



## Review Article

### Caffeine Citrate in Neonatal Intensive Care Unit

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#### Abstract

Apnea is a common condition in premature infants due to the immaturity of respiratory control mechanisms. Incidence increases with younger gestational age and lower birth weight, afflicting 25% of infants under 2500 g and 80% under 1000 g . Recurrent apnea can lead to respiratory failure, pulmonary hemorrhage , abnormal lung function, intracranial hemorrhage, abnormal neurodevelopment and even sudden death.

Caffeine is the most frequently used medication in the neonatal intensive care unit. It is used for the prevention and treatment of apnea, although this drug has been associated with lower incidence of bronchopulmonary dysplasia (BPD) and patent ductus arteriosus as well as intact survival at 18-21 months of life. The mechanism of action of caffeine on prevention of apnea and activation of breathing seems to be through central inhibition of adenosine receptors.

Caffeine has a long half-life of around 100 hours, thus it can be safely given once daily and has less toxicity than the other methyl xanthines. It has a wider therapeutic to toxic ratio and has reliable enteral absorption

**Key words:** Caffeine citrate, NICU, Apnea of prematurity, bronchopulmonary dysplasia

## **Introduction**

Caffeine citrate is a drug that is frequently used in the neonatal intensive care unit (NICU) to treat premature infants with apnea. It decreases the frequency of apneic episodes, thus reducing the need for mechanical ventilation [1].

The pharmacokinetic profile of caffeine in preterm infants, proof of its protection and efficacy of various doses of caffeine is a matter of debate. Polymorphisms in pharmacodynamics-associated genes have a huge effect at the interindividual variability in the clinical response to caffeine therapy [2, 3].

## **Therapeutic effect of caffeine**

### ***Apnea of prematurity***

Apnea of prematurity is a developmental disorder caused by immaturity of the respiratory control mechanisms, and consequently exhibited a widely variable. It was predicted to occur in almost all infants born at less than 28 wk gestation or extremely low birth weight infants (less than 1000 g). [4]

In the CAP trial [5], the reviewers concluded caffeine to be the “desired drug” for the treatment of apnea of prematurity. Besides apnea of prematurity, caffeine became additionally observed to be powerful in different causes of apnea like post-operative apnea, anesthesia-associated apnea, viral infection-associated apneas, and apneas related to obvious life-threatening events.

### ***Ventilation***

In a subsequent report of the CAP trial, the researchers observe a reduction of duration of mechanical ventilation in those who received caffeine in the first 3 d of life [5, 6].

### ***Bronchopulmonary dysplasia***

Bronchopulmonary dysplasia (BPD) is a well-known problem in preterm infants, which can be related to significant mortality, using early caffeine citrate within the first 3 days of life is related to a decrease occurrence of BPD compared with later use [7].

### ***Prevention of extubation failure***

Several trials proof that high dose caffeine in the periextubation period decreased extubation failure in addition to the mechanical ventilation duration. [8]

Caffeine might enhance breathing mechanics via enhancing breathing muscle strength, inducing diuresis and subsequently enhancing lung compliance [9].

#### ***Bronchiolitis-related apnea***

Premature infants are more vulnerable to bronchiolitis-related apnea. Randomized controlled trials have shown the efficacy and safety of caffeine as a treatment of bronchiolitis-related apnea [10].

#### ***Intermittent hypoxemia***

Intermittent hypoxemia (IH) is described as brief, repetitive episodes of reduced hemoglobin oxygen saturation from a normoxic baseline followed by reoxygenation. Caffeine use in late preterm infants (35–36 weeks) may reduce episodes of intermittent hypoxaemia and improve long-term outcomes for these infants [11, 12].

#### ***Patent ductus arteriosus***

Caffeine use has been related to PDA closure . Other researches additionally confirmed that early caffeine use ,within three days, was associated with less intervention for PDA in comparison to later caffeine use. The useful impact of caffeine on PDA can be correlated with its diuretic and anti-prostaglandin effects. [13]

#### ***Neurodevelopmental outcome***

Prolonged caffeine consumption might also have a neuroprotective effect, possibly via up regulating adenosine A1 receptors. The CAP trial confirmed decreased probability of death, and neurocognitive impairment at 18 months post menstrual age in babies weighing less than 1250 g. Follow up of CAP trial at 5 years, did not show any distinction in the final results of death or intense impairment. The actual mechanism may be related to the ability of caffeine to lessen intermittent hypoxia and possibly to its direct neuroprotective effect [14, 15].

