

eNeonatal Review

Jointly Presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing

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October 2006 VOLUME 4, NUMBER 2

Thanks and Congratulations...

We at eNeonatal Review would like to congratulate Daniel M. McCormick, a respiratory therapist at the Dartmouth-Hitchcock Medical Center in Lebanon, NH, for being the winner of an iPod Shuffle for our online Podcast Survey, and thanks to all of you who participated.

92% of you said that the podcast either greatly or somewhat enhanced their knowledge on the June 2006 edition on the subject of birth injuries. Because of your feedback, we are happy to announce that we will offer more podcasts in 2007.

In this issue...

Aminophylline and, more recently, caffeine have been used extensively for prevention of apnea in premature infants. Recent reports indicate that early use of caffeine results in reduced incidence of BPD. Also, caffeine dosages higher than the usual apnea dose have been shown to result in a doubling of the rate of successful extubation compared to normal apnea doses. Nevertheless, caffeine has adverse effects including reduced fetal and postnatal growth velocity, increased metabolism, and reduced cerebral and intestinal blood flow. While these changes have not been associated with observed adverse events, long-term studies have not been published.

In this issue we take a new look at an old remedy, reviewing several recent studies on the effectiveness and potential risks of caffeine use in neonates.

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Guest Editors of the Month

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Expiration Date
October 19, 2008

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Faculty Disclosure: Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

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Faculty Disclosure: Dr. Lehmann has indicated a financial relationship with Eclipsys Corporation.

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Faculty Disclosure: No relationship with commercial supporters.

Unlabelled/Unapproved Uses:

This presentation will include off-label and unapproved uses of caffeine based on a scientific literature review.

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Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CE activity.

At the conclusion of this activity, participants should be able to:

- Describe the effectiveness of caffeine usage for new purposes, including extubation and BPD prevention
- Discuss current data regarding the potential for adverse effects, especially for higher dose therapies
- Integrate the data presented into current treatment paradigms for using caffeine in ventilated VLBW infants

Commentary

In the current issue we review new information about an old friend that is used quite frequently to ameliorate apnea in premature infants. Three topics are highlighted: 1) new information regarding caffeine effects on outcomes other than apnea; 2) the effects of high dose caffeine when given to prevent reintubation; and 3) metabolic and blood flow changes following caffeine loading doses. These themes were chosen because the results of recently published trials are likely to further increase our usage of caffeine in premature infants. However, we continue to be blissfully unaware of adverse effects and their mechanisms that may temper our enthusiasm for this drug.

Of great interest are the results of the Caffeine for Apnea of Prematurity Trial Group (Schmidt et al), who found a significant decrease in BPD among infants treated with caffeine for apnea of prematurity. This decrease is likely the side effect of an earlier ability to extubate ventilated infants, resulting in decreased

ventilator/endotracheal tube injury. This would result in diminished need for later CPAP and oxygen usage, as well as reduced blood loss for laboratory tests. While these effects may account for the observed improvement in outcome for the caffeine treated patients, this trial also raises the issue of reduced growth among the treated infants.

Another positive effect of caffeine use is found in the two reports by Steer et al, who reported a reduction in the reintubation rate when large doses of caffeine were administered in the periextubation period. These results clearly demonstrate that loading and maintenance doses 3 to 4 times that of the dosage used for apnea of prematurity halves the incidence of reintubation. This is an unexpected finding despite the fact that many neonatologists already recommend caffeine administration at the time of extubation, a belief based largely on the logic that the caffeine will reduce the incidence of apnea. However, the larger dose used in these studies clearly demonstrates a greater beneficial effect in comparison with the usual apnea prevention dose, without increased incidence of recognized short-term adverse events. However, the Caffeine for Apnea Group also found a one week reduction in ventilatory duration VLBW infants similar to the Steer et al. findings, despite using a lower dose. The differences are that the Caffeine for Apnea group was using a non-treated control and Steer et al were comparing a conventional low dose with a higher dose. While the mechanism of this beneficial effect was not studied by these two groups, other human and animal studies have shown that aminophylline increases diaphragmatic EMG activity during fatigue in piglets⁽¹⁾ and that aminophylline also causes earlier contraction of upper airway muscles in premature humans⁽²⁾. This latter effect would serve to reduce inspiratory resistance and improve tidal volume.

