Prospective comparative trial of moxalactam versus ampicillin or chloramphenicol for treatment of Haemophilus influenzae type b meningitis in children

In a prospective, randomized study, moxalactam in 44 children was compared with ampicillin or chloramphenicol in 47 children for the treatment of Haemophilus influenzae *type b meningitis. Both groups were comparable in terms of clinical and laboratory findings at admission. The hospital course, neurologic sequelae including deafness, and number of deaths were the same for both groups. The incidence of adverse reactions also was the same except that diarrhea and thrombocytosis occurred significantly ($P \leq 0.04$) more frequently in children given moxalactam. Moxalactam was equivalent to ampicillin or chloramphenicol in the treatment of* H. influenzae *type b meningitis in children. (J PEDIATR 104:447, 1984)*

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HAEMOPHILUS INFLUENZAE TYPE B is the most common organism responsible for bacterial meningitis in children younger than 5 years. During the past 5 years in the United States, approximately 20% of HIB isolates have been resistant to ampicillin.[1] In some areas of the country, strains of HIB resistant to chloramphenicol have been reported.[2] Furthermore, there have been isolates of HIB resistant to ampicillin and chloramphenicol concomitantly.[3,4] Therefore, alternative antibiotics must be available in the event that ampicillin-chloramphenicol–resistant strains of HIB increase in incidence. Moxalactam is an oxa-β-lactam antibiotic that is highly active in vitro against HIB and penetrates into cerebrospinal fluid effectively.[5-8] Previous studies have demonstrated that moxalactam is a safe and effective antibiotic for the treatment of non–central nervous system infections caused by HIB in children.[9] In March 1981, we initiated a prospective trial of moxalactam compared with ampicillin or chloramphenicol for the treatment of HIB meningitis in children.

METHODS

Children admitted to Texas Children's Hospital (TCH) with bacterial meningitis caused by HIB were eligible for enrollment if they were 2 months of age or older. Signed, informed parental consent and the consent of the private physician were obtained prior to the enrollment of a child in this study. This study was approved by the Institutional Review Boards of Baylor College of Medicine and TCH.

Lumbar punctures were performed in the emergency room of TCH or outlying hospitals or in offices of private physicians, at which time a diagnosis of meningitis was established. When the diagnosis of bacterial meningitis

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CIE	Countercurrent immunoelectrophoresis
HIB	*Haemophilus influenzae* type b meningitis
MBC	Minimum bactericidal concentration
PRP	Polyribosephosphate

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Table I. Characteristics of study children

	Ampicillin-chloramphenicol (n = 47)		*Moxalactam (n = 44)*	
	$\bar{x} \pm 1$ *SD*	*Range*	$\bar{x} \pm 1$ *SD*	*Range*
Age (mo)	13.7 ± 9.1	2 to 40	12.6 ± 10.3	4 to 54
Duration of illness prior to admission (days)	2.1 ± 1.7	0.5 to 7	2.5 ± 2.5	0.5 to 14
Duration of fever prior to admission (days)	1.6 ± 1.6	0 to 7	2.0 ± 2.4	0.5 to 14
Level of consciousness on admission	n	%	n	%
Irritable/lethargic	38	81.0	40	91.0
Obtunded	5	10.5	3	6.8
Comatose	4	8.5	1	2.3
Seizures prior to admission	15	32.0	11	25.0
Prior antibiotic therapy orally	19	40.0	8	18.0

Table II. Initial CSF findings in study children

	Ampicillin-chloramphenicol		*Moxalactam*	
	$\overline{X} \pm 1$ *SD*	*Range*	$\overline{X} \pm 1$ *SD*	*Range*
Total WBC/mm³	6890 ± 8960	30 to 38,160	5802 ± 7804	54 to 42,500
Polymorphonuclear leukocytes (%)	87 ± 16	28 to 100	87 ± 13	50 to 100
Protein (mg/dl)	211 ± 170	4 to 738	188 ± 132	25 to 600
Glucose (mg/dl)	30 ± 25	0 to 80	38 ± 32	0 to 135
CSF:Blood glucose (%)	26 ± 20	0 to 77	27 ± 20	0 to 78
Positive culture	47		42	
β-Lactamase positive	8 (17%)		13 (31%)	
Quantitation of PRP (μg/ml)				
Mean	0.87 ± 2.0		0.54 ± 1.75	
Median	0.08		0.04	
Distribution				
0 to 0.16	30		33	
0.32 to 1.28	6		7	
2.56 to 10.24	6		3	

was established or suspected prior to admission to TCH, ampicillin and chloramphenicol were administered prior to transfer so as not to delay therapy. As soon as possible, Gram stain, countercurrent immunoelectrophoresis, or latex agglutination of the CSF was performed.

