Archives of Disease in Childhood, 1985, **60**, 360–364

Ceftazidime in neonatal infections

D C LOW, J G BISSENDEN, AND R WISE

Departments of Neonatal Paediatrics and Microbiology, Dudley Road Hospital, Birmingham

SUMMARY Ninety one neonates received 108 courses of intravenous ceftazidime (25 mg/kg, 12 hourly) over a study period of 15 months. Fourteen had clinically and bacteriologically proved infections. Only one of these had resistant organisms. Four (two with group B β haemolytic streptococcal infections, one with *Escherichia coli* meningitis, and one with *Staphylococcal aureus* septicaemia) failed to respond despite adequate treatment. Bacteriological eradication or clinical improvement, or both, were obtained in the remaining nine. Routine biochemical and haematological values were monitored and there were no side effects. High serum ceftazidime concentrations, well exceeding the minimum inhibitory concentration for most common neonatal pathogens were obtained and maintained throughout treatment. Penetration into the cerebrospinal fluid was excellent in eight of the nine cases studied. Ceftazidime has a theoretical role as a broad spectrum antibiotic suitable for neonatal use with no evident side effects. In this study, however, it was only appropriate for Gram negative infections, and was ineffective against Gram positive organisms. Ceftazidime cannot therefore be recommended as monotherapy before the results of bacteriological culture are known.

Penicillin and gentamicin are the usual initial antibiotics for the treatment of neonatal sepsis. Gentamicin, however, has several theoretical disadvantages—otoxicity,[1] nephrotoxicity,[2] poor cerebrospinal fluid penetration,[3] and the consequent need for the monitoring of blood values.[4] The recent development of the ureidopenicillins and third generation cephalosporins has aroused interest in their use as an alternative, first line treatment in the newborn.[5–11] One of the new cephalosporins is ceftazidime (Fortum) which has certain advantages. It has a wide spectrum of activity in vitro against most neonatal pathogens including *Pseudomonas aeruginosa* and also has no appreciable nephrotoxicity.[12] In addition, adequate penetration into cerebrospinal fluid has been described.[13]

Neonatal sepsis, though often suspected, is difficult to prove. It is therefore necessary to study a large number of babies before a sufficient number of infections with unequivocal clinical importance may be documented. The purpose of this study was to collect such a number of cases and to assess the efficacy and safety of ceftazidime in the newborn. A second aim was to confirm the correct dosage by pharmacokinetic studies.

Patients

Between January 1983 and March 1984, 91 of 470 babies admitted to the Special Care Baby Unit of Dudley Road Hospital (a regional referral centre) were treated with intravenous ceftazidime—25 mg/kg, 12 hourly. Their birth weights ranged from 740 to 3860 g and gestational age from 24 to 41 weeks. Twelve babies received more than one course of ceftazidime. Babies were given ceftazidime either because they were deemed to be at risk of infection or already had symptoms or signs of infection. Informed parental consent for this study was obtained and the project was approved by the local ethical committee.

Methods

Before starting antibiotics, samples of blood, urine, and superficial swabs were taken, and where indicated cerebrospinal fluid and endotracheal secretions were obtained. Treatment was stopped if these cultures were negative and the babies remained asymptomatic. Length of treatment varied between two and 10 days. Further cultures were taken where appropriate during treatment. Haematological values and renal function were monitored routinely and full intensive care support was given when necessary. For pharmacokinetic studies, up to four timed blood samples were obtained by heelprick over a 12 hour period on 42 babies. In a further 14

Table 1 *Babies with clinical and bacteriologically proved infections*

Case no	*Gestational age (wks)*	*Weight (g)*	*Symptoms*	*Day of onset*	*Organism*	*Site*	*Outcome*		
							Bacterial eradication		*Clinical improvement*
							Yes/no	*Day of treatment*	*Yes/no*
1	26	820	Apnoea, pneumonia	2	*Escherichia coli*	Blood	Yes	4	Yes, NEC day 7
2	26	880	Apnoea meningitis	34	*E coli*	Blood CSF	No	2·5	No, died
3	29	1000	Pneumonia	2	*E coli*	Blood	Yes	3	Yes
4	31	1720	PROM, hyaline membrane disease	1	*E coli*	Blood	Yes	2·5	Slight; gentamicin added day 3 treatment
5	35	2540	PROM asymptomatic	1	*E coli*	Blood	Yes	2	NEC day 3 treatment
6	31	1820	PROM hyaline membrane disease	1	*E coli* *Pseudomonas cepacia* *Streptococcus faecalis*	Blood	Yes	3	Yes; gentamicin added for 24 hours day 4 treatment in clinical error
7	26	820	Central venous catheter, neutrophilia	16	*Staphylococcus albus*	Blood	Yes	3	Yes
8	29	1140	Apnoea, collapse	29	Clostridium butyricum	Blood	No repeat culture		Yes; penicillin added on culture report, baby then asymptomatic
9	30	1120	Apnoea, collapse	3	*Staph aureus*	Blood	No No Yes	24 hrs 36 hrs 72 hrs	No; flucloxacillin added 48 hrs treatment, slow recovery
10	27	1020	Pulmonary interstitial emphysema, collapse	16	*Str faecalis* *Enterobacter cloacae*	Blood	No		No; died within 24 hrs treatment
11	30	1480	Apparent hyaline membrane disease	2	Group B streptococcus	Blood	No	16 hrs	No; penicillin added 15 hrs treatment. Died IVH day 11
12	40	2400	Apnoea, meningitis	2	Group B streptococcus	Blood+ CSF	Yes Blood No CSF	54 hrs 54 hrs	Slight; penicillin added 54 hrs treatment. Died day 23
13	29	1100	Apnoea, pneumonia	5	*Staph aureus*	Skin+pro-pharynx	Yes	3	Yes
14	31	1280	IPPV endotracheal secretions, peri-oral ulcers	15	*Ps aeruginosa*	ET+ ulcers	Yes	7	Yes