An old saying is "there is no free lunch". When visiting old friends such as caffeine, we should remember this aphorism even though we tend to use this drug in virtually all premature infants. Despite the benefits of caffeine, the cost may be the slow weight gain reported by Schmidt et al and Steers et al. While this effect was found to be generally short-lived, its cause is likely due to the higher metabolism and energy expenditure associated with caffeine use as demonstrated by Bauer et al (who also showed decreased weight gain). Whether or not we should be increasing caloric intake at the time of caffeine introduction remains speculative, but could have its own cost if increased enteral feeding results in adverse gastrointestinal outcomes. Indeed, the short-lived nature of the slow weight gain may be overcome by compensatory increases in caloric intake ordered by the caregivers. At present, without this increase in caloric intake, the reviewed studies showed no increase in NEC incidence associated with caffeine administration, despite the reduction in intestinal blood flow reported by Hoecker. The increased incidence of SGA babies from mothers with high caffeine intakes, as reported by Vik et al, tends to corroborate the growth effect of postnatal caffeine, and raises another issue to question mothers about regarding diagnostic investigation of small for gestational age infants. The potential for unrecognized "cost" when using the higher dose caffeine would seem to be even greater, indicating, at least, that the duration of higher dose therapy should be limited to the periextubation period until further studied. Does prudence dictate not using the higher dose until further trials are available?

References:

1. Mayock, D. E., et al. [The effect of aminophylline on diaphragm blood flow in the piglet](#). *Pediatr Res.* 26.3 (1989): 196-99.
2. Eichenwald, E. C., et al. [Developmental changes in sequential activation of laryngeal abductor muscle and diaphragm in infants](#). *Journal of Applied Physiology* 73 (1992): 1425-31.

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CAFFEINE REDUCES INCIDENCE OF BPD

Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W; Caffeine for Apnea of Prematurity Trial Group. **Caffeine therapy for apnea of prematurity.** *N Engl J Med.* 2006 May 18;354(20):2112-21.

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In a study of the short and long term benefits of caffeine on very low birth weight (VLBW) infants, Schmidt et al from the Caffeine for Apnea of Prematurity Trial Group randomly assigned more than 2000 infants with birth weights between 500g and 1200g to receive caffeine (20 mg/kg caffeine citrate bolus followed by 5-10mg/kg/d maintenance) or placebo in the first ten days of life. The study drug dose was adjusted weekly based on weight. To maintain blinding, blood caffeine levels were not obtained and the study drug titration was determined by clinical assessment of signs alone. The study drug was discontinued when the patient no longer needed caffeine for apnea of prematurity.

2006 infants underwent randomization (1006 treatment, 1000 placebo). Both groups received the first study drug dose at a median postmenstrual age (PMA) of 28 weeks and were weaned from the study drug by 35 weeks; the median number of treatment days was 37 in the caffeine and 36 in the placebo group. The investigators found that infants in the placebo group were statistically more likely to be switched to open-label methylxanthines. In the caffeine group, last use of an endotracheal tube, positive airway pressure, and supplemental oxygen were all discontinued one week earlier, and doxapram, postnatal corticosteroids, and red cell transfusions were used significantly less frequently.

The rates of death, brain injury, retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC) did not differ between the groups. However, using the definition of supplemental oxygen use after 36 weeks PMA, the incidence of bronchopulmonary dysplasia (BPD) was significantly lower in the caffeine group. (36.3% vs. 46.9%; Adjusted Odds Ratio (AOR) 0.63). During the first three weeks after the study drug initiation, infants in the caffeine group gained less weight. While this finding was statistically significant, the clinical differences were small (13 - 26 grams difference) and disappeared in weeks 4-6. In a post-hoc analysis, the authors found that infants in the caffeine group were significantly less likely to receive medical (AOR 0.67, 95% CI (0.55-0.81), $P < 0.001$) or surgical treatment (AOR 0.32, 95% CI (0.22-0.45), $P < 0.001$) for a patent ductus arteriosus (PDA).

While the benefits of caffeine use in the reduction of apnea of prematurity have been well established, the authors conclude that caffeine has additional and significant short-term benefits in VLBW infants, most notably the reduction of BPD incidence. Further, while safety concerns have been raised in the past with the use of caffeine, this study did not find an effect on death, NEC, brain injury or ROP; the only observed side effect was a temporary effect on weight gain. However, the authors caution against over-interpretation of the post-hoc finding of PDA reduction in the caffeine group, since echocardiograms were not performed routinely as part of the study protocol.

