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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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

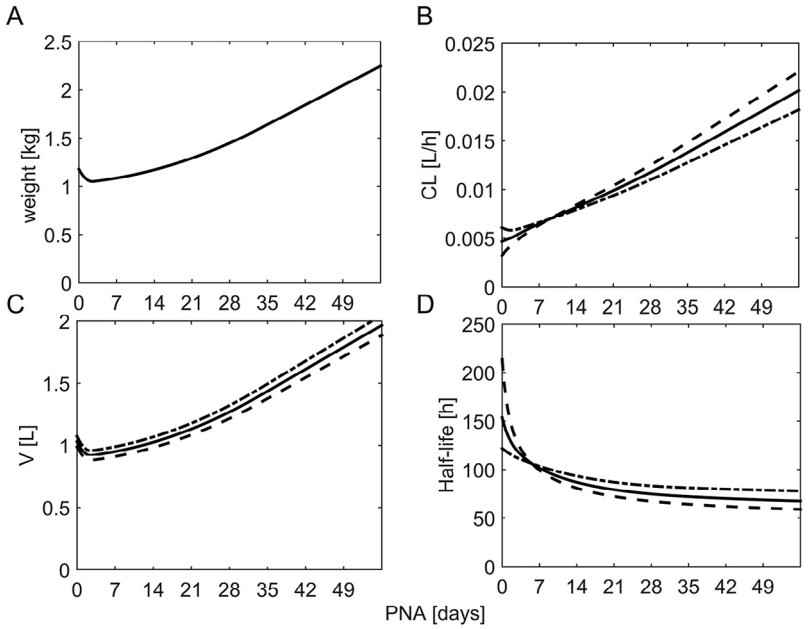

Figure 1. **A,** shows typical weight progression in a male preterm neonate of gestational age 28 weeks simulated by a mathematical weight change model. **B** and **C,** Clearance and volume of distribution predictions for model A (*dashed line*), model B (*dashed-dotted line*), and the applied integrated model (*solid line*). **D,** half-life is presented.

changes were computed, and subsequently clearance maturation and half-life development were predicted based on the final model using equations 1-6. Caffeine concentration profiles with the dosing regimen of 20 mg/kg loading and 5 mg/kg/day maintenance dose were simulated and adjustments of the maintenance doses to assure approximately stable caffeine concentrations with trough levels of 15 mg/L over the first 8 weeks were performed. In addition, a 10 mg/kg/day maintenance dose was investigated and simulations for various loading and maintenance doses of interest were performed. Finally, simulations after discontinuation of treatment at PNA of 7 and 28 days were produced to visualize the impact of decreasing half-life on remaining caffeine concentration exposure.

The weight change model, equation A1 (**Appendix**), captured weight loss, return to birth weight in the first 14 days, and an increase in weight to approximately 2000 g after 2 months (**Figure 1**, A). Changes in clearance (**Figure 1**, B), volume of distribution (**Figure 1**, C), and half-life (**Figure 1**, D) were based on weight and PNA for model A (equations A2-A3, **Appendix**), model B (equations A4-A5, **Appendix**), and the integrated model (using the average from models A and B), equation 6. The predicted average half-life of 120-130 hours in the first week together with a decrease toward approximately 60 hours after 8 weeks is in agreement with prior studies.[12,14] This serves as validation of the applied integrated model.

The caffeine concentration profile from the standard dosing regimen with 20 mg/kg loading and a fixed 5 mg/kg/day maintenance dose is shown in **Figure 2**, A. An increase in the first week is due to accumulation and a long half-life. The subsequent decline of approximately 35% from maximal concentration is caused by a decreasing half-life in the next weeks. The maximal concentration is predicted at PNA day 7 with a trough level of 15 mg/L, which corresponds to conservative therapeutic suggestions[16] and was chosen as the target trough concentration that should be preserved with adjusted maintenance doses.

To obtain a stable caffeine exposure over the entire treatment period with a trough level of at least 15 mg/L, an adjusted dosing regimen was generated. Because caffeine concentration has its peak after the initial week, the conventional dosing of 5 mg/kg/day was continued for the first week. Of the various tested maintenance dose strategies, the following was the simplest adjustment associated with stable trough caffeine concentrations: 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 (**Figure 2**, B). Our prediction suggests that caffeine concentration will remain in the range of 15-20 mg/L, corresponding to the standard therapeutic window.

