Absorption and excretion of cephalixin by the newborn infant

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Boothman, R., Kerr, M. M., Marshall, M. J., and Burland, W. L. (1973). *Archives of Disease in Childhood*, 48, 147. **Absorption and excretion of cephalixin by the newborn infant.** Blood levels and urinary excretion of cephalixin were studied in newborn infants who were given 3-day courses of the antibiotic prophylactically. These infants were born to mothers with intrapartum pyrexia or with membranes ruptured for 72 hours or longer.

Adequate blood levels of cephalixin were achieved after oral administration of 50 mg/kg every 12 hours, provided that the infant was not vomiting. Absorption was slower and probably less complete than in the adult. Persistently high levels of the antibiotic in the serum were associated with the low level of renal function normal in newborn infants.

It is suggested that oral cephalixin may be substituted for intramuscular cephaloridine in the newborn infant, but *only* when oral feeding has been firmly established.

Cephaloridine, both alone and with streptomycin, has been shown to be safe and effective for the prevention and treatment of infection in the newborn period (Burland and Simpson, 1967; Burland, Simpson, and Samuel, 1970; Gould, 1970; Keay and Fleming, 1970; Keay, Syme, and Barnes, 1967). These antibiotics are given by intramuscular injection every 12 or 24 hours, and the route ensures that blood and tissue levels are adequate and sustained. Cephalixin resembles cephaloridine in that it is a semisynthetic antibiotic derived from cephalosporin C but, unlike cephaloridine, it is well absorbed when given by mouth. To be effective in the newborn infant an orally administered antibiotic must be retained and well absorbed. Cephalixin, moreover, is bactericidal to a broad range of Gram-positive and Gram-negative organisms (Foord *et al.*, 1969; Nakazawa *et al.*, 1969) including those commonly encountered in the immediate newborn period. Marget (1971) found cephalixin to be well tolerated and without toxicity in infants. We decided therefore to measure the absorption and excretion of the antibiotic in the newborn infant.

Method

Infants born to mothers with intrapartum pyrexia or with ruptured membranes for 72 hours or more were considered to be at risk from infection. They were given cephalixin, in the form of a syrup, immediately after birth and for 3 days. Blood samples for cephalixin assay were taken at various intervals after the first dose of antibiotic. One 5 ml venous sample of blood was obtained from a peripheral vein or by fontanelle tap from each infant during the course of treatment. Blood was immediately centrifuged and the serum stored at -4°C . Urine was collected from a number of male infants for 24 hours during the second or third day of treatment, to determine the urinary excretion of the antibiotic. The samples were collected only from male infants for convenience. The total volume passed was measured and 10 ml samples were stored at -4°C . In an initial investigation 40 infants were given 15 mg/kg cephalixin every 8 hours. In a second series, 30 infants received 50 mg/kg every 12 hours.

Results

Dosage 15 mg/kg 8-hourly. Group 1. The levels of cephalixin in the serum of this group of infants, at 1½, 4, 6, and 8 hours after the first dose of the antibiotic, are shown in Fig. 1. The proportions of a day's dose excreted in the urine during 24 hours by 13 male infants are shown in

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FIG. 1.—Mean and individual serum cephalixin levels in newborn infants after one 15 mg/kg dose by mouth.

FIG. 2.—Mean and individual serum cephalixin levels in newborn infants after one 50 mg/kg dose by mouth.

Table I. The average amount of a day's dose excreted in this group of infants was 30%. Some regurgitation occurred in 5 infants, each of whom consequently had serum cephalixin levels below the average figure.

TABLE I

Urinary excretion of cephalixin by newborn male infants given 15 mg/kg 8-hourly by mouth

Group 1 infants	Urine		% of total daily dose excreted in 24 hr
	24 hr volume (ml)	Concentration cephalixin (µg/ml)	
1	124	465	39
2	38	139	5*
3	70	433	25
4	86	511	37
5	93	587	37
6	58	531	35
7	100	481	25
8	50	462	17
9	18	1113	11*
10	44	1518	34
11	90	468	41
12	127	768	59
13	40	766	17

*Vomited.

Dosage 50 mg/kg 12-hourly. Group 2. The levels of cephalixin in the serum of the second group of infants, at 1, 2, 3, 4, 8, and 12 hours after the first dose of the antibiotic, are shown in Fig. 2. Urinary excretion from 10 male infants during 24 hours is shown in Table II. Some minor regurgitation occurred in 5 infants. One, who vomited more severely, had no assayable cephalixin in the serum 1 hour after dosage. The average urinary excretion of a day's dose of cephalixin was 39%

for this group. Swabs were taken from nose, throat, groin, and rectum of each infant at birth and at 3, 5, 7, 14, and 21 days for bacteriological culture. Stomach aspirate at birth was also cultured. A range of Gram-negative and Gram-positive organisms was identified but no clinical infections occurred in the treated infants.

