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Caffeine for preterm infants: Fixed standard dose, adjustments for age or high dose?

Vivek Saroha, MD, PhD[1], **Ravi Mangal Patel, MD, MSc**[1]

[1]Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA

Abstract

Caffeine is an effective treatment for apnea of prematurity and has several important benefits, including decreasing respiratory morbidity and motor impairment. In this article, we focus on the dose of caffeine. We review the evidence regarding the efficacy and safety of standard caffeine dosing and alternative dosing approaches, including the use of high dose caffeine and routine dose adjustments for age. Current evidence suggests high dose caffeine may provide additional benefit in reducing the risk of bronchopulmonary dysplasia and extubation failure, but may also increase the risk of cerebellar hemorrhage and seizures. Increasing the standard caffeine citrate dose every 1 to 2 weeks to a goal dose of 8 mg per kilogram every 24 hours may help maintain therapeutic effect. We conclude by highlighting the need for additional trials before high dose caffeine is routinely used.

Keywords

Infant; neonate; preterm; caffeine; apnea; pharmacokinetics

Apnea is common problem among preterm infants, particularly for extremely preterm infants1. Caffeine is an effective treatment for apnea of prematurity and has a number of short- and long-term benefits. In this review, we focus on the dose of caffeine citrate. We start by discussing the history and evolution of the "standard dose" of caffeine, including studies evaluating the safety and efficacy of standard dosing. We then review two alternative dosing approaches: use of high-dose caffeine and routine caffeine dose adjustments for age.

A. History and Evolution of "Standard Dose" Caffeine

In 1973, Kuzemko and Paala reported on improvement in apnea among 10 preterm infants after the administration of 5 mg aminophylline suppositories[2]. Four years later, Aranda et al. published the first study of caffeine used to treat apnea of prematurity3. In this study, 18

*Corresponding author: **Dr. Patel**, Ravi Mangal Patel, M.D., M.Sc., 2015 Uppergate Dr. NE, Division of Neonatology, Atlanta, GA 30322. rmpatel@emory.edu.

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preterm infants with apnea were administered caffeine citrate and a marked reduction in apnea spells was observed from a mean of 14 per 24 hours before caffeine treatment to 2 per 24 hours following treatment. In this study, infants were initially administered a dose of 20 $mg.kg^{-1}$ of caffeine citrate once or twice daily by mouth. Following this, plasma caffeine concentrations of 50 to 60 mg per L were obtained and a prolonged elimination of caffeine was noted. Based on this data, the dosing for subsequent infants in the study was changed to a 20 mg per kg intravenous loading dose of caffeine citrate followed by a maintenance dose of 5 to 10 $mg.kg^{-1}$ once or twice per day started 2 to 3 days after the loading dose. The authors noted their goal was to maintain a plasma concentration in the range of 5 to 20 mg per L. This target plasma concentration was based on similar plasma concentrations of theophylline being effective for bronchodilation to reverse airway obstruction in adults with asthma and toxicity observed at plasma concentrations above 20 mg per L[4].

In 1979, Aranda et al. provided additional data on the pharmacokinetic profile of caffeine citrate using doses of 5 to 20 mg per kg in a dose finding study that highlighted the accumulation of caffeine[5]. Based on the goal range of plasma concentrations of 5 to 20 mg per L, the investigators recommended the use of a caffeine citrate loading dose of 20 mg per kg followed by a maintenance dose of 5 $mg.kg^{-1}$ per 24 hours. For this review, we refer to this as the “standard dose” regimen for caffeine. This standard dose regimen was used in additional small trials of 18 and 23 preterm infants in 1981 and 1986, respectively, that also demonstrated the efficacy of caffeine in reducing apnea.[6,7] The standard dose regimen was also used in trials in 1985 and 1987 showing caffeine citrate had similar efficacy in reducing apnea frequency as theophylline[8,9].

In subsequent trials around this time, two different dosing strategies were used that evaluated a maintenance caffeine citrate dose of 2.5 $mg.kg^{-1}$ per 24 hours as well as 10 $mg.kg^{-1}$ per 24 hours. The first trial enrolled 50 spontaneous breathing infants < 32 weeks’ gestation and used a loading dose of 20 mg per kg of caffeine citrate followed by a maintenance dose of 10 $mg.kg^{-1}$ per 24 hours and compared this to placebo[10]. The study reported no difference in hypoxemic episodes based on a decrease in transcutaneous oxygen measurement of 20% from baseline within 20 seconds and no overall decrease in bradycardia episodes, although there was a transient decrease in bradycardia within 12 hours after randomization with the use of caffeine. In 1992, Romagnoli et al. evaluated the use of a lower maintenance dose of caffeine citrate of 2.5 mg per kg, compared to a 5 mg per kg dose or placebo, and found no severe adverse effects with either dose and a reduction in apnea by both caffeine doses[11]. However, there was a lower incidence of tachycardia (heart rate > 180 beats per min) in the 2.5 mg per kg caffeine citrate study arm, compared to the 5 mg per kg arm. A study from 1991 of 15 preterm infants, provided additional support for a single daily maintenance dosing regimen, highlighting the long caffeine half-life[12].

