



Caffeine controversies

Samuel J. Gentle, Colm P. Travers, and Waldemar A. Carlo

Purpose of review

Caffeine use in preterm infants has endured several paradigms: from standard of care to possible neurotoxin to one of the few medications for which there is evidence of bronchopulmonary dysplasia (BPD) risk reduction. The purpose of the review is to analyze this dynamic trajectory and discuss controversies that still remain after decades of caffeine use.

Recent findings

Following concerns for caffeine safety in preterm infants, a large randomized controlled trial demonstrated a reduction in BPD and treatment for patent ductus arteriosus. The lower rate of death or neurodevelopmental impairment noted at 18–21 months was not statistically different at later timepoints; however, infants in the caffeine group had lower rates of motor impairment at 11-year follow-up. The time of caffeine therapy initiation is now substantially earlier, and doses used are sometimes higher than previously used, but there are limited data to support these practices.

Summary

Caffeine therapy for apnea of prematurity (AOP) remains one of the pillars of neonatal care, although more evidence to support dosing and timing of initiation and discontinuation are needed.

Keywords

apnea of prematurity, caffeine, methylxanthines

INTRODUCTION

Apnea of prematurity (AOP), the periodic cessation of respirations in preterm infants, is a common developmental disorder with an incidence that increases with decreasing gestational age [1]. Observational studies have demonstrated associations between apneic events with deficits in cerebral oxygenation [2], increased risk for retinopathy of prematurity [3], and death or disability [4]. The origin of apneic events can be central or obstructive, and most apneic events commonly have features of both. Rather than a pathologic condition, AOP is the physiologic result of immature chemoreception to carbon dioxide and hypoxia [5].

Several interventions decrease apneic event frequency and duration. These include respiratory interventions such as continuous positive airway pressure and pharmacologic therapies such as methylxanthines, which have been used for over 40 years. Meta-analyses of randomized controlled trials prior to 2001 supported the efficacy of caffeine for apnea reduction and a reduction in the need for mechanical ventilation without evidence of significant side effects including tachycardia or feeding tolerance [1]. However, concerns regarding potential long-term harms [6] led to one of the largest and most important randomized controlled trials in preterm

infants, the Caffeine for Apnea of Prematurity (CAP) trial [7]. In addition to safety, other controversies surrounding the therapy include which patients should receive caffeine, when to start and stop therapy, and the optimal dosing.

CAFFEINE MECHANISMS OF ACTION

Caffeine therapy works via several mechanisms including enhancing sensitivity to carbon dioxide via adenosine antagonism, improving diaphragmatic contractility, and increasing muscle tone [8,9]. Adenosine is a neurotransmitter with several physiologic roles including control of arousal and sleep as well as cerebrovascular homeostasis. Stimulation of adenosine receptors leads to inhibition of inspiratory neurons; therefore, antagonism of adenosine receptors is thought to be one of the primary

Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, USA

Correspondence to Samuel J. Gentle, MD, Department of Pediatrics, University of Alabama at Birmingham, 1700 6th Ave S: Suite 9380, Birmingham, AL 35249-7335, USA. Tel: +1 205 934 8793; e-mail: sjgentle@uabmc.edu

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KEY POINTS

- Caffeine is a very effective treatment for AOP.
- In infants with AOP, the use of caffeine is associated with decreased risk for BPD, PDA treatment, and neurological impairment.
- There is little to no evidence from randomized trials for the use of early caffeine (prior to the 3rd day after birth).
- High-dose caffeine reduces extubation failure and may also provide neurodevelopmental benefits.
- Caffeine therapy may be discontinued at around 34–36 weeks postmenstrual age in most infants, although infants born more prematurely may need a longer duration of therapy.

means by which caffeine prevents apnea. Polymorphisms in adenosine receptors may not only predispose certain preterm infants to apneic spells, but also predict responsiveness to caffeine therapy [10]. Clinical data support enhanced cortical cerebral activity following caffeine therapy with potential attenuation of cerebral blood flow and oxygenation [11,12].

