

Newborn Critical Care Center (NCCC) Clinical Guidelines

Caffeine Therapy for Apnea of Prematurity

INTRODUCTION

Apnea in the premature infant can be caused by decreased central respiratory drive, inability to maintain airway patency, and other causes. The treatment of choice for central apnea, when indicated, is caffeine, and upper airway obstruction leading to apnea may be effectively treated with CPAP. Caffeine is a methylxanthine that acts as a central nervous system stimulant. The effects are mediated by its antagonism of the actions of adenosine at cell surface receptors in the medulla. It increases chemoreceptor sensitivity to CO₂ and the output of the respiratory center in the medulla.

The use of caffeine in the CAP trial (Schmidt et al) was associated with decreased risk of bronchopulmonary dysplasia (at 36 weeks PMA) and cerebral palsy at 2 years.

DRUG INFORMATION

Caffeine Citrate

- *Loading dose:* 20 mg/kg
- *Maintenance dose:* Initial maintenance dose suggested - 5 mg/kg every 24 hours
- *Maintenance dosing range:* 5-10 mg/kg
- *Monitoring:* Clinical response; consider holding dose if HR >180
- *Adverse Effects:* Tachycardia, restlessness, vomiting, decreased seizure threshold

INDICATIONS TO START CAFFEINE

1. Ensure that there is no other attributable cause of apnea (i.e., infection, seizure, CNS abnormality).
2. <30 weeks gestation:
 - a. Administer caffeine for prophylaxis in the non-mechanically ventilated infant
 - b. Administer caffeine to infants demonstrating apnea
 - c. Administer caffeine to infants to be extubated in the first 10 postnatal days
 - d. Avoid routine use of caffeine in preterm infants likely to remain mechanically ventilated beyond 10 postnatal days (Amaro et al) because of non-statistically significant increase in mortality
3. ≥ 30 weeks gestation:
 - a. Administer caffeine if apnea persists after initiating respiratory support (e.g., on CPAP)
4. For all infants, regardless of gestational age or postnatal age, consider caffeine load prior to extubation

MAINTENANCE DOSING ADJUSTMENTS

In all above gestational age categories:

1. If worsening apnea, consider administering another loading dose of caffeine (10 mg/kg) and increase maintenance dose (up to 10 mg/kg/day) if:
 - a. No improvement in frequency or severity of apnea after initiation of caffeine
 - b. No improvement in frequency or severity of apnea after an increase in positive pressure support or if apneic episodes increase
2. Adjust maintenance dosing for weight weekly (Mondays) as needed.

DISCONTINUING CAFFEINE THERAPY

- Intubation and expected prolonged (> 48 hour) duration of mechanical ventilation
- Suggested end point of therapy is 32-34 weeks post menstrual age
- At the provider's discretion – former ELBW infants may have symptoms past 34 weeks PMA

APNEA FREE COUNTDOWN

Infants who have been treated with caffeine must complete an apnea free countdown prior to discharge.

- Countdown may be initiated once at least 3 days have passed since the infant's last dose of caffeine and the patient is no longer on positive pressure support or the infant is 36 weeks PMA, whichever is sooner.
- Patient should demonstrate at least 8 days without apnea prior to discharge. Document this in the chart as day 1 of 8 day apnea free countdown, day 2 of 8 apnea free countdown, etc.

POST OPERATIVE CAFFEINE FOR EXTUBATION

Discuss with Pediatric Surgery/Anesthesia prior to case whether postoperative caffeine to aid extubation is appropriate. In some cases, it may be more appropriate for the patient to return to the unit intubated to recover. If postoperative caffeine is administered, consider observing for a period of time for apnea prior to discharge.

References:

1. Amaro CM, Bello JA, Jain D, Ranmath A, D'Ugard C, Vanbuskirk S, Bancalari E, Claire N; Early Caffeine and Weaning from Mechanical Ventilation in Preterm Infants: A Randomized Placebo-Controlled Trial. *J Pediatr*, 2018, May; 196: 52-57.
2. 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.
3. Darnall RA, Kattwinkel J, Nattie C, Robinson M. Margin of safety for discharge after apnea in preterm infants. *Pediatrics*. 1997 Nov; 100 (5):795-801.
4. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for endotracheal extubation in preterm infants. *Cochrane Database Syst Rev*. 2010 Dec 8;(12):CD000139. Review .
5. Eichenwald EC. National and international guidelines for neonatal caffeine use: Are they evidence-based? *Semin Fetal Neonatal Med*. 2020 Dec;25(6):101177. Review .