CASE REPORT

Intraventricular Tobramycin in a Premature Infant with Pseudomonas Meningitis

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A 38-week postconceptional age (29-week gestational age) infant required the placement of an Ommaya reservoir following a grade IV intraventricular hemorrhage and progressive hydrocephalus. At 70 days of age, a cerebrospinal fluid (CSF) culture was positive for *Pseudomonas aeruginosa* and the infant was empirically treated with age-appropriate parenteral doses of ceftazidime and gentamicin. This antibiotic regimen was changed to meropenem and tobramycin following the results of sensitivity reports. The infection failed to respond despite aggressive systemic dosing of antibiotics and removal of the Ommaya reservoir. Intraventricular injections of tobramycin were added to the systemic antibiotic regimen at a dose of 2 mg daily with subsequent doses adjusted to maintain trough concentrations in the CSF of 20–30 μg/mL. The CSF was sterilized after three days of intraventricular injections. The infant completed seven days of intraventricular tobramycin plus a 24-day regimen of systemic antibiotics. No acute complications were noted with the addition of intraventricular injections.

KEYWORDS: intraventricular, meningitis, neonate, tobramycin

J Pediatr Pharmacol Ther 2003;9:55-62

INTRODUCTION

Gram-negative meningitis is associated with a high rate of morbidity and mortality in neonates and requires aggressive management with systemic antibiotic therapy. Reasons for high mortality rates can be attributed to poor antibiotic penetration into the central nervous system (CNS) and antimicrobial resistance associated with bacterial meningitis. Although an inflamed meninges enhances a moieties penetration into the CNS, CSF concentrations of tobramycin following systemic administration may be insufficient to produce a bactericidal effect, particularly in an environment deficient in opsonins and complement.[1,2] In such situations, instillation of an antibiotic directly into the CNS via intraventricular (IVT) or intrathecal (IT) administration may be necessary to achieve adequate concentrations in the CNS.[1] Vancomycin, gentamicin, tobramycin, amikacin, and amphotericin B are antimicrobials that have been administered via these routes.[1] Previous IVT administration of penicillins and cephalosporins have resulted in neurotoxicities (e.g., seizures, paraplegia) that have hindered their use.[1] Mortality from *Ps aeruginosa* sepsis or meningitis has also been reported to be inversely related to postnatal age at diagnosis.[3] This report describes a premature infant with hydrocephalus who developed pseudomonas meningitis that was successfully eradicated with the aid of IVT tobramycin.

CASE REPORT

A 38-week postconceptional age (29-week gestational age) neonate was born to a 30-year-old G_4P_3 by spontaneous vaginal delivery due to preterm labor and premature rupture of the membranes. He was admitted to the intensive care nursery for respiratory distress syndrome,

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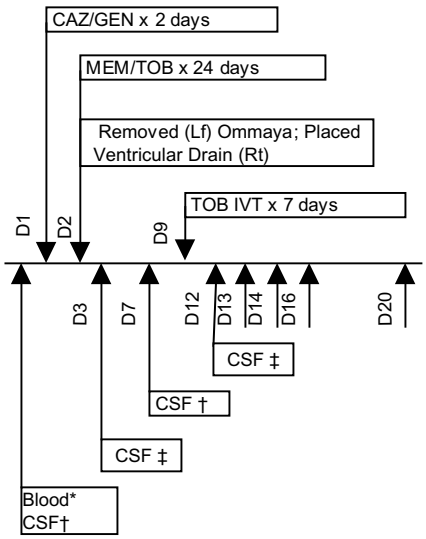
Figure 1. Antibiotic and Culture Timeline



