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Cefuroxime in the treatment of neonates

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SUMMARY The new broad spectrum cephalosporin, cefuroxime, was used to treat 28 neonates with suspected or proved infection. All of them had had complications at birth or in early neonatal life which were known to predispose to infection. The treatment regimen consisted of intramuscular or intravenous cefuroxime (50 mg/kg twice a day) for 5 days. Previously, such infants would have received gentamicin with penicillin or ampicillin. Pathogenic or potentially pathogenic bacteria were isolated from 7 (25%) of them. All of these organisms were sensitive to cefuroxime. None of the babies had meningitis, but blood cultures from 2 gave positive results. There was significant clinical improvement in 27 of them after 5 days of treatment and each was well on discharge from hospital. Serum urea, total protein, albumin, and alanine transaminase levels were estimated before, during, and after cefuroxime treatment. There were no changes attributable to cefuroxime nor were any changes in haemoglobin, packed cell volume, or total differential white cell counts observed. There were no adverse clinical side effects. One hundred and ninety-four samples of serum were assayed for cefuroxime. The mean peak level after intramuscular injection (42·7 mg/l) was reached in 0·8 hours, and the mean trough level was 10·5 mg/l. The mean half-life of cefuroxime in infants aged less than 4 days was 5·8 hours. In 4 infants older than 8 days, it ranged from 1·6–3·8 hours. Half-life was not associated with birthweight. Cefuroxime is a safe, well-tolerated, and rapidly-absorbed drug for the treatment of neonates with suspected or proved infections; it is a useful alternative to gentamicin, if the use of an aminoglycoside is not clearly indicated.

The vulnerability of preterm neonates to serious sepsis is so great that, often, the decision to initiate antimicrobial chemotherapy is based entirely on clinical suspicion. Bacterial cultures taken before treatment often fail to yield a pathogen. It is important therefore, that the antibiotic of first choice should be free from toxic side effects, and it is questionable if gentamicin is the ideal first line therapy for units that do not have a problem with infection caused by *Pseudomonas aeruginosa*.

The range of bacteria which may infect neonates is wide, and it is often considered necessary to use more than one antibiotic. With the introduction of the newer cephalosporins this has changed. Cefuroxime is active against a wide range of Gram-positive and Gram-negative bacteria—such as the Lancefield group B streptococcus, *Staphylococcus aureus*, *Escherichia coli*, as well as many other coliforms. Its potential toxicity is lower than that of gentamicin and, unlike most other β-lactam antibiotics, it requires only twice-daily injections.

This paper reports a study on the efficacy, safety, and pharmacology of cefuroxime used in the treatment of 28 neonates in a special care baby unit.

Subjects

Twenty-eight infants (15 boys, 13 girls) with a mean gestational age of 32·65±4·1 weeks and a mean birthweight of 2·00±0·85 kg were treated with cefuroxime. The mode of delivery of these infants included spontaneous vertex vaginal delivery (n=10), breech delivery (n=3), forceps delivery (n=2), elective lower segment caesarean section (n=9), and emergency lower segment caesarean section (n=2). Twenty-three babies were preterm; 6 of them were less than 30 weeks' gestation, 18 had birthweights less than 2·5 kg, and 3 were below the 10th centile for birthweight, head circumference, or length. Complications of birth or early neonatal life which contributed to suspicion of neonatal infection were prolonged (>24 hours) rupture of membranes (n=13), birth asphyxia (n=7), maternal pyrexia (n=2), meconium aspiration (n=2), and respiratory distress or hyaline membrane disease (n=8).

Previously, all babies would have received gentamicin with ampicillin or penicillin.

Treatment regimen

The dosage regimen was cefuroxime (50 mg/kg per

day) administered in two divided doses by intramuscular (n=23) or intravenous (n=5) injections for 5 days. Two infants initially treated intravenously, subsequently received intramuscular therapy. Treatment of one baby was changed to gentamicin and penicillin after 24 hours because of a deterioration in his clinical condition. Another baby who was still unwell after a 5-day course of cefuroxime continued on gentamicin and penicillin for a further 5 days.

