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Pharmacokinetics of Nafcillin in Infants with Low Birth Weights

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The pharmacokinetics of nafcillin were studied in 13 premature neonates with suspected sepsis. The mean weight of the infants studied was 1.19 kg (range, 0.73 to 2.21 kg). Infants less than 7 days of age were given 100 mg of nafcillin per kg per 24 h (every 12 h), and infants more than 7 days of age were given 100 mg of nafcillin per kg per 24 h (every 8 h). Blood samples were obtained before the first dose on day 3 of therapy and at 0.5, 1.5, 3, and 6 h thereafter. Nafcillin concentrations were measured by a microbiological assay. A mean volume of distribution of 326 ml/kg and an elimination rate constant of 0.2040 h^{-1} were obtained in 10 patients less than 21 days of age. Three patients from 24 to 68 days of age had a mean volume of distribution of 303 ml/min and a mean elimination rate constant of 0.3944 h^{-1} ($P < 0.05$). These data suggest that doses of nafcillin lower than those currently recommended may be adequate to achieve desired peak plasma levels of approximately 75 μg/ml in infants with low birth weights.

Nafcillin is a semisynthetic penicillin used for the treatment of infections caused by penicillinase-producing staphylococci. Despite the availability of nafcillin for pediatric use for over 10 years, studies of its pharmacokinetic properties in the newborn are limited and are nonexistent for the very small premature infant. Because of lower levels of nephrotoxicity, nafcillin may be a valuable alternative to methicillin (2). This paper reports nafcillin serum concentrations during therapy in 13 sick premature infants receiving nafcillin intravenously.

MATERIALS AND METHODS

Subjects were patients in the Newborn Center of the University of Tennessee Center for the Health Sciences. Informed consent was obtained from parents before the admission of children into the study.

Patients who weighed less than 2.5 kg and who received the combination of nafcillin and gentamicin were eligible for inclusion in the study. Sepsis was suspected in these infants on the basis of a deterioration in clinical status as indicated by apnea, bradycardia, hypotension, and increasing respiratory requirements or alterations in the leukocyte count and differential or both. Nafcillin was used therapeutically only in infants who had been in the nursery more than 4 days and who had no evidence of meningitis or necrotizing enterocolitis.

Infants received the regimen suggested in the American Academy of Pediatrics Report of the Committee on Infectious Diseases (1) which includes the intravenous administration of 100 mg of nafcillin per kg per 24 h in two divided doses for infants less than 7 days of age and three divided doses for infants more than 7 days of age. Measurements of blood urea nitrogen, serum glutamic oxalacetic transaminase, and total and fractionated bilirubin were taken, and a routine urinalysis was done, all immediately before drug administration. At 48 h after the initiation of treatment, blood was obtained by a heel stick or an umbilical artery catheter for a repeat laboratory evaluation and the determination of a nadir serum nafcillin concentration. The patient's usual nafcillin dose was then administered by an intravenous or intraarterial injection (1 to 2 min). The venous or arterial lines were flushed with saline after the injection was administered. Serial serum specimens were collected at 0.5, 1.5, 3, and 6 h postinjection.

Serum nafcillin concentrations were measured by the method of Simon and Yin with a disk diffusion modification of the agar cup method (13). The test organism was *Micrococcus luteus* (ATCC 9341), and standards were prepared in pooled human serum. The disk diffusion method was modified by adding calcium chloride (final concentration 50 mM) to the culture medium to inactivate gentamicin in the samples, as described by Ervin and Bullock (6). This concentration of calcium chloride is sufficient to inactivate at least 20 μg of gentamicin per ml.

A one-compartment model with first-order elimination was assumed for pharmacokinetic calculations. The postinfusion serum concentrations were plotted as log concentration versus time. By least-squares regression a line of best fit with slope $K_e/2.303$, where K_e is the elimination rate constant, was obtained. The half-life was determined with the relationship K_e = 0.693/half-life. For calculating the volume of distribution (V_d), the trapezoidal rule (8) was used with appropriate adjustments in the area under the curve

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for the steady-state nadir concentration. The V_d was calculated with the equation V_d = dose/(area under the curve × K_e). Data were statistically compared by the Student t test (one tailed).