Animal studies have shown both beneficial and detrimental effects of adenosine antagonism during hypoxia–ischemia. Adenosine may have a protective role during hypoxic events, which led to concerns that adenosine inhibition might impact neurodevelopment in preterm infants [13]. Adenosine receptors are expressed throughout the brain, including the hippocampus and cerebral cortex, and are increasingly expressed during periods of development [9^a]. As adenosine is produced by ATP degradation, levels of adenosine increase in brain tissue following hypoxia–ischemia due to resultant imbalances in ATP production and consumption. In adult animal models, adenosine antagonism (the pharmacologic effect of caffeine) and adenosine receptor knockouts are associated with increased mortality and brain injury [13]. In contrast, others using neonatal models have observed a reduction in brain injury [14,15] and improved neurobehavioral achievement [16] when adenosine antagonism preceded hypoxia ischemia. These latter studies provide evidence for which there may be potential benefit from adenosine antagonism therapies in AOP.

CLINICAL EVIDENCE FOR SAFETY

Clinical evidence has supported short-term safety of caffeine, but there have been concerns for potential long-term consequences. Meta-analyses

of methylxanthine use in AOP prior to 2001 concluded that reported side effects of caffeine including tachycardia or feeding tolerance were either not present or not statistically different enough to discontinue use [1]. An observational cohort study comparing extremely low birth weight infants receiving theophylline to those who did not suggested that infants exposed to therapy had higher rates of cerebral palsy (CP) [17]. However, differences in several characteristics of infants in the caffeine group compared with those not treated including mechanical ventilation (81.2 vs. 45.9%), birth weight (1106 vs. 1246 g), and gestational age (28.5 vs. 30.2 weeks) indicated that infants treated with caffeine were at higher risk for CP than those not treated. Concerns that caffeine may affect growth potential were based on calorimetry showing increased energy expenditure following theophylline therapy [18]. This was further supported by a small randomized controlled trial ($n = 18$) of caffeine or placebo in preterm infants 28–33 weeks showing higher daily weight gain in infants receiving placebo [19]. In the CAP trial, the caffeine group infants gained less weight during the first 3 weeks after randomization but then caught up by 4 weeks and beyond [7].

As adenosine provides potential brain protective effects during hypoxia–ischemia, the investigators of the CAP trial expressed urgency for a large randomized controlled trial due to the potential ability of methylxanthine therapy to exacerbate hypoxic tissue damage in preterm infants that would otherwise be masked by the baseline risk for adverse outcomes in the population [20]. Infants were eligible if they had a birth weight between 500 and 1250 g at birth, were less than 10 days old, and were considered a candidate for methylxanthine therapy by clinical staff based on the following indications: to prevent apnea, to treat apnea, or to facilitate extubation. Two thousand and six infants were randomized to either receive caffeine therapy or placebo. Prior to use of open methylxanthines, clinicians were instructed to use nonpharmacologic therapies including positive pressure or assisted ventilation.

Because infants were randomized if they met criteria for caffeine treatment and the intention was to restrict caffeine use, we report the outcomes in the placebo group compared with the usual care which was the caffeine group. The placebo group had higher rates of bronchopulmonary dysplasia (BPD) defined as oxygen need at 36 weeks postmenstrual age (PMA) (Table 1), received intubation/mechanical ventilation and oxygen supplementation until a later PMA, and received more postnatal steroids. The placebo group also had higher rates of patent ductus arteriosus (PDA) receiving medical or surgical closure [7].

Table 1. Outcomes from the Caffeine for Apnea of Prematurity trial

Outcome	Caffeine (%)	Placebo (%)	Unadjusted OR (95% CI)	OR adjusted for center (95% CI)
Pharmacologic therapy for PDA closure	29.3	38.1	0.67	0.67 (0.55–0.81)
Surgical PDA closure	4.5	12.6	0.33	0.32 (0.22–0.45)
Bronchopulmonary dysplasia	36.3	46.9	0.65	0.63 (0.52–0.76)
Composite death or disability at 18–21 months	40.2	46.2	0.78	0.77 (0.64–0.93)
Composite death or disability at 5 years	21.1	24.8	0.81 (0.65–1.02)	0.82 (0.65–1.03)
Composite death or disability at 11 years	31.7	37.6	0.77 (0.59–1.01)	0.78 (0.59–1.02)

CI, confidence interval. Adapted from [7,21,22,23*].

