Caffeine Use in Neonates: Indications, Pharmacokinetics, Clinical Effects, Outcomes

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Educational Gaps

1. Caffeine therapy in the NICU is beneficial and has both short- and long-term benefits, but the optimal time to initiate therapy in premature infants is unclear.
2. There are no objective criteria for determining the appropriate time to discontinue caffeine therapy in infants born preterm.

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Abstract

Caffeine is commonly prescribed in the NICU to treat apnea of prematurity. This review is an update based on current knowledge of the mechanisms of action, pharmacologic properties, clinical effects, and safety of caffeine in the neonatal population. Recent studies of caffeine in the neonatal population confirm its efficacy in treating apnea-related symptoms and reveal additional significant benefits with minimal short-term, and no long-term, adverse effects.

Objectives

After completing this article, readers should be able to:

1. Describe the mechanisms of action of caffeine.
2. Summarize the pharmacokinetics of caffeine treatment.
3. List the established and possible benefits of caffeine therapy in neonates.
4. Describe the short-term adverse effects associated with caffeine use.
5. Summarize the potential incremental benefits of early initiation of caffeine on a prophylactic basis.

Abbreviations

AOP:	apnea of prematurity
BPD:	bronchopulmonary dysplasia
CAP:	Caffeine for Apnea of Prematurity trial
CI:	confidence interval
GER:	gastroesophageal reflux
IH:	intermittent hypoxia
IQ:	interquartile range
PDA:	patent ductus arteriosus
PMA:	postmenstrual age
VLBW:	very low birthweight

Introduction

Initial studies documenting the efficacy of methylxanthines (aminophylline, theophylline, caffeine) for apnea of prematurity (AOP) were published more than 30 years ago. (1) The clinical effects of these methylxanthines are equivalent, and caffeine has now largely replaced aminophylline and theophylline for routine treatment because of its wider therapeutic index and longer half-life that allows once-daily administration. (2) Exclusive use of caffeine in very low birthweight (VLBW) infants increased from 26% of all methylxanthine use in 1997 to 96% in 2010. (3) Caffeine is now one of the most commonly prescribed drugs in the NICU, and has appropriately been described as a "silver bullet" in neonatology. (1)

Several reviews of caffeine therapy in neonates have been published recently. (1)(2) Recent data indicate that initiation of caffeine treatment

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before a postnatal age of 3 days may have incremental beneficial effects on later outcomes, and that higher maintenance doses may be associated with additional benefits without adverse effects. This review of caffeine utilization provides an update of current knowledge, with emphasis on (1) mechanisms of action, (2) pharmacologic properties, (3) clinical effects and safety, (4) optimum maintenance dosing, and (5) effects on later clinical outcomes.

Mechanisms of Action

Acting both centrally and peripherally, methylxanthines stimulate the medullary respiratory centers, increase carbon dioxide sensitivity, induce bronchodilation, and enhance diaphragmatic function, leading to increased minute ventilation, improved respiratory pattern, and reduced hypoxic respiratory depression. (2)(4) In preterm infants, theophylline increased tidal volume due to an increase in inspiratory drive. (2) Other effects of methylxanthines include stimulation of the central nervous and cardiovascular systems, increased catecholamine secretion, enhanced diuresis, and antagonism of prostaglandin activity. (2)

Caffeine is a trimethylxanthine that primarily exerts its effects by blocking adenosine A1 and A2A receptors. Blockage of adenosine receptors leads to important secondary effects on many classes of neurotransmitters, including noradrenaline, dopamine, serotonin, acetylcholine, glutamine, and gamma-aminobutyric acid. (5) Adenosine receptors are present in the brain, heart, blood vessels, kidneys, gastrointestinal tract, and respiratory system. Recent studies suggest that the primary mechanism by which methylxanthines reduce apnea is through antagonism of A2A receptors on GABAergic neurons. (6)(7) The effect of caffeine on carotid body chemoreceptors is less clear, but may be excitatory during early development by blocking adenosine A1 receptors located in nerves innervating the carotid body and resulting in increased respiratory drive. (8) Interestingly, adenosine receptor gene polymorphisms affect susceptibility to AOP and may account for the individual variability to caffeine response. (9)

