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Central Nervous System Chloramphenicol Concentration in Premature Infants

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Four premature infants under 1,500 g were treated with parenteral chloramphenicol for central nervous system infections due to organisms resistant to the penicillins. Serum, cerebrospinal fluid (CSF), and ventricular fluid concentrations of chloramphenicol were measured frequently during therapy and were used to maintain drug dosages in the safe and therapeutic range. Concentrations of chloramphenicol in the lumbar CSF and ventricular fluid had a mean of 23.3 ± 7.7 μg/ml, consistently greater than 45% of peak serum levels. These data show that chloramphenicol enters the CSF in both ventricular and lumbar regions in therapeutic concentrations when administered intravenously. The clinical usefulness of this drug remains to be investigated. The importance of monitoring serum drug levels during therapy is emphasized.

Despite the development of impressive facilities for intensive supportive care of sick premature infants and a recent dramatic fall in the mortality rate of premature infants, bacterial meningitis in premature infants still carries a mortality rate of 40 to 50%, and many survivors suffer significant sequelae. It has become apparent in recent studies that the aminoglycoside antibiotics may not reach the ventricular and cerebrospinal fluid in therapeutic concentrations when administered by the parenteral route (1). Furthermore, in a recent report from the National Meningitis Cooperative Study Group, it was shown that therapy with intrathecal gentamicin in conjunction with parenteral ampicillin and gentamicin was not statistically significantly superior to parenteral therapy alone (4). These data suggest that in the case of neonatal meningitis and ventriculitis due to organisms resistant to the penicillins, other antimicrobial therapy that reaches the intracranial infection sites in adequate concentrations may offer therapeutic benefits. Chloramphenicol, a valuable antibiotic associated with significant potential toxicity in the newborn infant, has been suggested to meet this requirement (1). Data regarding ventricular or spinal fluid concentrations, together with safe serum concentrations in immature infants, are needed to support this recommendation.

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MATERIALS AND METHODS

Four premature infants under 1,500 g with intracranial sepsis involving organisms resistant to penicillin and its semisynthetic derivatives were treated at Cardinal Glennon Memorial Hospital, St. Louis, Mo. Two of these infants had sepsis and meningitis, one due to *Escherichia coli* initially believed to be resistant to ampicillin and one due to *Staphylococcus aureus* resistant to methicillin. The other two infants had preexisting hydrocephalus secondary to intraventricular hemorrhage and developed ventriculitis after several therapeutic ventricular taps. The two organisms involved were again *E. coli* and *S. aureus* resistant to methicillin. The child with *S. aureus* ventriculitis initially received intraventricular gentamicin, to which the organism was sensitive in vitro, for 5 days without sterilization of the fluid and then became the first infant in the group who received parenteral chloramphenicol.

All four infants had normal blood counts and normal liver enzymes, and none was significantly jaundiced. Vital signs, blood counts, and clinical parameters were followed closely during the course of chloramphenicol therapy, and no child developed any evidence of toxicity from the drug during 6 to 21 days of treatment.

Chloramphenicol was administered in doses of 25 to 35 mg/kg per day in two divided intravenous infusions of 1 h each. Blood from three infants was obtained for chloramphenicol levels immediately before drug infusion and at the completion of the infusion on days 2, 5, and 8 of therapy and whenever else it was clinically indicated. These samples were designated trough and peak levels, respectively. Samples of lumbar cerebrospinal fluid (CSF) were obtained after drug infusion by the pediatric house staff. Ventricular fluid samples were obtained via ventricular tap by the neurosurgical staff.

Serum and CSF samples were immediately frozen and maintained at −20°C until assayed, usually within 24 h. Repeated refreezing of samples and testing 2 or 3 weeks later did not change the concentration of drug. Levels of chloramphenicol were measured by using a modification of the colorimetric assay of Kakemi et al. (3, 5). The modified assay uses serum rather than whole blood, thus eliminating the necessity to lyse erythrocytes and simplifying the colorimetric evaluation. The assay was demonstrated by Kakemi et al. to measure free chloramphenicol but neither the parent succinate compound nor the glucuronide metabolite, both of which reacted in older chemical determinations. Chloramphenicol-free CSF or serum gave no colorimetric reactions. Duplicate determinations were within 6% of each other.

RESULTS

Serum levels of chloramphenicol in three babies are shown in Table 1. Baby A had a mean peak level after infusion of 41.5 ± 8.2 μg/ml. The mean trough level before infusion was 29.1 ± 8.9 μg/ml. The mean concurrent CSF level was 21.3 ± 7.3 μg/ml. The baby's CSF was sterile on day 5 of treatment.