PROM=maternal membranes ruptured >24 hours; IPPV=intermittent positive pressure ventilation; NEC=necrotising enterocolitis; IVH=intraventricular haemorrhage.

babies only peak and trough serum concentrations were measured.

Serum ceftazidime concentrations were assayed by high performance liquid chromatography using an Applied Chromatography Systems pump and fixed wavelength detector (254 nm); a Z module fitted with a C18 cartridge (Waters); and a mobile phase of 35% methanol, 1% acetic acid, and 1 mM heptane sulphonic acid in water (flow rate 3·5 ml/minute). Patient samples and standards were treated with equal volumes of 7% perchloric acid, mixed and spun at 3000 rpm for five minutes to precipitate the protein. The clear supernatant was injected via a rheodyne valve (20 µl loop). Linearity of the method was determined for concenrations ranging from 2 to 100 mg/l.

The individual serum concentration data were fitted to a two compartment open model and the pharmacokinetic parameters were derived by standard methods using a computer program based on non-iterative procedures.

Minimum inhibitory concentrations for ceftazidime against all isolated pathogens were measured by an agar dilution procedure using Oxoid Iso-Sensitest agar (Oxoid) with an inoculum of 10^4 organisms per spot. The minimum inhibitory concentration was defined as that concentration of antibiotic at which there was a reduction to 10 or less colonies in the original inoculum.

Results

Fourteen babies had bacteriologically proved serious infections (12 septicaemias including two with meningitis, one pneumonia, and a peri-oral ulceration due to *P aeruginosa*). A further seven babies had strong clinical evidence of sepsis but no organisms were isolated and all improved on treatment. Twenty one other babies were colonised with various organisms (including five with group B β haemolytic streptococci) but never had symptoms attributable to these organisms.

Table 1 lists the babies with serious infections. For nine of these, the use of ceftazidime may be deemed successful. In three cases, however, other antibiotics were added, which in retrospect were probably unnecessary (cultures already sterile or patient improving).

For five babies, ceftazidime treatment was unsuccessful. Case 2 had *Escherichia coli* meningitis that had not responded to gentamicin or chloramphenicol. After two days of ceftazidime treatment organisms were still isolated from the cerebrospinal fluid despite very adequate concentrations (Table 2). Case 9 had a *Staphylococcus aureus* septicaemia. Despite adequate serum concentrations three to four times greater than the minimum inhibitory concentration, cultures were still positive after 48 hours, with clinical deterioration. Cases 11 and 12 had group B β haemolytic streptococcal infections. Again, in both of these patients excellent serum and cerebrospinal fluid concentrations, well in excess of the minimum inhibitory concentrations of the organisms were obtained, but the infection persisted (Table 3).

Finally, there was one septicaemia with resistant organisms. This baby was receiving respiratory support for pulmonary interstitial emphysema and had received eight days of ceftazidime and five days of penicillin and gentamicin. Twenty four hours after antibiotics were stopped he deteriorated.

Table 2 *Pharmacokinetic parameters for 42 neonates treated with ceftazidime (values mean (SD))*

Half life (T½ β) (hours)	7·57 (4·57)
Clearance (ml/kg/per minute)	1·02 (0·59)
Volume of distribution (ml/kg)	542 (201)
10–12 hour trough concentration* (mg/l)	14·5 (9·16)

*56 babies.