Rates of neurodevelopmental impairment (NDI) were examined at various time points after the CAP trial. Infants receiving placebo had higher rates of death or NDI (defined as CP, cognitive delay, hearing loss requiring amplification, and/or bilateral blindness) at 18–21-month follow-up (Table 1) [21]. In addition, infants receiving placebo had worse motor function both at 5 and 11 years of age; however, death or NDI at 5 and 11 years of age did not differ between infants receiving caffeine or placebo (Table 1) [22,23*].

Although the CAP trial proposed to evaluate the potential negative impact of caffeine on neurodevelopment, the results showed that when caffeine is indicated to prevent apnea, to treat apnea, or to facilitate extubation as used in this trial, not giving caffeine resulted in harms including increased risk for BPD, treatment for a PDA, and some long-term neurodevelopmental disabilities. Contrary to animal data suggestive of risk of methylxanthine treatment, this trial showed the benefits of caffeine therapy with nonpharmacologic therapies (including positive pressure or assisted ventilation) compared with nonpharmacologic therapies alone.

WHEN TO START CAFFEINE THERAPY?

In infants treated to prevent apnea, to treat apnea, or to facilitate extubation, is early caffeine beneficial when compared with placebo? An exploratory subgroup analysis by timing of commencement of caffeine in the CAP trial reported that infants receiving caffeine by day 3 after birth had a shorter duration of mechanical ventilation in infants receiving early compared with later caffeine use. However, the analysis was not controlled for clinical indication or level of respiratory support, and there were no differences in major outcomes by timing of treatment [24]. It is possible that infants meeting eligibility criteria earlier were less ill as two of the three indications required the infants to be extubated or about ready to be extubated. A randomized trial of early (1st day) caffeine in 87 preterm infants (23–30

week) found that caffeine did not facilitate extubation or reduce mechanical ventilation but resulted in a trend for increased mortality (caffeine 22% vs. placebo 12%) [25]. A randomized trial of early (first 36 h after birth) caffeine at standard vs. high dose (four times loading and maintenance doses) found increased incidence of cerebellar damage in infants who received high-dose caffeine [26]. A meta-analysis on prophylactic methylxanthine therapy found no benefit in apnea reduction [27].

Several observational studies from neonatal databases have reported differential outcomes between early and late caffeine use. A Canadian Neonatal Network found lower rates of BPD in infants receiving caffeine before day 2; however, infants receiving late caffeine had many factors associated with refractory respiratory failure including higher incidence of high frequency oscillatory ventilation (19.4 vs. 6.2%; $P < 0.01$), postnatal steroid use (28.4 vs. 15.5%; $P < 0.01$), and duration on mechanical ventilation (median of 4 vs. 2 days; $P < 0.01$) [4]. An analysis of a large cohort from the Alere Neonatal Database also reported decreased rates of BPD in preterm infants receiving early caffeine, but similarly those infants receiving late caffeine had higher respiratory requirements of which no adjustments were made, including more days on the ventilator (23.7 vs. 16.7%; $P < 0.001$), longer duration until attempted extubation (10.8 vs. 7.1 days; $P < 0.001$), and increased use of postnatal steroids (13.6 vs. 10.9%; $P = 0.04$) [28]. The largest observational study of early caffeine therapy utilized propensity score matching for many clinical variables including respiratory support, fraction of inspired oxygen, and need for high-frequency ventilation. Analysis showed a lower rate of death or BPD between infants receiving early and late caffeine therapy [28 vs. 34% odds ratio 0.74 (0.69–0.80)] [29], but marked baseline differences and residual biases cannot be completely overcome by this analysis.

Rather than concluding that early caffeine is associated with decreased risk for BPD or death, it

may be more likely that caffeine initiation is delayed in those patients requiring more support. Thus, early caffeine remains a controversial practice as the benefits are limited to observational data, whereas the randomized controlled trials have not reported benefits and harms cannot be excluded, although the trials reporting adverse outcomes were relatively small. The evidence for the timing of the initiation of caffeine is weak. Whereas 20 years ago, the starting time for therapy was an average of 10 days after birth, the majority of preterm infants now start therapy on or before the 2nd day after birth according to a recent retrospective review [29]. As meta-analyses and subgroup analyses have not demonstrated benefit from early or prophylactic caffeine therapy, delaying treatment until caffeine is indicated may be more appropriate.