Assuming that caffeine concentrations up to 30 mg/L are safe, a 2-fold higher, maintenance dose of 10 mg/kg/day was explored. This fixed maintenance dose produced concentrations above 15 mg/L with a maximal trough of 25 mg/L after 1 week and decreasing trough concentrations approaching 20 mg/L after 8 weeks (**Figure 2**, C).

Higher loading doses than 20 mg/kg were explored to test whether they are associated with maintaining caffeine trough concentrations above 15 mg/L. Simulations indicate that an

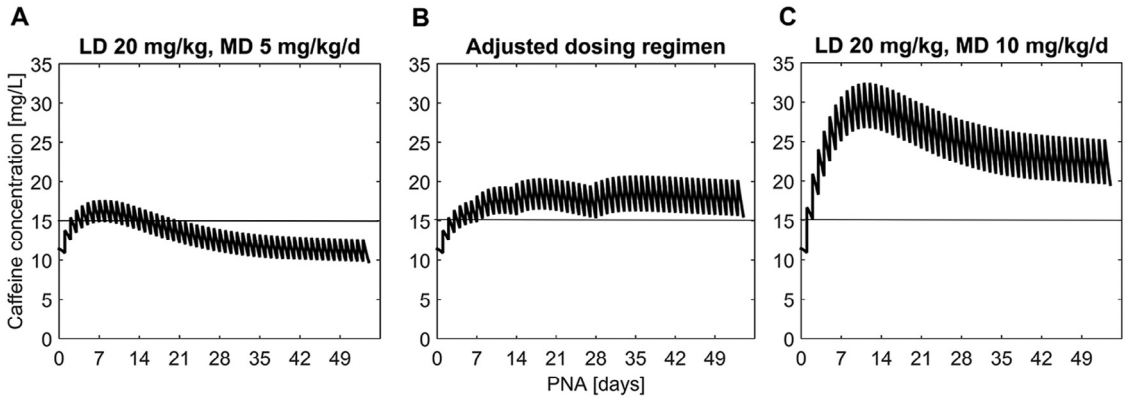

Figure 2. Prediction of caffeine concentration based on the integrated model with **A,** the standard caffeine citrate dosing regimen, **B,** an adjusted dosing regimen to produce a trough concentration of approximately 15 mg/L, and **C,** a maintenance dose (*MD*) of 10 mg/kg/day.

increase of the loading doses to 40, 60, or 80 mg/kg results in considerably higher concentrations during the initial week. However, as caffeine clearance increases these higher concentrations rapidly decrease with a maintenance dose of 5 mg/kg/day toward caffeine levels obtained with a loading dose of 20 mg/kg within 3-4 weeks (**Figure 3**).

In several clinical studies,[5,10,11,25,26,29] administrations of higher loading and maintenance doses such as 40 and 10, 40 and 20, and up to 80 and 20 were performed. Measured caffeine concentrations[5,26] suggest a linear relationship between dose and concentration. Consequently 40 and 10, 60 and 15, and 80 and 20 preserve the trough concentration above 20, 30, and 40 mg/L.

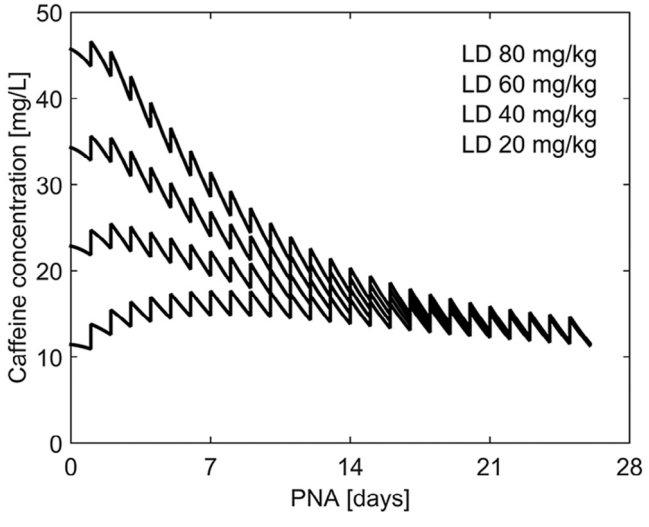

Figure 3. Prediction of caffeine concentration from the integrated model with escalating caffeine citrate loading doses (*LD,* 20, 40, 60, 80 mg/kg) and fixed maintenance dose of 5 mg/kg/day.

