Population pharmacokinetic analysis of caffeine in preterm infants considering pre- and postnatal period

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Background: Caffeine (CAF) is one of the most frequently prescribed drugs for treatment of apnea of prematurity (AOP) which commonly occurs in preterm infants. We previously reported that postmenstrual age (PMA) is a promising factor in describing and understanding the developmental change of caffeine (CAF) clearance, suggesting that developmental changes during gestation affect the CAF clearance after birth. In the present study, we tried to describe the CAF clearance in preterm infants with gestational age (GA) and/or postnatal age (PNA) instead of PMA alone for better understanding of the pharmacokinetics of CAF in preterm infants.

Methods: Preterm infants routinely treated with CAF were recruited with informed consent. Residual serum samples after biochemical tests were used and CAF concentrations were determined by LC-MS/MS. Based on assumption that no absorption phase and constant serum concentration at steady-state, a population pharmacokinetic model was developed and validated by the NONMEM software.

Results: A total of 115 samples were obtained from 52 patients. The mean values of GA, PNA and PMA were 194 ± 15.4, 34.3 ± 18.2 and 227 ± 12.8 days, respectively. We found that even with the same PMA, some patients had a small GA and a large PNA, whereas others had a large GA and a small PNA. There was a negative relationship between PNA and GA. NONMEM analysis provided the following final model of CAF:

$$CL/F = 0.00603 \cdot WT \cdot (PNA/31)^{0.210} \cdot 0.877^{(GA \leq 196)}$$

in L/hr, where CL/F and WT mean oral clearance and body weight, respectively. The numbers of 31 and 196 correspond to the median values for PNA and GA.

Conclusions: We developed the model describing CAF clearance in preterm infants based not only on PNA but also GA, suggesting that we should consider the maturation during gestational period in preterm infants. This study provides insights into the clinical management of CAF therapy as well as developmental changes during neonatal and/or childhood periods and their impact on the pharmacokinetics of drugs.

Key Words: caffeine, population pharmacokinetics, preterm infants, gestational age, postmenstrual age, postnatal age