Pharmacokinetics

Caffeine is metabolized in the liver, and the enzymes responsible for its metabolism mature progressively with increasing gestational age at birth and increasing postmenstrual age (PMA). (2) The N7-demethylation process is the primary caffeine metabolic pathway in premature infants, and girls have a higher rate of caffeine metabolism than boys. (2) There are four cytochrome P450 isoforms, including P450 isoforms of the CYP2C subfamily, which contribute to the metabolism of caffeine in the liver. (10) The 7-N-demethylation is catalyzed nonspecifically, mainly by CYP1A2 and, to a smaller extent, by CYP2C8/9 and CYP3A4. At higher caffeine concentrations, the contribution of CYP1A2 decreases in favor of CYP2C8/9.

Caffeine pharmacokinetic data are limited in VLBW infants. (11) Clearance in infants born preterm is markedly lower and the volume of distribution is higher than at term-equivalent age and beyond. (12) In preterm infants born at a mean gestational age of 29 weeks and receiving caffeine citrate at a dosage of 6 mg/kg per day intravenously, the 25th to 75th percentile range for the serum concentrations was 18 to 23 mg/L in the first 14 postnatal days. At this age, the serum caffeine concentrations were not dependent on PMA, weight, or postnatal age, and remained in a safe and therapeutic range over the ranges of renal and hepatic functions typically found in practice. (11)

In infants born at 24 to 29 weeks' gestation and birthweights of 570 to 1,570 g, oral caffeine was completely absorbed. Clearance increased nonlinearly with increasing postnatal age, whereas volume of distribution increased linearly with increasing weight. (12) The mean elimination half-life was 101 hours. Elimination of caffeine was initially depressed in extremely premature infants and then increased nonlinearly to final assessment at 6 weeks. However, the depressed clearance was not fully explained by body weight, and time-related developmental factors had an important effect on elimination of caffeine, as indicated by a significant impact of postnatal age.

In other studies of premature neonates receiving routine treatment with caffeine, clearance increased with increasing gestational age at birth and higher current weight and postnatal age, especially at more than 28 weeks' gestation. (2) No clinical factors were identified that influenced volume of distribution. Among all infants studied, clearance (L/d) = 0.14 × weight (kg) + 0.0024 × postnatal age (days) (±20%) and volume of distribution = 0.82 L (±24%).

Caffeine Dosing and Levels

The routine dosing for caffeine citrate has been a loading dose of 20 mg/kg (10 mg/kg of caffeine base) followed by a daily maintenance dose of 5 mg/kg. (11) Original approval by the Food and Drug Administration of caffeine for treatment for AOP was based on this dosing regimen. Some studies, however, have reported using higher maintenance dosages of 15 to 30 mg/kg per day. (2)(13) In a recent study, a daily maintenance dose of 20 mg/kg caffeine citrate beginning in the periextubation period was as well tolerated as the comparison dose of 5 mg/kg per day. (14)(15) Most US neonatal centers now use maintenance doses of 5 to 8 mg/kg and occasionally up to

10 mg/kg per day of caffeine citrate for routine therapy during the early postnatal weeks (Table 1). Some international centers use maintenance caffeine citrate doses as high as 20 mg/kg per day, but maintenance doses in excess of 10 mg/kg per day are rare in US NICUs. Treatment is typically discontinued by 33 to 34 weeks PMA, following resolution of clinically apparent AOP-related symptoms. Some centers continue caffeine beyond 34 weeks PMA, although little evidence supports the efficacy of this practice.

