Br J Clin Pharmacol 1995; **40**: 439–443

Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin

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1 The effects of postnatal age and postnatal exposure to indomethacin on the pharmacokinetic parameters of ceftazidime (CAZ) were investigated in 23 preterm infants (gestational age 28.7 ± 1.7 weeks; weight 1086 ± 311 g) on day 3 and day 10 after birth.

2 CAZ (25 mg kg^{-1}) was administered by intravenous bolus injection. Blood samples were drawn from an arterial catheter at 0, 0.5, 1, 2, 4, 8, and 12 h after the dose and CAZ concentrations in serum were determined by h.p.l.c. CAZ pharmacokinetics followed a one-compartment open model.

3 The glomerular filtration rate (GFR) of all infants was studied by means of the 24 h continuous inulin infusion technique.

4 The total body clearance of CAZ (34.7 ± 9.2 *vs* 50.6 ± 19.6 ml h^{-1}, $P < 0.05$; 30.7 ± 5.9 *vs* 41.6 ± 9.0 ml h^{-1} kg^{-1}, $P < 0.05$) and GFR (0.72 ± 0.11 *vs* 0.91 ± 0.15 ml min^{-1}, $P < 0.05$) increased, whereas the apparent volume of distribution (425 ± 147 *vs* 352 ± 108 ml, $P < 0.05$; 363 ± 59 *vs* 292 ± 44 ml kg^{-1}, $P < 0.005$) and the elimination half-life (8.7 ± 2.8 *vs* 5.0 ± 0.9 h, $P < 0.005$) decreased significantly between day 3 and day 10 after birth. Clearance of CAZ increased with increasing GFR ($r = 0.81$, $P < 0.001$).

5 In infants with postnatal exposure to indomethacin the changes in CAZ pharmacokinetics were markedly reduced.

6 These results indicate that the dosage regimen of CAZ should be adjusted after the first week of life except in infants who were postnatally exposed to indomethacin.

Keywords postnatal age indomethacin pharmacokinetics ceftazidime preterm infants

Introduction

Ceftazidime (CAZ) is frequently used for the treatment of infectious diseases in newborn infants. The currently recommended dosage in preterm infants less than 4 weeks of life with a birth weight of less than 1200 g is 25–50 mg kg^{-1} of body weight every 12 h [1–6]. Despite the fact that these dosage recommendations are derived from studies that did not stratify patients according to postnatal age, Prober *et al.* [6] recommend not to reduce dosage intervals for CAZ in preterm infants until after the fourth week of life. This recommendation was made on the assumption that no significant postnatal increment in GFR has been documented in these preterm infants. Previous studies on the postnatal development of GFR in preterm infants indeed show conflicting data [7–13]. However, several investigators report the presence of a significant increase in the GFR in the first 10 days after birth [8, 11, 13, 14]. This postnatal age dependent increase would be predicted to exert a major effect on the pharmacokinetics of drugs such as CAZ which are mainly eliminated by glomerular filtration.

Animal and human studies have indicated that the use of indomethacin results in an impaired blood flow and a concomitant reduction in the GFR [15]. Postnatal exposure to indomethacin which is administered to preterm infants in order to close a patent ductus

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arteriosus was therefore also thought to influence the developmental pharmacokinetics of CAZ between day 3 and day 10.

The purpose of the present study was to determine the effects of postnatal age, changes in GFR, and postnatal exposure to indomethacin on the pharmacokinetics of CAZ between day 3 and day 10 after birth in preterm infants with gestational ages of less than 32 weeks and to investigate if dosage adjustments are indicated additional to those suggested by Prober *et al.* [16].

Methods

Patients

Twenty-three preterm infants with gestational ages of less than 32 weeks, admitted to the neonatal intensive care unit with suspected or documented septicaemia or invasive infection, were eligible for study. The inclusion criteria on day 3 after birth were stability of haemodynamic function (diuresis, >1 ml kg^{-1} of body weight h^{-1}; systolic and diastolic blood pressure above the third percentile adjusted for gestational age), a normal liver function, and no history of prenatal exposure to indomethacin or betamethasone. Infants who received inotropic or nephrotoxic drugs were excluded. All patients had an indwelling arterial catheter. The partial pressure of oxygen in arterial blood was kept at higher than 50 mm Hg (6.66 kPa), and the oxygen saturation above 92%. The gestational ages of the 23 enrolled infants were estimated from the mother's menstrual history, early ultrasound if available and from physical examination using the criteria of Dubowitz *et al.* [17]. Study infants were given CAZ (25 mg kg^{-1} intravenously [i.v.]) every 12 h and amoxicillin (25 mg kg^{-1} i.v.) every 12 h. Patients with sterile blood cultures and without a focus of infection received a total of 72 h of therapy.

