Cefuroxime in bacterial meningitis

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SUMMARY In order to find an alternative antimicrobial treatment for childhood bacterial meningitis 30 infants and children with meningitis, due to *Haemophilus influenzae* (n=13), *Neisseria meningitis* (n=9), *Streptococcus pneumoniae* (n=5), or meningitis of unknown aetiology (n=3), were treated with cefuroxime, 200 mg/kg a day, as the only antibiotic. Prompt clinical and bacteriological responses were noted and every patient was cured. Cefuroxime concentrations in cerebrospinal fluid ranged from 1.1 to 18.8 (mean 7.0) mg/l at the beginning and from 0.5 to 4.1 (mean 1.6) mg/l at the end of treatment. Three infants developed symptomatic sterile subdural effusions which were managed by repeated subdural aspirations while still on antibiotics. Cefuroxime concentrations in the subdural fluid ranged from 17.4 to 32.4 mg/l. At follow-up 2 patients had moderate unilateral hearing loss and one had mild ataxia. We conclude that cefuroxime is effective and safe for the treatment of childhood bacterial meningitis caused by any of these common organisms.

Generally childhood bacterial meningitis is treated with ampicillin, chloramphenicol, or penicillin G. However these antibiotics, alone or in combination, have problems associated with them that limit their routine use in purulent meningitis caused by *Haemophilus influenzae*, *Neisseria meningitis* or *Streptococcus pneumoniae*. In addition to the increasing incidence of beta-lactamase producing, ampicillin-resistant strains of *H. influenzae*^{1,2} there are now reports of clinical isolates of beta-lactamase negative *H. influenzae* with inherent resistance to ampicillin.^{3,4} Occasionally *H. influenzae* strains resistant to chloramphenicol alone or resistant to both chloramphenicol and ampicillin are encountered.⁵⁻⁷ The potential toxicity of chloramphenicol in children is well known. It also has widely variable pharmacokinetics in them. Moreover there is experimental evidence of antagonism of chloramphenicol plus ampicillin against some strains of *S. pneumoniae* or *N. meningitis*.⁸ The most recent potential problem in the treatment of bacterial meningitis is the emergence of strains of *S. pneumoniae* that are insensitive (minimal inhibitory concentration 0.1-1.0 mg/l) and resistant (minimal inhibitory concentration >1.0 mg/l) to penicillin G.^{9,10}

These facts justify the search for another drug for use on its own in the treatment of bacterial meningitis in infants and children.

Cefuroxime (CXM), a cephalosporin antibiotic with excellent resistance to beta-lactamases, is highly active *in vitro* against the three main aetio-

logical agents of childhood bacterial meningitis: *H. influenzae* (ampicillin-susceptible and ampicillin-resistant), *N. meningitis*, and *S. pneumoniae*.^{11,12} Preliminary studies on cerebrospinal fluid (CSF) penetration of CXM have been promising.¹³⁻²⁰ For these reasons a prospective study to determine the efficacy and safety of CXM in the treatment of childhood bacterial meningitis was carried out.

Material and methods

Children aged over 3 months who had been admitted because of suspected or proved bacterial meningitis to the Department of Paediatrics, University of Berne, or to one of the children's hospitals at Lucerne or St Gallen, Switzerland, were eligible for study. Any patient with an allergy to beta-lactam compounds or with an underlying disease of the immune and haemopoietic systems, central nervous system, liver, kidney, heart, or lung was excluded. The study was approved by the ethical committee of the University Children's Hospital Berne.

Study protocol. This comprised the following: (1) The presence of purulent meningitis had to be confirmed by CSF analysis before treatment with CXM was started. Between 24 and 48 hours after the start of treatment a control lumbar puncture was done to find out if the CSF was sterile. Additional lumbar punctures were done if clinically indicated and at the end of antimicrobial therapy. Routine CSF examinations included cell count with differentiation, protein and glucose concentrations, Gram-stain, and

bacteriological cultures. (2) Antimicrobial therapy consisted of the administration of CXM 200 mg/kg a day, divided into 4 doses. The drug was given intravenously by slow bolus injection. No other antibiotic was used. The duration of treatment with the antibiotic as well as all other aspects of management (administration of fluids, electrolytes, corticosteroids, anticonvulsants, and monitoring) were handled as described previously.²¹ (3) Adverse or toxic reactions to CXM were assessed by clinical observation and by the following laboratory studies before and after treatment: complete blood cell count including platelets, prothrombin time, electrolytes, urea nitrogen, creatinine, AST, ALT, bilirubin, and alkaline phosphatase concentrations. (4) CSF and concurrent serum samples for determination of CXM concentrations were obtained at the time of the control lumbar punctures. All specimens were taken 2 hours after the last dose of CXM. CSF and serum specimens were kept frozen at -20°C until assayed. CXM assays were performed using a large plate agar diffusion technique.²² Antibiotic medium number 2 (Oxoid Limited) was seeded with spores of either *Bacillus subtilis* 1904E or *Bacillus subtilis* MB 32 SDR allowing determination of CXM concentrations in the range 5.0 to 0.3 and 0.5 to 0.03 mg/l, respectively. Standard solutions were used and, if necessary, samples were diluted in phosphate buffer (pH 7.0). *In vitro* susceptibility of the isolated meningitic pathogens to CXM and other antimicrobial agents was tested using Kirby-Bauer paper discs. (5) Clinical and bacteriological responses to treatment were carefully evaluated. Two to 6 weeks after treatment each patient had an auditory function test and a neurological examination.

