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Pharmacokinetics of Penicillin G in Very-Low-Birth-Weight Neonates▽

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Data on the pharmacokinetics (PKs) of penicillin G (PEN) in neonates date back to the 1970s and do not include data for very-low-birth-weight (VLBW) neonates. The aim of this study was to describe the steady-state PKs and to establish an optimal regimen for the dosing of PEN in neonates with gestational ages of less than 28 weeks and birth weights of less than 1,200 g. Two PEN dosing regimens were studied: 50,000 IU (30 mg)/kg of body weight every 12 h (q12h) (group 1; $n = 9$) and 25,000 IU (15 mg)/kg q12h (group 2; $n = 9$). Samples for PK analysis were drawn before the injection of PEN and at 2 and 30 min and 1.5, 4, 8, and 12 h after intravenous injection of the third to eighth PEN doses. The PEN concentration was measured by a high-performance liquid chromatography with UV detection technique. The median peak and trough concentrations of PEN were 147 μg/ml (lower and upper quartiles, 109 and 157 μg/ml, respectively) and 7 μg/ml (lower and upper quartiles, 5 and 13 μg/ml, respectively) after administration of the dose of 50,000 IU and 59 μg/ml (lower and upper quartiles, 53 and 78 μg/ml, respectively) and 3 μg/ml (lower and upper quartiles, 3 and 4 μg/ml, respectively) after administration of the dose of 25,000 IU. The PEN half-life (median and lower and upper quartiles for group 1, 3.9 h and 3.3 and 7.0 h, respectively; median and lower and upper quartiles for group 2, 4.6 h and 3.8 and 5.6 h, respectively) was longer in VLBW neonates than in adults and term infants. PEN renal clearance correlated with creatinine clearance ($R^2 = 0.309596$; $P = 0.038$). Only a median of 34% (lower and upper quartiles, 28 and 37%, respectively) of the administered dose was excreted in urine within the following 12 h. We conclude that in VLBW infants a PEN dose of 25,000 IU (15 mg)/kg q12h is safe and sufficient to achieve serum concentrations above the MIC_{90} for group B streptococci for the entire dosing interval.

Antibiotics are widely used in neonatal intensive care units (NICUs), and their widespread use has been associated with the development of antibiotic resistance. These developments have led to the preferred use of antibiotics known or assumed to have lower potentials for the selection of resistant microorganisms (22).

Penicillin G (PEN) is a safe and narrow-spectrum antibiotic that, in combination with gentamicin, is recommended for use for the empirical therapy of neonatal sepsis (31). It has many advantages over wide-spectrum penicillins and cephalosporins. First, it has demonstrated favorable efficacy against the majority of organisms that cause neonatal sepsis (14, 27); second, it is well tolerated and does not cause allergic reactions in neonates; third, compared to other beta-lactam antibiotics, penicillin has the least effect on the development of resistance by gram-negative bacteria (9); and fourth, narrow-spectrum penicillins have a minimal effect on the normal bowel colonization in neonates and young infants (4, 17).

The currently recommended PEN dosage for infants born at less than 29 weeks of gestation is 25,000 to 50,000 IU (15 to 30 mg)/kg of body weight twice a day (b.i.d.), but in the case of suspicion group B streptococcal (GBS) meningitis, the dose should be doubled (19, 26). However, the pharmacokinetic (PK) data behind this recommendation date back to 1973, when antibiotics were given intramuscularly (24). Furthermore, in that study the mean birth weight (BW) of the population was not reported, but it is likely that in the late 1960s or early 1970s very-low-birth-weight (VLBW) infants were not included in PK studies. Later studies have shown that the PK parameters of other beta-lactam antibiotics are dependent upon changes in body water and the development of renal function with increasing gestational and postnatal age and thus support the idea that the PKs of PEN in VLBW neonates cannot be extrapolated from data collected for more mature infants (8, 16, 20, 25, 33).

The aim of our study was to describe the steady-state PKs of the presently recommended intravenous PEN dosage of 50,000 IU (30 mg)/kg b.i.d. in VLBW infants and, if this dose appears to be suboptimal, to establish an optimal regimen for the dosing of PEN for VLBW infants. The tolerance and safety profile of PEN were monitored throughout the study.

