Caffeine Citrate Dosing Adjustments to Assure Stable Caffeine Concentrations in Preterm Neonates

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Objective To identify dosing strategies that will assure stable caffeine concentrations in preterm neonates despite changing caffeine clearance during the first 8 weeks of life.

Methods A 3-step simulation approach was used to compute caffeine doses that would achieve stable caffeine concentrations in the first 8 weeks after birth: (1) a mathematical weight change model was developed based on published weight distribution data; (2) a pharmacokinetic model was developed based on published models that accounts for individual body weight, postnatal, and gestational age on caffeine clearance and volume of distribution; and (3) caffeine concentrations were simulated for different dosing regimens.

Results A standard dosing regimen of caffeine citrate (using a 20 mg/kg loading dose and 5 mg/kg/day maintenance dose) is associated with a maximal trough caffeine concentration of 15 mg/L after 1 week of treatment. However, trough concentrations subsequently exhibit a clinically relevant decrease because of increasing clearance. Model-based simulations indicate that an adjusted maintenance dose of 6 mg/kg/day in the second week, 7 mg/kg/day in the third to fourth week and 8 mg/kg/day in the fifth to eighth week assures stable caffeine concentrations with a target trough concentration of 15 mg/L.

Conclusions To assure stable caffeine concentrations during the first 8 weeks of life, the caffeine citrate maintenance dose needs to be increased by 1 mg/kg every 1-2 weeks. These simple adjustments are expected to maintain exposure to stable caffeine concentrations throughout this important developmental period and might enhance both the short- and long-term beneficial effects of caffeine treatment. *(J Pediatr 2017;191:50-6).*

Apnea of prematurity in preterm neonates is primarily treated with caffeine,[1,2] including a large proportion of very preterm infants (<32 weeks of gestation).[3,4] A commonly used standard dosing regimen of caffeine citrate consists of a 20 mg/kg loading dose and a 5 mg/kg/day maintenance dose[5] (citrate/base relation 2:1). Based on several studies,[6-11] there is ongoing worldwide discussion of whether higher loading and/or maintenance doses would be beneficial to assure stable caffeine concentrations in preterm neonates. However, in increasing loading and/or maintenance doses, it might be prudent first to investigate the relationship between various dosing strategies and caffeine concentrations in this vulnerable patient population.

Caffeine clearance increases and the half-life decreases during the first postnatal weeks. This is primarily a function of the kidneys because of the immature metabolic capacity of the hepatic enzyme system.[12] As a result, the half-life of caffeine decreases from 120 to 60 hours within the first 8 postnatal weeks,[13] approaching half-life values observed in adults and in children 6 months and older.[13,14] The recommended therapeutic range for caffeine concentration has been increased several times in the last 40 years.[15] Initially, the recommended concentration ranges were 5-15 mg/L[13] and later increased to 8-20 mg/L.[16] Currently, minimal caffeine concentrations of 15-20 mg/L are recommended for treatment of apnea of prematurity.[17]

In this study, we address the following key questions: (1) What is the impact of increasing caffeine clearance on caffeine concentration based on current standard dosing with fixed maintenance doses during the first 8 weeks of life? (2) What adjustments in maintenance doses are necessary to assure a stable caffeine trough concentration during the first 8 weeks of life? (3) What peak and trough concentrations are associated with various loading (20-80 mg/kg) and maintenance (5-20 mg/kg/day) dosing strategies?

CL	Clearance
GA	Gestational age
PNA	Postnatal age
V	Volume of distribution

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The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.08.064

Methods

To address the formulated research questions, a 3-step simulation approach was followed: (1) a mathematical weight change model was developed based on weight distribution data published in literature; (2) a pharmacokinetic model was constructed based on published models that account for effects of individual weight, postnatal age (PNA), and gestational age (GA) on drug clearance and volume of distribution; and (3) caffeine concentrations were simulated with dosing strategies of interest and dosing regimens were identified that assure stable caffeine concentrations during the first 8 weeks of life.