In 2000, a double-blind randomized trial of caffeine citrate was performed in the US[13] using the dosing regimen initially recommended by Aranda et al.[5] (20 mg per kg loading followed by 5 $mg.kg^{-1}$ per 24 hours). In this trial, 85 infants who were 28 to 32 weeks’ post-menstrual age and at least 24 hours old were randomized to caffeine or placebo for up to 10 days. Of note, many infants in this trial were transferred to open-label caffeine use and < 50% completed at least 10 days of double-blind therapy. Caffeine treatment resulted in a >

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50% reduction in apnea in 69% of infants, compared to 43% of infants receiving placebo (P=0.02), with apnea eliminated in 24% of infants receiving caffeine compared to no infants receiving placebo. Caffeine levels ranged from 4.5 to 16.5 mg per L, consistent with the target range of 5 to 20 mg per L suggested by Aranda et al.[5]. This study was used for US Food and Drug Administration (FDA) approval of caffeine for the labeled indication of short-term treatment of apnea of prematurity in infants between 28 and <33 weeks' gestational age. On the FDA drug label, the following dose of caffeine citrate was recommended: a loading dose of 20 mg per kg of caffeine citrate followed by a 5 mg per kg caffeine maintenance dose every 24 hours[14] with a similar approval by the European Medicines Agency[15]. Although these studies demonstrated the beneficial effects of standard dose caffeine on apnea, there was concern based on pre-clinical studies of potential adverse neurocognitive effects of methylxanthines[16] and prior trials had not adequately assessed the long-term safety of caffeine.

B. Rigorous Evaluation of The Short- and Long-Term Safety and Efficacy of Standard-Dose Caffeine

The safety and efficacy of the standard dose regimen of caffeine was rigorously evaluated in the Caffeine for Apnea of Prematurity (CAP) trial[17]. In this trial, infants were randomized to placebo or caffeine citrate at a loading dose of 20 mg per kg, followed by a maintenance dose of 5 $mg.kg^{-1}$ per 24 hours, which could be increased to 10 $mg.kg^{-1}$ per 24 hours for persistent apnea. In the trial, 40 % of the infants randomized to caffeine group and 39% of the infants randomized to placebo group continued on the 5 $mg.kg^{-1}$ maintenance dose for the duration of the intervention (personal communication from Dr. Barbara Schmidt). This trial demonstrated several beneficial effects of caffeine, including a reduction in the risk of bronchopulmonary dysplasia, duration of mechanical ventilation and positive airway pressure respiratory support, severe retinopathy of prematurity, and the use of treatments to close a patent ductus arteriosus[17,18]. In addition, at 18–22 months follow-up, caffeine use, compared to placebo, resulted in a lower risk of cerebral palsy and cognitive impairment[18] with benefits in reducing motor impairment persisting into middle childhood[19]. Importantly, this trial found no serious harm with the use of a standard dose of caffeine.

C. Monitoring of Caffeine Levels to Guide Dosing

Caffeine has a wide therapeutic index and the CAP trial did not perform therapeutic drug monitoring of serum caffeine levels. Another study found the majority of preterm infants attain target plasma caffeine levels of 5 −20 mg per dL when treated with a median dose of caffeine citrate of 5.0 mg per kg (range 2.5 to 10.9 mg per kg), with 95% of measures within this range in a cohort of 101 preterm infants, including those with renal or hepatic dysfunction[20]. In another study of 115 preterm infants, there was no association between episodes of apnea and serum caffeine concentrations ($R^2 < 0.001$, P=0.97), although there was a significant, but weak correlation between caffeine concentrations and heart rate ($R^2 = 0.031$, $P = 0.04$).[21]

However, in a commentary in response to the aforementioned study, Gal reported a proportionally improved response in apnea, bradycardia or oxygen desaturation events as

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caffeine levels increased up to a serum concentrations of 40 mg per L, although toxicity in the form of tachycardia also increased with increasing caffeine concentrations[22]. A study by Alur et al. evaluated the association between caffeine concentrations and risk of chronic lung disease and, using receiver operator curves (ROC) and cut-points, suggested a concentration above 14.5 mg per L was associated with a lower chronic lung disease rate[23]. However, the overall area under the ROC curve for this study was low at 0.63.