MATERIALS AND METHODS

A prospective two-center study that planned to enroll 18 consecutive neonates in two groups was performed from 1 October 2005 to 30 April 2006 in the NICUs of Tartu University Clinic of Anesthesiology and Intensive Care, Tartu, Estonia, and Tallinn Children's Hospital, Tallinn, Estonia. Neonates were eligible for the study if they fulfilled the following criteria: (i) a gestational age (GA) of less than or equal to 28 weeks and a BW below 1,200 g; (ii) a postnatal age of less than 72 h; (iii) hemodynamic stability, defined as a mean arterial blood pressure equal to or above that appropriate for the GA, no signs of circulatory compromise (metabolic acidosis, poor perfusion, oliguria, food intolerance), and no need for inotropic/vasoactive support (7, 21); (iv) normal renal function, defined as urine output of >1 ml/kg/h (assessed within 6 h prior to inclusion), a serum creatinine concentration within the normal range for age (69 to 141 μmol/liter) (30), and no signs or suspicion of renal disease; (v) the need for early empirical antibiotic therapy, based on the CDC revised guidelines for the prevention of perinatal GBS disease (2); (vi) a clinical need for an arterial or central venous catheter; (vii) expectancy of survival for more than 3 days; and (viii) written informed

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consent signed by the parents or guardian. Subjects were excluded if they had major malformations or had received drugs, with the exception of gentamicin, that may significantly affect renal function.

Study drug administration and sample collection. PEN (Biochemie GmbH, Austria) was diluted in normal saline for no more than 30 min prior to administration to a final concentration of 50,000 IU (30 mg)/ml and was administered by a slow (about 2-min) intravenous bolus injection via a peripheral or central venous catheter. The first nine infants received PEN at a dose of 50,000 IU (30 mg)/kg every 12 h (q12h) (group 1). The dose administered was based on the BW, but the actual weight of the infants on the morning of sample collection was also recorded.

The study plan was for an interim PK analysis to be conducted after the first nine subjects were recruited. The dose of PEN for the next nine subjects (group 2) was expected to be 25,000 IU (15 mg) b.i.d. if the values of the PK parameters obtained after use of the initially chosen dose appeared to be significantly higher than those achieved in adults with the currently recommended dose of 1,000,000 IU (600 mg) and the trough levels were more than 10 times greater than the MIC_{90} for GBS.

Gentamicin was administered to all subjects at a dose of 5 mg/kg every 48 h by intravenous infusion over 1 h. To minimize the possible effect of gentamicin on renal function, all PK studies were performed at least 24 h after administration of the last dose of gentamicin.

For both groups samples for PK analysis were collected at steady state after administration of the third to eighth doses of PEN. A maximum of 0.3 ml of blood was drawn from an arterial or central venous catheter before the injection of PEN and at 2 and 30 min and 1.5, 4, 8, and 12 h after the end of the injection of PEN. Samples were immediately centrifuged at 2,000 × *g* for 5 min, and the plasma was stored at −20°C for up to 1 week, when it was transferred to −80°C. All samples in each group were analyzed at the same time. The actual sampling times were recorded and used for calculation of the PK parameter values if deviations from prespecified sampling times were more than 1 min for the first sample obtained postdosing and more than 10 min for all other samples.

For safety monitoring, serum sodium, potassium, calcium, glucose, albumin, creatinine, and urea levels were measured within 24 h before and 24 h after study drug administration. To calculate creatinine clearance, the creatinine concentration was measured in the blood sample collected 12 h after infusion of the study dose.

Urine samples were collected within 12 h after PEN study dose administration at 4-h intervals. The urine was collected in plastic urine bags. Simultaneously, possible losses were estimated by weighing the diapers. The urine collection method was considered adequate, and the data for urine were used for calculation of the PK parameter values when at least 90% of the total estimated urine output for the given 4-h period was collected.

Blood pressure, heart rate, and transcutaneous oxygen saturation were monitored continuously and were recorded every 30 min by the attending nurse. Blood pressure was measured via a peripheral arterial cannula or by oscillometry, as clinically appropriate. All infants were monitored for the occurrence of adverse reactions for at least 7 days after the study. In order to identify possible adverse effects from repeated blood sampling, the need for blood component transfusions throughout the intensive care period was registered.