Results

Between January 1979 and April 1981, 33 infants and children with purulent meningitis were studied.

Three of them, one with *H. influenzae* (6 years 2 months old), one with *N. meningitis* (11 months old), and one with *S. pneumoniae* meningitis (3 months old), died within a few hours of admission to hospital because of irreversible septic shock or fulminant brain oedema. These patients were excluded. The main clinical characteristics of the 30 remaining patients are listed in Table 1. All the bacterial strains of *H. influenzae*, *N. meningitis*, and *S. pneumoniae* isolated were susceptible *in vitro* to CXM and ampicillin.

Seven children had received short courses of oral antimicrobial treatment before admission to hospital: 4 with *H. influenzae* meningitis (amoxycillin, $n=2$; penicillin V, $n=1$; erythromycin, $n=1$), 2 with *S. pneumoniae* meningitis (erythromycin, $n=2$), and 1 with meningitis of unknown aetiology (amoxycillin, $n=1$).

All patients showed rapid clinical improvement (shock, convulsions, consciousness, meningitic signs) to CXM. Reduction in fever occurred between 1 and 17 days after treatment with CXM (mean $\pm$ SD, 5.4 ± 4.1 days). Prolonged fever, defined as temperature $> 38.3^{\circ}\text{C}$ for at least 10 days, was present in 4 (13%) patients. Secondary fever, defined as re-appearance of raised temperature after at least 48 hours without fever, occurred in 5 (17%) patients. The established causes were polyarthritides in 1, drug reaction with rash in 1, and subdural effusions in 3 patients.

All patients were cured and no second meningitic attack took place. The first control lumbar puncture 24 to 48 hours after treatment with CXM had begun showed sterile CSF in 29 patients. A 4-month-old boy with *H. influenzae* meningitis had a lumbar puncture after the fourth dose of CXM and the fluid still showed some slight growth of *H. influenzae*. The subsequent CSF 24 hours later was sterile.

Three infants (aged 4, 8, and 12 months) with *H. influenzae* meningitis developed subdural effusions

Table 1 Clinical and laboratory details, treatment, complications, and outcome

Aetiology	Gender		Average age (years)	Initial CSF (cells/mm ³) mean $\pm$ SD	Duration of treatment with cefuroxime (days) mean $\pm$ SD	Complications during treatment	Outcome	
	Male	Female					Normal	Sequelae
<i>H. influenzae</i> (n=13)	8	5	1 9/12	4097 $\pm$ 2897	11.6 $\pm$ 2.0	Subdural effusions, 3 Gastrointestinal bleeding, 1 Polyarthritides, 1	11	Unilateral hearing loss, 1 Mild ataxia, 1
<i>N. meningitis</i> (n=9)	8	1	4 8/12	9163 $\pm$ 10299	10.4 $\pm$ 1.8	0	9	0
<i>S. pneumoniae</i> (n=5)	2	3	4 8/12	6564 $\pm$ 5621	12.8 $\pm$ 1.6	0	4	Unilateral hearing loss, 1
Unknown (n=3)	3	0	3 2/12	10324 $\pm$ 11018	11.6 $\pm$ 2.1	0	3	0
Total (n=30)	21 (70%)	9 (30%)	3 3/12	6793 $\pm$ 7283	11.4 $\pm$ 2.0	5 (17%)	27 (90%)	3 (10%)

Table 2 Cefuroxime concentrations in CSF and serum and percentage penetration into CSF