Routine monitoring of caffeine levels is not recommended by the American Academy of Pediatrics Committee on Fetus and Newborn in their statement on apnea of prematurity.1 A letter in response to this statement described the experience of two authors that targeting of serum caffeine concentrations in the upper normal therapeutic range (15 to 20 mg per L) yields a greater response[24]. The study by Aranda et al. suggested that preterm infants tolerate caffeine concentrations as high as 50 to 84 mg per L based on clinical assessment of short-term cardiovascular and gastrointestinal effects[5] and the study by Lee et al. reported tolerance of levels of 70 mg per L or above and suggested a concentration > 35 mg per L was needed to effectively prevent apnea after extubation[25]. Caffeine toxicity is possible, as case reports of accidental caffeine overdose in premature infants have described acute neurological, gastrointestinal and metabolic consequences[26,27]. In the UK, the National Institute for Health and Care (NICE) guidelines recommend measuring plasma levels when high dose caffeine is used[28] to ensure that a safe plasma level is maintained, although the guidelines do not specify what levels of caffeine are considered safe. It is also important to note that there are other factors that may influence therapeutic response to caffeine, such as heritability of apnea of prematurity[29] and polymorphisms of adenosine receptors[30].

D. Use of Higher Caffeine Doses

Many infants persist with apnea despite caffeine treatment, even with serum concentrations within the target range of 5 to 20 mg per L[20]. Thus, some infants may need plasma levels > 15 mg per L to maximize therapeutic benefit of caffeine[22,23], providing some rationale for the use of higher doses of caffeine to improve therapeutic effect. In this section, we review and summarize data from trials examining the use of higher doses of caffeine citrate. We also summarize data from several meta-analyses that provide pooled effect estimates on reported outcomes among infants randomized to higher vs. lower doses of caffeine in clinical trials.

Multiple studies have evaluated higher vs. lower doses of caffeine citrate, with a variety of dosing regimens with loading doses as high as 80 mg per kg and maintenance doses as high as 20 $mg.kg^{-1}$ per 24 hours (Table 1). The study population has included preterm infants < 30–32 weeks' gestation. Of note, the single center trial by Steer et al.[31] was followed by a multicenter trial of 238 infants that evaluated caffeine dose on extubation success.[32] This study was followed by a report by the same group that included long-term outcomes of the 238 infants from the aforementioned trial plus an additional 49 infants who received caffeine for apnea[33]. All other trials have been conducted at single centers and additional trials from China are not shown in Table 1 but included in a meta-analysis by Chen et al.[34]. The primary outcome of trials has varied, but several had primary outcomes focused on the treatment or prevention of apnea or reduction in extubation failure. Individually, no clinical trials showed

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benefit in the reduction of BPD. One randomized, controlled trial showed an increased risk of cerebellar hemorrhage in preterm infants randomized to high dose caffeine along with the presence of neurobehavioral differences at term-equivalent age including increased tone and abnormal movements[35]. A secondary analysis of this trial also noted potential concern for a higher incidence of seizures and increased seizure burden among infants receiving higher doses of caffeine[36]. Importantly, this study initiated the higher dose of caffeine soon after birth, during a period at which infants are at highest risk of intracranial hemorrhage.

Four meta-analyses have synthesized the findings from the trials comparing higher vs. lower doses of caffeine (Table 2).[34,37–39] One meta-analysis reported a shortened duration of mechanical ventilation (mean difference −1.7 days; 95% CI −2.1, −1.2)37, two reported a decrease in apnea frequency[34,37], three reported a lower risk of extubation failure[34,37,39] and three reported a lower risk of BPD[34,37,38] (Table 2). Of note, the quality of the included studies varied and three of the meta-analyses used GRADE40 to evaluate the certainty of evidence and found all outcomes to have either low or very-low certainty of evidence. Thus, the effect estimates from these meta-analyses should be interpreted with caution. Regarding safety concerns, three meta-analyses reported a higher risk of tachycardia with high-dose caffeine[34,37,39], but no other adverse outcomes were increased with high-dose caffeine. While these meta-analyses suggest benefits from higher doses of caffeine, it is important to consider the quality of the studies and certainty of the evidence as well as the concerns for potential harm with an increased risk of cerebellar hemorrhage[35].

