

# PEDIATRIC PHARMACOTHERAPY

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## Caffeine Citrate for the Treatment of Apnea of Prematurity

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Methylxanthines (caffeine, theophylline, and aminophylline, the ethylenediamine salt of theophylline) have been used in the treatment of apnea of prematurity since the 1970s.<sup>1,2</sup> While theophylline was initially preferred in many neonatal intensive care units, the introduction of a preservative-free parenteral caffeine citrate product onto the market in 1999 resulted in a move to caffeine as the drug of choice. Caffeine citrate offers the advantages of once daily dosing and a wider therapeutic range, with a lower risk for toxicity. Several clinical trials have demonstrated the efficacy of caffeine in reducing apneic episodes and lessening the need for mechanical ventilation in preterm neonates.<sup>3-7</sup> This issue of *Pediatric Pharmacotherapy* will review the use of caffeine citrate in the treatment of apnea of prematurity, highlighting new research suggesting improved survival and addressing the current controversy over routine measurement of serum caffeine concentrations.

### Mechanism of Action

Caffeine (1,3,7-trimethylxanthine) acts as an antagonist to endogenous adenosine at A<sub>1</sub> and A<sub>2</sub> receptor subtypes. It inhibits phosphodiesterase, leading to increased levels of cyclic AMP and stimulation of the central nervous system (CNS). Caffeine relaxes bronchial smooth muscle, stimulates cardiac muscle, and acts as a mild diuretic. In infants with apnea, caffeine is believed to work by stimulating the central respiratory center, decreasing the carbon dioxide threshold and increasing the response to hypercapnea. Caffeine may also increase skeletal muscle tone and decrease diaphragmatic fatigue, aiding respiratory effort.<sup>1,8,9</sup>

### Pharmacokinetics

The pharmacokinetic profile of caffeine in infants has been evaluated in several studies. Caffeine is well absorbed after oral administration, with a bioavailability approaching 100%. In neonates, a 20 mg/kg caffeine citrate dose produces peak serum concentrations of 6 to 10 mcg/mL, with an

average time to peak of 30 minutes to 2 hours. Absorption does not appear to be affected by administration with feedings. Caffeine is widely distributed throughout the body, with a mean volume of distribution of 0.8 to 0.97 L/kg in neonates (compared to 0.6 L/kg in adults). It rapidly crosses the blood-brain barrier, achieving concentrations in the cerebrospinal fluid equal to serum concentrations.<sup>8-12</sup>

Caffeine is metabolized in the liver by cytochrome P450 1A2 (CYP1A2), as well as CYP2E1 and CYP3A3/4. Approximately 3 to 10% of a caffeine dose is converted to theophylline. In clinical trials, the mean elimination half-life of caffeine has been correlated to postconceptional age, postnatal age, and weight, reflecting the development of CYP1A2 activity in the growing infant. In preterm neonates, the half-life of caffeine is approximately 72 to 96 hours (range 40 to 231 hours). By 9 months of age, the half life has declined to approximately 5 hours, similar to that observed in adults. Likewise, the rate of caffeine clearance increases with age, from an average of 5 to 9 mL/hr/kg in neonates to 94 mL/hr/kg in adults.<sup>8-12</sup>

### Clinical Trials

A large number of papers have been published describing the use of caffeine in neonates with apnea of prematurity. While many are limited by small sample sizes, lack of controls, or short treatment durations, there are several well-designed studies. In 1981, Murat and colleagues published the results of a prospective controlled trial of 18 preterm neonates with apnea (mean gestational age 30 weeks).<sup>3</sup> The patients were randomized to receive caffeine citrate (20 mg/kg loading dose followed by 5 mg/kg/day) or placebo. The primary outcome measures were continued apneic episodes at 24 hours and at day 5. On both occasions, there was a significant decrease in the incidence of severe apnea requiring intervention (p<0.01) and mild apnea (p<0.001). The patients in the caffeine group required no additional treatment, while six of the

nine infants in the control group (67%) were determined to be treatment failures and were subsequently treated with caffeine.

In 1992, Scanlon and colleagues compared caffeine to theophylline in 44 preterm infants (mean gestational age 28 weeks).<sup>4</sup> Patients were randomized to receive either low-dose caffeine (12.5 mg loading dose followed by 3 mg/kg/day), high-dose caffeine (25 mg/kg loading dose followed by 6 mg/kg/day), or theophylline (7.5 mg/kg loading dose followed by 3 mg/kg given twice daily). Doses were administered intravenously (IV) or enterally and adjusted to maintain serum concentrations within the therapeutic range. At 48 hours, the number of apneic episodes had declined in all groups, but the decline was greater in the high-dose caffeine and theophylline groups. A greater than 50% reduction in apneic episodes occurred in 69% of the low-dose caffeine group, 86% of the high-dose caffeine group, and 86% of the theophylline patients. Only the high-dose caffeine and theophylline groups demonstrated a significant effect within the first 8 hours of therapy. The authors suggested that high-dose caffeine was as effective as theophylline and offered the advantages of once daily dosing and more predictable serum concentrations.

