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Clinical Pharmacokinetics of Caffeine in Korean Preterm Infants with Apnea of Prematurity

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ABSTRACT

Purpose: Caffeine shows wide interindividual pharmacokinetic (PK) variation, and therapeutic drug monitoring (TDM) may be needed. The PK profile of caffeine in Korean preterm neonates was investigated, and factors influencing the clearance of caffeine were analyzed.

Methods: Fifty-nine preterm neonates receiving caffeine for apnea of prematurity were enrolled in the study (gestational age, 29.5±2.2 weeks and birth weight [BW], 1,318±358 g). Caffeine (20 mg/kg) was intravenously administered to each neonate as a loading dose, followed by a maintenance dose of 5-10 mg/kg/d. A total of 190 serum concentrations were measured for population PK analysis and modeling using nonlinear mixed-effects model (NONMEM®) software.

Results: The mean serum concentration of caffeine was 15.4±4.5 mg/L (range 7.8-33.0 mg/L). High serum concentrations (>20 mg/L) were noted in 36 samples (29%). At the first measurement of serum caffeine, the mean postmenstrual age was 33.9±2.3 weeks, mean BW was 1,802±471 g, mean duration of treatment was 7.4±9.4 days, and mean sampling time after the last dose was 21.8±2.1 hours. In the population PK analysis, the clearance was 0.033 L/h and volume of distribution was 0.371 L. Typical clearance was calculated as $0.0293\times(BW/70)^{1.33}$. Among the subjects receiving 5 mg/kg/d caffeine, the most significant risk factor associated with high serum concentrations (>20 mg/L) was low BW (P=0.024).

Conclusion: BW was the only covariate that influenced caffeine clearance in preterm neonates. Preterm neonates with low BW should be carefully monitored for apnea and adverse reactions in addition to undergoing TDM.

Key words: Apnea of prematurity, Caffeine, Clearance, Pharmacokinetics

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INTRODUCTION

Caffeine is a methylxanthine that acts as a nonspecific inhibitor of adenosine receptors and is used to wean patients from ventilatory support or as a treatment for apnea[1]. Premature neonates receive a loading dose of 20-80 mg/kg in the initial 30 minutes, followed

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by a maintenance dose of 5-20 mg/kg/d 24 hours later[2,3]. The therapeutic dose range is 8-20 μg/mL, with toxic effects occurring at doses exceeding 20 μg/mL[4]. Caffeine interacts with drugs metabolized by the cytochrome P450 (CYP) 1A2 enzyme and is eliminated by renal excretion[4]. Therefore, caffeine pharmacokinetics (PK) may vary in neonates.

The PK profile of caffeine in neonates is characterized by a volume of distribution of 0.8-0.9 L/kg, which is larger than that of children or adults[4,5]. In addition, the half-life of caffeine in neonates is approximately 72-96 hours, which is longer than that of adults, and is further prolonged with decreased renal function. The kidney is the main pathway of caffeine clearance in neonates; thus, newborns have lower clearance rates than children or adults. The population PK data on neonates, especially premature neonates, have been reported for Chinese, Malaysian, and Caucasian populations; however, no population PK data on Koreans have been analyzed.

There are relatively fewer reports of the adverse effects of caffeine than there are for other drugs used for apnea treatment. Irritability, restlessness, jitteriness, and tachycardia can occur owing to central nervous system (CNS) and cardiovascular stimulation[6-8]. An increase in the caffeine levels in the body increases its potency and toxicity accordingly[9]. Therefore, when caffeine is administered to premature neonates with unstable metabolism, therapeutic drug monitoring (TDM) is indispensable. This study analyzes the population PK, including serum concentration in preterm neonates who received caffeine for apnea of prematurity, and the factors affecting serum caffeine levels.

MATERIALS AND METHODS

1. Patients

The data were obtained retrospectively from medical records and routine caffeine monitoring of 57 hospitalized neonates (34 female and 23 male neonates) in the neonatal intensive care unit of Severance Children's Hospital from December 2012 to July 2013, using 190 caffeine measurements. The covariate data collected for each patient included sex, birth weight (BW), current weight, birth height, gestational age (GA), postnatal age, postconceptional age, ventilator care, oxygen care, and Apgar score.

