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Gram-negative bacillary meningitis in neonates: a glimmer of therapeutic success

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A combination of gentamicin and ceftazidime was used to treat four neonates with Gram-negative bacillary meningitis. The causative organisms were *Escherichia coli* (3 cases) and *Enterobacter agglomerans* (1 case). The laboratory findings, including cerebrospinal fluid (CSF) ceftazidime levels and bactericidal activity demonstrated that penetration of the cephalosporin into the cerebrospinal fluid was adequate. The antibiotics caused no side effects and all the patients responded well. On follow up none of the patients exhibited neurological deficits.

Introduction

Neonates with meningitis caused by Gram-negative bacilli continue to have a poor prognosis despite the use of treatment regimens such as ampicillin plus gentamicin or chloramphenicol (Lorber, 1974; Kaiser & McGee, 1975; Mulhall, de Louvois & Hurley, 1983). However, the relatively recent emergence of the third generation cephalosporins offers new therapeutic opportunities for this serious condition (Landensman *et al.*, 1981; Diaz & Fernandez-Guena, 1982; Steele & Bradshaw, 1983). One such antibiotic, ceftazidime, a third generation amino-thiazolyl cephalosporin has a broad spectrum of activity against Gram-negative bacteria including Enterobacteriaceae and many strains of *Pseudomonas aeruginosa*. Ceftazidime has been previously reported for the treatment of serious infections including Gram-negative meningitis (Elliott, Ispahani & Choudhary, 1983; Modai, Meulemans & Vittecoq, 1983; Modai *et al.*, 1983). However, these reports do not describe in detail any cases of neonatal meningitis. In this study we present the clinical response and laboratory investigations of four neonates with Gram-negative bacillary meningitis who were treated with ceftazidime and gentamicin.

Materials and methods

Patients

All four neonates were admitted to the special care baby units either at the University Hospital or the City Hospital, Nottingham.

Patient 1. Born at full-term following a normal delivery weighed 2·24 kg. Within 24 h she developed an ileal volvulus, which was resected and an ileostomy fashioned. Five

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days post operatively she became pyrexial and lethargic. A lumbar puncture (LP) was performed and CSF examination showed a pleocytosis and numerous Gram-negative bacilli. Gentamicin, ampicillin and metronidazole were commenced. Twenty four hours later *Escherichia coli* was isolated from the CSF. It was resistant to ampicillin, but sensitive to gentamicin, ceftazidime and chloramphenicol. The ampicillin and metronidazole were stopped and ceftazidime started. This regimen was given for three weeks during which time serum levels of ceftazidime and gentamicin were monitored. The patient made a satisfactory clinical response and on follow-up after one year had no neurological deficits.

Patient 2. Born following a normal delivery after 32 weeks gestation, weighed 1·42 kg. On day 12 having overcome initial respiratory problems he became unwell showing little interest in feeds. An LP was performed and gentamicin with flucloxacillin started. After 24 h incubation *Enterobacter agglomerans* was grown from both blood cultures and CSF. The organism was sensitive to gentamicin and ceftazidime, but resistant to ampicillin and chloramphenicol. The flucloxacillin was stopped and ceftazidime started. CSF obtained 12 days later was culture negative. Three weeks treatment was given and the child recovered uneventfully. At six months he had no neurological problems.

Patient 3. Ten weeks premature, weighed 1·6 kg at birth. After six days she became disinterested in feeds. An LP was performed and the CSF showed pleocytosis and numerous Gram-negative bacilli. Parenteral gentamicin and ampicillin were commenced. After 24 h incubation *E. coli* was isolated from the CSF and blood cultures. The *E. coli* was sensitive to gentamicin, ceftazidime and chloramphenicol but resistant to ampicillin. The ampicillin was stopped and ceftazidime added. Treatment was continued for three weeks, and she improved, despite developing a hydrocephalus secondary to the meningitis. Isosorbide was given for the hydrocephalus. After one year, the child's development has been normal, with no evidence of neurological problems.

Patient 4. Full-term, weighed 4·4 kg at birth. After eight days he became lethargic, disinterested in feeds, and pyrexial. An LP was performed and the CSF showed marked pleocytosis and numerous Gram-negative bacilli. Treatment with ampicillin and chloramphenicol was commenced. *E. coli* was subsequently isolated from the CSF and blood cultures. It was sensitive to ampicillin, chloramphenicol, gentamicin and ceftazidime. The patient improved on the antibiotics and when a culture negative CSF was obtained at day 9, all antibiotics were stopped after a total of 11 days. However, within a further 24 h the neonate became irritable. A repeat LP was performed and a combination of parenteral ceftazidime and gentamicin was commenced. *E. coli* was isolated from this CSF. The child gradually improved and after 20 days of this combination therapy the antibiotics were stopped. On follow-up after one year the child exhibited no neurological deficits.