PEN assay. The PEN concentrations in plasma and urine were determined by high-performance liquid chromatography (HPLC) with UV detection, as described previously (13). Briefly, plasma samples were prepared by adding 50 μl of acetonitrile to 50 μl of sample. After the samples were vortexed, they were centrifuged at 13,000 × *g* for 10 min, and 40 μl of the supernatant was injected into the HPLC system. For measurement of the concentration in urine, 40 μl of a urine sample was injected directly into the HPLC system. The samples were analyzed at a flow rate of 1.1 ml/min in an isocratic elution with a mobile phase of 0.05 M sodium dihydrogen phosphate (pH 5.0) and acetonitrile (80/20; vol/vol). The absorbance of PEN in plasma and urine was detected at 200 nm and 240 nm, respectively. The HPLC system consisted of a Waters 717 plus autosampler (Waters Millipore), an Alltech 426 HPLC pump (Alltech Associates Inc.), and a Waters 486 tunable absorbance detector (Waters Millipore). An Inertsil ODS-3 C_{18} analytical column (150 by 4.6 mm [inner diameter]; GL Science Inc., Japan) with a 5-μm particle size was used. It was protected by a platinum C_{18} (7.5 by 4.6 mm [inner diameter]), 5-μm-particle-size precolumn (Alltech GmbH). The chromatography software Kromex (version 32S; Akrom-EX, Estonia) was used for data acquisition. The method was linear over the ranges of 0.78 to 400 μg/ml and 12.5 to 3,200 μg/ml for the analysis of PEN in plasma and urine, respectively, with intraday coefficients of variance 2.1% and 1.5% for plasma and urine, respectively. Each analytical run included quality control samples at three concentrations. All study samples were analyzed in six analytical runs. Within-study validation was shown as the coefficients of variation were 1.5 to 2.0% for plasma and 3.0 to 3.7% for the urine quality control samples at three concentrations.

TABLE 1. Demographic characteristics of subjects in study groups

Characteristic	Group 1 (n = 9)	Group 2 (n = 9)
Median BW (g)	823 (640–969)[a]	930 (880–1,030)
Median GA (wk)	26 (26–27)	26 (25–27)
No. of subjects delivered vaginally/no. of subjects delivered by cesarean section	5/4	5/4
Maternal chorionamnionitis (no. of subjects)	3	2
Male sex (no. of subjects)	5	6
Median first-minute Apgar score	5 (5–6)	5 (3–6)
Median fifth-minute Apgar score	6 (6–7)	6 (6–7)
No. of subjects with artificial ventilation/no. of subjects with CPAP[b]	7/2	8/1
Surfactant treatment (no. of subjects)	7	8
Median serum creatinine concn prior to inclusion (μmol/liter)	73 (62–83)	97 (72–106)
Median serum albumin concn (g/liter)	25 (22–27)	27 (26–28)

[a] Data in parentheses represent the lower-upper quartiles.
[b] CPAP, continuous positive airway pressure.

Statistical analysis and pharmacokinetic calculations. PK analysis was performed with WinNonlin software (version 5.0.1; Pharsight Corporation, CA) by applying a noncompartmental model that assumed the use of a bolus intravenous injection. The area under the concentration-time curve over the dosing interval of 0 to 12 h ($AUC_{0–12}$) was calculated by use of the log-linear trapezoidal rule. The $AUC_{0–12}$ was used to calculate the total body clearance (CL; the clearance at steady state). The apparent volume of distribution at steady state (V_{ss}) was determined by calculating the mean residence time extrapolated to infinity. The renal clearance (CL_R) of PEN was calculated as follows: $CL_R = A_e\tau/AUC_{0–12}$, where $A_e\tau$ is the amount of unchanged drug excreted into urine (A_e) during the dosing interval (τ). Creatinine clearance (CL_{CR}) was calculated directly from the urine and serum creatinine concentrations at 12 h. Multiple linear regression analysis (StatsDirect software, version 2.3.4; Cheshire, United Kingdom) was used to estimate the influence of GA, gender, CL_{CR}, and weight on $AUC_{0–12}$, CL_R, CL at steady state, and V_{ss}.

The study was approved by the Ethics Committee of Tartu University.

RESULTS

From October 2005 to April 2006, a total of 24 neonates eligible for the study according to the GAs and BWs were admitted to the participating NICUs. Six of them were excluded (three in each period) for the following reasons: major congenital malformation (n = 1), parental refusal (n = 1), and hemodynamic instability (n = 4). The first group was recruited from 1 October to 15 December 2005, and the second group was recruited from 1 February to 30 April 2006. As presented in Table 1, the baseline demographic data for the two study groups were similar. None of the study subjects had a positive blood culture prior to or during the study.