In 2000, Erenberg and colleagues published the results of a multicenter, double-blind, placebo-controlled caffeine trial in *Pharmacotherapy*.<sup>5</sup> This study formed the basis of the New Drug Application submitted to the Food and Drug Administration for caffeine citrate injection (Cafcit®). Eighty-five neonates between 28 and 32 weeks postconceptional age were enrolled in nine neonatal intensive care units. Patients were randomized to receive caffeine citrate (20 mg/kg IV loading dose followed by 5 mg/kg/day given IV or orally) or placebo for 10 days. At least a 50% reduction in apneic episodes during days 7-10 occurred in 68.9% of the neonates in the caffeine group, compared to only 43.2% of the placebo group (p=0.02). Elimination of apnea was reported in 24.4% of the patients given caffeine, but none of the controls (p=0.005). Adverse effects were not significantly different in the two groups. At the end of the study, 31% of the patients in the caffeine group and 43% of the controls transferred to open-label administration of caffeine. As with previous studies, the authors concluded that caffeine citrate was a safe and effective treatment for apnea of prematurity.

Schmidt and colleagues published the results of the largest study conducted on this topic to date in *The New England Journal of Medicine*.<sup>6,7</sup> This international multicenter, randomized, placebo-

controlled study was designed to evaluate both short and long-term effects of caffeine on survival and development in very low birthweight infants. The primary outcome, survival without neurodevelopmental disability, was chosen to address long-standing concerns over the risk for caffeine-induced reductions in cerebral blood flow and inhibition of adenosine function. A total of 2006 infants between 500 and 1250 grams were randomized to receive caffeine citrate (20 mg/kg loading dose given IV followed by 5 mg/kg/day IV or enterally) or placebo.

The results of this study were published in two parts. The first paper, published in 2006, focused on short-term outcomes including bronchopulmonary dysplasia (defined as the need for supplemental oxygen at 36 weeks postconceptional age), evidence of brain injury on ultrasound, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and growth. At 36 weeks, 350 of the 963 patients (36%) in the caffeine group were receiving supplemental oxygen, compared to 447 of the 954 controls (47%), with an adjusted odds ratio of 0.63; 95% CI 0.52 to 0.76 (p<0.001). Caffeine produced a transient reduction in the rate of weight gain, with the greatest difference occurring at 2 weeks (-32 grams in the caffeine group versus -13 grams in the controls; p<0.001). No significant differences in weight gain were found after 3 weeks. Mortality, brain injury, ROP, and NEC did not differ significantly between the groups.<sup>6</sup>

The second paper from this study was published in November 2007, with the results of the primary outcome, a composite of death, cerebral palsy, and cognitive delay at 18 to 21 months.<sup>7</sup> Of the 937 infants given caffeine, 377 (40.2%) died or survived with a neurodevelopmental disability, compared to 431/932 control infants (46.2%), with an adjusted odds ratio of 0.77 (95% CI 0.64 to 0.93; p=0.008). The rate of cerebral palsy was 4.4% in the caffeine group versus 7.3% in the placebo group, while the incidence of cognitive delay was 33.8% in the caffeine group and 38.3% in the controls. The rates of death, deafness, and blindness were not significantly different. Based on their results, the authors concluded that administration of caffeine citrate in this sample of very low birthweight infants improved the rate of survival without neurodevelopmental disability and reduced the rate of bronchopulmonary dysplasia.

#### Precautions

Caffeine has been shown to reduce cerebral and intestinal blood flow in preterm infants.<sup>13,14</sup> In a study of 16 infants (mean gestational age 31

weeks) given a 25 mg/kg dose of caffeine citrate, Hoecker and colleagues found that mean blood flow velocity in the internal carotid artery decreased by 17% at one hour and 22% at 2 hours.<sup>13</sup> Blood flow velocity in the celiac artery declined by 14% at one hour. The authors concluded from this preliminary study that caffeine administration may produce significant transient reductions in blood flow to vital organs, placing preterm neonates at risk for impaired cerebral and gastrointestinal perfusion.

Reduction in gastrointestinal blood flow could play a role in the development of NEC. Although a true causal relationship has not been established, the Erenberg study revealed an increased rate of NEC in preterm infants given caffeine.<sup>5</sup> There were six cases of NEC reported, with four cases occurring in the caffeine treatment group. Of the two remaining patients, one received only placebo, while the other had originally been in the placebo group but was transferred to caffeine during the open-label period. Conversely, the larger Schmidt study identified no difference in the rates of NEC between the caffeine and placebo groups.<sup>6</sup> While these newer study results are reassuring, it is still recommended that all infants receiving caffeine citrate be closely monitored for signs and symptoms of NEC.<sup>9</sup>

#### Adverse Effects

Caffeine citrate is generally well tolerated. Adverse effects reported in the Erenberg study which occurred more frequently in the caffeine-treated infants than in the controls included feeding intolerance (in 8.7% of patients), rash (8.7%), NEC (4.3%), and sepsis (4.3%). The following adverse effects were each reported in one patient (2.2%): hemorrhage, cerebral hemorrhage, gastrointestinal hemorrhage, disseminated intravascular hemorrhage, renal failure, acidosis, dyspnea, pulmonary edema, gastritis, dry skin, skin break-down, abnormal healing, and retinopathy of prematurity. There was no difference in the frequency of these adverse effects in the placebo group.<sup>5,9</sup>