Preterm infants at younger postmenstrual ages appear to safely tolerate caffeine concentrations as high as 50 to 84 mg/L. (2)(13) Routine maintenance caffeine doses are typically sufficient to achieve blood concentrations of 8 to 20 mg/L in infants less than 32 weeks PMA. After 32 weeks PMA, however, and especially at >33 weeks, levels will progressively decrease due to increasing caffeine metabolism unless the mg/kg dosage is increased. However, there are no data beyond 33 to 34 weeks PMA to establish the maintenance caffeine dose necessary to achieve a therapeutic blood level. Because clearance of caffeine progressively increases with increasing PMA, at the same maintenance dose per kilogram as at less than 34 weeks, caffeine levels at 36 weeks PMA would likely only be about half of levels achieved at 32 weeks PMA. (12)

Routine measurement of serum caffeine levels has not been shown to be necessary. (11)(16) In a study using a median maintenance dosage of 5 mg/kg per day at a median gestational age of 28 weeks, most plasma caffeine levels were between 5 and 20 mg/L, independent of gestational age, blood urea nitrogen, serum creatinine, or liver enzyme levels. (17)

Therapeutic Benefits

Although caffeine is most commonly used in the NICU to treat AOP-related symptoms and to facilitate extubation (Table 2), there are additional benefits of therapy. The Caffeine for Apnea of Prematurity (CAP) trial, a large, randomized clinical trial, provides the most recent and comprehensive data regarding caffeine and neonatal morbidities. (18)(19)(20) The CAP trial was conducted from 1999 to 2004 and randomized 2006 infants weighing 500 to 1,250 g to caffeine or placebo within the first 10 days of age, and treatment was continued until therapy was no longer clinically necessary. The caffeine group received a loading dose of 20 mg/kg of caffeine citrate and an initial maintenance dose of 5 mg/kg per day. The median age at initiation of treatment was 3 days (interquartile range [IQR] 2–5), the median duration of therapy was 37 days (IQR 24–46), and the median PMA at last dose was 34.4 weeks (IQR 33.0–35.9). (19) Specific results of the CAP trial are summarized in the relevant following sections.

Apnea of Prematurity

Apnea-related symptoms occur in as many as 85% of premature infants born at less than 34 weeks' gestation. (2) The Cochrane review of the six trials evaluating the use of methylxanthines (three trials of caffeine) concluded that methylxanthines were effective in reducing the frequency of apneic events and the use of mechanical ventilation. (21) Caffeine had a relative risk of treatment failure of 0.46 (95% confidence interval [CI], 0.27–0.78). (22) The CAP trial, already described, was not designed to directly assess the effectiveness of caffeine for the treatment of apnea-related symptoms but the post hoc analysis showed that infants treated with caffeine to prevent or treat apnea-related symptoms had better clinical outcomes. (19)(20)(23) The association of caffeine with improved outcomes combined with its better safety profile led the Cochrane reviewers to conclude that caffeine is the "preferred drug" for the treatment of AOP. (21)

Several studies have evaluated the efficacy of caffeine as prophylaxis to prevent apnea-related symptoms. Two studies, randomizing a total of 104 infants to caffeine or placebo, did not find any differences in the numbers of infants experiencing

Table 1. Recommendations for Caffeine Dosing

Age (PMA)	Usual Dosing, mg/kg*	Alternative Option, mg/kg*
Birth to 34 wk		
Loading dose	20	Up to 80
Maintenance dose (once daily)	5–10 (Usually start at 5–8, increase to maximum of 10 as needed)	Up to 20
Maintenance dose after 34 wk	None established	Not studied

There is no known minimum gestational age at birth for treatment. Age at initiation of treatment is variable, but typically within the first postnatal week. Treatment is typically discontinued following resolution of clinically apparent apnea of prematurity-related symptoms, hence by 33–34 weeks postmenstrual age. Please see text for references.
*All doses refer to caffeine citrate. The caffeine base dose is 50% of the caffeine citrate dose. Recommended doses are identical for parenteral and oral administration.