The values of the PK parameters for both groups are presented in Table 2, and individual time-concentration curves are presented in Fig. 1. One patient in group 1 accidentally received almost a double dose of PEN (83,300 IU/kg, equivalent to 50 mg/kg; shown as a dashed line in Fig. 1); the data for this patient were excluded from the calculations of the PK parameter values for the first dosing regimen (Table 2). Another infant, born at week 26 of gestation with a BW of 700 g, had a PEN elimination half-life ($t_{1/2}$) of 35.1 h (shown as a bold line

in Fig. 1). The baby was studied on day 2 of life, when she had lost only 3% of her BW and had clinical edema. She was diagnosed with late-onset sepsis 3 days after the PK study.

The interim PK analysis (group 1) demonstrated that with the dose of 50,000 IU (30 mg)/kg q12h, the values of various PK parameters, such as the maximum (peak) concentration of drug in serum (C_{max}), the minimum (trough) concentration of drug in serum (C_{min}), and AUC_{0-12}, in neonates were much greater than the respective values in adults after the administration of the doses recommended in most textbooks and that the median C_{min} of 7.4 μg/ml exceeded the MIC_{90}s for GBS by about 100 times. Therefore, for the second group, the PEN dose was reduced by half, to 25,000 IU (15 mg)/kg q12h. As expected, the dose reduction resulted in proportionally lower C_{max}s and C_{min}s and lower AUC_{0-12} values (Table 2). With both dosing regimens a significantly longer $t_{1/2}$ compared to those in adults and term infants was observed, but there was no difference between the two study groups (median $t_{1/2}$s, 3.6 and 4.1 h for groups 1 and 2, respectively).

After reduction of the dose to 25,000 U (15 mg)/kg q12h in group 2, the PEN C_{min} still remained well above the MIC for GBS (MIC_{90}, 0.062 to 0.094 μg/ml) for all patients (10, 11).

Urine samples were adequately collected (90% of the estimated urine output) from five subjects in the first group and seven subjects in the second group. Table 3 presents data on CL_{CR} and the urinary elimination of PEN. The CL_{CR} and 24-h creatinine excretion values were similar for both groups, with a wide range of variation, despite the relatively narrow range of BWs and GAs of the infants in our study. A higher PEN urinary recovery was observed with the dose of 50,000 IU (30 mg)/kg compared to that observed with the dose of 25,000 IU (15 mg)/kg (41% and 29%, respectively). To exclude drug degradation as a possible cause for the relatively low urinary recovery of PEN, we left urine samples that had been spiked with PEN in the incubator at the temperature usually needed for VLBW infants within the first days of life (36.2°C). No more than 10% of the drug was lost within 4 h, which was the urine collection interval in our study. There was a significant correlation between PEN CL_R and CL_{CR} (Fig. 2).

According to clinical and laboratory indices, all infants remained stable throughout the study. The study-related median blood loss was 2.3 ml/kg (lower and upper quartiles, 2.0 and 2.9 ml/kg, respectively), and the need for erythrocyte transfusion with a median of two transfusions (lower and upper quartiles, one and three transfusions, respectively) or 24 ml (lower and upper quartiles, 15 and 27 ml, respectively) per patient did not differ from the routine requirements for VLBW infants in both wards. One patient in each group did not require blood component transfusion throughout the intensive care period.

TABLE 2. Median PK parameters values for both study groups in comparison to the values for term infants and adults[a]

Group	Actual PEN dose (IU/kg)/route	Actual PEN dose (mg/kg)	$t_{1/2}$ (h)	C_{max} (μg/ml)	C_{min} (μg/ml)	CL (ml/min/kg)	V_{ss} (liter/kg)	AUC_{0-12} (min · μg/ml)
VLBW preterm neonates (present study)								
Group 1 (n = 8)	46,875 (46,440–48,143)/i.v.	28 (27.9–28.9)	3.8 (3.3–7.0)	145.5 (108.6–157.3)	7.1 (5.2–12.9)	1.2 (1.1–1.4)	0.41 (0.33–0.57)	23,360.2 (20,480.6–26,174.1)
Group 2 (n = 9)	23,913 (22.936–24.124)/i.v.	14.3 (13.8–14.5)	4.6 (3.8–5.6)	58.90 (52.9–77.5)	3.4 (2.9–3.6)	1.5 (1.3–1.8)	0.64 (0.50–0.71)	9,671.0 (8,180.0–10,180.0)
Term neonates, age <7 d (n = 23)	25,000/i.m.	15	3.4	22.0	2.3	ND	0.51	ND
Adults (n = 6)	1,000,000 per dose/i.v.	600	0.5	45	ND	ND	0.5	ND

[a] i.v., intravenous; i.m., intramuscular; ND, no data; data in parentheses represent lower-upper quartiles.

