Pharmacokinetics of cefuroxime in pregnant patients with preterm premature rupture of the membranes

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Introduction

Premature rupture of the membranes in preterm gestations is often the initiating event leading to preterm birth, which is associated with high rates of neonatal morbidity and mortality, mainly caused by respiratory distress syndrome [1 2]. Therefore, efforts to postpone delivery with or without tocolysis are favoured [3]. However, one of the risks of this management is the development of chorio-amnionitis and foetal-neonatal infection [4]. With the increase of the interval between onset of preterm premature rupture of the membranes and the date of delivery the risk of foetal-neonatal infection increases [5]. The uterine cavity can become infected via the ascending route from the vagina and cervix, or was infected before preterm premature rupture of the membranes via the haematogenous route [6]. Moreover, preterm premature rupture of the membranes is often caused by chorio-amnionitis [7].

Prophylactic administration of antibiotics to the mother with preterm premature rupture of the membranes to decrease the risk of chorioamnionitis and neonatal infection is a controversial issue [3 8]. Some investigators have found no difference in the incidence of neonatal infection, whereas others reported a significantly lower incidence after prophylactic use of antibiotics [9-11]. These controversial findings may be introduced by the type and dosage of the antibiotic used, the route of administration, and by colonization resistance as a result of long-term prophylaxis.

There are no published data on the use of cefuroxime for this special indication, although the broad spectrum of antibacterial activity of this cephalosporin, its low toxicity and its favourable pharmacokinetic properties make it suitable for use in pregnant women. Cefuroxime administration during spontaneous delivery or caesarean section at term, resulted in therapeutic concentrations in foetal blood and amniotic fluid, required for many common pathogens responsible for obstetrical infections [12-16]. However, cefuroxime levels in maternal plasma were significantly lower during pregnancy than during delivery or afterwards [16]. The present study was designed to establish the cefuroxime levels in maternal plasma and amniotic fluid during pregnancy in women with preterm premature rupture of the membranes, and in foetal plasma, placenta, and membranes after delivery.

Methods

Patients

6 Women with a singleton pregnancy and preterm premature rupture of the membranes at 27 to 33 weeks' gestation, volunteered for this study after informed consent. Premature rupture of the membranes was definitely diagnosed on demon-

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Abstract

To 6 pregnant patients with preterm premature rupture of the membranes, cefuroxime prophylaxis was given 1,500 mg three times daily intravenously. Cefuroxime concentrations were assayed in maternal plasma and amniotic fluid during pregnancy and in umbilical cord blood, placenta, and membranes after delivery. Our results showed a high rate of transplacental transfer of cefuroxime. Bactericidal levels could be demonstrated in maternal plasma, and in amniotic fluid leaking from the vagina. Therapeutically active levels were present in the newborns. The absorption of cefuroxime by the foetal membranes was high. Although the neonatal morbidity in this high-risk population was low, the data are still too preliminary to advise the routine prophylactic use of cefuroxime to pregnant patients with preterm premature rupture of the membranes.

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stration of amniotic fluid leaking from the vagina, by a positive Ferning test and determination of the prolactin concentration of the fluid. No vaginal examination was performed. The exclusion criteria were active labour, foetal distress and maternal complications conflicting with a delay of the delivery, use of antibiotics during the preceding week, and known allergy to cephalosporins.

The patients were hospitalized with recommended bedrest and vulvar hygiene. Routine vital sign assessment was done every 8 h, white blood count every 12 h, nonstress cardiotocography daily, and ultrasound weekly. Lecithin–sfingomyelin ratio and culture of the vaginal amniotic fluid were performed twice weekly, if possible. The patients did not receive any corticosteroids. Prophylactic tocolysis was performed with fenoterol (Partusisten®; Boehringer Ingelheim, Alkmaar, the Netherlands) 2.0 μg/min intravenously. The patients were treated with intravenous cefuroxime (Zinacef®; Glaxo, Nieuwegein, the Netherlands) three times daily 1,500 mg.

Tocolysis was discontinued and delivery accepted or induced at 34 weeks' gestation, in the case of clinical signs of chorio-amnionitis, and if foetal or maternal complications necessitating a delivery arised, for example, foetal asphyxia or pre-eclampsia. A cervial culture was taken at the beginning of labour. After delivery cultures were taken from both ears and the anus of each child, and from the maternal and foetal sides of the placenta. The placenta and membranes were sent for histopathological examination, with special attention for signs of chorio-amnionitis. The newborn infant was immediately transferred to the neonatal intensive-care unit.