On admission, children were randomized to either moxalactam plus penicillin or ampicillin plus chloramphenicol, based on a computer-generated table. Moxalactam was administered at a loading dose of 100 mg/kg, followed by 200 mg/kg/day in four divided doses intravenously. Aqueous penicillin G was administered at 12 million units/m²/day following one third of this dose as a loading dose. Penicillin was discontinued as soon as a diagnosis of HIB meningitis was documented by either CIE, latex agglutination, or culture. Ampicillin was infused as 300 mg/kg/day in six divided doses after a 100 mg/kg loading dose; the dose of chloramphenicol was 100 mg/kg/day in four divided doses intravenously. Chloramphenicol was discontinued once the HIB isolates were documented to be sensitive to ampicillin. Twenty-five children received one dose of ampicillin, and 23 of these 25 children also received one dose of chloramphenicol prior to enrollment in the moxalactam arm of the study. One parenteral dose of either antibiotic or both prior to admission did not exclude enrollment.

In the moxalactam group, a complete blood count with differential and platelet count was performed on admission, weekly during therapy, and at the conclusion of therapy. Blood urea nitrogen, serum creatinine, alkaline phosphatase, transaminases, and bilirubin levels (total and direct) were measured at admission and at conclusion of therapy. For the ampicillin-chloramphenicol group, a complete blood count with differential count and a platelet count were obtained in 35 of 44 children at the conclusion of therapy. Chloramphenicol serum concentrations were not monitored routinely. The patients were observed daily, and careful neurologic examinations were performed at hospital admission and discharge. Quantitation of the polyribose-phosphate concentration in the initial CSF was performed by twofold serial dilutions using CIE.[10]

Table III. Selected laboratory and clinical features of hospital course in study children

	Ampicillin-chloramphenicol		*Moxalactam*	
	$\bar{X} \pm 1$ *SD*	*Range*	$\bar{X} \pm 1$ *SD*	*Range*
Initial peripheral WBC count ($\times 10^{-3}$/mm^3)	13.6 ± 7.2	2.4 to 35.4	13.5 ± 8.4	3.5 to 36.2
Initial serum sodium (mEq/L)	134 ± 4	118 to 140	135 ± 4	124 to 147
Number <135 mEq/L	26 (55%)		19 (43%)	
Lowest serum sodium (mEq/L)	132 ± 3	118 to 139	133 ± 4	124 to 147
Duration of hyponatremia (hr)	18.5 ± 28.3	0 to 144	16.6 ± 38.4	0 to 240
Duration of fever (days)	5.0 ± 3.6	0 to 16	5.3 ± 4.6	0 to 20
Afebrile after 5 days	68%		67%	
Afebrile after 8 days	80%		84%	
Seizures in hospital	13 (28%)		10 (23%)	
Duration of antibiotic therapy (days)	10.8 ± 1.7	10 to 16	10.7 ± 1.7	10 to 17
>10 days	9/44		6/42	

Auditory brainstem responses were obtained at the end of therapy or within 1 month after discharge in all children, using a Nicolet CA-1000 Clinical Evoked Response System (Nicolet Instrument Corp., Madison, WI). A severe to profound sensorineural hearing loss by auditory brainstem response was defined as no response at equipment limits.

All children were admitted initially to the pediatric intensive care unit and received a standardized approach to supportive care of a child with bacterial meningitis.[10] Antibiotics were administered for a minimum of 10 days or longer at the discretion of the private physician. At the conclusion of antibiotic therapy, a repeat lumbar puncture was performed. Follow-up examinations were to be performed at 1, 3, 6, 12, and 24 months after discharge. Detailed psychometric evaluation was to be completed at 3 and 24 months after discharge.

For purposes of this study, fever was considered present if the temperature exceeded 38.1°C by rectum or 37.6°C by mouth. Diarrhea was defined to be caused by the antibiotic if the child had more than three loose stools per day and which persisted with antibiotic therapy. Neutropenia was defined as < 1500 total neutrophils/mm^3, eosinophilia as > 700 eosinophils/mm^3, and thrombocytosis as a platelet count > 800,000/mm^3. Statistical analysis of the data was performed using the Student *t* test, chi-square analysis, and the Fisher exact test.