The recommendations on caffeine dosing in current national and international guidelines1,[28,41] are reviewed elsewhere in this Issue.

E. Routine Adjustments of Caffeine Dose

Caffeine clearance in infants increases with postnatal age. In contrast to adults where renal excretion of caffeine is limited to 2.5% of total dose[42], renal clearance accounts of > 85% elimination of caffeine in infants up to one month of age[43] and hepatic elimination of caffeine increases with age as a result of developmental maturity of hepatic cytochrome P-450 monoxygenase system. To account for the increasing clearance of caffeine and the decreasing half-life over the first 8 postnatal weeks, Koch et al. performed pharmacokinetic model simulations to evaluate different dosing regimens that could ensure stable caffeine concentrations44. The authors developed a model that accounted for changes in weight and postnatal age and evaluated three caffeine citrate dosing regimens to maintain caffeine concentrations of at least 15 mg per L: 1) standard dose using a loading dose of 20 mg per kg, followed by 5 $mg.kg^{-1}$ per 24 hours maintenance; 2) high dose, using a loading of 20 mg per kg, followed by 10 $mg.kg^{-1}$ per 24 hours and, 3) an adjusted regimen. The investigators found that a standard dosing regimen resulted in caffeine concentrations falling below 15 mg per L after the second postnatal week, while the high dose regimen remained above 15 mg per L with levels reaching 30 mg per L and above. The adjusted dosing regimen was able to maintain trough caffeine concentrations above 15 mg per L but not generally exceed levels >20 mg per L. The adjustments involved increasing the maintenance caffeine citrate dose by 1 mg per kg every 1–2 weeks, with an increase to 6 $mg.kg^{-1}$ per 24 hours in the second postnatal week, 7 $mg.kg^{-1}$ per 24 hours in the third to fourth week and 8 $mg.kg^{-1}$ per 24

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hours in the fifth to eighth week. The authors also noted that an alternative would be to use a maintenance dose of 10 $mg.kg^{-1}$ per 24 hours initially, although this would lead to caffeine concentrations routinely above the desired range. A retrospective study of 89 neonates found treatment with a maintenance dose of > 7.9 $mg.kg^{-1}$ per 24 hours was associated with fewer clinical interventions (dose adjustment, mini-loading, or maintenance dose increases), compared to infants who received a maintenance dose of ≤ 7.9 $mg.kg^{-1}$ per 24 hours[45]. These data, in addition to the study by Koch et al.44 suggest that empiric increases in caffeine dose might reduce the need to respond to events by accounting for changes in clearance with postnatal age and assuring stable caffeine concentrations for caffeine.

In the concluding sections below, we highlight key practice points informed by the available evidence regarding dosing of caffeine. We also note opportunities for future studies.

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PRACTICE POINTS

- Current evidence supports the safety and efficacy of standard dose caffeine.
- Routine drug level monitoring of caffeine is unnecessary.
- Higher dose caffeine, compared to standard dose, may provide additional benefit in reducing the risk of BPD, but may increase the risk of cerebellar hemorrhage and seizures.
- Additional trials are needed before higher doses of caffeine can be routinely recommended.
- Increasing caffeine citrate by 1 $mg.kg^{-1}$ per 24 hours every 1 to 2 weeks to a goal dose of 8 $mg.kg^{-1}$ per 24 hours may help maintain therapeutic effect.

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RESEARCH DIRECTIONS

- Adequately powered trials are needed to evaluate the safety and efficacy of high dose caffeine (e.g. 20 $mg.kg^{-1}$ per 24 hours) compared to standard dose caffeine (e.g. 5 $mg.kg^{-1}$ per 24 hours). Such trials should include long-term neurodevelopmental assessments.
- Data from future trials may increase or decrease the confidence in the results from existing meta-analyses that a higher caffeine dose, compared to lower dose, reduces the risk of bronchopulmonary dysplasia, while increasing the risk of intracranial hemorrhage.
- Studies are needed to better understand why some infants persist with apnea despite increases in caffeine dose, and to determine how genetics may influence the efficacy of caffeine.

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Table 1.