Cefuroxime concentrations in maternal plasma were assessed twice weekly. One sample was taken 1 h after intravenous administration of cefuroxime and another just before the next dose, which was given 8 h after the previous one. During pregnancy and delivery, as many samples as possible were collected of the vaginal amniotic fluid leaking. After delivery, samples of umbilical cord blood, placenta and membranes were taken.

Analysis

Samples of maternal plasma, amniotic fluid, and umbilical cord blood were collected in sterile plastic tubes and centrifuged at 2,500 g. Supernatants were frozen at −20 °C for a maximum of 4 weeks. Cefuroxime levels in samples from 1 patient were assayed, simultaneously (Department of Clinical Pharmacy and Toxicology, De Wever Hospital, Heerlen, the Netherlands) using high pressure liquid chromatography (HPLC) [17].

After thawing and deproteinization with perchloric acid and methanol the samples were centrifuged at 10,000 g. An aliquot of the supernatant was mixed with phosphate buffer at pH 7, and injected onto a 5 μm Bondapack C18 column with water+methanol+tetramethyl ammonium hydrogen sulphate (vol/vol/vol) as mobile phase. Detection was achieved at 278 nm. The analysis was performed on a Hewlett-Packard HPLC (model 1084 B; Amstelveen, the Netherlands), fully equipped with autoinjector, autosampler, variable UV detector, integrator and oven. In view of the linearity in the concentration range 1-75 mg/l, and a maximal standard deviation of 5% in this range, the use of an internal standard was judged unnecessary. Calculations were made by comparison, using a standard curve, with results from the analysis of freshly prepared spiked serum samples.

The samples of placenta and membranes of all patients were frozen at −20 °C in sterile plastic tubes and assayed simultaneously (Department of Clinical Pharmacy, University Hospital Nijmegen, the Netherlands). After thawing, 5 ml of 0.9% NaCl solution were added to 1 g of membrane or placental tissue and homogenized in an Ultra Turrax (Ystel, FRG). The homogenous mixture was, subsequently, centrifuged for 10 min at 2,600 g and 0.2 ml of the supernatant were deproteinized by vortexing with 0.2 ml trichloroacetic

Table 1
Clinical data of 6 patients

Patient	Age (years)	Gravidity parity	Amenorrhoea at premature rupture of the membranes (weeks + days)	Duration of premature rupture of the membranes (days)	Amenorrhoea at delivery (weeks + days)	Reason delivery	Kind of delivery
A	34	2-1	28+4	9	29+5	clinical chorio-amnionitis	caesarean section
B	23	1-0	32+1	3	32+3	transverse presentation oligohydramnios	caesarean section
C	45	3-2	27+0	9	28+2	contractions	spontaneous
D	31	3-2	28+1	9	29+2	haemorrhage	spontaneous
E	28	4-3	29+5	5	30+2	solutio placentae	caesarean section
F	23	3-2	31+0	8	32+0	abnormal nonstress cardiotocography	caesarean section

Table 2
Pregnancy outcome, cultures and histopathologic results in 6 patients

Patient	Gender of child	Weight of child (g)	Apgar score (min) 1	5	10	Umbilical artery pH	Neonatal cultures	Neonatal follow-up	Cervical cultures	Placental cultures	Histopathologic chorio-amnionitis
A	F	1,310	3	10	10	7.11	sterile	uneventful	sterile	sterile	no
B	F	1,760	3	9	10	7.15	sterile	uneventful	–	sterile	yes
C	M	1,530	9	9	8	7.32	*Enterococcus faecalis* (both ears)	uneventful	sterile	sterile	yes
D	F	1,310	5	7	8	7.17	*Enterococcus faecalis* (both ears and anus)	respiratory distress syndrome *Enterococcus faecalis* infection	–	*Entero-coccus faecalis*	yes
E	M	1,120	7	9	8	7.22	sterile	uneventful	*Gardnerella vaginalis*	sterile	no
F	M	1,560	6	10	10	7.21	sterile	uneventful	sterile	sterile	no

acid 5%. After centrifugation for 5 min at 2,600 g, 20 μl of the clear supernatant was injected onto the HPLC column. To membrane and placental tissue free of cefuroxime, known concentrations of cefuroxime were added and left overnight in the refrigerator. The standard samples were similarly prepared.

The HPLC apparatus consisted of the following parts: Autosampler SP 8780 XR, isocratic pump SP 8810, Applied Biosystems UV detector 757, integrator SP 4290 (Spectra Physics, Eindhoven, the Netherlands). The column was 150 × 4.6 mm i.d. packed with Lichrosorb RP8 5 μm with a guard column 100 × 2.1 mm packed with pellicular phase 10 μm. Detection was achieved at 278 nm. The mobile phase consisted of 425 ml 0.067 *M* KH_2PO_4+75 ml methanol (vol/vol). The flow rate was 1.2 ml/min.