The accurate dosing history including date, dose, and route of administration was collected. The typical loading and maintenance doses of caffeine citrate administered intravenously were 20 and 5 mg/kg once daily, respectively. However, because of the clinical condition of the neonates, the maintenance caffeine dose ranged from 5 to 10 mg/kg once daily. The exclusion criteria were major congenital abnormalities, blood culture-proven sepsis, major neurological conditions, liver or renal disorders, or term neonates. The study protocol was approved by the Institutional Review Board of Yonsei University Severance Hospital. The requirement for informed consent was waived because the study was conducted retrospectively.

2. Serum sampling and analysis

Actual sampling and treatment times were recorded by a nurse on a data sheet and were checked independently. The serum caffeine concentrations were assayed by chromatography/mass spectrometry (MS) using an API 4000TM liquid chromatography-tandem MS (LC-MS/MS) system (Applied Biosystems, Foster City, CA, USA). The working assay range was 0.2-50 mg/L, and the inaccuracy and between-day and within-day variance were <10% across this range. Samples containing >20 mg/L caffeine were diluted in drug-free serum and re-assayed.

3. PK model

The concentration time course of caffeine was described using a one-compartment model with either zero- or first-order (infusion vs. oral) absorption and first-order elimination, assuming a permanent non-steady-state condition. The modeling was performed using non-linear mixed-effects model software (NONMEM, version 5.1.1, Globomax LLC, Hanover, MD, USA). The influence of mean-centered covariates was evaluated by adding these to the base model, and in turn, noting the changes in the objective function value (OFV). The inclusion of a covariate was considered to have improved the fit of the data to the model if there was a decrease in the OFV. The differences between a pair of OFV values when a covariate was included (full model) and excluded (nested reduced model) were tested for significance (a=0.01) using the χ^2 statistic with 1 degree of freedom.

4. Statistical analysis

The continuous variables were presented as means±standard deviation (SD) and were compared using Student's *t*-test. The categorical variables were presented as percentages and frequencies and compared using the chi-square or Fisher's exact test. The risk factors were analyzed using multivariable linear

regression analysis adjusted for GA and BW to estimate the odds ratios (ORs) with 95% confidence intervals (CIs). A $P<0.05$ was considered statistically significant.

RESULTS

The patient characteristics are described in Table 1. The results of blood chemistry at the time of caffeine level measurement showed parameters within normal limits as follows. The blood urea nitrogen (BUN) was 7.1±5.4 mg/dL; creatinine, 0.4±0.3 mg/dL; aspartate transaminase (AST), 28.1±29.0 IU/L; alanine transaminase (ALT), 14.8±21.5 IU/L; albumin, 3.2±0.3 g/dL; and the C-reactive protein was 1.8±3.8 mg/L (Table 2). The mean caffeine concentration was 15.4±5.0 mg/L, and the distribution of serum caffeine levels is shown in Figure 1, with different shapes depicting data for different therapeutic doses. The sample analysis that showed toxicity potential (with serum caffeine levels >20 mg/L) indicated that 6 (4.5%), 7 (41.2%), and 23 (60.5%) of such samples were associated with 5, 7.5, and 10 mg/kg maintenance doses, respectively. When analyzing samples with serum caffeine levels <20 mg/L, 129 (95.5%), 10 (58.8%), and 15 (39.5%) samples were associated with 5, 7.5, and 10 mg/kg maintenance doses, respectively. The overall drug concentration depended on the dose administered, but varied within the same dose.