Serum caffeine concentrations greater than 20 mcg/mL are often associated with an increase in irritability, jitteriness, feeding intolerance, increased urine output, and tachycardia. At serum concentrations greater than 50 mcg/mL, there is an increased risk for fever, tachypnea, hypertonia, vomiting, hyperglycemia, increased blood urea nitrogen values, elevated white blood cell counts, arrhythmias, and seizures.<sup>8,9</sup>

#### Drug Interactions

Administration of caffeine with cimetidine, fluconazole, ketoconazole, mexiletine, or phenylpropanolamine may decrease the rate of caffeine metabolism and result in increased serum concentrations. Neonates requiring these medications should have their caffeine dose reduced during concomitant treatment. Drugs that induce CYP1A2 activity, including phenytoin and phenobarbital, increase the rate of caffeine metabolism and may result in subtherapeutic concentrations. Concomitant administration of caffeine and beta-adrenergic agonists may result in an additive increase in heart rate. Caffeine reduces the efficacy of adenosine by blocking adenosine receptor sites. Neonates receiving caffeine may require higher adenosine doses to achieve cardioversion.<sup>8,9</sup>

#### Dosing Recommendations

The recommended loading dose for caffeine citrate is 20 mg/kg given IV or enterally (equivalent to 10 mg caffeine base). If administered IV, the loading dose should be infused over 30 minutes. Maintenance therapy should be initiated with a dose of 5 mg/kg given IV over 10 minutes or enterally every 24 hours, beginning 24 hours after the loading dose. Therapy should be titrated based on clinical response and to maintain caffeine concentrations between 5 and 20 mcg/mL.<sup>1,8,9</sup>

Routine serum concentration monitoring has recently been challenged.<sup>15,16</sup> While still standard practice in most neonatal intensive care units, two recent papers have suggested that it may be unnecessary. Natarajan and colleagues conducted an observational study of 101 preterm neonates with apnea of prematurity (gestational age 23 to 32 weeks).<sup>15</sup> The median caffeine dose was 5 mg/kg/day, with a range of 2.5 to 10.9 mg/kg/day. Caffeine levels ranged from 3 to 23.8 mcg/mL, with 94.8% of the levels falling within the desired 5 to 20 mcg/mL range. All of the infants with hepatic dysfunction and 91% of the infants with renal dysfunction had levels within the desired range. Based on these results, the authors suggested that routine monitoring of steady-state serum caffeine concentrations was not required in infants without clinical signs of apnea or toxicity.

Concha Leon and colleagues came to similar conclusions in their prospective study of caffeine concentrations in 154 preterm neonates (mean gestational age 29 weeks).<sup>16</sup> Treatment was initiated with a 20 or 25 mg/kg caffeine loading dose followed by 6 mg/kg/day. Serum concentrations were evaluated 4 to 8 days after initiation of caffeine. The mean serum

concentration in the infants without renal or hepatic dysfunction was 20.87±4.37 mcg/mL. No infant had a caffeine level greater than 33 mcg/mL or less than 11 mcg/mL.

Gal, in an editorial published in *The Journal of Pediatric Pharmacology and Therapeutics*, suggested that there may still be benefit to serum concentration monitoring.<sup>17</sup> The author proposed that knowing a caffeine concentration was subtherapeutic may avoid unnecessary procedures or laboratory testing to determine if an increase in apneic episodes was the result of sepsis. Conversely, knowledge of an elevated caffeine concentration may prompt a reduction in dose prior to the onset of adverse effects.

#### Availability and Cost

Caffeine citrate is available as Cafcit® (Mead Johnson) and as generic products (American Pharmaceutical Products and Paddock Labs) in a 20 mg/mL injection and a 20 mg/mL oral solution. All products are available in 3 mL preservative-free vials and may be stored at room temperature. Caffeine products containing sodium benzoate should not be used in neonates.<sup>8,9</sup> The average wholesale price for caffeine citrate injection or oral solution is approximately \$45.00 to \$50.00 per vial.<sup>18</sup>

#### Summary

Caffeine citrate is an effective therapy for neonates with apnea of prematurity. Clinical trials have demonstrated its benefit and a relatively low rate of adverse effects. Newer research also suggests an improved rate of survival without neurodevelopmental disability in neonates receiving treatment.

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#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/23/08:

1. Insulin glargine prefilled pens (Lantus® SoloSTAR®) were added to the Inpatient Formulary.
2. The restriction on bevacizumab was amended to include intravitreal use for macular degeneration, edema, and neovascularization.
3. Aprotinin, immediate-release galantamine, octreotide LAR, and pegaptanib were deleted from the Inpatient Formulary.
4. Ondansetron orally disintegrating tablets were added to both the Inpatient and Outpatient Formularies and the oral solution was removed due to lack of use.
5. Immediate-release galantamine and alendronate/cholecalciferol were also deleted from the Outpatient Formulary.

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