Gestational age was estimated by the method of Dubowitz et al. (4).

RESULTS

For purposes of comparison the patients were grouped into those less than 3 weeks of age and those more than 3 weeks of age. The kinetic data for the 13 patients are listed in Table 1, and the mean nafcillin concentrations with respect to time are shown in Fig. 1. Patients under 3 weeks of age, although having differing mean nafcillin concentrations because of the frequency of dose administration, had similar values for V_d and K_e. The three infants more than than 3 weeks of age showed significantly greater K_e values ($P < 0.05$), but the V_d values remained approximately the same. The relationship of total body clearance to age is shown in Fig. 2. The patient who was 68 days of age at the time of the study was the only subject who did not exceed a peak level of 80 μg/ml. Bilirubin, blood urea nitrogen, and serum glutamic oxalacetic transaminase had no relationship to nafcillin clearance or distribution, and no adverse clinical or laboratory changes were associated with drug administration. Blood cultures were positive for *Staphylococcus aureus* in three of the patients with suspected sepsis. These three infants experienced clinical and bacteriological cure while receiving nafcillin. The remainder of the patients had sterile blood cultures.

DISCUSSION

Previous studies (10–12) of nafcillin kinetics in the neonatal period have been based on the following three assumptions: (i) the administration of a single dose is representative of steady-state kinetics; (ii) healthy full-term newborns provide data to guide drug use in compromised premature newborns; and (iii) nafcillin administered intramuscularly is rapidly and completely absorbed. The first two assumptions have not been tested. The third was studied in an animal model in which it was demonstrated that nafcillin administered intramuscularly was slowly and incompletely absorbed (9). The design of this study circumvents these problems by specifying intravenous administration of the drug in a premature infant population and the study of drug kinetics at steady state.

O'Connor et al. (12) found that nafcillin excretion in the urine of newborns was over the range of 8.17% to 25.32% and concluded that biliary excretion was the principal route of elimination. The clearance of other hepatically eliminated drugs appears to increase with postnatal age (3). Figure 2 suggests that this is also the case for nafcillin. The paucity of data in the current study for infants more than 3 weeks of age precludes pharmacokinetic analysis; however, the group of 10 infants less than 3 weeks of age appears to represent a homogeneous group for analysis.

Although it is difficult to determine concentrations of an antibiotic which are appropriately therapeutic, it seems reasonable to attempt to achieve concentrations found to be efficacious in older children. Based on the data of Feldman et al. (7), a peak of 80 μg/ml was selected to derive an appropriate dose of nafcillin for the neonate based upon our data for newborns less than 3 weeks of age. According to the formula for peak serum concentration, $C_{p\max}$ = [dose/V_d(1 − e^{-KT}], where K is the elimination rate constant

TABLE 1. *Pharmacokinetics of nafcillin*

Patient	Age (days)	Gestational age (wk)	Wt (kg)	Serum half-life (h)	K_e (h^{-1})[a]	V_d (ml/kg)[b]	Total body clearance (ml/min per kg)
1	5		2.210	3.08	0.225	366	1.37
2	5	30	1.220	4.28	0.162	342	0.92
3	6	32	0.980	3.45	0.201	313	1.05
4	7	31	1.065	4.39	0.158	281	0.74
5	8	29	0.730	3.54	0.196	273	0.89
6	8	30	1.520	2.63	0.263	282	1.24
7	11	28	0.790	2.23	0.311	242	1.25
8	13	30	1.040	5.46	0.127	534	1.13
9	16	29	1.175	3.25	0.213	317	1.13
10	17	32	0.940	3.75	0.185	313	0.96
11	24	33	1.520	2.18	0.318	342	1.81
12	28	30	1.390	2.26	0.307	275	1.40
13	68	31	1.940	1.24	0.559	293	2.72

[a] The mean K_e was 0.204 for patients 1 to 10 and 0.394 for patients 11 to 13.