In the case of the 5 mg/kg administration group, the 6 and 129 samples with serum caffeine levels >20 and <20 mg/L (high and normal concentration groups), respectively, were compared. The average BWs in the normal and high concentration groups were 1,784±466 g and 1,350±332 g, respectively, which differed significantly (P=0.026, Table 3). No significant differences were observed in GA (28.9 and 28.8 weeks for normal and high concentration groups, respectively, P=0.876, Table 3), postnatal age, birth weight, and Apgar score. In the univariate and multiple linear regression analyses (Table 4), the BW was a significant parameter (P=0.024), whereas the GA, postconceptional age, and Apgar score were not significant. The PK parameters determined were clearance (0.033 L/h), the volume of distribution (0.371 L),

Table 1. Characteristics of Study Patients

Characteristic	Mean±SD	Range
Number of Patients, n	57	
Male, n	23	
Gestational age (wks)	29.49±2.22	24.4-33.6
Postconceptional age (wks)	33.94±2.28	27.6-39.3
Postnatal age (d)	36±23	5-89
Birth weight (g)	1,318±358	530-2,210
Current weight (g)	1,802±471	770-2,995
Birth height (cm)	38.93±3.56	29.5-44
Apgar score - 1 min	4.05±1.19	2-7
Apgar score - 5 min	6.12±1.33	3-10
Ventilator care (d)	18.14±23.10	3-10
Oxygen care (d)	42.97±30.32	1-133
Number of Samples, n	190	
Sample time after medication (h)	21.8±2.1	12-24
Caffeine dose (mg/kg)	6.2±2.0	
5 mg/kg, n (%)	135 (71%)	
7.5 mg/kg, n (%)	17 (9%)	
10 mg/kg, n (%)	38 (20%)	

Plus minus values are mean±SD.

Table 2. Laboratory Data

	Mean±SD	Range
BUN (mg/dL)	7.1±5.4	1.0-35.0
Creatinine (mg/dL)	0.4±0.3	0.2-3.2
AST (IU/L)	28.1±29.0	11-377
ALT (IU/L)	14.8±21.5	2-258
Albumin (g/dL)	3.2±0.3	2.3-4.0
CRP (mg/L)	1.8±3.8	0.3-27.4

Normal range of CRP is 0-8 mg/L.
Abbreviations: BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase; CRP, C-reactive protein.

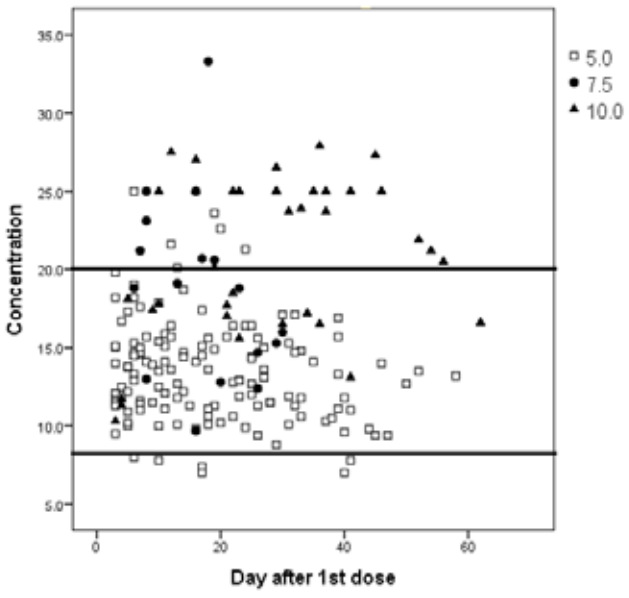

Figure 1. The distribution of serum caffeine levels at the days after 1st dose is shown with different shapes depicting data of different therapeutic doses.