Characteristics of Randomized Trials of Higher vs. Lower Doses of Caffeine

First author (ref)	Scanlon[46]	Romagnoli[11]	Steer[31]	Steer[32]	Gray[33]	McPherso n[35]	Mohammed[47]	Wan[48]
Year published	1992	1992	2003	2004	2011	2015	2015	2020
Design (sample size)	single center (n=44)[a]	single center (n=37)[b]	single center (n=127)	multicenter (n=234)[c]	multicenter (n=287)[c]	single center (n=74)	single center (n=120)	single center (n=111)
Population, GA, weeks	<31	<32	≤31	<30	<30	≤30	<32	<30
Higher LD	50	10	60, 30 (intermedia te dose)[d]	80	80	80	40	20
Higher MD	12	5	30, 15 (intermedia te dose)[d]	20	20	10	20	10
Lower LD	25	10	6	20	20	30	20	20
Lower MD	6	2.5	3	5	5	10	10	5
Primary study outcome	Apnea	Apnea	Extubation failure	Extubation failure	Cognitive outcome at 1 year	Brain structure by MRI and neurobehavioral outcome at 2 years[e]	Extubation failure, apnea	Extubation failure, apnea

Abbreviation: GA, gestational age; LD, loading dose in mg per kg; MD, maintenance dose in mg.kg^{-1} per day; MRI, magnetic resonance imaging.

[a] Trial also included a theophylline arm.

[b] Trial included a control group and direct comparisons between caffeine dosing arms were not performed.

[c] Studies include overlapping populations. The study by Gray et al.[33] includes 234 infants from the multicenter trial by Steer et al.[32] plus 49 additional infants (190 of whom underwent 12 month follow-up).

[d] Trial includes high, intermediate and low dose arms (doses shown).

[e] A secondary study evaluated seizure burden[36].

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Table 2.

Results from Meta-Analyses of Trials of Higher Vs. Lower Caffeine Doses

Study (ref)	**Vliegenthart 39**	**Brattstrom 37**	**Chen[34]**	**Pakvasa[38]**
Year published	2018	2018	2018	2018
Trials included[a], n	6	6	13	3
Infants studied[a], n	620	816	1515	432
Apnea frequency		**−5.7 (−6.2, −5.2)**[b]	**−1.5 (−2.7, −0.4)**[b]	
Extubation failure	**0.51 (0.37–0.70)**	**0.51 (0.36–0.71)**	**0.50 (0.35–0.71)**	
MV duration, d		**−1.7 (−2.1, −1.2)**[b]		
BPD	0.81 (0.63–1.04)	**0.76 (0.60–0.96)**	**0.79 (0.68–0.91)**	**0.65 (0.43–0.97)**[c]
Death before discharge	0.92 (0.51–1.65)	0.85 (0.53–1.38)	0.74 (0.51–1.09)	
BPD or death	0.89 (0.65–1.21)			
IVH		0.90 (0.63–1.27)	0.98 (0.76–1.27)	
Severe IVH	1.24 (0.65–2.36)	1.41 (0.71–2.79)		
PVL		1.33 (0.48–3.70)	1.35 (0.59–3.07)	
CBL hemorrhage		3.33 (1.00–11.2)[d]		
Abnormal neuroimaging		0.95 (0.75–1.22)		
Seizures		1.47 (0.86–2.50)[d]		
PDA treatment		1.00 (0.66–1.52)[d]		
NEC	0.82 (0.36–1.90)	0.78 (0.39–1.55)	0.54 (0.26–1.12)	
SIP	1.00 (0.22–4.64)[d]			
ROP			0.74 (0.52–1.05)	
Severe ROP	0.60 (0.28–1.29)	0.57 (0.27–1.20)		
Growth ($g.kg^{-1}$ per 24 hours)[b]		−1.1 (−2.4, 0.1)[b]		
Tachycardia	**3.39 (1.50–7.64)**	**2.56 (1.45–4.50)**	**2.02 (1.30–3.12)**	
Electrolyte disturbance			0.75 (0.17–3.28)	
Feeding intolerance			1.13 (0.84–1.51)	
Hypertension			1.75 (0.52–5.89)	
Hyperglycemia	1.92 (0.47–7.94)		0.80 (0.32–1.98)	
Restlessness			1.22 (0.52–2.85)	
Death before 1 year	0.93 (0.47–1.85)			
Major disability	0.58 (0.26–1.25)[d]	0.63 (0.28–1.39)[d]		
Death or disability	1.19 (0.37–3.77)			

Effect estimates are relative risks with 95% confidence intervals in parenthesis, comparing higher vs. lower doses of caffeine, unless otherwise noted. Significant effect estimates noted in boldface.

Abbreviations: MV, mechanical ventilation; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; CBL, cerebellar; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; SIP, spontaneous intestinal perforation; ROP, retinopathy of prematurity.

[a] Number of trials and infants used to pool estimates varied depending on the outcome.

[b] Estimates are mean differences.

[c] Estimate is an odds ratio with 95% confidence interval.

[d] Only 1 study informed this estimate.

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