Long-term follow up on a composite of death, cerebral palsy, cognitive delay, deafness or blindness at 18-21 months is currently in progress, with expected completion by December of 2006.

CAFFEINE REDUCES THE INCIDENCE OF EXTUBATION FAILURE

Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG. **Periextubation caffeine in preterm neonates: a randomized dose response trial.** J Paediatr Child Health. 2003 Sep-Oct; 39 (7): 511-5.

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Steer P, Flenady V, Shearman A, Charles B, Gray PH, Henderson-Smart D, Bury G, Fraser S, Hegarty J, Rogers Y, Reid S, Horton L, Charlton M, Jacklin R, Walsh A; Caffeine Collaborative Study Group Steering Group. **High dose caffeine citrate for extubation of preterm infants: a randomized controlled trial.** Arch Dis Child Fetal Neonatal Ed. 2004 Nov; 89 (6): F499-503.

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The two articles by Steer et al report the effects of caffeine on extubation. The first, with data collected 1993-1995, reports on a randomized double-blind trial performed at an Australian maternity teaching hospital of

three dose regimens of caffeine citrate (3, 15 and 30 mg/kg) for periextubation management. 127 infants of 31 weeks gestation or less (without congenital anomaly, sepsis, major neurologic condition, Grade III/IV intraventricular hemorrhage or previous exposure to methylxanthines), who received mechanical ventilation (≥ 48 hrs but < 28 days), were randomly assigned to one of the three regimens. Infants in the three groups were similar with regard to gestational age, birth weight, age, days of mechanical ventilation, gender, presence of respiratory distress syndrome, and the use of surfactant and antenatal steroids.

A loading dose of caffeine citrate (6, 30 or 60 mg/kg) was administered intravenously (IV) with maintenance doses (3, 15 or 30 mg/kg IV or enterally) at 24 hr intervals for 6 days, with extubation to nasopharyngeal continuous partial airway pressure (NCPAP) with chest physiotherapy and theophylline therapy as indicated. Monitoring parameters included recordings of vital signs, apnea/bradycardia events, and Day 5 serum caffeine levels. The main outcome measure was failure of extubation, defined as inability to extubate within 48 hours of caffeine loading or the need to reintubate or to use doxapram within 7 days of caffeine loading.

In the 3, 15 and 30 mg/kg groups, extubation failure rates were 45%, 25% and 24% ($P < 0.06$) respectively. There were significantly more documented apneas in the 3 mg/kg group than in the 15 and 30 mg/kg groups over the 7-day period (1.3, 0.4, 0.2; $P < 0.01$). Tachycardia (defined as a HR > 200 bpm in 4 consecutive hours) and feeding intolerance (defined as a clinical decision to withhold feedings) were higher, and weight gain was lower in the 15 mg/kg and 30 mg/kg groups, but these findings were not statistically significant. There were no statistical differences in neonatal morbidity. The authors concluded that there was short-term benefit in apnea reduction in the postextubation period at the higher doses of caffeine for the infants studied.

The second paper, using data collected 1996-1999 at four tertiary neonatal units, was an associated Australian multi-center randomized double-blind trial. Infants of less than 30 weeks gestation who received or were expected to receive 48 hours of mechanical ventilation were randomly assigned to one of two caffeine dose regimens (5 mg/kg or 20 mg/kg), with similar exclusion criteria as previously described. Infants received a loading dose of (20 mg/kg or 80 mg/kg) caffeine intravenously with subsequent maintenance doses (5 mg/kg or 20 mg/kg) by IV or enteral route as tolerated, with postextubation to NCPAP as indicated. In this study, 121 infants were assigned to the 5 mg/kg group and 113 to the 20 mg/kg group (all were similar gestational age, birth weight, postnatal age at study entry, and exposure to exogenous surfactant and antenatal steroids). The primary outcome measure was failure of extubation, with secondary outcome measures of apnea frequency, tachycardia and jitteriness, feeding intolerance, incidence of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), and chronic lung disease of prematurity. Enrolled infants were reviewed at 12 months (corrected age) by general physical examination, neurologic assessment and Griffiths mental developmental scales.