DISCUSSION

To the best of our knowledge, this is the first study of the PKs of intravenous PEN in VLBW infants, the majority of whom were artificially ventilated. The main finding of our study is that the currently recommended regimen for the dosing of PEN for neonates led to extremely high C_{max}s and C_{min}s. The C_{max} of PEN after the administration of 50,000 IU (30 mg)/kg q12h exceeded the MIC_{90} for GBS, the leading cause of early-onset neonatal sepsis, by more than 1,000-fold, whereas

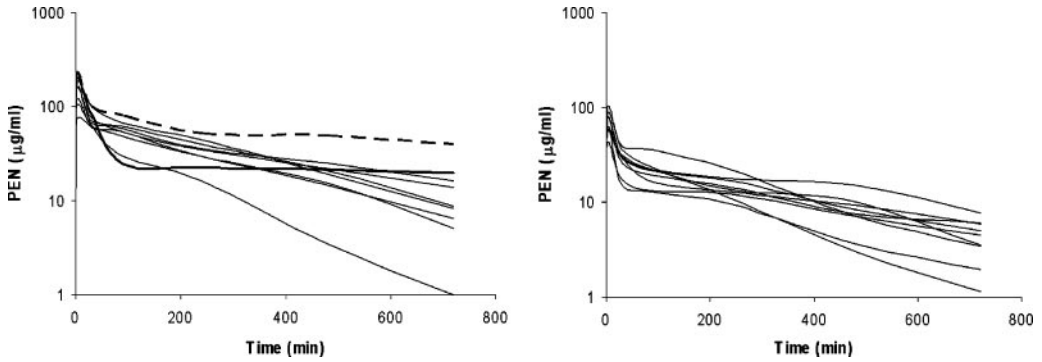

FIG. 1. Individual time-concentration curves of intravenous PEN in VLBW infants receiving PEN doses of 50,000 IU/kg (left) and 25,000 IU/kg (right). Dotted line, the patient accidentally received PEN at a dose of 83,300 IU (50 mg)/kg; the data for this patient were excluded from calculations of the PK parameter values for group 1; bold line, an infant born at the 26th week of gestation with a BW of 700 g had clinical edema and a PEN $t_{1/2}$ of 35.1 h; the data for this patient were included in the calculations of the PK parameter values for group 1.

the dosing regimen with a two-times-lower dose of 25,000 IU (15 mg)/kg q12h ensured C_{min}s above the MIC for GBS in all patients (12, 18). Considering the relatively high prevalence of meningeal involvement in early neonatal sepsis and the nonspecificity of the clinical symptoms of meningitis in VLBW infants, the PEN dosing regimen recommended should ensure the presence of adequate antibiotic concentrations in cerebrospinal fluid (CSF). There are very limited data on the PKs of antibiotics in the CSF of neonates, especially premature infants. However, one may assume that the penetration of an antibiotic through the blood-brain barrier (BBB) in neonates is not much different from that in adults and, if anything, might be even better (29). Thus, considering that the penetration of PEN through the inflamed BBB is about 10% and that the principal determinant of antibiotic effectiveness is the relation between the antibiotic concentration in CSF and the minimal bactericidal concentration (MBC) for the infecting organism, in which the required time above the MBC is 100%, the PEN dose of 25,000 IU (15 mg)/kg q12h is likely to be adequate in most cases; and even when meningitis is suspected, an additional increase in the dose may not be required in VLBW neonates (15, 23, 32). Assuming a 50% protein binding of PEN and an MBC of two times the MIC (0.12 to 0.18 μg/ml) (18, 28), the active non-protein-bound concentration of PEN would still exceed the MBC two times. However, such calculations should be interpreted with caution, as the true PKs of PEN in CSF may be influenced by a variety of additional factors.