All HIB isolates recovered from these children were tested for their susceptibility to moxalactam by macrotube dilution technique and to ampicillin and chloramphenicol by disk; β-lactamase activity was determined by acidometric assay.[11,12]

RESULTS

Forty-seven children were enrolled in the ampicillin-chloramphenicol group, and 44 children received moxalactam therapy. The age, sex, and racial distribution of the patients at admission, the days of illness and duration of fever prior to admission, the level of consciousness at the time of admission, and the percentage of patients with seizures prior to admission were not significantly different between the children who received ampicillin or chloramphenicol compared to those who received moxalactam (Table I). Forty percent of the children in the ampicillin-chloramphenicol group received prior antibiotic therapy orally, compared with 18% in the moxalactam group ($\chi^2 = 5.39$, $P = 0.02$). One child in each group had buccal cellulitis in association with the meningitis.

Table IV. Adverse effects of antibiotics in study children

	Ampicillin-chloramphenicol (n = 35)		*Moxalactam (n = 41)*	
	n	%	*n*	%
Neutropenia				
<1500/mm^3	4	11.4	9	22.0
<1000/mm^3	2	5.7	3	7.3
Eosinophilia >700/mm^3	5	14.3	6	14.6
Thrombocytosis	3	8.6	11	26.8
Thrombocytopenia	1	2.9	1	2.4
Diarrhea	4	11.4	11	26.8
Mild elevation in transaminases*	ND		7	

ND, Not done.
*Less than two times normal values.

The CSF findings at admission were not significantly different between the two groups (Table II). Two of the children in the moxalactam group had sterile CSF cultures and a CIE test negative for HIB, but the latex agglutination was positive for HIB in the CSF. All HIB isolates from both groups were sensitive to moxalactam: $MBC_{50} = 0.016$ μg/ml, $MBC_{90} = 0.06$ μg/ml; MBC range < 0.001 to 0.5 μg/ml.

The hospital course in both groups was similar (Table III). The mean serum sodium concentration at the time of

admission, the lowest serum sodium concentration in the hospital, and the duration of hyponatremia and fever were equivalent for both groups. One child developed a warm, swollen elbow on day 5 of moxalactam therapy. The joint fluid was positive for HIB by CIE, but culture negative. The patient was given 14 days of moxalactam, with complete resolution of the arthritis. The CSF findings obtained within 24 hours of discontinuing antibiotic therapy were the same except that the total WBC count in the ampicillin-chloramphenicol group was significantly greater ($t = 2.79$, $P < 0.01$) than that in the moxalactam group.

Adverse effects. Neutropenia was noted in four of 35 children in the ampicillin-chloramphenicol group (Table IV). All four children had received ampicillin. In the moxalactam group, the incidence of neutropenia was not significantly different than in the control group. In five instances, the neutrophil count increased during moxalactam therapy. No complications of the neutropenia were noted in either group. Eosinophilia was noted in five patients in the ampicillin-chloramphenicol group (four of five associated with ampicillin) and in six patients in the moxalactam group. The incidence of thrombocytosis was significantly greater ($\chi^2 = 4.19$, $P = 0.04$) in the moxalactam group than in the ampicillin-chloramphenicol group. Diarrhea was noted in 11 of the 42 surviving patients who received moxalactam, compared with four of the 44 surviving patients given ampicillin-chloramphenicol ($\chi^2 = 4.36$, $P = 0.037$). In many instances the diarrhea improved during moxalactam therapy. Six patients in the moxalactam group had a *Candida* diaper rash. There were no episodes of bleeding in either group.

Outcome. One half of the patients in each group have been seen in follow-up for at least 1 year after discharge. Forty of the children in the ampicillin-chloramphenicol group have had no physical sequelae in follow-up from between 1 month and 2 years after discharge. One of these children is hyperactive. Three children have severe to profound bilateral sensorineural deafness, and two of these children have ataxia, which has improved. Two children have profound neurologic sequelae from their disease. One child was 1½ years of age when he was hospitalized with a 6-day history of fever and lethargy. We was semicomatose with a right hemiparesis at the time of admission, and the initial quantitative CIE was 10.24 μg/ml. The child at follow-up has bilateral profound sensorineural hearing loss, severe developmental delay, a right hemiparesis, and cortical blindness. A second child was 2½ months of age and had a 24-hour history of illness with seizures and a respiratory arrest prior to admission. She has profound developmental delay and microcephaly and requires exogenous vasopressin. One child with normal neurologic examination results had a single, generalized seizure 9 months after discharge. His EEG findings are normal, and he continues to take phenobarbital without additional seizures.