In comparison to the lower dose, the 20 mg/kg group showed significant reduction in extubation failure (15% vs 29.8% RR 0.51 {95% CI 0.31-0.85}, $p < 0.01$). There was significant reduction in the number of apneas within 7 days of beginning treatment (4 {1-12} vs 7 {2-22}, $p < 0.01$) in the 20 mg/kg group. Infants less than 28 weeks gestation showed a larger difference with the higher caffeine dose in reduction of extubation failure (17% vs 49% RR 0.36 {95% CI 0.2-0.65}) as well as significant reduction in the duration of ventilation (mean days {SD}: 14.4 {11.1} vs 22.1 {17.1}, $p < 0.01$). There were no statistical differences in the adverse effects: tachycardia, jitteriness, feeding intolerance, duration of intravenous nutrition, major morbidity or pre-discharge mortality. While there was a significant difference in the time for infants to regain birth weight (mean {SD} 14.8 {5.3} vs 12.9 {5.0} days, $p < 0.01$), there was no difference in the overall weight gain over the duration of therapy. At 12 months, there was no statistical difference in death, disability or mean general quotient.

The authors conclude that caffeine at 20 mg/kg/day for infants of less than 30 weeks gestation may have significant short-term benefits with no evidence of harm at 12 months.

MATERNAL CAFFEINE INTAKE AND SGA

Vik T, Bakketeig LS, Tryggv KU, Lund-Larsen K, Jacobsen G. **High caffeine consumption in the third trimester of pregnancy: gender-specific effects on fetal growth.** Paediatr Perinat Epidemiol. 2003 Oct; 17 (4): 324-31.

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In a population-based case-control study from Norway, 858 pregnant Caucasian women (Para 1, 2) with singleton births, registered prior to 20 weeks gestation, were divided into two groups according to small for gestational age (SGA) risk factors (previous low birth weight infant, cigarette smoking at conception, maternal pre-pregnancy weight =50 kg, previous perinatal death, chronic maternal disease). Dietary information was recorded for 3 consecutive days during the second (week 17-20) and third (week 33) trimesters for all subjects. At birth, infants were weighed and classified as SGA (<10th percentile) or non-SGA. Of 858 infants included in the study, 111 were SGA with equal boy/girl proportions in both groups (SGA: 56/55; non-SGA: 368/379).

Subjects were divided into three groups: low, media and high caffeine intake. Median caffeine intake was defined as 232 mg/day at week 17-20 and 205 mg/day at week 33. Mothers of SGA infants had higher mean caffeine intake than mothers of non-SGA infants at week 33 (mg/day +/- SD: 281 +/- 210 vs 212 +/- 150; P<0.001). The odds ratio (OR) for SGA birth with high maternal caffeine intake was OR 1.8 (95% CI) [1.2, 2.5] (overall), which was mainly in boys OR 2.8 [1.5, 5.2] but not girls OR 1.2 [0.7, 2.1], after adjustment for cigarette smoking and other risk factors. The OR of SGA birth increased with increasing caffeine intake overall in mothers having a male child, but not those having a female child.

The authors conclude that high caffeine intake in the third trimester is associated with increased risk of SGA birth among male fetuses.


CAFFEINE INCREASES OXYGEN CONSUMPTION

Bauer J, Maier K, Linderkamp O, Hentschel R. **Effect of caffeine on oxygen consumption and metabolic rate in very low birth weight infants with idiopathic apnea.** Pediatrics. 2001 Apr; 107 (4): 660-3.

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In a study from a German academic medical center, 9 very low birth weight (VLBW) infants at 28-33 weeks gestation (median 30 weeks) with severe idiopathic apnea receiving caffeine were compared to a control group of 9 matched (for age and weight) infants with apnea but no caffeine exposure. O₂ consumption and CO₂ production were measured by indirect calorimetry: before therapy (1st week of life), 48 hrs on therapy, every other week for 4 weeks, and 6 days after stopping therapy. Other causes of apnea were excluded, and the decision to prescribe caffeine was made by an independent neonatologist. Caffeine citrate (10 mg/kg loading, 5 mg/kg q 24 hrs) was given intravenously (with serum levels ranging between 10-15 mcg/ml). No other stimulant drugs or supplemental O₂ were given during the study. All infants received full enteral feedings by the second week of life and were on 8 feedings per day by the third week. Calorimetry was started 45 minutes after each feeding and lasted 60 minutes, with measures for O₂ consumption (VO₂), CO₂ production (VCO₂) and energy expenditure (EE: a linear combination of VO₂ and VCO₂).