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Table 3. Comparison of Patient Characteristics between Normal and High Concentration Group

	Normal group (N=129)	High group (N=6)	*P*-value
Gestational age (wks)	28.9±2.3	28.8±2.1	0.876
Postconceptional age (wks)	33.9±2.3	32.3±0.9	0.099
Birth weight (g)	1,212±366	1,298±363	0.575
Body weight (g)	1,784±466	1,350±332	0.026
Postnatal age (d)	35.1±23.9	25.0±12.9	0.308
Apgar score – 1 min	3.89±1.38	4.83±0.41	0.098
Apgar score – 5 min	6.00±1.34	6.67±0.82	0.230
Ventilator care	22.9±29.0	34.3±34.7	0.318
Oxygen support	49.0±30.0	37.0±6.7	0.331
Measurement after n dose	15.9±25.1	12.3±4.4	0.729
BUN (mg/dL)	7.1±5.8	10.8±11.9	0.148
Creatinine (mg/dL)	0.37±0.28	0.74±1.21	0.019
AST (IU/L)	28.8±34.0	32.0±10.9	0.817
Albumin (g/dL)	3.14±0.59	3.22±0.25	0.748
CRP (mg/L) (normal 0-8)	2.08±4.32	0.48±0.19	0.368

Data are expressed Mean±SD.
Normal range of CRP is 0-8 mg/L.
Abbreviations: BUN, blood urea nitrogen; AST, aspartate transaminase; CRP, C-reactive protein.

Table 4. Multiple Linear Regression Analysis

	Beta	*P*-value
Gestational age (wks)	2.495	0.149
Postconceptional age (wks)	-2.946	0.093
Body weight (g)	-0.371	0.024
Apgar score – 1min	-0.015	0.885
BUN (mg/dL)	-0.139	0.286
Creatinine (mg/dL)	0.123	0.322
Albumin (g/dL)	-0.206	0.026
CRP (mg/L)	-0.026	0.769

F= 2.794, *P*-value= 0.008.
Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein.

and half-life (22.6 h). Based on these results, a clearance formula for each population was obtained using the following formula: typical clearance=0.0293×(BW/70)$^{1.33}$. The clearance was significantly correlated with the current weight, and the model was fitted with an OFV of 885.53 (Table 4).

DISCUSSION

For over 20 years, caffeine has been successfully used to treat apnea in premature neonates[1,10]. However, limited data on caffeine PK parameters and dosage schedules in premature neonates are available. The population approach is an effective way to determine the safety and efficacy of caffeine, but has not been previously applied to Korean neonates. This study is the first to investigate the population PK of caffeine in Korean preterm neonates.

The clearance and half-life of caffeine change rapidly in the postnatal period, and it may be necessary to adjust dosage regimens as neonates grow older. Controversies exist among various neonatal intensive care units in terms of dosage regimen, time of initiation, duration of therapy, and value of TDM. One recommended regimen reduces the dosage interval from once daily for neonates younger than a month to every 12, 8, or 6 hours for infants aged 1 to 2 months, 2 to 4 months, or 4 months and older, respectively[11]. In a previous study, the recommended loading dose of caffeine citrate was 20 mg/kg and the maintenance treatment (5 to 10 mg/kg once a day) should be administered orally or by intravenous infusion. In this study, the dosage interval was not adjusted based on postnatal age. Instead, a loading dose of 20 mg/kg caffeine was administered, followed by a maintenance dose of 5 mg/kg administered every 24 hours, and increased to 10 mg/kg based on the symptoms and serum caffeine levels.

Caffeine is metabolized in the liver by CYP1A2[12]. The metabolism of caffeine is limited in neonates because of their immature hepatic enzyme system; approximately 86% of caffeine dose is excreted unchanged in the urine[13,14]. Therefore, physiological variables related to renal function would influence caffeine clearance in newborns. Several other factors including genetic variation in hepatic metabolic enzymes and caffeine receptors may also contribute to the variability in pharmacodynamic responses[15-17]. This study included neonates with normal AST, ALT, BUN, and creatinine levels, and excluded newborns with kidney or liver disease.