Laboratory investigations

Before the study started and during it, all bacterial isolates from patients within the special care baby unit were tested for sensitivity to cefuroxime. Surface swabs and blood cultures were collected from all babies before treatment, and cerebrospinal fluid was taken from 9 infants with suspected meningitis. Capillary blood samples were collected before, during, and after the 5-day course for estimation of serum urea, protein, albumin, and alanine transaminase. The results of other microbiological and haematological investigations requested by paediatricians before and during the treatment period were also analysed.

Cefuroxime assay

Timed series of blood were collected after the midday injection on day 3 or 4 of treatment for cefuroxime estimation. Assay was performed by an agar diffusion technique using antibiotic medium no 2 (Oxoid) with the addition of 0·25% sodium citrate. The indicator organism was *Bacillus subtilis* 1904 E (Glaxo Laboratories) prepared as a spore suspension which was incorporated before pouring at a concentration of 10^4 spores per ml agar. Cefuroxime standards in the range 0·62 to 10·0 mg/l were prepared in phosphate buffer pH 7·0 and test samples appropriately diluted in the same medium. Four-millimetre agar wells were filled with test and standard solutions in quadruplicate and after overnight incubation at 37°C, zone diameters were measured on a magnified zone reader. The standards were plotted on semilog paper, and the tests read from the resulting straight line graph.

Serum concentration of cefuroxime was measured in 194 samples from 28 infants. The results from 23 of the infants (184 samples) were analysed using a logarithmic transformation and linear regression[1] to calculate the terminal half-life. There were insufficient data from the remaining 5 infants to warrant inclusion. The infants analysed had a mean birthweight of $1·98 \pm 0·78$ kg and a mean gestational age of $32·48 \pm 3·84$ weeks. The median concentration curve after intramuscular injection was assumed to be adequately described by a 1-compartment open model as found in adults.[2]

Sensitivity of clinical isolates to cefuroxime was determined by the disc diffusion technique on DST agar (Oxoid) pH 7·2 using *E. coli* NCTC 10418 as control.

Results

Bacteriological specimens from 7 of the 28 infants showed pathogenic or potentially pathogenic bacteria. Two infants had positive blood cultures, one yielding *Listeria monocytogenes* and the other *Klebsiella pneumoniae*. The endotracheal tubes of both these infants were colonised with *K. pneumoniae*. One infant had a urinary tract infection due to *E. coli* and another a respiratory tract infection due to *Haemophilus influenzae*. *Staphylococcus epidermidis* was isolated from an arterial line removed from the fifth infant and 2 others were superficially colonised with *E. coli*. All organisms were sensitive to cefuroxime. The only cefuroxime-resistant organisms occasionally encountered in the special care baby unit before or during the study were pseudomonads from environmental swabs.

Cefuroxime had no discernible effects on serum urea, protein, albumin, or alanine transaminase as measured in blood collected before, during, and after the treatment period, nor were there any changes in haemoglobin, packed cell volume, or peripheral leucocyte count associated with therapy.

Twenty-six of 27 infants showed clinical improvement after treatment. One infant who remained unwell at the end of 5 days of cefuroxime therapy was then treated with gentamicin and penicillin. All the infants were well when discharged from hospital.

Timed blood samples were obtained from 10 infants on 2 separate days, after at least 24 hours of treatment. Paired semilog plots of serum concentration against time for individual patients resulted in graphs that were very similar in shape and showed no consistent shift, indicating that a steady state existed.

The data on 17 infants (mean birthweight $2·11 \pm 0·75$ kg, mean gestational age $33·29 \pm 3·82$ weeks) treated with intramuscular cefuroxime are shown in Table 1. Average concentrations were taken for each sampling time for the 10 infants with two timed series. Using a logarithmic transformation and linear regression, estimates of half-life in individual patients were determined. The median half-life was 6·0 (SD 2·1) hours and the range 2·1–10·8.