To assess the impact of clearance increase (half-life decrease), caffeine concentrations were simulated after discontinuation of treatment with the adjusted dosing regimen assuming treatment starts at PNA = 0, and treatment discontinues at PNA = 7 or 28 days. As expected a shortened half-life after discontinuation of treatment at PNA = 28 days (half-life = 86 hours), compared with a treatment discontinuation at PNA = 7 days (half-life = 112 hours), results in a shorter time to reach the lower limit of therapeutic concentrations. **Figure 4**

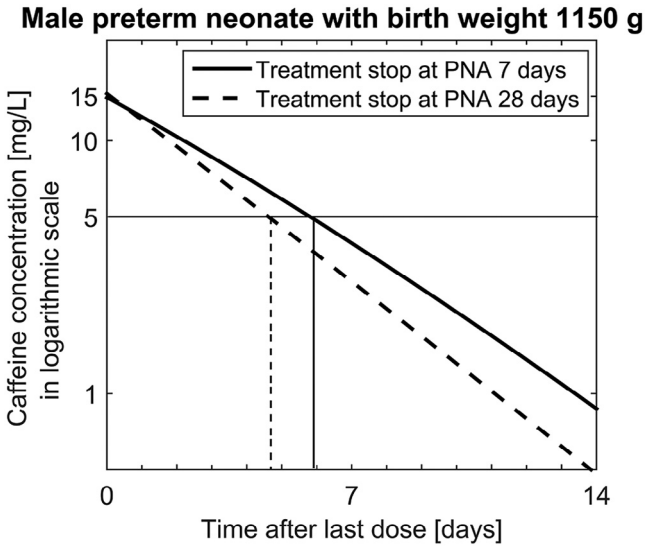

Figure 4. Decreases in caffeine concentration with the adjusted caffeine citrate dosing regimen after treatment discontinuation at PNA 7 days (*solid line*) and PNA 28 days (*dashed line*) in a male preterm neonate with birth weight of 1150 g (GA 28 weeks). Caffeine concentrations below 5 mg/L are reached after approximately 6 (discontinuation at PNA 7 days) and approximately 4.5 days (discontinuation at PNA 28 days).

illustrates that a minimal target concentration of 5 mg/L is reached within approximately 4.5 days in neonates with a treatment discontinuation at PNA = 28, whereas concentrations stay above 5 mg/L for almost 6 days if treatment is discontinued at PNA = 7. Subtherapeutic concentrations of 1 mg/L or lower are reached after 11 days (with treatment discontinuation at PNA = 28) and 14 days (with treatment discontinuation at PNA = 7), respectively.

Discussion

Since the introduction of caffeine for preterm infants, there have been ongoing discussions of whether it would improve outcomes if preterm infants were exposed to higher loading or maintenance doses of caffeine. However, the use of higher caffeine doses is controversial as the literature on the topic is rather sparse with conflicting results.[7-11] Schmidt et al performed a randomized control trial involving 2006 preterm neonates (median GA 27 weeks) with 50% of the patients treated with caffeine (median administration time 37 days).[6] This study showed that the duration of positive airway pressure and supplemental oxygen were reduced as well as rates of bronchopulmonary dysplasia and severe retinopathy of prematurity. The percentage of infants with cerebral palsy and cognitive delay was significantly lower in those who received caffeine compared with those who did not after 1-2 years of age, whereas neurodevelopmental outcomes such as motor impairment and behavioral problems were similar in both groups at 5 years of age. Other studies have demonstrated that median maintenance caffeine citrate doses higher than 7.9 mg/kg/day were associated with a reduction in clinical interventions including mechanical ventilation for persistent apnea in neonates (mean GA 26 weeks)[7] and that caffeine concentrations above 14.5 mg/L were correlated with reduced chronic lung disease in infants born with a GA of less than 29 weeks.[8] However, high caffeine loading doses (80 mg/kg) administered in the first 24 hours of life have been associated with a higher incidence of cerebellar hemorrhage, increased muscle tone, and more abnormal movements compared with standard dosages.[11]

Although it is known that apnea frequency decreases with maturation, there is no evidence that the caffeine exposure-apnea response relationship changes and that lower caffeine concentrations are needed to prevent and treat apnea after the first 2-3 weeks of life. Thus, if the goal of caffeine therapy remains the same (ie, to prevent and treat apnea), the same caffeine concentrations should be targeted during the first weeks of life.