These 23 infants were also studied on day 10 after birth. The inclusion criteria on day 10 after birth were stability of haemodynamic function, and a normal liver function. Infants with suspected or documented septicaemia or invasive infection were excluded. All infants had an indwelling catheter on day 10 and received a single dose of CAZ (25 mg kg^{-1} i.v.). Twelve of the 23 infants had postnatally (days 4 or 5) been exposed to indomethacin. Eleven infants were not postnatally exposed to indomethacin (controls).

The study protocol was approved by the Medical Ethics Committee of the University Hospital Rotterdam. Patients were only enrolled after informed consent was obtained from the parents.

Pharmacokinetic study

The multiple-dose pharmacokinetics of CAZ were determined on day 3 after birth. Single-dose pharmacokinetics of CAZ were studied on day 10 after birth. Blood samples were taken from indwelling arterial lines before administration of an i.v. bolus injection (t = 0) and at 0.5, 1, 2, 4, 8, and 12 h after the administration. These sampling times were selected based on the known disposition profile for CAZ. Serum samples obtained after centrifugation (Merck type Eppendorf 5414, 3000 g for 1 min) were stored at −70° C.

Measurement of the glomerular filtration rate

The GFR was measured by the continuous inulin infusion technique on day 3 and day 10 after birth [13, 14]. A 10% glucose-inulin solution containing 25 g inulin l^{-1} was infused at a rate of 0.6 ml kg^{-1} h^{-1}, beginning at time (t) zero of the pharmacokinetics study. After 24 h, the inulin clearance (CL_{in})was calculated from the infusion rate (R), the inulin concentration in the infusate (I), and the serum inulin concentration (P_{in}) by the equation $CL_{in} = (I \times R)/P_{in}$. The determination of the inulin in serum was performed after acid hydrolysis in 0.3 mmol l^{-1} perchloric acid for 15 min at 70° C. The fructose thus formed was measured enzymatically.

Ceftazidime assay

Analysis of serum CAZ concentrations was performed according to the method described by Ayrton with minor modifications [18]. To a 50 µl aliquot of the serum sample, an equal volume of 6% (v/v) perchloric acid containing 50 mg l^{-1} cephaloridine as an internal standard was added. Samples were centrifuged at 1550 g for 5 min. Subsequently 25 µl was transferred by an automatic sample injector to the column. A calibration curve was made by dissolving 4, 12, 25, 50, 100, and 200 mg CAZ l^{-1} in serum. These spiked standard samples were processed according to the procedure mentioned above. A linear calibration curve was obtained over a range of 4 to 400 mg CAZ l^{-1}. Spiked samples of the calibration curve underwent the same processing procedure as clinical samples. Hence, clinical samples were directly converted from the calibration curve to actual CAZ concentrations l^{-1} of serum. The lower limit of detection of CAZ in serum was 0.5 mg l^{-1}. The coefficients of interassay variation at different concentrations were less than 7%. The intraassay values were less than 5%. Recovery of 95% of CAZ, which had been incubated for 24 h at room temperature, was established.

Pharmacokinetic analysis

Kinetic data were described using a one-compartment open model. Visual inspection of individual model fits gave no indication that a model more complex than a one-compartment open model was required. Pharmacokinetic parameters were calculated with the multiple-dose equations described by Rowland & Tozer [19]. The basic equation used was C_t = dose/V × $(1 - r^N)/(1 - r) \times e^{-kt}$. In this formula, C_t is the plasma concentration of CAZ at given times t, V is the apparent volume of distribution, N is the dose number, $r = e^{-k\tau}$, in which k is the elimination rate constant and τ the dosing interval. The conversion factor for CAZ to SI units is: 1 mg l^{-1} = 1.83 nmol l^{-1}. Because doses were given twice daily, the CAZ concentration *vs* time curve on day 3 after birth was assumed attributable to the 7th dose (and the trough level at t = 0 was assumed

to be attributable to the 6th dose). Total body clearance (CL) was calculated with the following equation: $CL = k.V$. Concentration-time plots showed linear decrease over time and no indication of levelling off. Scatter was evenly distributed on a log-scale indicating the need for $1/(Ycal)^2$ weighting. The CAZ concentration *vs* time curve on day 10 after birth was attributable to the 1st dose. All calculations were carried out using the non-linear regression module of SPSS/PC + V 4.0.1 (SPSS, Inc, Chicago, Ill.), which uses a Levenberg-Marquardt algorithm.