Over a period of 6 months, as part of a separate bacteriological survey, 28 separate isolations of *Pseudomonas pyocyanea* occurred in the neonatal unit where the investigations were undertaken. The isolations came from infants aged 1 to 14 days and from various body sites. 10 of these infants were among those who had received cephalixin, 10 others had received ampicillin and cloxacillin, and 8 had received no antibiotic. In only one instance was illness in the infant considered to be related to the presence of the organism.

TABLE II

Urinary excretion of cephalixin by newborn male infants given 50 mg/kg 12-hourly by mouth

Group 2 infants	Urine		% of total daily dose excreted in 24 hr
	24 hr volume (ml)	Concentration cephalixin (µg/ml)	
1	14.5	4067	24
2	49	1365	25
3	38	2486	30
4	120	1832	64
5	58	1441	20
6	105	2373	66
7	73.5	2283	51
8	71	1810	36
9	51.5	1318	18
10	37	3847	54

No untoward effects were noted in either group of infants during cephalixin treatment. All the infants, whose birthweights ranged from 2 kg to 4.3 kg, remained free from infection during the period of treatment.

Discussion

There is at present no general agreement regarding the necessity for prophylactic antibiotic therapy in the newborn after a birth which has been possibly complicated by uterine infection. Many clinicians, remembering the problems in maternity units in the 1950s, are probably reluctant to abandon prophylaxis when there has been prolonged rupture of membranes and/or fetal distress (Bound, Butler, and Spector, 1956). Davies (1971) advises that prophylactic antibiotics should be withheld from the majority of infants, even though they emerge from an apparently infected environment, and treats only those who appear ill at birth.

However, since infection in the newborn may be overwhelming or so insidious in onset as to make prompt diagnosis difficult, it remains the practice at this hospital to give newborn infants a suitable antibiotic for 3 days when the membranes have been ruptured for more than 72 hours, or when there has been maternal pyrexia of 37.0 °C or more, during labour.

The serum levels of cephalixin achieved after a dosage of 15 mg/kg 8-hourly were lower than the average minimum inhibitory concentration (MIC) for many of the Gram-negative organisms encountered in the neonatal period. In contrast, the levels achieved after 50 mg/kg 12-hourly resembled more closely those seen in adults receiving 1 g doses (O'Callaghan, Toothill, and Robinson, 1971), though peak levels occurred later, at about 2 hours after dosage, indicating slower absorption by the infants. The high levels of cephalixin in the serum 8 or 12 hours after a single dose reflect a phenomenon seen with other antibiotics, including cephaloridine (Burland and Simpson, 1967), in newborn infants and result from reduced renal function, normal in this age group. Higher serum and tissue levels of cephalixin may be required in certain infections and could be achieved with higher dosage. No changes in bacterial isolations were experienced as a result of introducing cephalixin into the neonatal unit; the isolations of *Ps. pyocyanea* were equally distributed between infants receiving cephalixin, those receiving other antibiotics, and those receiving none.

Urinary excretion of cephalixin in 24 hours ranged widely from 5 to 66% of the total daily dose. The lowest amounts excreted by infants taking

15 mg/kg 8-hourly were from the ones with the lowest serum levels and in whom regurgitation had occurred. Urinary excretion of the antibiotic must be related to the amount of drug absorbed and its persistence at significant levels in the serum and tissues. The excretion of antibiotic by the infants studied was below that expected from adults with normal renal function. This probably reflects the limited powers of absorption and renal excretion seen in newborn infants, especially within the first 24 hours of life. On the basis of the urinary excretion levels obtained it appears that some 50 to 60% of the administered dose of cephalixin is absorbed by the newborn infant. 9 infants were bled at various intervals after multiple doses of cephalixin. Table III shows that there was no significant accumulation of antibiotic in the serum.

TABLE III

Serum cephalixin in newborn infants after multiple 50 mg/kg doses given 12-hourly by mouth

Group 2 infants	No. of previous doses	Time since last dose (hr)	Serum cephalixin (µg/ml)
1	2	12	8.8
2	3	3	28.0
3	3	8	15.9
4	3	12	15.9
5	3	12	24.4
6	4	4	24.1
7	6	1	14.1
8	6	4	21.6
9	6	8	27.7

It is not the purpose of this communication to suggest that, for the newborn infant, an orally administered antibiotic is to be preferred to one given by intramuscular injection. Many paediatricians advise that even prophylactic antibiotics should be given by the intramuscular route for at least the first 24 hours of life. It seems reasonable, therefore, to substitute oral cephalixin for intramuscular cephaloridine in the newborn infant *only* when oral feeding has been firmly established.

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