In adults <2% of a caffeine dose is eliminated unchanged in urine, the remainder is metabolized primarily in the liver to a series of partially demethylated xanthines and methyl uric acids. In contrast, during the first month of human life more than 85% of administered caffeine is excreted unchanged in urine of the newborn infant.[12] These observations indicate that newborn infants have a severe deficiency in their caffeine metabolizing capacity, and this deficiency persists for several months because caffeine will remain the most abundant component in the urine of infants up to the age of 3 months. Not until 3-5 months of age is the capacity to produce demethylated metabolites and caffeine clearance comparable with adults.

Hence, factors such as body weight, GA, and PNA are expected to have an important influence on changes in the dose-concentration relationship of caffeine during the first 8 weeks of life in these rapidly maturing neonates. Therefore, it seemed important to investigate how body weight, GA, and PNA influenced this dose-concentration relationship with the ultimate goal to assure a stable plasma concentration of caffeine. For these reasons, we developed a model to simulated caffeine concentration based on available published models that takes these demographic factors into account. Caffeine concentration profiles are well described by mono-exponential decay. Such a 1-compartment model has 2 essential components: clearance and volume of distribution. Because these 2 parameters dramatically change in neonates, 2 previously published models for clearance and volume of distribution[24,26] were chosen and integrated to our final model. In both approaches, clearance was dependent on PNA and weight, and volume of distribution on weight. Because GA is correlated to weight, the effect of GA is indirectly included as well.

Although tables with complex adjustments of maintenance doses based on weight and PNA to achieve prespecified average target concentrations have been published (Falcao et al targets a 12 mg/L for 10 weeks and Lee et al a 35 mg/L average concentration for 3 weeks), such tables are rarely used because of their clinical impracticability.[24,25] Therefore, caregivers often continue to use a fixed maintenance dose and make dose adjustments based on clinical signs such as apneic events rather than prespecified target concentrations and therapeutic drug monitoring.

Our goal was to understand the impact on caffeine concentrations for different dosing regimens. Therefore, simulations for a typical neonate with a birth weight of 1150 g (corresponding to GA 28 weeks) were performed to answer the initially formulated questions:

What is the impact of increasing clearance on caffeine concentrations based on current standard dosing (loading dose of 20 mg/kg) with fixed maintenance doses (5 mg/kg/day) during the first 8 weeks of life? Our data show that this commonly used dosing regimen produces caffeine concentrations that increase during the first week to a trough level of 15 mg/L, which is considered to be the lower therapeutic level,[17] but subsequently decrease up to 35% in the next 7 weeks creating peak and trough concentration below 15 mg/L.

What adjustments in maintenance doses are necessary to assure a stable caffeine trough concentration during the first 8 weeks of life? Stable concentrations in the currently recommended therapeutic range (trough of 15 mg/L and a peak of 20 mg/L in the first 8 weeks of life[17]), are generated by increasing the maintenance doses by 1 mg/kg/day at weeks 2, 3, and 5. More precisely, the adjusted maintenance doses are 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. This dosing schedule is easy to apply in daily clinical practice because of its simple and elementary adjustments.

Which peak and trough concentrations are associated with various loading and maintenance dosing approaches? An alternative dosing strategy to our adjusted dosing regimen is to directly apply a maintenance dose of 10 mg/kg/day at start of treatment producing trough levels above 20 mg/L. This simple dosing strategy may be applied if caffeine concentrations up to 30 mg/L are considered to be safe. An escalating loading dose of 40, 60, and 80 mg/kg with a maintenance dose of 5 mg/kg/day provides higher caffeine concentrations during the initial week of treatment. However, those higher caffeine concentrations rapidly decrease approaching caffeine levels obtained with the standard loading dose of 20 mg/kg within 3-4 weeks. Increasing the loading dose to 40, 60, or 80 mg/kg together with increased maintenance doses of 10, 15, and 20 mg/kg/day preserves the trough concentrations above 20, 30, and 40 mg/L, respectively.