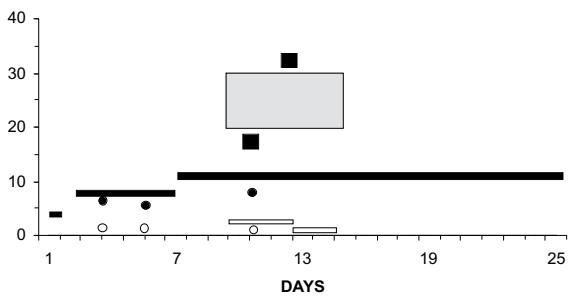
CAZ, Ceftazidime; GEN, Gentamicin; MEM, Meropenem; TOB, Tobramycin
** Blood cultures negative for pseudomonas*
† CSF cultures positive for pseudomonas: (S: Amikacin <16 mg/mL; Ciprofloxacin <1 mg/mL; Imipenem <4 mg/mL; Tobramycin <4 mg/mL; I: Gentamicin=8 mg/mL; R: Aztreonam >16 mg/mL, Ceftazidime >16 mg/mL; Piperacillin/tazobactam >64 mg/mL)
‡ CSF cultures negative

suspected sepsis, and VATER association. His initial APGAR scores were 4, 6, and 9 at 1, 5, and 10 minutes, respectively. The newborn was intubated, placed on a ventilator, and given age-appropriate doses of ampicillin and gentamicin as empiric therapy for 14 days. The patient required a thoracotomy with ligation of the tracheoesophageal fistula and G-tube placement on the third day of life. At 6 days of age, the initial neurosonogram showed the patient had developed a right-sided grade IV and left-sided grade III intraventricular hemorrhage (IVH). A repeat neurosonogram 14 days later showed dilated ventricles and bilateral grade IV IVH with progressive hydrocephalus, which required repeated CSF removal and the placement of an Ommaya reservoir on the 25th day of life.

During his first two months in the intensive care nursery, the infant was treated with numerous courses of ampicillin, gentamicin, tobramycin, cefotaxime, ceftazidime, and vancomycin for various infections. A CSF culture grew *P aeruginosa,* and empiric treatment with ceftazidime and gentamicin was initiated on day 70 of life (Figure 1, Day 1). In response to a sensitivity report indicating a highly resistant organism, the systemic antibiotic regimen was changed from ceftazidime (50 mg/kg every 8 hours) and gentamicin (4 mg/kg every 24 hours) to meropenem (40 mg/kg every 8 hours) and tobramycin (4 mg/kg every 24 hours) (Figure 1). The following day the tobramycin dosage was changed to 4 mg/kg every 12 hours and the Ommaya reservoir was removed. Despite aggressive dosing with antibiotics and removal of the Ommaya reservoir, the CSF cultures continued to grow *P aeruginosa.* The tobramycin dosage was again increased to 5.5 mg/kg every 12 hours, and IVT preservative-free tobramycin was initiated at 2mg daily.

Systemic and IVT dosing of tobramycin as well as CSF and serum tobramycin concentrations are in Figure 2. Intraventricular and tobramycin dosing was adjusted to maintain the CSF trough concentrations between 20–30 μg/mL. Doses were administered immediately after CSF sampling. Trough concentrations achieved in the CSF ranged from 17.5 to 32.4 μg/mL. Four days after beginning IVT tobramycin, CSF cultures indicated that the fluid was sterilized. Repeat CSF cultures remained negative. The patient received 24 days of systemic antibiotics in conjunction with seven days of IVT tobramycin. No acute complications were observed with the IVT injections. Despite eradication of the organism from the CSF, the patient died from cardiorespiratory failure at 118 days of age.

Figure 2. Systemic and IVT Tobramycin Dosing Accompanied by Serum and CSF Concentrations



Systemic dosing of tobramycin (mg/kg/d); ● Tobramycin peak serum concentration (μg/mL); ○ Tobramycin trough serum concentration (μg/mL); ▭ IVT dosing of tobramycin (mg/day); ■ CSF concentration of tobramycin; □ Reference range for CSF tobramycin concentration

DISCUSSION

Although systemic antibiotics failed to treat pseudomonas meningitis in this premature infant with severe hydrocephalus, concurrently administered IVT tobramycin was effective. The presence of a highly resistant organism was likely a result of exposure to numerous antimicrobial courses throughout his neonatal life. The use of IVT aminoglycosides in the management of resistant meningitis is controversial. Despite the successful eradication of the organism in this case with the regimen employed, there are many questions regarding the appropriate indications and dosing of IVT aminoglycosides.