Body weight influences caffeine clearance and volume of distribution in a neonatal patient. A preterm neonate experiences up to 10% weight loss in the first days after birth, approximately 14 days are necessary until birth weight is regained, and doubling the birth weight occurs after 2 months. Different weight change models for full term[18] and preterm[19] neonates are available. Ehrenkranz et al[19] characterized the weight change with a mathematical function (**Appendix**, equation A1; available at www.jpeds.com) over 7-8 weeks for different birth weights ranging from 500 to 1500 g. To describe the median weight change for a typical preterm male neonate with GA of 28 weeks and mean birth weight of 1150 g,[20] the corresponding growth curve[19] was digitized and necessary model parameters for equation A1 were estimated. Note that in general, body weight is correlated with GA.[21]

Caffeine concentration profiles are well described by mono-exponential decay,[5,22] and several 1-compartment models to characterize caffeine clearance and volume of distribution in preterm neonates were developed.[23-26]

First, the mathematical representation of a 1-compartment model was introduced. Second, the clearance and volume of distribution of caffeine was investigated in 4 models (**Appendix**) to see if the findings of these models underscored the goal to simulate different caffeine dosing regimens to assure stable caffeine concentrations during the first 8 weeks of life. Third, a final integrated model was constructed to perform caffeine concentration simulations.

The 1-compartment model[27] assumes a rapid homogenous distribution of the drug throughout the body. The rate of change of drug amount A [mg] reads

$$\frac{d}{dt}A(t) = In(t) - k_{el}A(t), \quad A(t_0) = 0 \tag{1}$$

where In(t) describes the administration of total doses [mg] and k_{el} [1/h] is the elimination rate depending on individual covariates such as weight, PNA or GA. By time t_0 the start of caffeine treatment is denoted. Caffeine citrate is usually administered by intravenous infusion over a short time period (eg, duration of 15 minutes) or a gastric tube (eg, with an absorption time of 30-60 minutes). Because of these relatively short time periods compared with the daily drug administration, we can approximate both administrations by an intravenous bolus administration:

$$In(t) = \sum_{i=1}^{n} d_i \delta(t - t_i) \tag{2}$$

where n is the number of doses, d_i is the administered dose at time t_i for i = 1,. . .,n, and δ is the Dirac delta impulse function. Caffeine concentration is obtained by dividing the drug amount with volume of distribution (V) [L]:

$$C(t) = \frac{A(t)}{V} \tag{3}$$

The elimination rate k_{el} is controlled by clearance (CL) [L/h] and volume of distribution V:

$$k_{el} = \frac{CL}{V} \tag{4}$$

Finally, caffeine half-life $T_{1/2}$ is obtained by

$$T_{1/2} = \frac{ln(2)}{k_{el}}. \tag{5}$$

Individual patient characteristics determine CL and V in equation 4. In the 4 available models[23-26] (A-D, **Appendix**), both parameters are controlled by the covariates body weight, PNA, and GA. As model selection criterion, the typical reported values[13,28] were used. Models for CL and V from Charles et al[26] (model A; n = 110 preterm neonates) and Falcao et al (model B; n = 75 preterm neonates) predicted these typical reported values and were chosen for our final model.[24] In both models, CL is driven by weight and PNA, and V depends on weight only. The model from Lee et al predicted an unusually high V and the model from Thomson et al assumed a constant V.[23,25] Therefore, these 2 models were not selected. Because GA is correlated to weight, the selected models indirectly also account for GA. We averaged CL and V obtained from the 2 selected models by

$$CL = \frac{CL_A + CL_B}{2}, \quad V = \frac{V_A + V_B}{2} \tag{6}$$

to obtain our integrated pharmacokinetics model. Such a combination has the advantage that it incorporates results from different clinical studies. From equation 6, the elimination rate in equation 4 is computed.

With the final model equations 1-6, we performed simulations to (1) investigate the caffeine concentration profiles of the standard dosing regimen; (2) construct an alternative dosing regimen by adjusting the maintenance dose; and (3) examine other dosing regimens proposed in literature. All simulations and figures were performed in Matlab (MATLAB 2014R1, The MathWorks Inc, Natick, Massachusetts).

Results

Simulations were performed for a typical preterm male neonate with birth weight of 1150 g (GA of 28 weeks) receiving caffeine treatment immediately after birth (PNA = 0). Weight