Although PEN is generally well tolerated and we did not observe any drug-related adverse events throughout the study, serious dose-related organ toxicities have been reported, including central nervous system toxicity in the form of myoclonic seizures (3, 6). With their large central nervous system volume, higher BBB permeation, and immature renal function, preterm infants are likely to be especially vulnerable, although the clinical manifestations may not be easy to recognize (1, 26). Unnecessarily high drug concentrations clearly carry a higher risk because of these factors. Serious encephalopathy with seizures has been described in an adult with a serum PEN concentration of 100 μg/ml, similar to the peak concentrations seen by us after administration of the dose of 50,000 IU (30 mg)/kg (27). There is also a potential risk of a paradoxical effect, described in vitro by Eagle and Musselman in 1948 (10); however, the clinical relevance of this is still not completely clear.

Our results, which showed a longer $t_{1/2}$ and higher C_{max}s and C_{min}s of PEN in VLBW infants compared to those in adults and even term neonates, are well consistent with the results of previous studies of the PKs of beta-lactam antibiotics in VLBW infants and are most likely the result of the higher body water content and different compartmental distribution of the body water in VLBW infants, as well as their immature renal function (1). Similar recommendations for the use of lower-dose, longer-interval drug administration regimens for VLBW infants have been reported for several beta-lactam antibiotics, like amoxicillin, ampicillin, carbenicillin, and meropenem (16, 20, 25, 33).

In adults PEN is predominantly excreted unchanged by the kidneys, primarily by tubular secretion, with other elimination routes accounting for less than 20% of the total dose administered (6). In preterm neonates with immature renal function

TABLE 3. Median creatinine and PEN CL_R values

Group(s)	Creatinine excretion in 24 h (μmol/24 h/kg)	CL_R				PEN urinary recovery (% of administered dose)
		Creatinine		PEN		
		ml/min	ml/min/kg	ml/min	ml/min/kg	
1 (n = 5)	50.6 (50.6–73.7)[a]	0.26 (0.18–0.44)	0.30 (0.30–0.63)	0.27 (0.26–0.41)	0.46 (0.32–0.59)	41 (35–48)[b]
2 (n = 7)	70.6 (60.0–70.8)	0.53 (0.39–0.58)	0.57 (0.55–0.59)	0.31 (0.27–0.40)	0.38 (0.33–0.41)	29 (25–34)
1 and 2 (n = 12)	66.0 (54.9–71.6)	0.42 (0.28–0.56)	0.56 (0.34–0.60)	0.30 (0.26–0.41)	0.39 (0.32–0.46)	34 (28–37)

[a] Data in parentheses present lower-upper quartiles.
[b] The difference from the results for group 2 was significant (P = 0.0288).

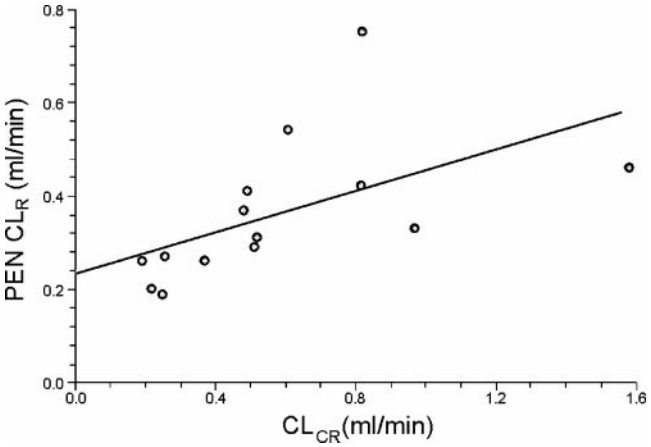

FIG. 2. Correlation between PEN and creatinine CL_R: PEN CL_R (ml/min) = 0.221987 CL_{CR} (ml/min) + 0.233152 (R^2 = 0.309596; P = 0.038).

and especially immature tubular function, the renal elimination of other beta-lactam antibiotics within the first week(s) of life has been shown to be proportional to the glomerular filtration rate, with total CL_R exceeding the glomerular filtration rate only after several weeks, when significant maturation of tubular function has been achieved (5, 16, 25). A significant correlation between the amount of PEN excreted into urine and CL_{CR} was demonstrated in more mature neonates by McCracken et al. (24) and was also shown in this study, suggesting that as with other beta-lactam antibiotics, glomerular filtration is the predominant renal excretion mechanism of PEN in VLBW neonates.