Baby B sustained an intraventricular hemorrhage on day 7 of life and subsequently developed hydrocephalus, requiring daily therapeutic ventricular taps. An *E. coli* urinary tract infection was diagnosed on day 14 and was treated with ampicillin and gentamicin. On day 17, *E. coli* was isolated from the ventricular fluid and chloramphenicol was begun at 25 mg/kg per day. The ventricular fluid was sterile 8 days later, and the patient was treated for a total of 18 days. Relapse with positive ventricular fluid cultures occurred 3 days off therapy, and the remainder of the baby's life was a progression of sepsis and ventriculitis that could not be satisfactorily treated with any combination of antibiotics and supportive care. One set of serum and CSF levels after reinitiation of chloramphenicol is designated day 2'. Initial serum levels on day 2 of chloramphenicol were 14.1 μg/ml (peak) and 11.7 μg/ml (trough), and the dosage was thereafter maintained at 35 mg/kg per day, after which mean levels were 20.4 ± 6.4 μg/ml (peak) and 13.6 ± 6.6 μg/ml (trough). The mean of concurrent ventricular fluid levels measured was 16.6 ± 6.3 μg/ml throughout therapy. It should be noted that this infant's ventricular fluid was always bloody and showed no clearing during the time of treatment.

TABLE 1. *Serum levels of three babies*

Infant	Treatment day	Serum (μg/ml)		CSF (μg/ml)	CSF: peak serum (%)
		Peak	Trough		
A[a]	2	45.9	32.5		
	3	54.4	16.4	29.5[b]	54
	5	43.9	40.9	25.3[b]	57
	8	33.4	27.2	15.0[b]	45
	11	37.9			
	14	33.6	28.7	15.4[b]	46
	Mean ± SD[c]	41.5 ± 8.2	29.1 ± 8.9	21.3 ± 7.3	50
B[d]	3	14.1	11.7		
	5	14.6	10.0	13.0[e]	89
	6			26.9[e]	
	7			36.6[e]	
	8	27.2	22.4	23.8[e]	87
	9			19.2[e]	
	10			29.9[e]	
	12			31.7[e]	
	13			19.3[e]	
	17			29.3[e]	
	20			14.7[e]	
	2'	19.3	14.7	12.9[e]	67
	Mean ± SD[c]	20.4 ± 6.4	13.6 ± 6.6	16.6 ± 6.3[e]	66.5
C[f]	3	35.4	26.2	30.8[b]	87

[a] Baby A: 15 days old, 800 g; *S. aureus* sepsis/meningitis.
[b] Lumbar CSF.
[c] SD, Standard deviation of the mean.
[d] Baby B: 17 days old, 840 g; *E. coli* ventriculitis, preexisting hydrocephalus.
[e] Ventricular CSF.
[f] Baby C: 6 weeks old, 1,200 g; *E. coli* meningitis.

Baby C had *E. coli* sepsis and meningitis and was treated for 6 days with chloramphenicol before switching to ampicillin when tube dilution studies of the organism's susceptibility showed that drug would be adequate. The CSF was sterile on day 3 of chloramphenicol treatment. Peak and trough levels were 35.4 and 26.2 μg/ml, respectively, and the CSF level was 30.8 μg/ml.

A ventricular fluid level was determined on one occasion in a fourth infant, with hydrocephalus and *S. aureus* ventriculitis, whose ventricular fluid had not become sterile after 5 days of parenteral and intraventricular gentamicin and who was then treated with intravenous chloramphenicol. The ventricular fluid level was 23.4 μg/ml on day 2 of chloramphenicol therapy, at which time the fluid was also sterile. Concurrent serum levels were not obtained.

DISCUSSION

Serum levels of active chloramphenicol in these small, immature infants were in the therapeutic and nontoxic range (above 15 and under 50 μg/ml [2]) with the dosage of 25 mg/kg per day used as recommended by the manufacturer. No infant demonstrated any apparent toxic effects from chloramphenicol.

Levels of chloramphenicol in CSF and ventricular fluid were also in the therapeutic range, and mean CSF levels were 66.5% of peak serum levels in each individual patient. Higher levels were seen in patients with bloody CSF. No diminution in the proportion of serum levels of active chloramphenicol was found in the CSF concentration over the course of treatment, despite the resolution of CSF pleocytosis and sterilization of CSF. CSF protein determinations were consistently elevated in all patients and did not correlate with drug concentration. This differs from the data of Windorfer and Pringsheim (2), which are based on determinations of total chloramphenicol concentrations, including inactive metabolites. Their data may reflect accumulation over time of metabolic products, thus suggesting decreased passage of chloramphenicol into CSF with healing of the meninges. Our results suggest consistent passage of chloramphenicol from serum into CSF, regardless of the degree of inflammation. CSF concentrations of chloramphenicol were not influenced by the presence or absence of hydrocephalus.

Two of the four infants survived the neonatal period and were doing well at 8 to 10 months of age, one with a ventriculoperitoneal shunt in place. The remaining two infants who had preexisting hydrocephalus succumbed: one after satisfactory clearing of his infection, to further intraventricular hemorrhage, and the other to the complications of intraventricular hemorrhage and infection.

We conclude from these determinations that biologically active chloramphenicol reaches the spinal and ventricular fluid of small immature infants in therapeutic concentrations. The value of chloramphenicol in the treatment of intracranial sepsis of a newborn remains to be determined by comparative studies in larger numbers of infants treated in modern intensive care units. It must be emphasized that if toxicity is to be minimized in these infants, then careful monitoring of serum concentrations of chloramphenicol is mandatory. Dosages must be adjusted to assure therapeutic and nontoxic drug levels.

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