Tables 1 and 2 review those published case reports and studies regarding the use of IVT or IT aminoglycoside antibiotics in pediatric patients. Our initial dose of 2 mg was selected using previously published case reports[4-9] and studies.[10-16] Doses of IVT tobramycin ranging from 1.5–2 mg were used in our patient to achieve CSF concentrations of 20–30 μg/mL. The initial dose of 2 mg was selected using previously published case reports[4-9] and studies.[10-16] Similar to earlier reports,[8,11,14,16] we employed a CSF goal concentration of 20–30 μg/mL in order to achieve tobramycin concentrations that were at least five times the minimal inhibitory concentration (MIC) of the organism in the CSF (<4 μg/mL). Traditionally, aminoglycosides are dosed by targeting a serum peak-to-MIC ratio of 5:10. Whether or not a similar approach should be used to "target" antibiotic CSF concentrations (i.e., peak concentration:MIC ratio) remains controversial. High antimicrobial concentrations in the CSF are required to achieve bactericidal effects due to the relative lack of local immune system function.[1,2]

Table 1. Case Reports of Previous Experience with IVT/IT Aminoglycoside Antibiotics in the Pediatric Population

References	Demographics	Antibiotic Therapy	CSF Concentration (μg/mL)	Outcome
Newman 1967[4]	3 infants; ventriculitis, (n=2), meningitis (n=1); *P pyocyanea* *K aerogenes*	GEN 1–2 mg/kg/d IM x 12–16 d *plus* GEN 0.1–2 mg IVT daily x 5–12 d	During IVT therapy <0.1–7	All cured
Moellering 1972[5]	16 mo; meningitis; *Proteus morganii*	GEN 29 mg IM q 8 hr x 11 d *plus* GEN 1mg IT qd x 4		CSF (+)
		2nd regimen: GEN 11mg IM q 8 hr x 5 d *plus* GEN 1–2 mg IT qd x 4 d	3 hr after 2mg dose=1.2	CSF (+)
		3 rd regimen: GEN 11 mg IM q 8 hr x 5 d *plus* GEN 2 mg IVT qd x 5 d	6 hr later=0.2 21–30 hr=2.4–10	CSF (-) within 24 hours after IVT initiated; Cured
Olsen 1977[6]	8 mo; ventriculitis; *P aeruginosa*	GEN 3 mg/kg/day IM x 12 d *plus* GEN 1 mg IVT qd x 12 d		CSF positive
		2nd regimen: GEN 5 mg/kg/day IM x 23 d *plus* GEN 3 mg IVT qd x 23 d	24 hr=25–35, single peak of 76	Cured
Pickering 1978[7]	6 mo; ventriculitis; *P aeruginosa*	GEN IV x 25 d (Unknown dose) GEN 2 mg IVT q 24–36 hr x 19 d	1 hr=15; 24 hr=1–5	Cured
		GEN IV x 14–17 d (Unknown dose)	1 hr=>20; 36 hr=8–14	All Cured
	3 infants: 1, 2, and 3 mo; ventriculitis; *Staphylococcus* sp.	MET IV x 3–5 d (Unknown dose) GEN 1 mg IVT q 24–48 hr x 10–19 d		
Katz 1980[8]	4 mo; VPshunt infection; *Enterobacter doacae*	GEN 2, 4, 6 mg IVT qd x 14 d *plus* CAR 400mg/kg/d IV x 21d	2 mg=1.7* 4 mg=0.7* 6 mg=19.6*	Cured
Masvosva 2003[9]	4mo; ventriculitis VP shunt; *P aeruginosa*	TOB 2.5mg/kg q 8 hr x 23 d TOB 5mg IVT qd x 21 d (intermittent) CAZ 50mg/kg q 8 hr x 38 d	During IVT therapy 1–130.8	Cured