At 48 hours of caffeine therapy, there was a significant increase in O₂ consumption, CO₂ production and EE in the treatment group in comparison to both pre-caffeine measures and to the non-caffeine group. Infants in the treatment group required lower environmental temperatures to maintain normal skin and rectal temperatures. There was a significant decrease in apnea for the treatment group from 20 +/- 3 episodes/day to 8 +/- 5 (p<0.05), compared with 12 +/- 4 and 11 +/- 3 in the control group, without significant change in RR, HR or SaO₂. O₂ consumption and caloric intake increased with growth in both groups, with consistently higher O₂ consumption in the treatment group until the end of the study. Weight gain in the treatment group averaged 12 +/- 2 g/d compared to 21 +/- 4 g/d in the control group.

The authors conclude that long-term administration of caffeine is associated with increased O₂ consumption and reduced weight gain, with implications for nutritional adjustment during therapy.

CAFFEINE IMPACTS CEREBRAL AND INTESTINAL BLOOD FLOW

Hoecker C, Nelle M, Beedgen B, Rengelshausen J, Linderkamp O. **Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants.** Arch Dis Child Fetal Neonatal Ed. 2006

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Hoecker C, Nelle M, Poeschl J, Beedgen B, Linderkamp O. **Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants.** Pediatrics. 2002 May;109(5):784-7.

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In two papers, Hoecker et al from Heidelberg, Germany evaluated the effect of high dose caffeine loading doses on neonatal cerebral and intestinal blood flow. While high dose caffeine has been shown to be more effective in the treatment of apnea, its effect on perfusion had been unclear. Considering the newly discovered benefits of caffeine, its safety profile is ever more important.

In 2002, 16 premature infants (29-33 weeks) were given an enteral loading dose of caffeine (25 mg/kg) via NG tube. Doppler ultrasound examinations were performed 1 and 2 hours after the dose to determine left ventricular output. Cerebral blood flow was measured in the internal carotid (ICA) and the anterior cerebral artery. Intestinal blood flow was assessed in the superior mesenteric artery and the celiac artery. To minimize the effect of feeding on cerebral and intestinal blood flow, caffeine was given 2 hours after the last feeding and the next feeding was skipped.

While left ventricular output, blood pressure, heart rate and transcutaneous PCO₂ did not change, cerebral blood flow velocity as measured in the ICA decreased by 15% at 1 hour and 20% at 2 hours after caffeine administration. Two hours after the caffeine, the cerebral blood flow velocity had decreased in 11 of 15 infants. In the superior mesenteric artery, blood flow velocity was reduced significantly by 25% at 1 hour and by 30% 2 hours after administration, but in the celiac artery blood flow had reduced 15% at 1 hour and returned to baseline levels by 2 hours.

Because of the concerns that reduced blood flow associated with a single loading dose of caffeine may increase the risk of cerebral and intestinal ischemia in premature infants, the authors conducted a second study in which the single loading dose of 25 mg/kg was divided into two doses of 12.5 mg/kg four hours apart.

Sixteen infants (gestational age 24-33 weeks) were studied. Caffeine levels were measured at 31 mg/l two hours after the second loading dose. One hour after the first caffeine loading dose none of the circulatory variables were significantly changed; however, one hour after the second loading dose, cerebral blood flow was reduced by 17% in the internal carotid and 19% in the anterior cerebral artery. The anterior cerebral artery blood flow velocity reduction was still reduced by 19% two hours after the second loading dose, but by 20 hours blood flow velocity did not differ from baseline. Unlike the single loading dose, the divided loading doses had no effect on intestinal blood flow as measured in the superior mesenteric artery and the celiac artery.

The investigators observed that heart rate and diastolic blood pressure increased significantly at the end of the 24 hour observation period while left ventricular output, respiratory rate and PCO₂ were unchanged, and also noted an increase in total vascular resistance at one and two hours after the second loading dose.

The authors concluded that a single oral loading dose of caffeine (25 mg/kg) significantly reduces cerebral and intestinal blood flow velocity. Caffeine — at high doses — is a potent inhibitor of the vasodilator adenosine and may explain the reduction in cerebral blood flow. The mechanism of decreased intestinal blood flow is less clear and is explained by the authors by local vasoconstriction. Dividing the loading dose into two smaller doses four hours apart removed the effect on intestinal blood flow, but the effect on cerebral blood flow remained unchanged. Reduced blood flow may be of particular concern considering that oxygen consumption increases by 20% during caffeine treatment.