Three children in the ampicillin-chloramphenicol group died. One death occurred in a 1½-year-old child with a 12-hour history of illness prior to admission. She was unresponsive, in shock, and immediately required ventilatory support at the time of admission; on the third hospital day, an EEG showed no cortical activity. A second child was 2 years of age with a 1-day history of fever and vomiting, and on admission was comatose, in shock, and had fixed dilated pupils; the child expired on the second hospital day. The third death occurred in a 1½-year-old child with a 12-hour illness and seizures prior to admission. The patient had anisocoria and was semi-comatose on admission; an EEG was isoelectric within 24 hours of admission.

In the moxalactam group, 37 children were considered normal at follow-up, although two did exhibit hyperactivity. Two children had profound, bilateral sensorineural hearing losses with ataxia, which has improved. One of these children developed seizures 9 months after discharge. Three children had other significant neurologic sequelae. A 4-month-old infant was ill < 12 hours prior to admission, required ventilatory support, and had prolonged focal seizures during the hospitalization. At follow-up he has developmental delay and generalized hypotonia. A second 4-month-old child had fever for 6 days prior to admission and also had prolonged focal seizures during the hospitalization. At follow-up she has quadriparesis and global retardation. A 6-month-old child had a 4-day history of fever and on admission was noted to have a right hemiparesis. In the hospital, the patient had generalized persistent seizures, and at follow-up has generalized hypotonia and developmental delay.

Two patients in the moxalactam group died. A 5-month-old infant had a 4-day history of irregular breathing, and was obtunded and in shock on admission. Initial CSF quantitation of PRP by CIE was 10.24 μg/ml. The hospital course was complicated by prolonged seizures, pneumonia and empyema, pyogenic arthritis, and diabetes insipidus. A ventricular tap done prior to death revealed sterile ventricular fluid. A second child was 2¾ years of age, and on admission was comatose with fixed, dilated pupils and no spontaneous respirations. An EEG showed brain death 12 hours after admission to the hospital.

Five of 86 (5.8%) surviving children had severe to profound bilateral hearing loss as a result of the HIB meningitis (Table V). There was no association between duration of illness prior to admission and the occurrence of severe hearing loss in this group of patients. Two of 59

Table V. Selected characteristics of children with profound sensorineural hearing loss

Age at onset (yr)	*Duration of illness prior to admission*	*Seizures*	*CSF cell count (/mm³)*	*CSF glucose (mg/dl)*	*Quantitative PRP determination in CSF (gm/ml)*	*Prolonged fever (days)*	*Therapy*
1½	36 hr	−	3,039	4	5.12	9	Chloramphenicol
½	48 hr	+	Clumped	2	5.12	−	Ampicillin
2½	3 day	−	3,800	15	0.64	−	Moxalactam
1½	5 days	+	42,500	<10	5.12	−	Moxalactam
1½	6 days	+	38,160	5	10.24	11	Chloramphenicol

(3.4%) children who were ill 2 or fewer days, compared with three of 27 (11.1%) who were ill 3 days or more prior to admission, had significant hearing losses (Fisher exact test, $P = 0.19$). However, both the initial CSF glucose concentration and quantitative PRP concentration by CIE were associated with hearing losses. One of 63 (1.6%) children with a CSF glucose concentration > 10 mg/dl, compared with four of 22 (18%) with an initial CSF glucose concentration < 10 mg/dl, had severe hearing deficits (Fisher exact test, $P = 0.016$). One of 72 children with CSF PRP concentrations up to 1.28 μg/ml and four of 8 with values between 2.56 and 10.24 μg/ml had severe hearing loss (Fisher exact test, $P = 0.002$).