Statistical analysis

Data given are mean ± s.d. unless indicated otherwise. Correlation coefficients given are Pearson's. Comparison of outcomes on day 3 and day 10 was performed using the paired *t*-test. *P* values $\leqslant 0.05$ were considered significant.

Results

The demographic and clinical parameters of indomethacin-treated and control infants on day 3 of life are shown in Table 1. None of the infants had a positive blood culture or another invasive infection. All neonates had serum trough concentrations above 5 mg l^{-1}. In control infants CL_{in} (as a parameter of the GFR) increased significantly between day 3 and day 10 of life (0.72 ± 0.11 ml min^{-1} *vs* 0.91 ± 0.15 ml min^{-1}, $P < 0.05$). In these infants a positive linear relationship ($r = 0.81$, $P < 0.001$) was demonstrated between the clearance of CAZ and the GFR. The clearance of CAZ (34.7 ± 9.2 *vs* 50.6 ± 19.6 ml h^{-1}, $P < 0.05$), and clearance of CAZ kg^{-1} (30.7 ± 5.9 *vs* 41.6 ± 9.0 ml h^{-1} kg^{-1}, $P < 0.05$) increased significantly. The apparent volume of distribution (425 ± 147 *vs* 352 ± 108 ml, $P < 0.05$), volume of distribution kg^{-1} (363 ± 59 *vs* 292 ± 44 ml kg^{-1}, $P < 0.005$), and the serum half-life decreased significantly (8.7 ± 2.8 *vs* 5.0 ± 0.9 h, $P < 0.005$) between day 3 and day 10 (Table 2).

In the indomethacin-exposed infants CL_{in} did not change significantly between day 3 and day 10 of life (0.67 ± 0.13 ml min^{-1} *vs* 0.80 ± 0.14 ml min^{-1}, $P = 0.066$). Clearance of CAZ increased significantly (32.7 ± 14.5 *vs* 39.9 ± 20.4 ml h^{-1}, $P = 0.049$) between day 3 and day 10 after birth, whereas CL of CAZ kg^{-1}, *V* and *V* kg^{-1}, and $t_{1/2}$ did not change in this 7 day period (Table 3).

Table 1 Demographic and clinical parameters of study infants*

	Indomethacin-exposed (n = *12*)	*Controls* (n = *11*)
Gestational age (weeks)	28.4 ± 1.7	29.1 ± 1.1
Weight (g)	1024 ± 319	1154 ± 301
Appropriate for gestational age	10 (83%)	9 (82%)
Artificial ventilation	10 (83%)	8 (73%)
Respiratory distress syndrome	4 (33%)	3 (27%)

*Values are mean ± s.d. or numbers (%) of patients.

Discussion

The data presented in this paper indicate that GFR values in preterm infants with gestational ages of less than 32 weeks, and without postnatal exposure to indomethacin increase significantly between days 3 and 10 of life. These findings are consistent with the results of several other studies [8, 11, 13, 14], although some investigators could not find a postnatal age dependent increase of the GFR [7–9]. However, all these studies did not specify whether infants were postnatally exposed to indomethacin. GFR values in infants who are not exposed postnatally to indomethacin increase by a mean of 0.19 ml min^{-1} during the 7 day period between days 3 and 10 after birth. Recently we reported that the GFR undergoes a weekly intrauterine increase of 0.035 ml min^{-1} [14]. This indicates that the postnatal increase of the GFR in the first days of life is 5.4 times higher in comparison with the intrauterine increase. Therefore postnatal age seems to be associated with an acceleration of the development of the GFR. However, the possible impact of invasive bacterial infection on these postnatal-age induced changes in the GFR could not be investigated, because none of the infants enrolled in this study had a proven bacterial infection.

The positive relationship ($r = 0.81$, $P < 0.001$) between the GFR and the clearance of CAZ indicates the important role of the GFR in the clearance of CAZ. The increase in the GFR results in a significant increase in the clearance of CAZ. These findings are consistent with the results of some investigators [3, 20], whereas other studies could not find any rela-

Table 2 Pharmacokinetic parameters of CAZ and CL_{in} (inulin clearance) on day 3 and day 10 after birth of eleven infants without postnatal exposure to indomethacin[a]

	Day 3	*Day 10*	P *value*	*Mean difference (95% CI)*
CL (ml h^{-1})	34.7 ± 9.2	50.6 ± 19.6	< 0.05	15.8 (3.5, 28.1)
CL (ml h^{-1} kg^{-1})	30.7 ± 5.9	41.6 ± 9.0	< 0.05	10.9 (2.4, 19.5)
V (ml)	425 ± 147	352 ± 108	< 0.05	−74 (−37, −111)
V (ml kg^{-1})	363 ± 59	292 ± 44	< 0.005	−71 (−42, −101)
$t_{1/2}$ (h)	8.7 ± 2.8	5.0 ± 0.9	< 0.005	−3.7 (−1.8, −5.5)
CL_{in} (ml h^{-1})	43.2 ± 6.6	54.6 ± 9.0	< 0.05	12.4 (4.6, 20.3)

[a]Values are mean ± s.d. with 95% confidence interval between parentheses.