Results

Clinical data

The clinical data of the 6 patients with a median age of 29.5 years are presented in Table 1. 5 Patients were multiparous. The median amenorrhoea at premature rupture of the membranes was 29 weeks and 1 day, the median duration of premature rupture of the membranes was 8.5 days. In 5 patients pregnancy was terminated or delivery accepted for serious obstetrical pathology, and in 1 patient for clinical signs of a chorio-amnionitis. In 4 patients caesarean section was performed for foetal reasons.

Table 2 shows the pregnancy outcome of the 6 patients, and the results of culture and histopathologic investigations. The median birth weight of the newborns was 1,410 g (range 1,120-1,760). Although the 1-min Apgar scores of most children were low, the 5- and 10-min Apgar scores of 5 children were 8 or higher. The umbilical artery pH of all children was higher than 7.10, the median artery pH was 7.19. The neonatal course of only 1 child was not uneventful. This child suffered from a respiratory distress syndrome and an *Enterococcus faecalis* infection without sepsis; the placental cultures

Table 3
Cefuroxime concentrations after intravenous injection of 1,500 mg cefuroxime in 6 patients

Patient	Maternal plasma after 1 h (mg/l)	Maternal plasma after 8 h (mg/l)	Delivery (hours, minutes after injection)	Umbilical cord blood (mg/l)	Placenta (mg/kg)	Membranes (mg/kg)
A	38.0	2.0	8 h 17′	3.0	25.5	52.9
	24.0	–				
B	28.2	1.2	8 h 16′	2.3	4.4	58.8
C	14.7	1.0	7 h 0′	1.6	6.6	80.0
	23.5	0.7				
D	33.0	2.0	8 h 8′	1.8	14.1	53.9
	31.0	0.8				
	32.0	–				
E	36.0	–	10 h 20′	–	17.5	11.2
F	28.0	1.3	1 h 36′	17.0	8.0	18.3
	27.0	1.2				

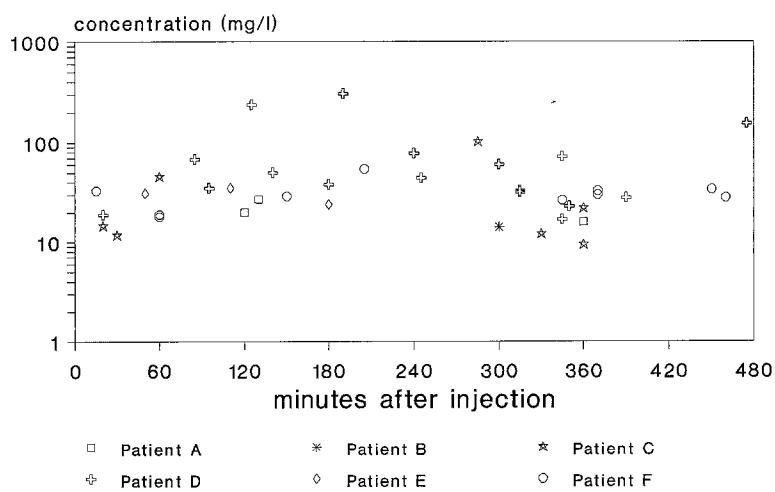
were positive for *Enterococcus faecalis*. In 3 patients histopathologic signs of chorioamnionitis could be demonstrated.

Pharmacokinetics

The pharmacokinetic data of cefuroxime in maternal plasma, umbilical cord blood, placenta, and membranes of the 6 patients are shown in Table 3. The median cefuroxime level in maternal plasma 1 h after intravenous administration of 1,500 mg cefuroxime, was 28.2 mg/l. Except for one sample all levels were higher than 16 mg/l, which is the breakpoint for bacterial susceptibility. The median cefuroxime level in maternal plasma was 1.2 mg/l after 8 h. In 5 children, the cefuroxime level could be measured in umbilical cord blood at delivery. In 1 child the cefuroxime level was 17.0 mg/l, 1.5 h after intravenous injection in the mother. The median concentration in other cord blood samples was 1.9 mg/l, 7 to 8 h after injection. In placental tissue and in the membranes the cefuroxime concentrations showed a wide variation. The median concentration was 11.1 mg/kg (range 4.4-25.5 in placenta, and 53.4 mg/kg (range 11.2-80.0) in the membranes. In 5 patients, the concentration of cefuroxime in the membranes was much higher than in placental tissue.