Finally, we demonstrated that discontinuation of treatment at different PNAs has an impact on remaining time with therapeutic caffeine concentration. As half-life of caffeine decreases with PNA in preterm neonates, treatment discontinuation at later time points (eg, PNA = 28) is associated with a decreased duration of therapeutic caffeine concentrations compared with discontinuation of caffeine after the first week of life. This finding is of clinical relevance as the drug-related "protection period" after the last caffeine dose is reduced in neonates receiving treatment for several weeks.

The results of this data analysis show that higher maintenance doses than 5 mg/kg/day should be considered if the goal is to maintain target caffeine concentrations above 15 mg/L beyond the first week of life. A clinical study is warranted to understand whether a gradual increase in maintenance dose (eg, 1 mg/kg/day every 1-2 weeks) or a 2-fold higher fixed maintenance dose (ie, 10 mg/kg/day) has a superior efficacy–safety balance.

Our data illustrate that the combined application of neonatal clinical pharmacology principles and pharmacometric tools[30,31] may allow for a tailored approach to the optimal use of drugs in neonates that display an increased clearance during the early stages of life. Moreover, applying this newly proposed dosing regimen of caffeine use in preterm infants will allow us to investigate prospectively the impact of different disease states (eg, patent ductus arteriosus, perinatal asphyxia, septicemia, congenital heart disease) and treatment modalities (eg, mechanical ventilation, surfactant administration) on the metabolism and clearance of caffeine in preterm infants through 44 weeks of postmenstrual age. This may facilitate implementation of optimal precision medicine in this vulnerable population. ■

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References

1. Dobson NR, Patel RM. The role of caffeine in noninvasive respiratory support. Clin Perinatol 2016;43:773-82.
2. Atik A, Harding R, De Matteo R, Kondos-Devcic D, Cheong J, Doyle LW, et al. Caffeine for apnea of prematurity: effects on the developing brain. Neurotoxicology 2017;58:94-102.
3. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112-21.
4. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357:1893-902.
5. Aranda JV, Cook CE, Gorman W, Collinge JM, Loughnan PM, Outerbridge EW, et al. Pharmacokinetic profile of caffeine in the premature newborn infant with apnea. J Pediatr 1979;94:663-8.
6. Schmidt B, Anderson PJ, Doyle LW, Dewey D, Grunau RE, Asztalos EV, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012;307:275-82.
7. Francart SJ, Allen MK, Stegall-Zanation J. Apnea of prematurity: caffeine dose optimization. J Pediatr Pharmacol Ther 2013;18:45-52.
8. Alur P, Bollampalli V, Bell T, Hussain N, Liss J. Serum caffeine concentrations and short-term outcomes in premature infants of 29 weeks of gestation. J Perinatol 2015;35:434-8.
9. Steer P, Flenady V, Shearman A, Charles B, Gray PH, Henderson-Smart D, et al. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2004;89:F499-503.
10. Gray PH, Flenady VJ, Charles BG, Steer PA, Caffeine Collaborative Study G. Caffeine citrate for very preterm infants: effects on development, temperament and behaviour. J Paediatr Child Health 2011;47:167-72.
11. McPherson C, Neil JJ, Tjoeng TH, Pineda R, Inder TE. A pilot randomized trial of high-dose caffeine therapy in preterm infants. Pediatr Res 2015;78:198-204.
12. Aldridge A, Aranda JV, Neims AH. Caffeine metabolism in the newborn. Clin Pharmacol Ther 1979;25:447-53.
13. Le Guennec JC, Billon B, Pare C. Maturational changes of caffeine concentrations and disposition in infancy during maintenance therapy for apnea of prematurity: influence of gestational age, hepatic disease, and breast-feeding. Pediatrics 1985;76:834-40.
14. Aranda JV, Collinge JM, Zinman R, Watters G. Maturation of caffeine elimination in infancy. Arch Dis Child 1979;54:946-9.
15. Aranda JV, Gorman W, Bergsteinsson H, Gunn T. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr 1977;90:467-72.
16. Pesce AJ, Rashkin M, Kotagal U, National Academy of Clinical Biochemistry. Standards of laboratory practice: theophylline and caffeine monitoring. Clin Chem 1998;44:1124-8.
17. Kahn DJ, Godin R. Is it time to embrace the caffeine level? Pediatrics 2016;137.
18. Wilbaux M, Kasser S, Wellmann S, Lapaire O, van den Anker JN, Pfister M. Characterizing and forecasting individual weight changes in term neonates. J Pediatr 2016;173:101-7, e10.
19. Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999;104:280-9.
20. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010;125:e214-24.
21. Keirse MJ. International variations in intrauterine growth. Eur J Obstet Gynecol Reprod Biol 2000;92:21-8.
22. Gorodischer R, Karplus M. Pharmacokinetic aspects of caffeine in premature infants with apnoea. Eur J Clin Pharmacol 1982;22:47-52.
23. Thomson AH, Kerr S, Wright S. Population pharmacokinetics of caffeine in neonates and young infants. Ther Drug Monit 1996;18:245-53.