Although our study was conducted at steady state, only 22 to 74% of the administered PEN dose was excreted in urine within 12 h. Similar results for PEN elimination in neonates were reported by McCracken and coworkers (24), who found that 26.4 to 36.8% of the drug is excreted in urine within 12 h after intramuscular administration of 16,650 to 25,000 IU (10 to 15 mg)/kg of PEN, with larger amounts of the drug excreted after the administration of larger doses. These results may suggest that elimination routes other than renal excretion play a role in PEN elimination in neonates.

Conclusions. In VLBW infants a PEN dose of 25,000 IU (15 mg)/kg q12h is safe and is sufficient to achieve concentrations in serum and, most likely, CSF above the MIC_{90} for GBS for the entire dosing interval.

Our study underlines the fact that the values of the PK parameters of drugs in extremely immature infants are different from those in adults, older children, and even term infants. In order to avoid unnecessary adverse effects or insufficient efficacy, there is an urgent need for more extensive studies of the PKs of drugs in this population. A study evaluating the clinical efficacy of the PEN dose recommended above for the empirical treatment of early neonatal sepsis is ongoing.

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REFERENCES

1. **Alcorn, J., and P. J. McNamara.** 2003. Pharmacokinetics in the newborn. Adv. Drug Deliv. Rev. **55:**667–686.
2. **American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn.** 1997. Revised guidelines for prevention of early-onset group B streptococcal (GBS) infection. Pediatrics **99:**489–496.
3. **Barrons, R. W., K. M. Murray, and R. M. Richey.** 1992. Populations at risk for penicillin-induced seizures. Ann. Pharmacother. **26:**26–29.
4. **Bennet, R., M. Eriksson, and C. E. Nord.** 2002. The fecal microflora of 1-3-month-old infants during treatment with eight oral antibiotics. Infection **30:**158–160.
5. **Capparelli, E., C. Hochwald, M. Rasmussen, A. Parham, J. Bradley, and F. Moya.** 2005. Population pharmacokinetics of cefepime in the neonate. Antimicrob. Agents Chemother. **49:**2760–2766.
6. **Chambers, H.** 2005. Penicillins, vol. 1, 6th ed. Churchill Livingstone, Philadelphia, PA.
7. **Cunningham, S., A. G. Symon, R. A. Elton, C. Zhu, and N. McIntosh.** 1999. Intra-arterial blood pressure reference ranges, death and morbidity in very low birthweight infants during the first seven days of life. Early Hum. Dev. **56:**151–165.
8. **de Hoog, M., J. W. Mouton, and J. N. van den Anker.** 2005. New dosing strategies for antibacterial agents in the neonate. Semin. Fetal Neonatal Med. **10:**185–194.
9. **de Man, P., B. A. Verhoeven, H. A. Verbrugh, M. C. Vos, and J. N. van den Anker.** 2000. An antibiotic policy to prevent emergence of resistant bacilli. Lancet **355:**973–978.
10. **Eagle, H., and A. Musselman.** 1948. The rate of bactericidal action of penicillin in vitro as a function of its concentration and its paradoxically reduced activity at high concentrations against certain organisms. J. Exp. Med. **88:**99–130.
11. **Fernandez, M., M. E. Hickman, and C. J. Baker.** 1998. Antimicrobial susceptibilities of group B streptococci isolated between 1992 and 1996 from patients with bacteremia or meningitis. Antimicrob. Agents Chemother. **42:**1517–1519.
12. **Figueira-Coelho, J., M. Ramirez, M. J. Salgado, and J. Melo-Cristino.** 2004. Streptococcus agalactiae in a large Portuguese teaching hospital: antimicrobial susceptibility, serotype distribution, and clonal analysis of macrolide-resistant isolates. Microb. Drug Resist. **10:**31–36.
13. **Giachetto, G., M. C. Pirez, L. Nanni, A. Martinez, A. Montano, G. Algorta, S. L. Kaplan, and A. M. Ferrari.** 2004. Ampicillin and penicillin concentration in serum and pleural fluid of hospitalized children with community-acquired pneumonia. Pediatr. Infect. Dis. J. **23:**625–629.
14. **Hall, M. A., D. A. Ducker, J. A. Lowes, J. McMichael, P. Clarke, D. Rowe, A. Gordon, and D. S. Cole.** 1988. A randomised prospective comparison of cefotaxime versus netilmicin/penicillin for treatment of suspected neonatal sepsis. Drugs **35**(Suppl. 2)**:**169–177.
15. **Hieber, J. P., and J. D. Nelson.** 1977. A pharmacologic evaluation of penicillin in children with purulent meningitis. N. Engl. J. Med. **297:**410–413.
16. **Huisman-de Boer, J. J., J. N. van den Anker, M. Vogel, W. H. Goessens, R. C. Schoemaker, and R. de Groot.** 1995. Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. Antimicrob. Agents Chemother. **39:**431–434.
17. **Jaureguy, F., M. Carton, P. Panel, P. Foucaud, M. J. Butel, and F. Doucet-Populaire.** 2004. Effects of intrapartum penicillin prophylaxis on intestinal bacterial colonization in infants. J. Clin. Microbiol. **42:**5184–5188.
18. **Jokipii, L., P. Brander, and A. M. Jokipii.** 1985. Reverse inoculum effect in bactericidal activity and other variables affecting killing of group B streptococci by penicillin. Antimicrob. Agents Chemother. **27:**948–952.
19. **Jung, T. E., and B. Magnum (ed.).** 2004. Neofax: manual of drugs used in neonatal care, 17th ed. Acorn Publishing, Raleigh, NC.
20. **Kaplan, J. M., G. H. McCracken, Jr., L. J. Horton, M. L. Thomas, and N. Davis.** 1974. Pharmacologic studies in neonates given large dosages of ampicillin. J. Pediatr. **84:**571–577.
21. **LeFlore, J. L., W. D. Engle, and C. R. Rosenfeld.** 2000. Determinants of blood pressure in very low birth weight neonates: lack of effect of antenatal steroids. Early Hum. Dev. **59:**37–50.
22. **Levy, S. B., and B. Marshall.** 2004. Antibacterial resistance worldwide: causes, challenges and responses. Nat. Med. **10:**S122–S129.
23. **Lutsar, I., G. H. McCracken, Jr., and I. R. Friedland.** 1998. Antibiotic pharmacodynamics in cerebrospinal fluid. Clin. Infect. Dis. **27:**1117–1127.
24. **McCracken, G. H., Jr., C. Ginsberg, D. F. Chrane, M. L. Thomas, and L. J. Horton.** 1973. Clinical pharmacology of penicillin in newborn infants. J. Pediatr. **82:**692–698.
25. **Morehead, C. D., S. Shelton, H. Kusmiesz, and J. D. Nelson.** 1972. Pharmacokinetics of carbenicillin in neonates of normal and low birth weight. Antimicrob. Agents Chemother. **2:**267–271.