* *trough concentration*

IVT, intraventricular; IT, intrathecal; IM, intramuscular; IV, intravenous; CAZ, ceftazidime; CAR, carbenicillin; GEN, gentamicin; TOB, tobramycin

Olsen and colleagues advocated the need for 24-hour post-dose CSF concentrations of at least 25–35 μg/mL for *P aeruginosa* ventriculitis.[6] The use of high trough concentrations in the CSF was also supported by Lorber et al.[10] This group reported a correlation between successful treatment and a trough (i.e., 24-hour post-IVT dose) gentamicin CSF concentration that 'exceeded manyfold the MIC' of the organism. Pickering and colleagues targeted a goal CSF trough gentamicin concentration that was four times the minimal bactericidal concentration (MBC) of the organism.[7] Unlike the MBC of 3.12 μg/mL reported by Pickering et al. the gentamicin MIC of the or-

Table 2. Studies of Previous Experience with IVT/IT Aminoglycoside Antibiotics in the Pediatric Population

Reference	Demographics	Antibiotic Therapy	CSF Concentrations (μg/mL)	Outcome
Lorber 1970[10]	14 infants; ventriculitis; *E coli, Proteus* sp. *P pyocyaneus*	GEN 0.5–8 mg/kg/d IM (Max 22 d) *plus* GEN 0.5–8 mg IVT qd (Max 11 d)	24 hr=0.5–80	7 cured; 7 died
Kaiser 1975[11]	6 pts, ventriculitis; *E coli*, *Klebsiella* sp. *Pseudomonas stutzeri*	TOB/GEN 5–10 mg IVT d x 10 d *plus* TOB/GEN 3–4.5 mg/kg IV qd	Within 1st 6 hrs=12.8–40 24 hrs=4–6	All cured; 1 relapse x3
Yeung 1976[12]	16 infants; 1–27*; meningitis; *E. coli*, *Pseudomonas*, *Klebsiella, Flavobacteriu, Bacillus subtilis, S aureus*	Term: GEN 4 mg IT/IVT qd x at least 7 d LBW: GEN 2mg IT/IVT qd x at least 7 d All: GEN 8 mg/kg IM qd *plus* AMP 200–400mg/kg IV qd at least 3 wks or 1 wk after IT/IVT therapy D/C	No levels	All cured; 1 had hearing loss at 5th week that returned to normal
McCracken 1976[13]	52 infants; <2yr; meningitis; gram- negative enteric	AMP 50 mg/kg IV q12 hr (≤7*) or 70 mg/kg IV q 8 hr (>7*) and GEN 2.5 mg/kg IM q12 hr (≤7*)/q8 hr (>7*) ± GEN 1 mg IT qd x at least 3 d	2–4 hr=18.4≥40 18–24 hr=0.5-3.4	No benefit of IT/IVT over systemic therapy
Wald 1980[14]	8 pts; 1mo–19yr; shunt infection or ventriculitis; *E coli*, *Enterococcus* sp. *Klebsiella* sp. *Staphylococcus* sp.	GEN 3–55 mg IV q 8 hr *plus* GEN 1–6 mg IVT qd x 4–16 d	24 hr=5.3–12.6 48 hr=1.74–13.6	7 cured; 1 relapse then cured
McCracken 1980[15]	52 infants; meningitis and ventriculitis, 28 pt; ventriculitis: 9 pt w/o ventriculitis: *E coli*, *Klebsiella* sp. *Enterobacter* sp. *Citrobacter* sp. *Salmonella* sp.	All: GEN 2.5 mg/kg IM q12 hr (≤7*) q 8 hr (>7*) plus AMP 50 mg/kg IV q12 hr (≤7*) or 70 mg/kg IV q 8 hr (>7*) GEN 2.5 mg IVT qd x at least 3 d GEN 2.5 mg IT qd x at least 3 d	1–6 hr: IVT=10–130; IT: 8–85 16–24 hr: IVT=1–24; IT=1.8-2.4	Higher mortality with IVT in meningitis group study stopped
Wright 1981[16]	8 infants; 1–10 wks; ventriculitis: *E. coli, C diversus P morganii P aeruginosa Streptococcus faecalis*	Previous therapy: Varied (IV or oral) or no antibiotics; addition of AMK 5 mg IVT qd to all patients	2–4 hr >100	6 cured; 2 died