Cefuroxime level could be assessed in 41 amniotic fluid samples. A logarithmic representation of the results is shown in Figure 1. There was a wide variation. The minimum and maximum levels were 9.4 mg/l and 304 mg/l, respectively. The median cefuroxime level in amniotic fluid was 31.0 mg/l. Cefuroxime concentrations were lower than 16.0 mg/l in 1 sample of patient B, and in 4 samples of patient D. In all other samples (n = 36) cefuroxime concentrations were higher than 16.0 mg/l. Although the median concentration was highest 4 h after injection (61.0 mg/l), and lowest after 8 h (23.5 mg/l), a dose–concentration curve of cefuroxime in amniotic fluid could not be detected.

Figure 1
Logarithmic representation of cefuroxime levels (mg/l) in 41 amniotic fluid samples of 6 patients with preterm premature rupture of the membranes, after an intravenous dose of 1,500 mg cefuroxime, three times daily



Discussion

Kinetics

The highest levels of cefuroxime in plasma of pregnant patients with preterm premature rupture of the membranes, 1 h after intravenous injection of 1,500 mg cefuroxime, were similar to those of other investigators [13]. Also the plasma levels found 8 h after injection, and the levels in vaginal amniotic fluid were similar [13]. As expected, the amniotic fluid cefuroxime levels were higher than those reported by other investigators, who injected 750 mg cefuroxime intramuscularly or intravenously, or 1,000 mg cefuroxime intravenously [12 14-16]. 36 Out of 41 amniotic fluid cefuroxime concentrations were higher than 16.0 mg/l, which is the breakpoint for intermediate susceptibility to cefuroxime. A dose–concentration curve in the amniotic fluid could not be determined. Although cefuroxime appears to be concentrated in the amniotic fluid, it is not accumulated. The responsible mechanisms are not clear yet. One can suppose a homeostasis between the continuous excretion of cefuroxime by the foetal kidneys and its absorption by the membranes. The high cefuroxime levels in the membranes, which were higher than placental tissue levels and also higher than those found by other investigators, support supposition [13]. Yet, cefuroxime concentrations depend on the total volume of amniotic fluid. In the case of ruptured membranes, the total volume is determined by the rate of fluid synthesis and loss by leakage. Thus, despite the steady state by kidney excretion and tissue reabsorption, cefuroxime concentrations depend on the diluting effect of fluid leakage and synthesis.

The cefuroxime levels in the umbilical cord blood were in agreement with other reports [12-16]. After an initial high concentration all levels were lower than 4 mg/l after 7 to 8 h, which sufficiently covers against β-haemolytic streptococci group B.

Clinics

The good condition of the newborns at birth was demonstrated by their 5- and 10-min Apgar scores and artery pH. The low 1-min Apgar score of most newborns must be related to the caesarean delivery [18]. The courses of the newborns were uneventful, except for one child, who developed a respiratory distress syndrome. *Enterococcus faecalis* was cultured from the ostia of this child, but cultures from blood, skin, and liquor cerebrospinalis were negative. During pregnancy, 3 amniotic fluid cultures from this patient were positive for *Enterococcus faecalis* and resistant to cefuroxime. However, in 5 out of 6 patients several bacteria belonging to the common vaginal flora were cultured. As these cultures were taken from vaginal amniotic fluid and bacterial growth was insignificant, they were judged as contaminants rather than pathogens. After delivery, the newborn was treated with amoxicilline, intravenously. The further course was uneventful.

In 3 patients, histopathological evidence of chorio-amniotitis was found. Although this

finding is not always caused by bacterial infection, it is possible that chorio-amnionitis was in fact the cause of preterm premature rupture of the membranes. 2 Of these patients had negative placental cultures after cefuroxime treatment.

Conclusion

Our results showed a high rate of transplacental transfer of cefuroxime. Bactericidal levels could be demonstrated in maternal plasma and in vaginal amniotic fluid. Therapeutically active levels were also present in the newborns. The absorption rate of cefuroxime by the foetal membranes was high. However, double-blind, randomized, placebo-controlled trials are required to determine the clinical utility of cefuroxime prophylaxis in pregnant patients with preterm premature rupture of the membranes.

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Discussion

Verbrugh: Have you tried to find control patients who were closely matched to the patients treated with cefuroxime?

Roumen: We have tried to make two randomized groups of 10 patients. By chance, the first 3 patients were all in the control group. It took so long before more patients could be included into the study that we decided to give cefuroxime to all patients that met the eligibility criteria.

Hekster: In fact, this is clearly an open, uncontrolled study, both groups are not comparable.

Jonker: This is primarily a pharmacokinetic study, since no data were available on the behaviour of cefuroxime in these patients. A number of 7 to 10 patients is usual for this purpose.

Roumen: The clinical efficacy can only be shown in controlled, double-blind, randomized, multi-centre studies. The data we presented must be regarded as a pilot dose-finding study.