Table 2. Therapeutic Effects of Caffeine in Infants Born Preterm

Established benefits

1. Treats apnea of prematurity (AOP)
2. Facilitates extubation, with shorter duration of intubation and noninvasive respiratory support
3. Reduces incidence of bronchopulmonary dysplasia/chronic lung disease
4. Decreases need for treatment of patent ductus arteriosus
5. Improves motor function and visual perception at 5-year follow-up
6. Reduces severity of retinopathy of prematurity

Possible or apparent benefits

1. Prevention of AOP-related symptoms, including intermittent hypoxia
2. Prevention of postoperative apnea in preterm infants undergoing general anesthesia
3. Prevention of apnea associated with viral bronchiolitis in young infants
4. Induction of anti-inflammatory cytokine profile
5. Incremental overall benefits if treatment initiated before 3 days of age

Adverse effects

1. Short-term: Mild transient symptoms, including tachycardia, irritability, diminished weight gain
2. Long-term: None known

Unknown

1. Potential benefits of extended duration of treatment after resolution of apparent apnea-related symptoms after 33–34 weeks postmenstrual age (PMA)
2. Potential adverse consequences of extended duration of treatment after resolution of apparent symptoms after 33–34 weeks PMA

apnea, bradycardia, and hypoxemic events, or in the use of positive pressure ventilation. (24) However, these studies relied on bedside reporting of apnea and less sophisticated monitoring techniques to define hypoxemic events. A recent study comparing caffeine and theophylline showed that caffeine prophylaxis appeared to control apnea in infants at risk but not initially symptomatic, but after the first week of treatment, the benefits of caffeine and theophylline were comparable. (16) Although the current Cochrane review concludes that the available evidence does not support the use of caffeine as prophylaxis to prevent apnea, the CAP trial and the other benefits of early caffeine therapy with minimal risk, as discussed later in this article, justify the use of early caffeine prophylaxis in premature infants. (24)

Postoperative Apnea

Infants born prematurely, especially those with a history of AOP or chronic lung disease, are at increased risk for postoperative apnea, associated hemoglobin oxygen desaturation, and bradycardia following administration of general anesthesia. (25) Several small clinical trials of caffeine administration at doses of 5 to 10 mg/kg during or immediately after induction of anesthesia revealed a reduction in postoperative apnea. (26) Because caffeine has minimal adverse effects at these doses, caffeine is often administered to preterm infants to prevent postoperative apnea after general anesthesia.

Apnea-Related Symptoms in Other Clinical Conditions

Caffeine therapy has been used to manage other forms of apnea and related symptoms in infants. Apnea associated with Arnold-Chiari malformation has been successfully treated with caffeine. (27) In addition, caffeine may play a role in the management of infants with viral bronchiolitis, including its development secondary to respiratory syncytial virus infection. Young infants with bronchiolitis are at significant risk for apnea, especially if born prematurely. Several small case series have reported reduction of bronchiolitis-related apnea with administration of caffeine, (28) but this has not been studied in the context of a randomized controlled trial. Similar to earlier results with theophylline, caffeine has also been used successfully to correct later apnea-related symptoms in infants at risk for, or having already experienced, an apparent life-threatening event requiring intervention. (29)

Extubation

The Cochrane review of the effects of prophylactic methylxanthine treatment to facilitate weaning from mechanical ventilation and extubation concluded that treatment results in a significant reduction in failure of extubation within 1 week (relative risk 0.48, 95% CI 0.32–0.71). (30) The CAP trial did not report directly extubation success rates, but the caffeine group had younger PMAs at last use of oxygen therapy, positive pressure ventilation, and endotracheal intubation. (19) A randomized, double-blind trial of 3 different maintenance dosing regimens of caffeine citrate (3, 15, and 30 mg/kg) for periextubation management of 127 infants born at less than 32 weeks' gestation revealed no difference in extubation failure between groups, but infants in the 2 higher dose groups had significantly less documented apnea compared with the lowest dose group. (13) Another trial by the same investigators comparing maintenance dosing regimens of

20 and 5 mg/kg per day of caffeine citrate for periextubation management showed a significant reduction in extubation failure in the high-dose group (relative risk 0.51, 95% CI 0.31–0.85). (15) In addition, in the subgroup of infants with a gestational age of less than 28 weeks at birth, the duration of mechanical ventilation was significantly less in the high-dose group. There were no incremental adverse effects of the higher dose and no longer-term adverse effects were observed during the first year of life. (14)(15)

The mechanisms for improved extubation success rates are not well understood. A recent study in preterm infants assessing respiratory muscle function showed improvements in functional residual capacity, maximum pressures generated during occlusions at end inspiration and expiration, and compliance, and decreased respiratory system resistance after caffeine administration. (31) These results suggest that caffeine improves respiratory muscle strength, which may facilitate weaning from mechanical ventilation.