** Days of life; AMK,amikicin; AMP, ampicillin; GEN, gentamicin; IM, intramuscular; IV, intravenous; IVT, intraventricular; IT, intrathecal; LBW, low birth weight; TOB, tobramycin*

ganism in our patient was considerably higher at 8 μg/mL.[7] Although aminoglycoside antibiotics exhibit concentration-dependent killing, numerous reports of successful clinical cure have occurred by targeting high 24-hour post-IVT dose CSF concentrations.[6,10,14,16]

CSF antibiotic concentrations and dosing requirements have been shown to vary based upon patient disease characteristics (e.g., hydrocephalus), type, and severity of infection.[4-15] Olsen and colleagues described a 6-month-old infant with hydrocephalus and a ventriculoperitoneal (VP) shunt who developed *P aeruginosa* ventriculitis.[6] Monotherapy with intramuscular (IM) and IVT gentamicin was initiated at a daily dose of 3 mg/kg and 1 mg, respectively. After 12 days of therapy, the CSF cultures remained positive, and gentamicin was increased to 5 mg/kg IM and 3 mg IVT daily. Sterile CSF cultures were achieved, and the infant received gentamicin for a total of 35 days. CSF concentrations 24 hours post dose (3 mg) ranged from 25–35 μg/mL with a single peak value of 76 μg/mL. The infant showed no signs of toxicity or reinfection at a one-year follow-up.

Another case report described a 4-month-old female with a VP shunt infection due to–*Enterobacter cloacae*. The organism was effectively eradicated by IVT gentamicin and intravenous carbenicillin.[8] Gentamicin was initiated at a dose of 2 mg/day IVT. During therapy, the daily IVT dose was increased to 6 mg in order to achieve the goal CSF trough concentration that was 30–50 times the MIC of the organism. Gentamicin CSF trough concentrations ranged from 1.7–19.6 μg/mL and no toxicities were reported during therapy. The authors concluded that patients with patent VP shunts may require two to three times the usual IVT gentamicin dose of 0.5–2 mg, and those with enlarged ventricles may need four to five times the normal dose. The purpose of their report, however, was to document successful IVT therapy and not to provide specific dosing recommendations for patients with VP shunts.

Masvosva and colleagues describe a 4-month-old infant with ventriculitis (post-VP shunt repair) who was treated with IVT tobramycin (5-mg dose), IV tobramycin, and ceftazidime for *P aeruginosa*.[9] Goal CSF concentrations were troughs between 5–10 μg/mL, and actual tobramycin concentrations in the CSF ranged from 1–130.8 μg/mL. The patient was cured; however, it was noted that four seizure episodes occurred during therapy. These events may also have been due to a concomitant brain abscess or shunt placement.

Kaiser and McGee reported six episodes of ventriculitis that were cured with the combined use of IVT and systemic administration of tobramycin or gentamicin.[11] Infections were caused by *Escherichia coli* (n=2), *Klebsiella* species (n=3), and *Pseudomonas stutzeri* (n=1) and were treated with 5 mg of an aminoglycoside administered daily through an Ommaya or Rickhan reservoir. The CSF aminoglycoside concentrations ranged from 12.8–40 μg/mL within the first six hours after administration. Concentrations remained between 4–6 μg/mL for most of the following 18 hours. No toxicities were reported in any episode.