Assays

The minimum bactericidal concentration (MBC) of gentamicin and ceftazidime against the infecting bacteria were determined by doubling dilutions of the antibiotics in Oxoid nutrient broth. Overnight broth cultures of the bacteria were diluted in fresh broth to give 10^5 organisms/ml and 25 µl was added to 1 ml of the antibiotic in broth. The tubes were incubated aerobically for 18 h at 37°C. The broths were subcultured into blood

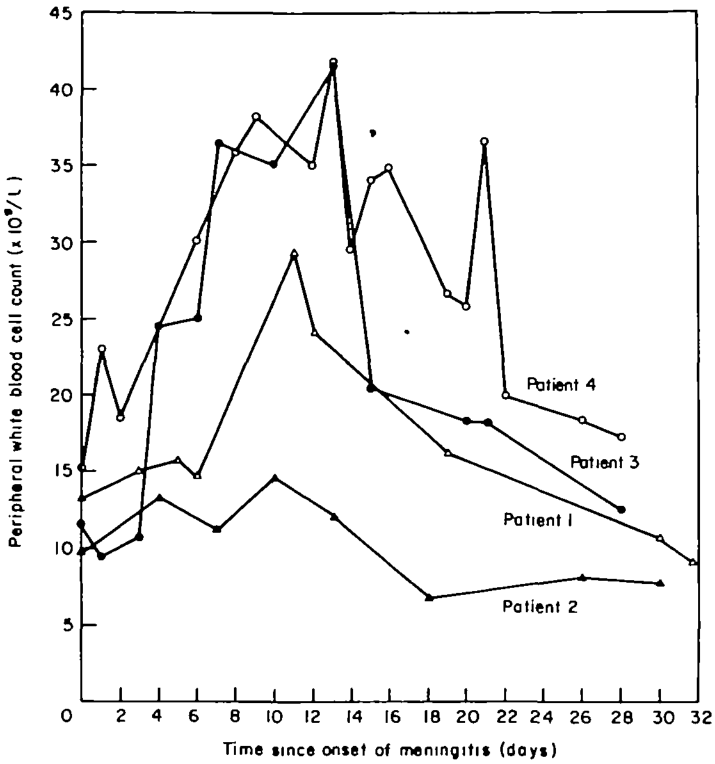

Figure 1. Sequential venous white cell counts of 4 neonates with Gram-negative bacillary meningitis.

agar plates, which were incubated for 18 h at 37°C. Bactericidal activity of the patients CSF against the infecting bacteria was determined by inoculating 1 ml of a range of dilutions of the CSF with 25 µl of a fresh broth containing 10^6 organisms/ml. After incubation at 37°C the bactericidal activities were determined as above.

The amount of gentamicin and ceftazidime in the patients' CSF and serum was determined using a modified plate diffusion technique (Reeves *et al.*, 1978). A strain of *Ent. cloacae* which was resistant to ceftazidime up to a concentration of 100 mg/l but sensitive to aminoglycosides was used for the gentamicin assay. For the ceftazidime assays an *E. coli* which was sensitive to ceftazidime but resistant to gentamicin at a concentration of >64 mg/l was used.

The patients peripheral white cell counts (Figure 1) were monitored during their illness. A reduction in count corresponding to clinical recovery took up to 3 weeks.

Results

The MBC of the bacteria isolated from the patients CSF (Table I) against ceftazidime and gentamicin were within the range of 0·12–2·0 mg/l. The ceftazidime levels attained in the CSF are given in Table I. The CSF bactericidal activity against the bacteria isolated from the CSF of the neonates is also shown in Table I with all the values being >1/32. The amount of ceftazidime given in divided doses was between 90 to 150 mg/kg body weight daily and the resulting serum levels were all higher than the MBC for the infecting organisms. The dose of ceftazidime had to be adjusted to maintain the recommended serum levels; trough <40 mg/l peak >100 mg/l (R. D. Foord, personal communication).

Table I. Minimum bactericidal concentrations (MBC) of the bacteria isolated from the patients CSF, dose of ceftazidime (mg/kg) used, CSF bactericidal activity and CSF ceftazidime concentrations in 4 neonates with Gram-negative bacillary meningitis

Patient	Bacteria isolated from CSF	Ceftazidime MBC (mg/l)	Gentamicin MBC (mg/l)	*Total daily dose of ceftazidime (mg/kg body wt)	CSF bactericidal activity	CSF ceftazidime level (mg/l)	Time since last dose of ceftazidime (h)
1	*E. coli*	0·25	2·0	150 180	1/32 1/32	22·0 25·0	4 3
2	*Ent. agglomerans*	1·0	0·12	150	1/64	30·0	2
3	*E. coli*	0·5	2·0	150	ND	ND	—
4	*E. coli*	0·12	1·0	110 150	1/160 1/160	25·0 22·9	4 4

ND, Not done.
*Divided into three doses.

Serum gentamicin levels throughout the course of the patients illness were also monitored and the levels were kept between 5 to 10 mg/l for the peak, at 1 h post dose, and around 2·0 mg/l for the trough.

Discussion

Previous reports from clinical trials have suggested that ceftazidime in combination with an aminoglycoside may be useful in the treatment of Gram-negative bacillary meningitis (Modai *et al.*, 1983; Elliott *et al.*, 1983; Williams & Foord, 1985). Gentamicin was given with ceftazidime because of the possible emergence of resistant bacteria whilst using this cephalosporin alone (Hudson & Ingham, 1985). In this present study, the four neonates with Gram-negative bacillary meningitis responded well to their treatment regimens. The efficacy of this combination was emphasized by patient 4, whom relapsed after ampicillin and chloramphenicol had been given whereas with ceftazidime and gentamicin the patient was cured.

The penetration of ceftazidime into the CSF, as in previous reports (Fong & Tomkins, 1984), was adequate. This was confirmed both by the CSF ceftazidime concentration attained and the CSF bactericidal activity (Table I). The combination of antibiotics was well tolerated with no adverse effects noted, including renal function, despite having levels of ceftazidime 1 h post dose of over 200 mg/l.

The findings indicate that the combination of ceftazidime and gentamicin is suitable for treating Gram-negative meningitis and that perhaps the mortality rate will be reduced with such a combination.

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