Lung Function and Bronchopulmonary Dysplasia

Caffeine improves lung function by increasing central respiratory drive and diaphragmatic activity, as well as by inducing diuresis and bronchodilation. In prematurely delivered baboons with respiratory distress syndrome, early caffeine therapy in combination with surfactant reduced airway resistance and improved lung compliance, ventilator efficiency index, and arterial/alveolar pO_2 ratio in the first 24 hours after birth. (32) A recent study in premature infants showed that caffeine improved respiratory muscle strength. (31) In the CAP trial, caffeine treatment was associated on average with 1 week less of endotracheal intubation, positive pressure ventilation, and supplemental oxygen use, and less use of postnatal corticosteroids. (19) In addition, the rates of bronchopulmonary dysplasia (BPD) were significantly lower in the caffeine group compared with in the placebo group (36.3% versus 46.9%; adjusted odds ratio, 0.63; $P < .001$). (19) Of note, the benefits of caffeine were most significant when treatment was initiated in the first 3 days after birth. (23) This benefit has also been evident in two recent retrospective cohort studies in which caffeine therapy in the first 3 days of age was associated with approximately one-half the incidence of BPD compared with later initiation of therapy. (3)(33)

Intermittent Hypoxia

Intermittent hypoxia (IH) is defined as brief, repetitive cycles of decreased hemoglobin saturation from a normoxic baseline followed by reoxygenation and return to normoxia. IH occurs commonly in premature infants but data confirming the clinical significance of IH in neonates and early infancy are limited. There is an association between IH and severity of retinopathy of prematurity. (34) Later assessments of neurodevelopmental outcome have shown impairments associated with frequent recurrent decreases in hemoglobin oxygen saturation at term equivalent age and in early infancy. (35)(36) In a recent study of preterm infants nearing NICU discharge, caffeine significantly reduced the number of IH episodes, especially in infants at 35 to 36 weeks PMA. (37) Whether extended duration of caffeine treatment in VLBW infants to term-equivalent age has any later adverse effects, or any improved long-term benefits due to reductions in extent of IH, requires further study.

Cardiovascular Effects and Patent Ductus Arteriosus

Methylxanthines increase heart rate, heart rate variability, stroke volume, and blood pressure. (38) In adults, tolerance to the cardiovascular effects of caffeine usually develops within a few days, but it is not known if the same phenomenon occurs in premature infants. Heart rate alone cannot be used to predict toxic drug levels, and high drug levels will not necessarily cause tachycardia. (2)

In the CAP trial, infants in the caffeine group required less intervention for PDA closure compared with infants in the placebo group (29% versus 38%; $P < .001$; adjusted odds ratio 0.67). (19) Moreover, only 4.5% of infants in the caffeine group required PDA ligation compared with 12.6% in the placebo group ($P < .001$; adjusted odds ratio 0.32). (19) Two retrospective studies found that early caffeine therapy within the first 3 days of age was associated with fewer infants requiring treatment for PDA compared with later initiation of therapy. (3)(33) The beneficial effects of caffeine on PDA closure may be related to enhanced diuresis and antagonism of prostaglandin activity. (2)

Central Nervous System Effects and Neurodevelopmental Outcomes

Adenosine is critical for maintaining ATP levels, especially in the brain. During hypoxia and inflammation, adenosine levels in brain tissue increase dramatically. Adenosine protects the brain during experimental hypoxic-ischemic injury in animal models, and activation of adenosine A1 receptors protects against excitotoxic (glutamate) injury. (2) Acute caffeine administration would thus be expected to interfere with the normal neuroprotective effects of adenosine, and in animal models, short-term exposure to caffeine often alters developmental processes and worsens neuronal injury. (2)(39) Chronic caffeine intake, however, appears to

have a neuroprotective effect, presumably by up-regulating adenosine A1 receptors. (40) In P3–P12 mouse pups (equivalent to third trimester of human pregnancy), adenosine A1 receptor activation contributed to hypoxia-induced reduction in cerebral myelination and ventriculomegaly. (41) Caffeine treatment attenuated the effects of hypoxia, presumably through blockade of adenosine A1 receptors. (42) Additionally, caffeine altered the morphology of neuronal synapses and increased the size of dendritic spines. (43)