The median and range of serum levels were determined at each sampling time and the results are

Table 1 *Serum concentrations (mg/l) of cefuroxime in 17 neonates after intramuscular injection of 25 mg/kg*

Case	*Time (hours)*							
	0·25	*0·5*	*0·75*	*1*	*3*	*5*	*6*	*12*
2	30	39	53	—	25	22	—	—
3	38	42		—	—	—	16	—
6	28	30		32	23	—	—	—
7	69	75		—	43	—	—	—
8	39	52	30	46	39	29	—	—
10	57	58		65	61	46	—	—
11	33	48		45	44	31	—	—
12	19	55		39	27	19	—	—
13	46	50		42	42	28	—	—
16	13	15		15	12	—	3	—
17	—	—	49	—	38	—	—	13
19	51	55		56	55	—	—	17
20	37	—	49	45	32	—	21	16
22	—	40		42	37	24	—	—
24	—	—		33	—	—	—	11
26	32	38		42	33	22	—	10
27	21	27		28	20	13	—	0
Median concentration	35	45	—	42	35	26	—	10·5

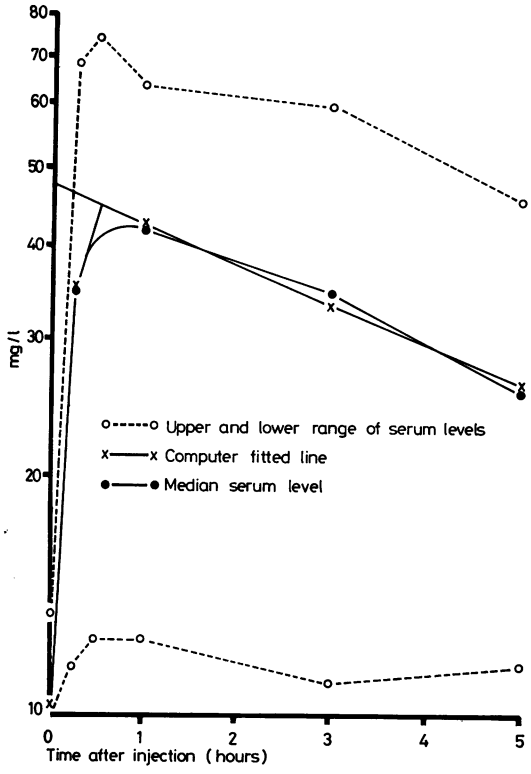

Figure *Median and range of cefuroxime levels in serum after intramuscular injection.*

presented graphically in the Figure. The median time from injection to peak serum concentration was 0·8 hours, and the half-life determined from the terminal portion of the median curve was 5·8 hours. This compares well with the median half-life obtained from results on individual patients. The median trough level 12 hours after injection was 10·5 mg/l (23·5 μmol/l).

On the assumption that absorption is complete 12 hours after injection and that the trough concentration will continue to drop according to $C_T e^{-ket}$ (where C_T (trough concentration) = 10·5 mg/l, k_e (elimination rate constant) = 0·12h), a computer was used to determine the portion of each serum concentration that was due to residual drug. The data were further analysed using the CSTRIP computer program of Sedman and Wagner[3] and this produced a best fit line (Figure) described by the equation

$$C = A(e^{-ket} - e^{-kat}) + C_T e^{-ket} \text{ given that } C_T = 10{\cdot}5 \text{mg/l}$$

$$\text{and } k_e = 0{\cdot}12\text{h from } k_e = 0{\cdot}693/t\tfrac{1}{2}$$

From this, a theoretical concentration at time zero (Co) of 48·5 mg/l (108·6 μmol/l) and a half-life of 5·8 hours were derived. This provided an estimate of the serum concentration after a single dose in a 1-compartment open model from the equation:

$$C = A(e^{-ket} - e^{-kat}) \text{ where } A = \frac{k_a D}{V(k_a - k_e)}$$

(k_a (absorption rate constant)=4·7h, t=time zero, D=dose administered, V (volume of distribution)= 0·67 l/kg). Using this model, the values obtained for trough levels after 1, 2, and 3 injections were 9·0 mg/l (20·2 μmol/l), 11·1 mg/l (24·9 μmol/l), and 11·6 mg/l (26 μmol/l), providing further support for the assertion that a steady state existed after the first 24 hours of treatment.

Results from 4 infants who were older than 9 days when treatment with cefuroxime was started were analysed separately (Table 2). Firm conclusions cannot be drawn from such a small series but it is clear that elimination is more rapid in older babies. Estimates of half-life in these infants ranged between 1·6 and 3·8 hours. There were insufficient data on the infants treated with intravenous cefuroxime for

Table 2 *Serum concentrations (mg/l) of cefuroxime in 4 preterm neonates after intravenous injection of 25 mg/kg*

Case	*Time (hours)*				
	0·25	*0·5*	*1*	*3*	*5*
1	41	—	47	34	20
4	30	36	36	25	12
5	44	46	38	22	9
28	24	36	36	22	10

analysis but serum levels one hour after injection were similar to those obtained by intramuscular injection.

Discussion

This study confirms the suggestion made in earlier reports[4 5] that cefuroxime is appropriate for single drug antimicrobial therapy of neonates with suspected or proved infections. Twenty-seven of 28 neonates showed clinical improvement after 5 days of treatment and all were well on discharge from hospital. In previous reports on cefuroxime during the neonatal period, treatment has either been combined with other antimicrobial drugs[4] or has been used at a lower dosage or with a shorter interval between injections.[6] Thus, comparison of results is difficult.

In the present study an intramuscular injection of 25 mg/kg twice daily resulted in median serum levels of 45 mg/l (100·8 μmol/l) after half an hour and 10·5 mg/l after 12 hours and a median half-life of 5·8 hours. The time to peak concentration, 0·8 hours (Figure), is shorter than that occurring in older patients and the plasma clearance, 1·35 ml/min per kg, is about half that demonstrated in healthy adults, reflecting the immature renal function of neonates.

The lower dosage regimen used by Renlund and Pettay[6] (10 mg/kg, three times a day) resulted in elimination of the drug from the blood within 8 hours. After a higher dose (33 mg/kg three times a day) used by Wilkinson *et al.*[4] the preinjection level was so high (10–40 mg/l) that there was risk of accumulation of the drug. No evidence of accumulation was noted in the present study and the results suggest that after 24 hours of treatment, a steady state exists with regard to excretion.

The excretion of cefuroxime is slower in neonates than in infants and adults. In this study 82% of infants were preterm and the median half-life for those who started treatment during the first 3 days of life was 5·8 hours. In 4 infants treated after the eighth postnatal day, the half-life ranged from 1·6 to 3·8 hours. Similar results were reported by Dash *et al.*[5] who, in a study of neonates up to 3 weeks of age, reported that the half-life fell from about 5 hours on the first postnatal day to 2–3 hours on the sixth day. Unlike an earlier report,[5] no association between half-life and birthweight was noted in the present study. Some results suggest that the half-life of cefuroxime is longer in preterm than term infants and that as renal function develops the half-life falls.[4 5] In some infants the half-life at age 3–4 weeks may be as low as 1–1½ hours[4] which compares with a half-life in adults of 1·1 hours.[7] The treatment regimens for neonates and infants must therefore be modified accordingly. The safety of cefuroxime for neonates as measured by the absence of adverse clinical, biochemical, or microbiological changes in this study matches that reported previously for older infants,[8] and we consider it to be a safe and effective first line antimicrobial drug for the treatment of neonates with suspected or proved infections.

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