DISCUSSION

Previous investigations have demonstrated that moxalactam is an effective agent in the treatment of a wide variety of infections, including meningitis caused by gram-negative enteric organisms, in both adults and children.[9,13-18] In one study, six of seven children with HIB meningitis (none ampicillin resistant) who were given moxalactam had a satisfactory clinical response.[16] In a second report of 27 children with HIB meningitis treated with moxalactam, 26 survived and neurologic sequelae were noted in four.[19] None of these initial reports compared moxalactam with established antibiotics for the treatment of HIB meningitis. Moxalactam does not appear useful for the treatment of meningitis caused by gram-positive agents such as *Streptococcus pneumoniae* or group B streptococcus.[15]

Moxalactam was shown to be equivalent to ampicillin or chloramphenicol for the treatment of HIB meningitis in children. Many of the clinical and laboratory variables that correlate with outcome of bacterial meningitis were the same in both groups. The only significant difference was that more children in the ampicillin-chloramphenicol group than in the moxalactam group received antibiotics orally prior to admission. The clinical courses in the hospital were virtually identical. Both groups of children have been observed carefully, and more than half of the children in each group have been seen for up to a year after discharge from the hospital. Forty of 44 (91%) survivors in the ampicillin-chloramphenicol group and 37 of 42 (88%) survivors in the moxalactam group were considered to have no neurologic abnormalities as a result of meningitis at their last follow-up visit. In particular, moxalactam was effective in the treatment of ampicillin-resistant HIB meningitis in 13 children. We do not believe that the outcome of the five children who died and of the five who have significant neurologic damage in the combined group could have been altered by antimicrobial therapy.

Five children (5.8%) in the total group of survivors have severe to profound, bilateral sensorineural hearing loss. This incidence of severe hearing loss is equivalent to that noted previously after HIB meningitis.[20] Furthermore, this study confirms the association between low CSF glucose on admission and subsequent severe hearing loss related to meningitis.

In a previous report, we noted that neutropenia occurred in a high percentage (43%) of children who received moxalactam for non–central nervous system infections.[9] In this study, neutropenia developed in nine of 41 (22%) children who received moxalactam, but this was not different than the incidence of neutropenia in the ampicillin-chloramphenicol group. None of the children experienced any adverse effects referable to the neutropenia. Thrombocytosis and diarrhea occurred more commonly in the children given moxalactam. The cause of moxalactam-induced neutropenia or thrombocytosis is not known.

We did not encounter any episode of bleeding in these children, and vitamin K was not administered to any patient. However, inasmuch as prothrombin or bleeding times were not performed, we could not determine specifically the effect of moxalactam on hemostasis in children. Vitamin K–dependent hypoprothrombinemia, abnormalities in platelet aggregation, and significant hemorrhage have been described in patients receiving moxalactam.[21,22] Currently, prophylactic administration of vitamin K is recommended once a week, and bleeding times should be determined in patients who receive high doses of moxalactam for longer than 3 days. Further experience in chronically ill children with serious infection is required before

the importance of alterations of hemostasis induced by moxalactam can be determined.

Moxalactam at a dose of 200 mg/kg/day in four divided doses intravenously proved to be equivalent to ampicillin or chloramphenicol in the treatment of HIB meningitis in children. Moxalactam *should not be used alone* as the initial therapy of meningitis in children because of its relatively poor activity against *S. pneumoniae.* Aqueous penicillin G or ampicillin should be administered with moxalactam until the cause of the meningitis has been proved to be *H. influenzae* type b.

We continue to recommend ampicillin for the treatment of infections caused by ampicillin-susceptible HIB. Moxalactam should be considered a drug of choice for the treatment of meningitis caused by HIB resistant to both ampicillin and chloramphenicol. Cefotaxime and ceftriaxone are two other cephalosporins that appear to be promising agents for the treatment of HIB meningitis.[23] A more difficult question is the role of moxalactam and the other newer antibiotics in treating infections caused by ampicillin-resistant HIB. The known risks of chloramphenicol as well as the recommendations to monitor serum levels are disadvantages to its use.[24, 25] On the other hand, chloramphenicol has been used safely for many years in the treatment of HIB meningitis, can be administered orally, and costs less than moxalactam.[25] On the basis of available data, we believe that moxalactam is equivalent to chloramphenicol in the therapy of meningitis caused by ampicillin-resistant HIB in children.

ADDENDUM

Since acceptance of this article, an additional six children (three ampicillin resistant) have been given moxalactam; four, ampicillin; and one, chloramphenicol. Clinical characteristics, hospital course, and outcome in these children were the same as reported above.

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