24. Falcao AC, Fernandez de Gatta MM, Delgado Iribarnegaray MF, Santos Buelga D, Garcia MJ, Dominguez-Gil A, et al. Population pharmacokinetics of caffeine in premature neonates. Eur J Clin Pharmacol 1997;52:211-7.
25. Lee TC, Charles B, Steer P, Flenady V, Shearman A. Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity. Clin Pharmacol Ther 1997;61:628-40.
26. Charles BG, Townsend SR, Steer PA, Flenady VJ, Gray PH, Shearman A. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. Ther Drug Monit 2008;30:709-16.
27. Koch G, Schropp J, Pfister M. Facilitate treatment adjustment after overdosing: another step toward 21st-century medicine. J Clin Pharmacol 2017;57:704-11.
28. Picone S, Bedetta M, Paolillo P. Caffeine citrate: when and for how long. A literature review. J Matern Fetal Neonatal Med 2012;25(Suppl 3):11-4.
29. Mohammed S, Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. Eur J Pediatr 2015;174:949-56.
30. Wilbaux M, Fuchs A, Samardzic J, Rodieux F, Csajka C, Allegaert K, et al. Pharmacometric approaches to personalize use of primarily renally eliminated antibiotics in preterm and term neonates. J Clin Pharmacol 2016;56:909-35.
31. Koch G, Schropp J. Mathematical concepts in pharmacokinetics and pharmacodynamics with application to tumor growth. In: Kloeden PE, Poetzsche C, eds. Nonautonomous dynamical systems in the life sciences. Springer; 2013.

50 Years Ago in *The Journal of Pediatrics*

Public Knowledge of Ipecac Syrup in the Management of Accidental Poisonings

Alpert JJ, Levine MD, Kosa J. J Pediatr 1967;71:890-4

At one time, ipecac was considered the preferred first aid treatment for gastric decontamination in children with accidental poisoning. The Massachusetts Pharmaceutical Association even sponsored a program to distribute syrup of ipecac, free of cost, to be used as an emetic in the event of accidental poisoning in young children. A 1-oz bottle of syrup of ipecac also could be purchased without a prescription.[1] The authors studied 2 samples of families from the target areas of Massachusetts to ascertain their knowledge of home use and possession of ipecac syrup. They concluded that the program had increased families' knowledge of the use of ipecac syrup. For years after this study, the American Academy of Pediatrics continued to support the home use of syrup of ipecac.[2]

Fifty years later, we have made a complete U-turn on the policy on home use of syrup of ipecac. Questioning the utility of ipecac, Vale et al[3] argued that although its use "may satisfy the innate desire of parents, doctors, and nursing staff to do something, there is no evidence that it prevents drug absorption or systemic toxicity." In November 2003, for the first time, the American Academy of Pediatrics issued a statement advocating against the use of ipecac for the home management of poison ingestion, based on the landmark study by Bond[4] that concluded that ipecac neither reduced the number of Emergency Department visits nor improved the final outcome of poisoning. Following this report, the use of ipecac decreased from 15% of all human poison exposures reported to American Association of Poison Control Centers in 1985 to only 0.02% in 2009.[5]

In a 2013 position paper, the European Association of Poison Centres and Clinical Toxicologists[6] also advocated for the avoidance of routine administration of ipecac, noting that it may delay the effectiveness of other, more suitable procedures for gastric decontamination. Shannon,[7] in a 2003 "obituary" for ipecac, commented that "the drug may be missed briefly, but it is unlikely its absence will create more concerns than its presence has," and I agree.