Wald and McLaurin described eight patients (ages 1 month to 19 years) with a shunt infection or ventriculitis who were successfully treated with systemic and IVT administration of gentamicin.[14] IVT gentamicin was dosed at 1–6 mg daily (six patients) or every other day (two patients) for 4-16 days. Gentamicin CSF concentrations ranged from 5.3–12.6 μg/mL at 24 hours post-dose. These concentrations were 1.6–42 times above the MIC of the causative organisms. No seizures, neurological deficits, or other toxicities were seen with the administration of intraventricular gentamicin.

Controlled studies of the use of IT and IVT antibiotics in neonates have been performed. The Neonatal Meningitis Cooperative Study Group was formed to evaluate the role of IT- administered antimicrobials in the treatment of gram-negative meningitis.[13] This multicenter, prospective, randomized controlled trial evaluated 117 infants with gram-negative meningitis. Causative organisms included *E coli* (n=82), *Salmonella* sp. (n=7), *Citrobacter diversus* (n=5), *Proteus mirabilis* (n=5), *Serratia* sp. (n=5), *Klebsiella* sp. (n=4), *Enterobacter* sp. (n=4), and *P aeruginosa* (n=1). [note: total = 113] All patients received systemic antibiotics, and 52 patients received concomitant IT gentamicin. IT therapy (1 mg daily) was administered for a minimum of three days or until CSF cultures became sterile. CSF gentamicin concentrations were measured at two to four hours after a 1-mg ITdose in four infants. The authors did not specify concentration goals,

but did report that CSF concentrations were 18.4, 25, 36.8, and >40 μg/mL. CSF samples from 43 infants showed gentamicin concentrations that ranged from 0.5–3.4 μg/mL at 18-24 hours after a 1-mg IT dose. The authors did not report an infection eradication rate but stated 80 (68.4%) of the 115 infants survived. The addition of IT antibiotics to systemic therapy for meningitis did not improve patient outcomes in this study. Twenty-one (32%) infants on systemic antibiotics alone and 14 (28%) infants receiving IT plus systemic antibiotics died secondary to meningitis. Mortality rates did not differ significantly between the two groups (P=0.769). Additionally, there was no correlation between causative organisms and mortality rate in either group. No acute adverse effects were seen with IT gentamicin, but one infant who received three days of this therapy developed hyperreflexia and left lower extremity weakness 12 months after therapy. The child showed some neurologic improvement but was still impaired at three and one half years of age.

Subsequently, the Second Neonatal Meningitis Cooperative Study Group examined the role of IVT administration of gentamicin.[15] They hypothesized that the IVT route would sterilize the CSF quickly and decrease meningitis case-mortality rates. This multicenter, prospective, randomized controlled trial included 71 infants diagnosed with gram-negative meningitis with or without ventriculitis (n=52 and n=19, respectively). Twenty-eight of the 52 infants with ventriculitis were randomized to receive 2.5 mg/day of gentamicin IVT for a minimum of three days in conjunction with systemic antibiotics. In addition to systemic antibiotics, 10 of 19 infants without ventriculitis were randomized to receive IT gentamicin 2.5 mg daily for a minimum of three days. Infants who received IVT therapy had gentamicin CSF concentrations ranging from 10–130 μg/mL and 1–24 μg/mL, 1-6 hours and 16-24 hours post-dose, respectively. This study was discontinued because of increased mortality in patients who received IVT antibiotics when compared to systemic antibiotics alone. In the patients with ventriculitis, 12 (42.9%) infants who received IVT died versus three (12.5%) infants receiving systemic therapy alone (P=0.016). In the subset of patients without ventriculitis, no deaths were seen in the nine patients who received IT antibiotics, but two patients who only received systemic therapy died. Overall mortality was higher in the patients with meningitis and ventriculitis (29%) versus patients with meningitis alone (10.5%). The authors' explanations for this high mortality rate with IVT therapy included the presence of resistant organisms, cyst formation from repeated ventricular taps, or gentamicin toxicities. The outcome of this study provides the greatest concerns regarding the administration of IVT antibiotics and warrants their cautious use.

