of Lee, et al., in which 10 of 16 CSF cultures were still positive after 24 hours of therapy, and one was positive as long as 10 days after initiation of therapy. A prolonged period of positive CSF cultures despite antibiotic concentrations well in excess of the amount necessary to kill the infecting organism is a feature of some cases of Gram-negative meningitis treated with a variety of antibiotics. It is important to obtain multiple peak and trough antibiotic concentrations periodically during therapy to ensure that antibiotic levels are consistently above the minimum inhibitory concentrations of the organism (Fig. 1). If the cultures remain positive, a change in antibiotic susceptibility of the infecting organism may be a possible explanation. However, if the patient is clinically improving and antibiotic levels are adequate, the antibiotic regimen should not be altered just because sterilization of the CSF is delayed.

Amikacin was effective in curing all four patients treated and no adverse effects of parenteral or intraventricular administration were detected. No bacteria developed in vivo resistance during therapy. Its use was especially valuable in the patient whose infecting bacterium had already developed resistance to gentamicin. Indeed, amikacin is the drug of choice in Gram-negative infections known to be caused by gentamicin-resistant organisms or in initial therapy of infections suspected to be caused by gentamicin-resistant organisms because the infections occur in settings such as intensive care units where such organisms are known to be present. If the infecting organism is not resistant to gentamicin or tobramycin or if there are no such organisms in the environment, either gentamicin or tobramycin in appropriate dosage (roughly one-third that of amikacin) may also be effective in the therapy of Gram-negative bacillary meningitis. Recent data indicate that amikacin is no more ototoxic or nephrotoxic than gentamicin.

Amikacin levels in the CSF and serum can easily be obtained for monitoring purposes, either by the zone-inhibition method or commercially available radioimmunoassay.

It has been particularly difficult to cure meningitis associated with VP or ventriculoatrial (VA) shunts, without removal of the shunt apparatus. Although the cure rate is increased from about 10% (with parenteral therapy alone) to about 40% with the addition of intraventricular therapy, the proportion of failures of therapy is still quite large. A possible explanation for...
Intraventricular therapy of Gram-negative meningitis

the failure of intraventricular therapy to improve the cure rate even more is that a drug administered into the ventricles fails to reach the lumbar area in the presence of a shunt. This explanation is supported by the finding of Larson, et al.,4 that the flow of radioactive tracer from the ventricle into the lumbar area was diminished or absent if the shunt was functioning. In this regard it was of interest to study the pharmacodynamics of amikacin in our Case 4 in which the drainage of CSF to an external receptacle resembled in many respects the drainage of CSF in the presence of a shunt. In this patient, the clamping of the catheter for 2 hours after administration of amikacin into the ventricles was associated with the achievement of therapeutic concentrations of amikacin in the lumbar CSF (Fig. 1). More studies are needed to determine if clamping of a VP or VA shunt following intraventricular administration of antibiotics results in more effective delivery of antibiotic into the lumbar area and a higher cure rate, as suggested by McGee and Kaiser.16

The daily intraventricular dose of 0.1 mg/ml estimated CSF, although empirical, achieved CSF concentrations that were adequate at their peak and usually not more than 4 to 8 times the minimum inhibitory concentration of the infecting organism at the end of the interval between doses. A problem with this dosage scheme is that there currently is no reliable and accepted means of measuring total CSF volume in the individual patient. Computerized tomography has recently been used to calculate the volume of the cerebral ventricles;14 however, in the absence of hydrocephalus the ventricular volume is only 5% to 30% of the total CSF volume into which an antimicrobial agent is distributed.4,9,18 The total CSF volume has been estimated to be 40 to 60 ml in babies, 60 to 100 ml in young children, 80 to 120 ml in older children, and 110 to 160 ml in adults.10,18 The dynamics of antimicrobial agents in the CSF would also be expected to be influenced by the rate of CSF production and absorption, the changing status of the blood-brain barrier with varying degrees of meningeal inflammation, and serum antimicrobial concentration. An initial dose based on estimated CSF volume of drug distribution would therefore still require surveillance of CSF drug levels and the frequent use of determinations of the minimum inhibitory and bacteriocidal concentrations for the infecting organisms for precisely establishing the optimal intraventricular dose.

Acknowledgment
Audiometric and intelligence testing was kindly performed by Ms. Ann B. Silton at the Bill Wilkerson Hearing and Speech Center, Nashville, Tennessee.

References


Address reprint requests to: William F. Meacham, M.D., Department of Neurosurgery, Vanderbilt University Hospital, Nashville, Tennessee 37232.