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References

1. Alpert JJ, Heagarty MC. Evaluation of a program for distribution of ipecac syrup for the emergency home management of poison ingestions. J Pediatr 1966;69:142-6.
2. American Academy of Pediatrics. Faculty childhood safety counseling schedule. The injury prevention program. EIK Grove Village (IL): American Academy of Pediatrics; 1985.
3. Vale JA, Meredith TJ, Proudfoot AT. Syrup of ipecacuanha: is it really useful? BMJ 1986;293:1321.
4. Bond GR. Home syrup of ipecac use does not reduce emergency department use or improve outcome. Pediatrics 2003;112:1061-4.
5. Albertson TE, Owen KP, Sutter ME, Chan AL. Gastrointestinal decontamination in the acutely poisoned patient. Int J Emerg Med 2011;4:65.
6. Haijer J, Troutman WG, Hoppu K, Erdman A, Benson BE, Macgrabane B, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. Clin Toxicol 2013;51:134-9.
7. Shannon M. The demise of ipecac. Pediatrics 2003;112:1180-1.

Appendix

First, the model for weight change in the first 8 weeks is presented. Second, the 4 available models for clearance and volume of distribution developed based on a 1-compartment model are presented and compared among each other.

Model for Weight Change

Weight change was described by a combination of quadratic and linear functions:[19]

$$WT = \begin{cases} b + \beta_1 t + \beta_2 (T_1 - t)^2 + \beta_3 (T_2 - t)^2, & for\ t \le T_1 \\ b + \beta_1 t + \beta_3 (T_2 - t)^2, & for\ T_1 < t \le T_2 \\ b + \beta_1 t, & for\ t > T_2 \end{cases} \quad (A1)$$

where t is day of life. Because no explicit parameter values were listed, the presented curve of the 1150 g birth weight patient was digitized and parameters in equation (A1) were refitted.

Available Models for Clearance and Volume of Distribution

Charles et al[26] (model A) established the following equations for clearance $CL\left[\frac{L}{h}\right]$ and volume of distribution $V[L]$ based on current weight $WT\ [kg]$ and $PNA\ [d]$:

$$CL_A = 0.167 \left(\frac{WT}{70}\right)^{0.75} \left(\frac{PNA}{12}\right)^{0.358} \quad (A2)$$

$$V_A = 58.7 \cdot \left(\frac{WT}{70}\right) = 0.84 \cdot WT. \quad (A3)$$

Equation (A2) is a multiplication of 2 nonlinear models, one depending on weight and the other on PNA, and equation (A3) is a linear approach including weight only. Please note that equation (A3) corresponds to the final model equation from the Results part and Table 2 from Charles et al[26] and not to the equation presented in their Abstract. The applied 1-compartment model was additionally extended with an absorption compartment, which we neglected because of the rapid absorption compared to once-a-day dosing. Falcao et al[24] (model B) presented the following linear equations for $CL\left[\frac{ml}{h}\right]$ and $V[ml]$ based on $WT\ [kg]$, $PNA\ [wk]$ and $GA\ [wk]$

$$CL_B = (5.81 \cdot WT + 1.22 \cdot PNA) \cdot \begin{cases} 0.757 & if\ GA \le 28 \\ 1 & if\ GA > 28 \end{cases} \quad (A4)$$

$$V_B = 911 \cdot WT. \quad (A5)$$

Note the close relationship of equation (A3) and equation (A5). Moreover, simulation showed that also equation (A2) and equation (A4) are in close agreement. Lee et al[25] (model C) constructed the combination of linear equations as follows:

$$CL_C\left[\frac{L}{h}\right] = 0.00000399 \cdot WT[g] + 0.000128 \cdot PNA[d] \quad (A6)$$

$$V_C[L] = \begin{cases} 0.000764 \cdot WT[g] + 0.0468 \cdot PNA[d]\ if\ GA > 28\ weeks \\ 0.000755 \cdot WT[g] + 0.0224 \cdot PNA[d]\ if\ GA \le 28\ weeks \end{cases} \quad (A7)$$

Equation (A6) is qualitative also close to equations (A4) and (A2). Equation (A7) is the only approach that includes weight, PNA, and GA. However, equation (A7) predicts higher values than equations (A3) and (A5). Finally, Thomson et al[23] (model D) presented:

$$CL_D\left[\frac{L}{d}\right] = 0.14 \cdot WT[kg] + 0.0024 \cdot PNA[d] \quad (A8)$$

$$V_D[L] = 0.82. \quad (A9)$$

Again equation (A8) is in good agreement with the other clearance models equations (A2), (A4), and (A6), but volume of distribution does not dependent on any covariate.