[b] The mean V_d was 326 for patients 1 to 10 and 303 for patients 11 to 13.

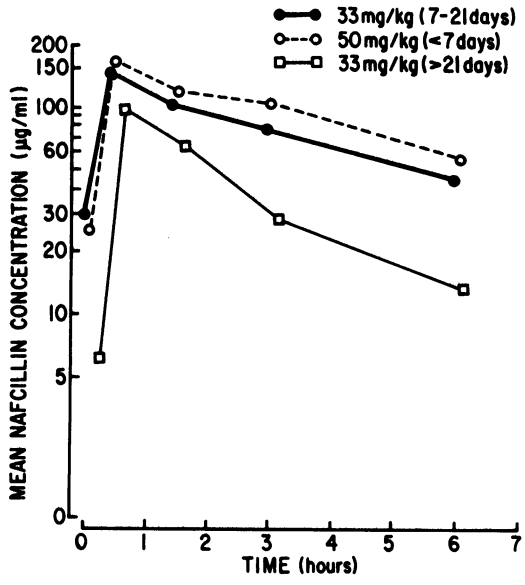

FIG. 1. *Mean nafcillin concentration with respect to time after intravenous administration in 13 infants weighing less than 2.5 kg.*

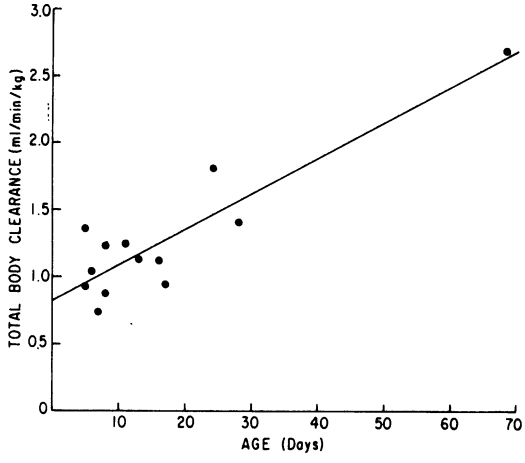

FIG. 2. *Relationship of total body clearance of nafcillin to age after intravenous administration in 13 infants weighing less than 2.5 kg.*

and T is the dosing interval (h) and the mean V_d and K_e for this group, a dose of 20.5 mg/kg administered every 8 h theoretically would achieve a mean peak concentration of 80 μg/ml and a steady-state nadir concentration of 17 μg/ml. In the patients we studied, the computed range of peak concentrations with this reduced regimen would be 59 to 90 μg/ml. Feldman et al. (7) found that this level corresponded to a serum inhibitory titer of ≥1:128 when serum was tested against the patient's own pathogen. The range of predicted nadir concentrations would be 7 to 21 μg/ml. Therefore, this regimen would seem to maintain most neonates less than 3 weeks of age within the chosen range of efficacy without exposing them to unnecessarily high concentrations of drug.

In previous studies on neonates receiving nafcillin intramuscularly, detailed pharmacokinetic analyses were not done (10, 11); however, it appears that the infants in our study achieved disproportionately high serum concentrations. Only 1 of 13 infants failed to achieve a peak nafcillin concentration of greater than 80 μg/ml. In one study of nafcillin administration in neonates (12) mean K_e values ranged from 0.1473 to 0.1631 h^{-1}. Considering the differences in methodology, this correlates well with the mean of 0.204 h^{-1} obtained in the present study.

Although this was not a study of drug efficacy, no therapeutic failures or adverse effects were observed. Bacteremia with *S. aureus* was documented in only three cases with clinical evidence of sepsis before the administration of nafcillin.

A recent review of antibiotic therapy (5) has recommended methicillin as an antistaphylococcal drug in the neonate. That recommendation was based on the lack of pharmacokinetic data on nafcillin. The data presented suggest that nafcillin can be used in newborns with reduced dosage requirements. In view of the known toxicity of methicillin, (2) comparative efficacy and toxicity studies of methicillin and nafcillin in this age group are indicated.

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