Caffeine is a generalized central nervous system excitant. Acute neurologic effects of methylxanthine administration included jitteriness, tremor, and hypertonia. (2) Several small studies evaluating sleep architecture in preterm infants have yielded conflicting results on the effect of caffeine on sleep organization. (44)(45) In a recent study in preterm infants, amplitude-integrated electroencephalography amplitudes increased after caffeine administration, but the clinical implications of this increased cerebral cortical activity are unknown. (46)

The effect of caffeine on cerebral hemodynamics has been extensively evaluated. Several studies have shown reductions in cerebral blood flow after caffeine administration, (47)(48) although other studies have found no such effect. (49) In the CAP trial, the rates of intraventricular hemorrhage and periventricular leukomalacia did not differ between the caffeine-treated and placebo groups. (19)

Early studies suggested that caffeine treatment in the NICU was not associated with adverse long-term outcomes. (2) The CAP trial reported that caffeine therapy from a median age of 3 days until 34 weeks PMA in infants weighing less than 1,250 g at birth reduced the likelihood of death, clinical disability, or neurocognitive impairment at 18 months PMA. The primary outcome of death or survival with a significant neurodevelopmental disability occurred in 40.2% of infants in the caffeine group compared with 46.2% of infants assigned to the placebo group (adjusted odds ratio, 0.77; $P = .008$). (20) Subsequent follow-up of the CAP trial infants at 5 years revealed no difference in the composite outcome of death or severe impairment, but there was statistically significant improvement in motor coordination and visual perception in the caffeine-treated group. (18) Furthermore, these improvements in motor function were associated with improved cerebral white matter microstructural development on magnetic resonance imaging at term equivalent age. (50)

The CAP trial was not designed to assess mechanisms for the observed improvements in later neurodevelopment. However, the observed neuroprotective benefits of caffeine could possibly be related to reduced incidence and severity of IH due to its respiratory stimulatory effects and/or to direct neuroprotective mechanisms.

Retinopathy of Prematurity

In the CAP trial, severe retinopathy of prematurity occurred in 5.1% of the caffeine-treated group versus 7.9% of the placebo group (adjusted odds ratio 0.61, 95% CI 0.42–0.89). (20) The authors speculated that the reduction in severe retinopathy of prematurity resulted from shorter duration of positive airway pressure and supplemental oxygen. In addition, however, intermittent hypoxia has been associated with severe retinopathy of prematurity and caffeine has been reported to decrease extent of intermittent hypoxia. (34)(37)

Other Effects

Oxygen Consumption and Growth

Infants born at 28 to 33 weeks' gestation and treated with caffeine had increased oxygen consumption and energy expenditure over a 4-week period and the daily weight gain was significantly less compared with a control group. (2) The CAP trial found similar effects on weight gain initially, with caffeine-treated infants gaining significantly less weight during the first 3 weeks after randomization. (19) By 4 weeks after randomization, however, there was no difference in weight gain, and at 18 to 21 months, the mean percentiles for weight, height, and head circumference did not differ between infants in the caffeine and placebo groups. (20) In a study comparing maintenance caffeine citrate doses of 5 and 20 mg/kg per day, infants randomized to the higher dose required longer time to regain birthweight, but the mean difference was only 1.9 days (14.8 vs 12.9 days). (15)

Renal Effects

Methylxanthines induced diuresis by increasing renal blood flow and glomerular filtration. Later studies in preterm infants confirmed the diuretic effect of caffeine, and also revealed a significant increase in creatinine clearance and urinary calcium excretion. Caffeine did not affect serum sodium, potassium, calcium, or phosphorus concentrations. (2)

Gastrointestinal Effects: Reflux and Necrotizing Enterocolitis

Methylxanthines may worsen gastroesophageal reflux (GER) by increasing gastric secretions and relaxing lower esophageal sphincter tone by enhancement of intracellular cyclic AMP levels. (2) In studies completed

in the late 1980s, approximately half of the infants treated with methylxanthines exhibited an increase in reflux time during esophageal pH monitoring that was independent of plasma xanthine concentration and resolved after stopping therapy. (2) These physiologic studies generated concern among some neonatal clinicians. However, symptoms attributable to GER are common in preterm infants and correlate poorly with proven GER. No study has shown worsening of GER symptoms related to caffeine treatment.