Table 3 *Concentrations of ceftazidime in cerebrospinal fluid (CSF)*

Case no	*No of doses*	*Time after dose (hrs)*	*Blood concentration (mg/l)*	*CSF concentration (mg/l)*	*Ventricular fluid concentration (mg/l)*
2*	4	1·25	360		115·3
5	5	6·0	29·5	<1·0	
10	2	10·75	32·5	9·0	
11	15	11·0	11·3		10·3
12†	1	6·75	153	142	
	3‡	1·0	117	92	
	22		25	18	21·5
35	11	2·0	40·0	19·5	
42§	3	4·0			30·0
68**	4	18·0	41·5	11·5	
89	2	2·0	48·5	7·0	

* 100 mg/kg per 12 hrs; † 50 mg/kg per dose; ‡ 2×50 mg/kg per dose+1×25 mg/kg per dose; § 40 mg/kg per 12 hrs; ** 25 mg/kg per 12 hrs.

Ceftazidime was restarted but he died 24 hours later. *Enterobacter cloacae* and *Streptococcus faecalis* were later isolated in a blood culture. *Str faecalis* colonisation occurred in 13 babies altogether. Initially there were not many cases but by the end of the study the frequency of colonisation became a worrying feature, there being 10 cases in five months.

Table 2 shows the pharmacokinetic data on 56 babies. Only in one baby who had a severe metabolic acidosis was there any evidence of drug accumulation. Two babies in renal failure with serum creatinine values of 324 and 243 μmol/l (3·67 and 2·75 mg/100 ml) respectively received ceftazidime, 25 mg/kg, 18 hourly, with satisfactory serum values and no deterioration in renal function. The mean serum concentration of samples taken between one and two hours after a dose of 25 mg/kg intravenously in 47 neonates was 46 mg/l (range 250 to 8 mg/l). This concentration exceeded the minimum inhibitory concentration for *P aeruginosa* by over 40 fold and for *Staph aureus* by at least six fold.

Table 3 shows the concentrations of ceftazidime in cerebrospinal fluid for nine babies. For varying dosage regimens, good and sometimes very high cerebrospinal fluid concentrations were achieved, ranging from 92·8% of the serum value for case 12 with meningitis to less than 3·4% for case 5 whose meninges were not inflamed. The mean percentage penetration into cerebrospinal fluid was 45·7% of the serum value at that time.

In no cases were adverse changes seen in any biochemical or haematological values.

Discussion

This study was designed to evaluate experience with ceftazidime over a long period, treating a wide variety of infections. It was not a controlled study comparing ceftazidime with another antibiotic. Because of the variety of infection encountered in a neonatal unit, it was considered that such a study would give an inconclusive result.

Indeed, controlled studies[8 9] comparing various antibiotic regimens have been inconclusive as regards the relative efficacy of the antibiotic because of the very low septicaemia rate and the variety of organisms in the groups compared. Also, certain open studies on the new cephalosporins[10 11] have concluded that the antibiotic was safe but because of only two cases of septicaemia in each study, this was not a true test. In our study there were 12 proved cases of septicaemia, and therefore some assessment of the effectiveness of ceftazidime may be made.

On the positive side, ceftazidime cured five of six babies with Gram negative septicaemia. The baby that died had *E coli* meningitis and gentamicin and chloramphenicol treatment had failed. A major difference between ceftazidime and other cephalosporins is its activity against *P aeruginosa*. Only one case was encountered where this pathogen was invasive. This baby (case 14) had severe peri-oral ulceration after endotracheal tube fixation; this resolved with treatment and the organism cleared.

On the negative side, two babies with group B β haemolytic streptococcal infection died and a baby with *Staph aureus* septicaemia failed to respond, despite the organisms being sensitive to ceftazidime. One baby with group B β haemolytic streptococcal septicaemia (case 11) was treated late as his symptoms had been ascribed to hyaline membrane disease. Case 12 had meningitis and the mortality for this condition, whatever antibiotic used, lies between 35 and 50%.[14 15] Nevertheless, although excellent blood and cerebrospinal fluid concentrations were obtained, exceeding the minimum inhibitory concentration more than 40 fold, the infection persisted in cerebrospinal fluid. Although tolerance of this organism to penicillin is recognised,[16] exacerbated by extremely large numbers of infecting organisms,[17] no tolerance to ceftazidime could be shown in this patient. Perhaps combination treatment with an aminoglycoside would have had synergistic action as has already been suggested for the combination of ampicillin and gentamicin.[18 19]

The value of studying ceftazidime over a long period of time was emphasised by the colonisation of an increasing number of babies in our unit with *Str faecalis*. This is a well known phenomenon associated with the widespread use of cephalosporins.[20] Such colonisation has been reported not to have caused clinical problems,[11] but one baby in our study developed septicaemia in conjunction with *Ent cloacae* and died.

Despite a wide range of values, pharmacokinetic studies showed that 25 mg/kg, 12 hourly by intravenous injection was a suitable regimen for the treatment of neonatal sepsis. The values were not affected by gestational age. No comment may be made on the effect of postnatal age, as almost all babies treated were within the first week of life.