HOW MUCH CAFFEINE?

Several studies have evaluated dosing of caffeine. The CAP trial used a loading dose of 20 mg/kg followed by maintenance dosing of 5 mg/kg daily which could be increased to 10 mg/kg. Among infants receiving caffeine, 2.3% had their dose reduced due to suspected toxicity, and 9.0% received additional open-label methylxanthines [7]. A retrospective analysis of preterm infants receiving caffeine suggested that infants receiving a dose less than 7.9 mg/kg required additional clinical interventions compared with those infants receiving a higher dose [30].

A randomized trial ($n = 287$) of caffeine for AOP or for preextubation in mechanically ventilated infants born at less than 30 weeks gestation compared a loading dose of 80 mg/kg followed by 20 vs. 20 mg/kg followed by 5 mg/kg daily and assessed cognitive development at 1 year as the main primary outcome [31]. A higher general quotient was found in the high-dose caffeine group ($P = 0.05$). There were no other statistically significant differences, but the point estimates and confidence intervals (CIs) suggest possible clinically important benefits in death or disability at 12 months of age, severe BPD, and cerebral cystic changes or hydrocephalus (Table 2). A limitation of this study is that neurological evaluations at 1 year are not as predictive of outcomes as later evaluations. Conversely, as previously mentioned, a randomized study of early high-dose caffeine reported increased cerebellar hemorrhage in infants receiving high-dose caffeine [26].

In summary, higher doses of caffeine compared with lower doses of caffeine may reduce extubation failure, but high doses early after birth may result in cerebellar injury, although the trials of later use

Table 2. Selected outcomes from the Caffeine Collaborative Study Group

Outcome	20 mg/kg	5 mg/kg	P value
Apneic episodes (median)	4	6	0.05
Moderate to severe BPD (%)	33	45	0.07
Cerebral cystic changes or hydrocephalus (%)	5	11	0.12
General quotient at 12 months (mean)	98	93.6	0.048
Death or disability at 12 months (%)	15.4	24.2	0.16

CI, confidence interval. Adapted from [31].

of high-dose caffeine show potential reduction in adverse neurodevelopmental and other important outcomes.

WHEN TO STOP THERAPY AND DISCHARGE HOME?

The clinical practice of the timing of methylxanthine discontinuation varies widely as trials have not been conducted to address the issue. Furthermore, the PMA at which apnea resolves differs between patients depending on their gestational age at birth [32]. Complete maturation of the respiratory center does not occur until as late as 44 weeks in preterm infants [33], particularly those born at the lowest gestations [34]. In the CAP trial, successful discontinuation occurred at a median of 34 weeks gestation [7]. The general recommendation is to discontinue therapy at a time point following apnea resolution, after which an infant would be apnea free for 5–7 days prior to discharge [35]. Such time points for discharge may differ for infants born at gestational ages less than 26 weeks as epidemiologic data suggest that as many as 13 days of observation may be required before apnea resolution in these infants [34].

There may also be subclinical benefit for extending the duration of caffeine therapy. A randomized trial in which preterm infants on caffeine therapy had either an extended course until 40 weeks PMA or stopped therapy following apnea resolution between 34 and 37 weeks PMA reported that prolonged therapy resulted in fewer episodes of intermittent hypoxia and more time at goal saturation [36].

Given these data, it is appropriate to discontinue caffeine once infants are less symptomatic and of an appropriate maturational age. The appropriate maturational age may vary depending on gestational age at birth with a longer course of caffeine in more premature infants. Discharge decisions based on confidence that AOP has truly resolved should

similarly not only consider PMA but gestational age at birth. Further evidence is needed to determine whether longer courses of caffeine therapy are beneficial.

CONCLUSION

The use of caffeine in combination with respiratory therapies for the treatment of AOP provides many benefits: a reduction in BPD, a reduction in need for PDA treatment, and a potential reduction in NDI. There is limited evidence to use early or prophylactic caffeine for AOP. High-dose caffeine reduces extubation failure and may provide further neurodevelopmental benefit. The timing of caffeine discontinuation depends on gestational age at birth, PMA, and the maturation of an infant's respiratory center.

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Conflicts of Interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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