Individualized therapy is necessary for all patients being administered intraventricular antibiotics. The presence of hydrocephaly, an Ommaya reservoir, or a VP shunt complicates dosing regimens. Patients with a lower degree of hydrocephalus than our patient may require lower doses of IVT antimicrobials due to a decreased volume of distribution. Also, removal of CSF through repeated intermittent sampling or continuous drainage may alter drug clearance and distribution. Administration technique may also impact drug distribution in patients with shunts. A rapid, forceful injection may open the valve and deliver the drug into the distal shunt or peritoneal cavity.[8] However, a slow, gentle injection will ensure that the drug enters the ventricles.[8] Wright and colleagues evaluated the pharmacokinetics of amikacin and found a large variation in the volume of distribution and clearance.[16] They correlated large CSF volumes with hydrocephalus, meningomyelocele, and occipital abscess and recommend individualizing patient dose and regimen.

The use of IT and IVT antibiotics does not go without reservation – particularly in children with developing nervous systems. Nephrotoxicity and ototoxicity are well-documented adverse effects that are associated with systemic use of all aminoglycosides. Previous experience indicates potential risks of administering IVT aminoglycosides.[1,8,12,13,15-18] Yeung reported an infant who exhibited signs of deafness during the fifth week of therapy for *E coli* meningitis.[12] The infant was only receiving systemic gentamicin and ampicillin, but had previously received 20 days of IVT and 16 days of IT gentamicin therapy. The systemic gentamicin was discontinued when the infant failed to respond to rattles and a music box as he had earlier during therapy. No objective hearing tests were performed at the time, but follow-up with audiometry testing at 2.5

years of age was normal.

Neurologic and morphologic changes have also been reported in adult patients and animals.[17-19] Incidental findings in an adult at autopsy revealed multiple brainstem lesions. This patient was previously treated with IV and IT gentamicin for *P aeruginosa* meningitis.[17] Neuropathological changes have also been seen in rabbits after intracisternal and IVT administration of gentamicin.[17,18] It is unclear how toxicities from IVT or IT aminoglycoside administration may affect the growth and development of the premature infant brain.

Target serum tobramycin peak and trough concentrations in our patient were 6–8 μg/mL and <2 μg/mL, respectively. Due to a lack of standard dosing, the degree of hydrocephalus, and risk of adverse effects, we initiated IVT therapy with 2 mg of tobramycin. Our target CSF trough tobramycin concentration was 20–30 μg/mL. After 4 days of IVT therapy, the CSF tobramycin concentration rose to 32.4 μg/mL, and the dose was reduced to 1.5 mg. At this time, the patient was clinically improving and the CSF was sterilized. (CSF cultures showed no growth.) When three successive CSF cultures were reported as no growth, the IVT tobramycin was discontinued. No evidence of acute adverse effects (e.g., nephrotoxicity, seizures) or secondary infections were noted following IVT or IV tobramycin. Testing for ototoxicity was not performed due to eventual death of the infant.

CONCLUSION

The lack of medically based evidence to support the use of IVT antibiotic mandates that caution be exercised any time this route of administration is employed. Intraventricular therapy may be used as a treatment of "last resort" for patients in whom aggressive conventional therapy fails to eradicate gram-negative meningitis or in those whose infecting organism is only susceptible to antimicrobials that have poor CNS penetration.[1] Potential neurological complications in the premature infant warrant a careful assessment of the risks and benefits of IVT antibiotic therapy before this therapeutic modality is used.

ACKNOWLEDGEMENTS Poster Presentation at the 10th Annual Pediatric Pharmacy Advocacy Group Annual Meeting, October 2001, St. Louis, Missouri.