### **Renal**

Caffeine exerts a diuretic effect via increasing creatinine clearance, as a hallmark of GFR, within 12 h of administration. caffeine has no effect on serum calcium, phosphorus, sodium, or potassium concentrations [16].

### **Retinopathy of Prematurity (ROP)**

The CAP trial showed reduced incidence of severe retinopathy of prematurity in caffeine group when compared to placebo (5.1% vs. 7.9% with adjusted odds ratio 0.61). This effect would perhaps be explained by reduced oxygen and ventilation days and reduced incidence of intermittent hypoxia with caffeine group [17].

### **Gastrointestinal**

Methylxanthines might also worsen reflux through delayed gastric emptying and reducing tone of lower oesophageal sphincter, in addition they increase gastrin secretion. Researches did not prove increase of gastro esophageal reflux symptoms in preterm infants treated by caffeine [18,19].

Caffeine citrate administration in a single loading dose 20 mg/kg intravenous did not cause significant modification in mesenteric blood flow velocities, whereas at a higher dose (25 to 50 mg/kg) had been reported to be associated with a reduction of mesenteric blood flow velocities [20,21].

### **Inflammatory effect**

Caffeine has an immunomodulatory effects which may be related to blocking of adenosine receptors located on the surface of immune. Chavez Valdez et al [22]. Results revealed that caffeine levels within (10-20 mg/L) were associated with a decrease in pro-inflammatory cytokines (interleukin-6, TNF $\alpha$ ) levels, and an increase in anti-inflammatory cytokine (interleukin) levels. However, caffeine levels outside the therapeutic range have been related to a proinflammatory profile [23].

### **Anti-in Growth**

The CAP trial found out that infants under the caffeine therapy gained less

weight than those in the control group during the first 3 wk after treatment [5].

### Indications to start Caffeine

Ensure that there is no other attributable cause for apnea (i.e., infection, seizure, CNS abnormality).

#### 1) **Less than 30 weeks gestation:** birthweight less than 1250 g

- 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

#### 4) **Equal or More than 30 weeks gestation:**

- Administer caffeine if apnea persists after initiating respiratory support (e.g., on CPAP)

**5) Facilitate extubation** from mechanical ventilation: For all infants, regardless of gestational age or postnatal age, consider caffeine load prior to extubation [25].

### Administration

- 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 [26]
- Higher maintenance doses of caffeine citrate (10-20mg /kg/day) mg was more effective and safer than low maintenance doses (5mg-10mg /kg/day) for treatment of premature apnea, despite a higher incidence of tachycardia [27].

### Discontinuing Caffeine therapy

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

- The countdown may begin once at least 3 days have passed since the child's last caffeine dose, the patient is off positive pressure support, or the child is 36 weeks gestational age, whichever comes first. [26]
- Patient should demonstrate at least 8 days without experiencing any 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.

However, caffeine may not reach sub-therapeutic levels until 11-12 days post-cessation [28].

The degree of respiratory stability and signs of caffeine-induced toxicity can both influence a clinician's decision to discontinue caffeine therapy [29].

### Contraindications

- Simultaneous administration of other xanthine preparations .

- gastrointestinal bleeding, liver or renal dysfunction
- Heart rate greater than 180 beats per minute.
- Approximate time to reach steady state blood levels is 5–6 days (i.e. apnoea may occur until steady state is reached, despite loading dose) [29]

### Practical points

- **European Consensus Guidelines on the Management of Respiratory Distress Syndrome:** Caffeine should be used to facilitate weaning from MV (High quality; Strong recommendation for using intervention) [30]
- Early caffeine should be considered for babies at high risk of needing MV such as those on non-invasive respiratory support (Low quality; Strong recommendation for using intervention).
- **AAP Committee on fetus and newborn:** Caffeine citrate is a safe and effective treatment of apnea of prematurity when administered at a

20-mg/kg loading dose and 5 to 10 mg/kg per day maintenance [31]

### Impact

- Extremely premature neonates with a lower birth weight may require higher weight-based caffeine dosing due to their higher weight-adjusted clearance and shorter half-lives.
- Higher caffeine citrate dosing (e.g. 10 mg/kg/day maintenance dose) than the standard dose (5 mg/kg/day maintenance dose ) may be needed to further prevent bronchopulmonary dysplasia. [26]

### Conclusions

Caffeine citrate is not only considered as the preferred drug for treatment and prevention of apnea of prematurity, it also used in treatment of other types of apnea. It may be used as a therapeutic drug in NICU for reduction in chronic lung disease, improvement in extubation failure within 7 days, prevention of postoperative apnea and its diuretic effect.

### Conflict of interest

The author had no conflict of interests to declare.

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