	Aetiology	No of patients (n=30)		Mean CSF cells per mm ³	Cefuroxime concentration (mg/l)		CSF/serum penetration (%)†
		Studied	Treated		CSF†	Serum†	
Concentration 24–48 hours after start of treatment with CXM (2 hours after dose)	<i>H. influenzae</i>	13	13	5223	8.8±1.5 (2.7–18.8)	57.4±3.8 (40.4–86.0)	14.5±1.8 (5.5–26.4)
	<i>N. meningitis</i>	8	9	2920	4.6±0.8 (1.9–6.8)	61.6±8.0 (34.9–91.9)	7.6±1.3 (3.3–14.3)
	<i>S. pneumoniae</i>	4	5	2080	7.9±3.1 (3.1–16.8)	40.8±10.0 (16.3–65.1)	21.9±8.2 (7.2–43.3)
	Unknown	3	3	4608	4.7±3.5 (1.1–11.8)	30.5±3.8 (25.5–38.0)	13.2±8.9 (3.9–31.1)
	Total	28	30	4051	7.0±1.0 (1.1–18.8)	53.3±3.6 (16.3–91.9)	13.4±1.8 (3.3–43.3)
Concentration at completion of treatment with CXM (2 hours after dose)	<i>H. influenzae</i>	11	13	112	1.9±0.3 (0.6–4.1)	13.9±1.2 (8.1–21.6)	14.6±2.8 (3.2–36.0)
	<i>N. meningitis</i>	8	9	16	1.4±0.2 (0.5–2.2)	19.1±2.3 (7.8–28.2)	8.3±2.0 (3.1–20.5)
	<i>S. pneumoniae</i>	5	5	20	1.6±0.7 (1.3–2.4)	25.7±4.1 (20.1–41.6)	6.4±0.4 (5.8–7.9)
	Unknown	2	3	60	1.1±0.2 (0.9/1.2)	15.0±1.1 (13.9/16.0)	7.0±0.5 (6.5/7.5)
	Total	26	30	41	1.6±0.2 (0.5–4.1)	17.9±1.4 (7.8–41.6)	10.5±1.5 (3.1–36.0)

†Mean value±standard error of mean; figures in parentheses represent range of observed values.
Conversion: traditional units to SI—cefuroxime 1 mg/l ≈ 2.24 µmol/l.

between days 6 and 8 of treatment, with fever, irritability, vomiting, and an increase in CSF white cell count. Both CSF and subdural effusion fluid remained sterile. In the first of these infants antibiotic treatment was changed to ampicillin and chloramphenicol but in the remaining 2 CXM was continued. All 3 patients were successfully managed by repeated subdural punctures and continued antimicrobial treatment for a total course of between 14 and 21 days. CXM concentrations determined in 6 specimens of subdural effusion aspirates between 1½ hours and 3 hours after the last CXM dose ranged from 17.4 to 32.4 (mean±SD, 22.4±5.5) mg/l.

A 15-month-old boy with *H. influenzae* meningitis developed a severe upper gastrointestinal bleeding on day 5 of treatment which was thought to be a result of stress and corticosteroid therapy. The haemorrhage was managed by transfusions and cimetidine, CXM was continued, and the patient recovered. A 4-year-old boy with *H. influenzae* meningitis suffered an episode of febrile polyarthritis from days 11 to 15 of therapy. Cultures of blood, CSF, and joint aspirates remained sterile and no reason could be found.

Intravenous CXM administration was well tolerated and phlebitis was only rarely observed. A 17-month-old patient developed a macular rash with fever on day 6 of treatment which disappeared within 3 days under continued CXM treatment. A transient mild increase in the alkaline phosphatase

concentration was noted at the end of treatment in one 10-year-old patient. Laboratory studies did not show any other abnormality.

Neurological follow-up examination and auditory function test performed 2 to 6 weeks after stopping CXM were judged to be normal in all patients except three. In one a mild ataxia was still present and in 2 others moderate, unilateral hearing loss was noted.

CXM concentration in concurrent CSF and serum samples, CSF/serum penetration (%), and CSF cell count 24 to 48 hours after start of treatment (available in 28 of them) and at completion of CXM treatment (available in 26 of them) are shown in Table 2. Eight CSF samples obtained 2 hours after the dose between days 4 and 7 from 6 patients were also available for antibiotic assay. The CXM levels in these CSF specimens ranged from 1.1 to 9.8 (mean±SD, 4.2±3.3) mg/l.

Discussion

CXM is active *in vitro* against the three major pathogens of childhood bacterial meningitis. The minimal inhibitory concentration values against both ampicillin-susceptible and ampicillin-resistant *H. influenzae* strains are between 0.25 and 0.5 mg/l, against *N. meningitis* strains between 0.016 and 0.064 mg/l, and against *S. pneumoniae* between ≤0.03 and 0.25 mg/l.^{11 12} Data on CSF penetration and efficacy of CXM in meningitis are generally