DISCLOSURE The authors declare no conflicts of interest or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

REFERENCES

1. Wen DY, Bottini AG, Hall WA, Haines SJ. The intraventricular use of antibiotics. Neuro Clin North Amer 1992;3:343-54.
2. Rahal JJ, Simberkoff MS. Host defense and antimicrobial therapy in adult gram-negative bacillary meningitis. Ann Intern Med 1982;96:468-74.
3. Leigh L, Stoll BJ, Rahman M, McGowan J Jr. Pseudomonas aeruginosa infection in very low birth weight infants: a case-control study. Pediatr Infect Dis J 1995;14:367-71.
4. Newman RL, Holt RJ. Intrathecal gentamicin in treatment of ventriculitis in children. Br Med J 1967;2(551):539-42.
5. Moellering RC Jr, Fischer EG. Relationship of intraventricular gentamicin levels to cure of meningitis. Report of a case of Proteus meningitis successfully treated with intraventricular gentamicin. J Pediatr 1972;81:534-7.
6. Olsen L, Grotte G, and Nordbring F. Successful treatment of Pseudomonas aeruginosa-ventriculitis with intraventricular gentamicin in a child with hydrocephalus. Scand J Infect Dis 1977;9:243-5.
7. Pickering LK, Ericsson CD, Ruiz-Palacios G, Blevins J, Miner ME. Intraventricular and parenteral gentamicin therapy for ventriculitis in children. Am J Dis Child 1978;132:480-3.
8. Katz MD, Rapp RP, Walsh JW. Infection in a functioning ventriculoperitoneal shunt treated with intraventricular gentamicin. Am J Hosp Pharm 1980;37:268-71.
9. Masvosva P, Buckingham SC, Einhaus S, Phelps SJ. Intraventricular and intravenous tobramycin with ceftazidime for ventriculitis secondary to pseudomonas aeruginosa. J Pediatr Pharmacol Ther 2003;8:137-43.

10. Lorber J, Kalhan SC, Mahgrefte B. Treatment of ventriculitis with gentamicin and cloxacillin in infants born with spina bifida. Arch Dis Child 1970;45:178-85.
11. Kaiser AB, McGee ZA. Aminoglycoside therapy of gram-negative bacillary meningitis. N Eng J Med 1975;293:1215-20.
12. Yeung CY. Intrathecal antibiotic therapy for neonatal meningitis. Arch Dis Child 1976;51:686-90.
13. McCracken GH Jr, Mize SG. A controlled study of intrathecal antibiotic therapy in gram-negative enteric meningitis of infancy. Report of the neonatal meningitis cooperative study group. J Pediatr 1976;89:66-72.
14. Wald SL, McLaurin RL. Cerebrospinal fluid antibiotic levels during treatment of shunt infections. J Neurosurg 1980;52:41-6.
15. McCracken GH Jr, Mize SG, Threlkeld N. Intraventricular gentamicin therapy in gram-negative bacillary meningitis of infancy. Report of the Second Neonatal Meningitis Cooperative Study Group. Lancet 1980;1(8172): 787-91.
16. Wright PF, Kaiser AB, Bowman CM, McKee KT, Trujillo H, McGee ZA. The pharmacokinetics and efficacy of an aminoglycoside administered into the cerebral ventricles in neonates: implications for further evaluation of this route of therapy in meningitis. J Infect Dis 1981;143:141-7.
17. Watanabe I, Hodges GR, Dworzack DL, Kepes JJ, Duensing GF. Neurotoxicity of intrathecal gentamicin: a case report and experimental study. Ann Neuro 1978;4:564-72.
18. Hodges GR, Watanabe I, Singer P, Rengachary S, Reeves D, Jusetesen R, et. al. Central nervous system toxicity of intraventricularly administered gentamicin in adult rabbits. J Infect Dis 1981;143:148-55.
19. Tauber MG, Shibl AM, Hackbarth CJ, Larrick JW, Sande MA. Antibiotic therapy, endotoxin concentration in cerebralspinal fluid, and brain edema in experimental Escherichia coli meningitis in rabbits. J Infect Dis 1987;156:456-62.