Several studies have documented a reduction in mesenteric blood flow velocities in preterm infants after administration of a loading dose of 25 to 50 mg/kg caffeine citrate. (2) (47) However, a recent study using a loading dose of 10 mg/kg caffeine base (equivalent to 20 mg/kg caffeine citrate) revealed no significant changes in superior mesenteric artery flow velocities. (51) One trial of caffeine therapy for apnea in preterm infants reported a trend toward more necrotizing enterocolitis in the caffeine group compared with the placebo group, although it was not statistically significant. (22) In the CAP trial, however, the incidence of necrotizing enterocolitis was similar in the two groups: 6.3% in the caffeine group compared with 6.7% in the placebo group ($P = .63$; adjusted odds ratio 0.93). (19) Likewise, the incidence of necrotizing enterocolitis was not increased with a maintenance dose of 20 mg/kg per day of caffeine citrate compared with 5 mg/kg per day. (15)

Inflammation

Adenosine receptors are expressed on immune cells. Caffeine therapy has been shown to modulate immune cell functions in vitro by adenosine receptor antagonism. (52) A recent study in preterm infants born at <31 weeks' gestation reported that caffeine treatment induced changes in the cytokine profile. (53) Caffeine levels within the therapeutic range of 10 to 20 mg/L were associated with an anti-inflammatory profile (decreased concentrations of interleukin-6 and tumor necrosis factor-α, increased concentrations of interleukin-10), whereas caffeine levels above 20 mg/L were associated with a proinflammatory profile. (53) This anti-inflammatory cytokine profile may contribute to the reduced incidence of BPD observed in caffeine-treated infants in the CAP trial, (19) but the clinical implications of the proinflammatory profile at higher caffeine levels are unknown and are not associated with any known adverse consequences.

Adverse Effects and Toxicity

The CAP trial did not reveal any significant short- and long-term adverse effects of caffeine therapy in the NICU. (18)(19)(20) Case reports of accidental caffeine overdose in premature infants have described a variety of acute neurologic, cardiovascular, and metabolic abnormalities. (54) Neurologic symptoms associated with an overdose included agitation, irritability, tremor, opisthotonus, and hypertonia, as well as tonic-clonic movements and nonpurposeful jaw and lip movements representative of seizure activity. Cardiorespiratory signs of caffeine toxicity included tachycardia and tachypnea.

Cost-Effectiveness

An economic analysis of the CAP trial showed that caffeine therapy is cost-effective in premature infants. (55) In comparison with placebo treatment, the mean cost per infant was reduced by $9,039 (Canadian dollars) in the caffeine group, and "cost-effectiveness analysis showed caffeine to be a dominant or 'win-win' therapy … caffeine-treated infants had simultaneously better outcomes and lower mean costs. These results were robust to a 1,000% increase in the individual resource items, including the price of caffeine citrate." (pg e146) (55).

Conclusions

Caffeine is widely used in the NICU to treat or prevent apnea-related symptoms and facilitate weaning from mechanical ventilation. Published data document that caffeine is safe, cost-effective, has significant benefits for premature infants, and is well tolerated at all doses used. Based on the overwhelming positive results from the CAP trial with no evidence of harm, VLBW infants should routinely receive caffeine therapy, in particular if birthweight is less than 1,250 g. Importantly, emerging evidence suggests that early caffeine therapy initiated before 3 days of age may improve neonatal outcomes compared with later initiation, but these findings need to be validated in randomized prospective studies of caffeine prophylaxis.

Caffeine levels do not need to be obtained as part of routine clinical management.