This study shows that ceftazidime is a good antibiotic to use for most neonatal infections. It is effective against Gram negative infections, it penetrates cerebrospinal fluid well, and its minimal toxicity obviates the need for blood monitoring. Reservations exist about its role in the group B β haemolytic streptococcal infections, so its use as a single first line antibiotic is not recommended until more experience has been accumulated.

We thank Mrs Jenny Andrews for assaying the ceftazidime values

and Miss Pauline Lowe for the bacteriological surveillance. We are grateful to Glaxo Group Research for their support, and in particular Mr Keith Williams.

References

[1] Elfving J, Pettay O, Ravio M. A follow up study on cochlear, vestibular and renal function in children treated with gentamicin in the newborn period. *Chemotherapy* 1973;**18**:141–53.

[2] Itsarayoungens S, Riff L, Shauf V, Hamilton L, Otrembiak J, Vidyasagar D. Tobramycin and gentamicin are equally safe for neonates: results of a double blind randomised trial with quantitative assessment of renal function. *Pediatr Pharmacol* 1982;**2**:143–55.

[3] Chang MJ, Escobedo M, Anderson DC, Hillman L, Feigin RD. Kanamycin and gentamicin treatment of neonatal sepsis and meningitis. *Pediatrics* 1975;**56**:695–9.

[4] Mulhall A, de Louvois J, Hurley R. Incidence of potentially toxic concentrations of gentamicin in the neonate. *Arch Dis Child* 1983;**58**:897–901.

[5] Schaad UB, McCracken GH, Threlkeld N, Thomas ML. Clinical evaluation of a new broad spectrum oxa-beta-lactam antibiotic, moxolactam, in neonates and infants. *J Pediatr* 1981;**98**:129–36.

[6] Kafetzis DA, Brater CD, Kapiki AN, Papas CV, Dellagrammaticas H, Papadatos CJ. Treatment of severe neonatal infections with cefotaxime. Efficacy and pharmacokinetics. *J Pediatr* 1982;**100**:483–9.

[7] Yamauchi T, Hill DE, Steele RW. The use of ceftizoxime in neonates. *J Antimicrob Chemother* 1982;**10(Suppl C)**:297–301.

[8] Placzek M, Whitelaw A, Want S, Sahathevan M, Darell J. Piperacillin in early neonatal infection. *Arch Dis Child* 1983;**58**:1006–9.

[9] Snelling S, Hart CA, Cooke RWI. Ceftazidime or gentamicin plus benzylpenicillin in neonates less than 48 hours old. *J Antimicrob Chemother* 1983;**12(Suppl A)**:353–6.

[10] de Louvois J, Mulhall A, Hurley R. Cefuroxime in the treatment of neonates. *Arch Dis Child* 1982;**57**:59–62.

[11] de Louvois J, James J, Mulhall A. Latamoxef and the newborn. *Arch Dis Child* 1984;**59**:346–50.

[12] Capel-Edwards K, Pratt DAH. Renal tolerance of ceftazidime in animals. *J Antimicrob Chemother* 1981;**8(Suppl B)**:241–5.

[13] Walstad RA, Hellum KB, Blika S, *et al.* Pharmacokinetics and tissue penetration of ceftazidime: studies on lymph, aequous tumour, skin blister, cerebrospinal and pleural fluid. *J Antimicrob Chemother* 1983;**12(Suppl A)**:275–82.

[14] Mayon-White RT. The incidence of neonatal group B streptococcal disease in Britain. In: Holm SE, Christensen P, eds. *Basic concepts in streptococci and streptococcal diseases*. Chertsey: Reedbooks, 1982:305–6.

[15] Baker CJ. Summary of the workshop on perinatal infection due to Group B streptococcus. *J Infect Dis* 1977;**136**:137–52.

[16] Kim KS, Anthony BF. Penicillin tolerance in group B streptococci isolated from infected neonates. *J Infect Dis* 1981;**144**:411–9.

[17] Feldmann WE. Concentrations of bacteria in cerebrospinal fluid of patients with bacterial meningitis. *J Pediatr* 1976;**88**:549–52.

[18] Schauf V, Deveikis A, Riff L, Serota A. Antibiotic–killing kinetics of group B streptococci. *J Pediatr* 1976;**89**:194–8.

[19] Deveikis A, Schauf V, Mizen M, Riff L. Antimicrobial therapy of experimental group B streptococcal infection in mice. *Antimicrob Agents Chemother* 1977;**11**:817–20.

[20] de Louvois J. Use of some new antibiotics in the newborn. *Hospital Update* 1983;**9**:1291–9.

Correspondence to Dr D Low, Department of Paediatrics, Dudley Road Hospital, Birmingham B18 7QH.

Received 12 December 1984