Table 3 Pharmacokinetic parameters of CAZ and CL_{in} (inulin clearance) on day 3 and day 10 after birth of twelve infants with postnatal exposure to indomethacin[a]

	Day 3	*Day 10*	P *value*	*Mean difference (95% CI)*
CL (ml h^{-1})	32.7 ± 14.5	39.9 ± 20.4	< 0.05	7.2 (0.3, 14.1)
CL (ml h^{-1} kg^{-1})	31.1 ± 6.0	34.3 ± 10.3	0.31	3.3 (−2.9, 9.5)
V (ml)	337 ± 132	354 ± 106	0.39	17 (−27, 61)
V (ml kg^{-1})	327 ± 71	317 ± 37	0.70	−11 (−61, 40)
$t_{1/2}$ (h)	7.4 ± 1.3	6.8 ± 1.8	0.43	−0.5 (−2.0, 0.9)
CL_{in} (ml h^{-1})	42.0 ± 7.8	48.0 ± 8.4	0.07	7.0 (−1.7, 15.7)

[a]Values are mean ± s.d. with 95% confidence interval between parentheses.

tion with postnatal age [21, 22]. Kenyon *et al.* have previously reported that postnatal renal function maturation exerts a significant influence on the developmental pharmacokinetics of amikacin. These authors speculate however that the rapid maturation of the renal function in the first week of life is not present in the extremely preterm population [22]. Our data show that the rapid postnatal change in the GFR is equally present in very young premature infants and is primarily responsible for the increase in the clearance of CAZ.

The volume of distribution of CAZ decreased significantly between day 3 and day 10 of life in control infants. During the first week of life a significant decrease of the extracellular water volume has been observed [23]. This may have caused the decrease of the *V* of CAZ in this 7 day period because CAZ is mainly distributed into the extracellular water compartment. Both the postnatal age dependent increase in the clearance of CAZ and the decrease of the volume of distribution contribute to the decrease in serum half-life between days 3 and 10 as was shown in this study.

In infants with postnatal exposure to indomethacin the increase in the GFR between days 3 and 10 of life was not seen. Consequently, the increase of the clearance of CAZ was markedly less (CL in ml h^{-1}) or absent (CL kg^{-1}) in infants with postnatal exposure to indomethacin compared with the controls. After normalisation for weight the previously significant (P = 0.049) increase in CL between days 3 and 10 was not present anymore. This was probably caused by the increase in the mean body weight from 1052 to 1163 g. The decrease of *V* of CAZ during this 7 day period was also not seen in the indomethacin-exposed infants. This may be explained by the dependence of postnatal changes in extracellular water on renal function [24], and the impairment of the GFR with the use of indomethacin. Elimination half-life of CAZ, influenced by both CL and *V*, did not show any change between days 3 and 10 in infants with postnatal exposure to indomethacin. The differences observed between indomethacin-exposed and control infants are probably not only caused by the postnatal use of indomethacin alone. The question remains whether the persistence of a patent ductus arteriosus, which may lead to congestive heart failure, can be held partially responsible.

Once daily dosing of 25 mg kg^{-1} CAZ or twice daily administration of 10–15 mg kg^{-1} seem appropriate in the first week of life [25, 26]. In the second week of life the dosage of CAZ should be adapted to twice daily 25 mg kg^{-1} CAZ because of the rapidly improving neonatal renal capacity. We conclude that dosage recommendations in the first 4 weeks of life should be based on postnatal age induced changes in the GFR. However, both the existence of a patent ductus arteriosus and postnatal exposure to indomethacin may alter this developmental process. This probably will delay the need for dosage adjustment of CAZ during the first 2 postnatal weeks in these preterm infants. Finally further studies will be necessary to determine if these dosage recommendations can also be applied to infants with invasive bacterial infections.

This study was financially supported by a research grant from Glaxo B.V., The Netherlands.

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(Received 27 April 1995, accepted 28 June 1995)