Routine clinical caffeine treatment is typically discontinued by 33 to 34 weeks PMA, following cessation of overt apnea-related symptoms. The longer-term safety and efficacy of extended caffeine treatment beyond the age at which symptomatic apnea has resolved, and the optimal dose to use, are unknown at this time but merit further study.

Note: The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Army, Department of Defense, or the U.S. Government.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the management of apnea of prematurity.
- Know the effects of various therapeutic measures, including use of drugs (eg, indomethacin, caffeine, dopamine) on cerebral blood flow.

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NeoReviews Quiz
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1. Which of the following is a physiologic response to caffeine in preterm infants?
   A. Decrease in carbon dioxide sensitivity.
   B. Stimulation of the medullary respiratory centers.
   C. Inhibition of bronchodilation.
   D. Decreased minute ventilation.
   E. Promotion of prostaglandin activity.

2. A 24-weeks'-gestational-age male infant was started on caffeine therapy on the second day after delivery and is now 5 weeks old. Which of the following statements is true regarding caffeine therapy dosing for this patient?
   A. The dosing should be based on the gestational age and birthweight at the time of delivery and remain constant until it is discontinued.
   B. Compared with similar female infants, this patient is likely to have higher rate of caffeine metabolism due to relatively increased N7-demethylation activity.
   C. Caffeine clearance in preterm infants is considerably higher than in term infants.
   D. If the patient is still experiencing apnea, the dosing should remain intravenous until improvement is clearly seen, as oral absorption is likely to be suboptimal for this infant.
   E. The volume of distribution of caffeine increases linearly with increasing weight.

3. A female infant born at 26 weeks' gestational age with birthweight of 900 g who was on mechanical ventilation for the first week after delivery is now 8 weeks old. She has been on caffeine therapy since 2 days after delivery and is now in room air. Which of the following is true regarding the potential impact of caffeine on this patient?
   A. Caffeine is likely to have reduced the frequency of apnea events in this patient compared to if she had received no treatment.
   B. Caffeine treatment is unlikely to have had any effect on duration of mechanical ventilation for this patient.
   C. The impact on duration of ventilation of caffeine is an all or none effect and dosing regimen would not have any significant influence on clinical course.
   D. The effect of caffeine for this type of patient is purely neurological at the level of the brainstem, and does not have any relationship to lung function.
   E. Although the patient is in room air at this time, an observed adverse effect of caffeine has been an increase in chronic lung disease in recipients.

4. A 4-day-old 29-weeks'-gestational-age infant was given his first caffeine dose yesterday and is now on maintenance dosing. He is noted to have a heart rate ranging from 180 to 220. Which of the following statements regarding caffeine and cardiovascular effects is true?
   A. The absence of tachycardia in a patient receiving caffeine is a good indicator of safe levels for treatment.
   B. Although caffeine may have some clinical benefits, one potential adverse effect is increased risk of the requirement for dopamine or epinephrine for hypotension.
   C. A high heart rate in this patient is a definitive indicator of a toxic caffeine level.
   D. Caffeine treatment has been associated with decreased likelihood of patent ductus arteriosus requiring treatment.
   E. Tachycardia in this patient is closely related to brain injury and caffeine should be discontinued.

5. You are talking to the mother of a 24-weeks' gestational age infant who is worried about the potential side effects of caffeine on the brain. Which of the following statements is true and may help inform the mother during counseling?
   A. Caffeine in small spurts is unlikely to have any adverse effect, but chronic intake may cause adverse neurologic outcomes.
   B. At the dosing used for preterm infants, caffeine specifically stimulates the breathing center of the brain, but has no impact on the general central nervous system.
   C. Several studies have demonstrated fairly conclusively that caffeine reduces the incidence of intraventricular hemorrhage and periventricular hemorrhage compared with placebo.
   D. The Caffeine for Apnea of Prematurity (CAP) trial, a large randomized trial on caffeine therapy, demonstrated that caffeine therapy for premature infants reduced likelihood of death, but had no effect, either positive or negative, on neurocognitive outcomes at 18 months of age.
   E. In the CAP trial, there were lower rates of severe retinopathy of prematurity in the caffeine-treated group compared with the placebo group.

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