favourable but rather scant. Norrby *et al.*¹³ found in 7 CSF specimens of two adults with bacterial meningitis due to *Klebsiella* sp. and *S. pneumoniae* CXM concentrations between 8 and 38 mg/l. Renlund and Pettay¹⁴ reported CSF levels of 2.3, 3.2, and 5.3 mg/l in 3 newborn infants with *Escherichia coli* (2 patients) and *Staphylococcus aureus* (1 patient) meningitis. Wilkinson *et al.*¹⁵ measured a CXM concentration of 20 mg/l in the CSF of a neonate with *E. coli* meningitis. Kuzemko and Walker¹⁶ reported 6 CSF levels in 3 children with bacterial meningitis (*H. influenzae*, 2 patients; *N. meningitis*, 1 patient) of between 1.5 and 9.0 mg/l. Corbeel *et al.*¹⁷ added 6 CSF levels of between 0.2 and 1.2 mg/l at the end of treatment in 6 children with purulent meningitis. Calonghi *et al.*¹⁸ successfully treated 12 cases of bacterial meningitis by continuous intravenous plus intrathecal administration of CXM. Hoffstedt *et al.*¹⁹ gave CXM plus ampicillin to 3 children with bacterial meningitis (*H. influenzae*, 1 patient; *N. meningitis*, 1 patient; *S. pneumoniae*, 1 patient) and measured 4 CSF CXM levels between 2.3 and 6.4 mg/l. Müller *et al.*²⁰ reported CSF levels after single 1.5 g doses of CXM ranging from 1.5 to 3.7 mg/l on 6 adults with bacterial meningitis. All these data of *in vitro* activity and CSF penetration in patients with purulent meningitis suggest that CXM is an attractive candidate for single-drug treatment of childhood meningitis due to *H. influenzae*, *N. meningitis*, or *S. pneumoniae*.

In our study prompt clinical and bacteriological response to CXM therapy was observed in the 30 patients, and there were no cases of recurrence or relapse. All bacterial isolates were susceptible *in vitro* to CXM. Time to reduction of fever (average, 5.4 days) and incidence of both prolonged (13%) and secondary fever (17%) were comparable with values found in other series.²³ Sterile subdural effusions became manifest in 3 infants with *H. influenzae* meningitis, contained high levels of CXM (17.4–32.4 mg/l), and were successfully managed by repeated subdural punctures and continued antibiotics. *In vitro* susceptibility of the aetiological agent and neither concentration nor penetration of CXM in CSF showed any abnormality in the 3 patients who developed subdural effusions between days 6 and 8 of therapy compared with the remaining patients. The incidence of symptomatic subdural effusions in childhood bacterial meningitis is reported to be from 10 to 15%,²⁴ which is in accordance with the incidence of 10% in these patients. The two other complications noted during treatment were gastrointestinal bleeding (probably caused by stress and administration of corticosteroids) and sterile, probably allergic, polyarthritis. The tolerance of intravenous CXM administration was good. One

patient developed a transient macular rash and another a transiently increased alkaline phosphatase level. No other adverse or toxic reaction to CXM was observed. Sequelae on follow-up examination 2 to 6 weeks after treatment with CXM had ended were noted in 3 (10%) of the 30 patients: one child showed mild ataxia and in 2 children moderate unilateral hearing loss was found. Adequate audiometric studies performed several months to years after *H. influenzae* meningitis detected sensorineural hearing defects in 14 to 16% of children.²⁵ In this study the incidence of hearing loss after *H. influenzae* meningitis was 1 (8%) of 13 patients.

Most CXM CSF levels in our series greatly exceeded the susceptibilities of the principal pathogens that cause bacterial meningitis in childhood.^{11,12} These CSF concentrations compare well with the values reported earlier.^{13–17,19,20} Our CXM CSF levels at the end of treatment were about four times lower than those 24 to 48 hours after the start. This reduction was mainly explained by about three times lower CXM levels in serum and only to a lesser extent by reduced percentage penetration into CSF. The lower serum levels were thought to be the result of improved renal function and thus of increased CXM elimination. Average CXM penetration into CSF at 2 hours after the dose was about 13% on days 2–3 and about 10% on days 8–13 of therapy. There seems to be some correlation between CSF percentage penetration and degree of meningeal inflammation expressed by CSF cell count, but it is statistically not significant.

Conclusions

On the basis of these clinical and laboratory data we conclude that CXM is effective and safe in the treatment of childhood meningitis due to *H. influenzae*, *N. meningitis*, or *S. pneumoniae*. A dosage schedule of 200 mg/kg a day given in 4 doses is suggested. It must however, be stressed that the experience with CXM in the treatment of meningitis is limited and its use should still be reserved for well controlled clinical evaluations.

Addendum

Since the study ended, 20 more children with bacterial meningitis (*H. influenzae*, 11; *N. meningitis*, 5; *S. pneumoniae*, 2; unknown aetiology, 2) have been successfully treated with CXM in Berne. Except for one subdural effusion no complications were noted.

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