26. **Paap, C. M., and M. C. Nahata.** 1990. Clinical pharmacokinetics of antibacterial drugs in neonates. Clin. Pharmacokinet. **19:**280–318.
27. **Raichle, M. E., H. Kutt, S. Louis, and F. McDowell.** 1971. Neurotoxicity of intravenously administered penicillin G. Arch. Neurol. **25:**232–239.
28. **Ruess, M., U. Muller, A. Sander, and R. Berner.** 2000. Antimicrobial susceptibility patterns of Streptococcus agalactiae in a German university hospital. Scand. J. Infect. Dis. **32:**623–626.
29. **Saunders, N. R., M. D. Habgood, and K. M. Dziegielewska.** 1999. Barrier mechanisms in the brain. II. Immature brain. Clin. Exp. Pharmacol. Physiol. **26:**85–91.
30. **Sonntag, J., B. Prankel, and S. Waltz.** 1996. Serum creatinine concentration, urinary creatinine excretion and creatinine clearance during the first 9 weeks in preterm infants with a birth weight below 1500 g. Eur. J. Pediatr. **155:** 815–819.
31. **Swingle, H. M., R. L. Bucciarelli, and E. M. Ayoub.** 1985. Synergy between penicillins and low concentrations of gentamicin in the killing of group B streptococci. J. Infect. Dis. **152:**515–520.
32. **Trijbels-Smeulders, M. A., J. L. Kimpen, L. A. Kollee, J. Bakkers, W. Melchers, L. Spanjaard, W. J. Wannet, and M. A. Hoogkamp-Korstanje.** 2006. Serotypes, genotypes, and antibiotic susceptibility profiles of group B streptococci causing neonatal sepsis and meningitis before and after introduction of antibiotic prophylaxis. Pediatr. Infect. Dis. J. **25:**945–948.
33. **van Enk, J. G., D. J. Touw, and H. N. Lafeber.** 2001. Pharmacokinetics of meropenem in preterm neonates. Ther. Drug Monit. **23:**198–201.