Ask the Authors

LAST MONTH'S Q & A October 2006 - Volume 4 - Issue 2

Last issue we reviewed several recent studies on the effectiveness and potential risks of caffeine use in neonates.



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The eNeonatal Review Team asked the October faculty a few questions.



Has evidence shown monitoring of caffeine levels to be of any value while treating apnea of prematurity?



Caffeine levels used for the short-term prevention/treatment of apnea of prematurity (AOP) have been cited as 5-20 mg/l, with the goal of providing adequate therapy while minimizing toxicity. Two reports of accidental overdose show transient physiologic changes associated with and without caffeine levels being obtained.

One case report^[1] of short-term toxicity from an accidental overdose of 160 mg/kg in a premature infant documented hypertonia, sweating, tachycardia, cardiac failure, pulmonary edema and metabolic acidosis with hyperglycemia (plus elevation of creatine kinase and gastric dilatation) at a caffeine level of 217 mg/l at 36 hours post-dose, with resolution of signs at a corresponding level of 60-70 mg/l. Another case report^[2] of an accidental dose of 300 mg/kg in a 30 day old premature infant described similar signs with resolution after 96 hours without levels being obtained (due to lack of facilities).

In a pharmacologic study^[3] of caffeine metabolism in premature infants, researchers measured caffeine metabolites and associated higher clearances with higher weights, higher post-natal ages and female gender. Another study of premature Asian infants with apnea^[4] documented levels of 10-20 mg/l with tolerable adverse effects (gastrointestinal disturbances, diuresis and hyperglycemia), and researchers concluded that weight was the sole parameter associated with therapeutic dosing.

Caffeine levels may be an important adjunct for monitoring the balance between adequate therapy and toxicity. Less invasive methods of measuring plasma caffeine levels such as urinary caffeine levels^[5] are being explored and may be of interest and clinical utility.

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5. Cattarossi L, Violino M, Macagno F, Logreco P, Savoia M. [Correlation between plasma and urinary caffeine levels in preterm infants](#). J Perinat Med. 2006;34(4):344-6.



While there are "encouraging" results from the CAP study regarding the potential effect of caffeine on neurodevelopmental outcomes of preterm infants, other studies suggest alteration of cerebral blood flow after caffeine administration, which in theory could adversely affect the brain. How premature are we in reassuring ourselves that caffeine is indeed safe for these infants?



Such questions are aims of the international CAP trial^[1] to examine the long-term effects and safety of caffeine in the management of AOP. Mortality and neurodevelopmental morbidity, including cerebral palsy, cognitive deficit, bilateral blindness and deafness, are measured at 18 months and are planned for follow up (mortality and morbidity in cognition, neuromotor function, behavior, vision, hearing, and general health) at 5 years.

Methylxanthines increase oxygen consumption and inhibit/alter the expression of receptors for adenosine, which is neuroprotective in hypoxia/ischemia of the developing brain. Experimental evidence shows that mice deficient in these receptors display anxious and aggressive behavior, but its effect on the growth, neurologic and cognitive development and childhood behavior of premature infants is unknown^[1,2]. Continuing follow-up data from the CAP trial will provide the data for rigorous evaluation of this neonatal therapy to answer the question.

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1. Schmidt B. [Methylxanthine therapy for apnea of prematurity: evaluation of treatment benefits and risks at age 5 years in the international Caffeine for Apnea of Prematurity \(CAP\) trial](#). Biol Neonate. 2005;88(3):208-13.
2. Millar D, Schmidt B: [Controversies surrounding xanthine therapy](#). Semin Neonatol 2004; 9:239-244.

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This activity has been developed for Neonatologists, NICU Nurses and Respiratory Therapists working with Neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives • [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe the effectiveness of caffeine usage for new purposes, including extubation and BPD prevention
- Discuss current data regarding the potential for adverse effects, especially for higher dose therapies
- Integrate the data presented into current treatment paradigms for using caffeine in ventilated VLBW infants

Statement of Responsibility · [back to top](#)

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- Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.
- Dr. Lehmann has indicated a financial relationship in the form of honorarium from the Eclipsys Corporation.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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No faculty member has indicated that their presentation will include information on off label products.

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