The serum concentration of caffeine should be monitored periodically, especially in critically ill neonates with unexplained adverse effects, and the therapeutic range is 8-20 mg/L[18,19]. In a study of neonates with GA of 27.6 weeks, groups that maintained caffeine dosing at 5 and 20 mg/kg had a mean serum caffeine concentration of 14.7 μg/mL (4.8-25.1 μg/mL) and 47.4 μg/mL (18.9-79.8 μg/mL), respectively[2]. In another study, the mean serum caffeine levels of 75 preterm neonates were 11.8 μg/mL (4.75-26.1 μg/mL), with less than 4% >20 μg/mL[20]. In this

study, based on neonates at 29.5 weeks GA, the mean serum concentration was 15.48 μg/mL (7.8-33.0 μg/mL). Among the neonates receiving maintenance caffeine doses of 5 and 10 mg/kg, 6 (3%) and 23 (12%) showed serum caffeine levels >20 μg/mL. The blood concentration of caffeine varies, and careful monitoring for toxicity is required. The serum concentration of caffeine tends to be high in underweight neonates, and extra caution is required with this population.

Caffeine toxicity has not been reported at the therapeutic plasma concentrations required to treat apnea of prematurity. Caffeine is a CNS and cardiovascular stimulant and has been associated with irritability, restlessness, jitteriness, tachycardia, and other cardiovascular effects[4]. Other side effects are feeding intolerance, increased urine output, and necrotizing enterocolitis[21].

Serum caffeine levels >50 μg/mL have been associated with fever, tachypnea, hypertonia, vomiting, hyperglycemia, elevated BUN, leukocytosis, seizures, and other symptoms[4,22]. In another study, the heart rate and caffeine serum concentrations were significantly correlated (P<0.05), which is consistent with the increased probability of tachycardia with increased caffeine serum concentration[23]. TDM monitoring should be considered in critically ill neonates with unexplained adverse effects such as tachycardia therefore it has been done in our institution and since the highest serum caffeine concentration was 33 μg/mL in our study, it was not possible to assess side effects at levels greater than 50 μg/mL. In this study, no definite adverse effects were found. Moreover, no cases of serum caffeine levels >50 μg/mL were recorded, and with constant observation, the dosage proved to be safe.

It is widely known that drug disposition in premature neonates can differ markedly from that in older children and adults[19,24]. The half-life of caffeine in preterm neonates (<33 weeks GA) was 87 hours, compared to 72-96 hours in the term neonate group[20]. The elimination of caffeine was severely suppressed in premature neonates but increased nonlinearly after birth up to 6 weeks of age, and reached adult values at approximately 60 weeks postmenstrual age[2]. The caffeine half-life observed for neonates in this study was shorter than that reported in other studies, which may have been caused by differences in the postnatal days.

Individual estimates of clearance were obtained using the population estimates and a post hoc Bayesian analysis of the individual concentration measurements. The mean clearance estimate was 1.8 mL/h/kg, which was lower than the average clearance values (7.9-8.9 mL/h/kg) reported by other studies[20,25,26]. The estimate of the population mean volume of distribution of caffeine (748 mL/kg) is similar to values reported by other studies (911 mL/kg)[2,27]. For estimation of the parameters in the preterm neonate population, the NONMEM program was used to assess the PK profile information for caffeine. The assessment showed that postnatal age, regardless of current weight, was the continual variable that yielded the best adjustment of data in a clearance model. Thomson et al.[27] modeled clearance as a simple function of current weight and postnatal age without the effect of any other covariate. Based on the analysis of the population PK of premature Korean neonates, the caffeine clearance was proven to be affected by current BW, in accordance with previous results. Using the proportional error model for the random effects parameters, this study showed an OFV of 885.53. The interindividual variability of clearance was 14.87%, and the residual variability was 18.44%. Moreover, the estimated values for the final parameters presented a typical pattern with a precision within acceptable limits for both the fixed and random effects parameters (<20 and <50%, respectively)[28]. The limitations of this study are the small sample size and insufficient variation in sampling times. In addition, the study was retrospectively conducted, and the toxicity symptoms could not be verified.

A comparison of the PK data of Koreans with that of other ethnicities revealed similarities in the clearance and volume of distribution values. The neonates had lower BWs than normal, which may have increased the caffeine serum levels. Therefore, the caffeine blood levels should be carefully monitored only in neonates with low BW who have apnea or signs of toxicity.

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