Methylxanthines: Caffeine Citrate, Aminophylline, Theophylline

What are Methylxanthines?

Methylxanthines are stimulant medications that act both centrally and peripherally to stimulate respiration. They are the first-line regimen in the management of apnea of prematurity in neonates.

The drug in this class include;

- Caffeine citrate,
- Aminophylline and,
- Theophylline.

Apnea of prematurity is one of the complications of preterm births.

What is the mechanism of action of methylxanthines?

Methylxanthines work by activating the medullary respiratory centers and increase chemoreceptor carbon dioxide sensitivity, induce bronchodilation, enhancing diaphragmatic function, leading to an increased minute ventilation, oxygen consumption, improved respiratory pattern, and reduced hypoxic respiratory depression.

Apnea is a cessation in ventilation lasting longer than 15 to 20 seconds, especially if associated with bradycardia and/or desaturation.

They have also been known to act on cardiac muscles, increasing metabolic rate, and stimulating diuresis.

Caffeine citrate is also thought to improve lung mechanics through its diuretic effects. Apnea of prematurity the improves as brainstem respiratory control centers progressively mature.

Methylxanthine drugs are non-specific inhibitors of two of the four known adenosine receptors. Adenosine is recognized as being an important regulator of sleep and arousal states.

In older children and adults, methylxanthines such as theophylline have been proven to achieve bronchodilation for asthmatics.

The study clearly showed substantial benefits from caffeine citrate in treating AOP, as well as a beneficial impact on neonatal short-term morbidities such as a decrease in incidence of bronchopulmonary dysplasia (BPD); the need for surgical ligation of patent ductus arteriosus (PDA); and long-term impairments such as cerebral palsy, severe retinopathy of prematurity, and neurocognitive defects.

Pharmacokinetics

Methylxanthines may be administered by either the oral or the intravenous route.

Why Caffeine Citrate?

All methylxanthines effectively reduce the incidence of apnea, but caffeine citrate is generally preferred due to;

- Fewer side effects therefore generally safe,
- Wider therapeutic index, and
- Long half-life that allows once-daily dosing
- It does not require routine serum therapeutic drug monitoring.

Caffeine citrate is considered to be safer than theophylline, demonstrating that blood levels of caffeine as low as 3 to 4 mg/L seem to be effective in abolishing apnea.

Caffeine also appears to be safer and more effective than other methods of treating apnea, such as kinesthetic stimulation and pharmacological stimulants such as doxapram.

Theophylline, however, is well-known to have a narrow therapeutic range, with toxicity becoming evident when excessive serum levels are greater than 20 mg/L.

For neonates, there was a concern that the therapeutic range for theophylline might be even narrower, observing control of apnea spells at plasma concentrations of theophylline of 6.6 mg/L but noting cardiovascular toxicity (HR greater than 180 bpm) with ranges between 13 and 32 mg/L.

Methylxanthines facilitate extubation and reduce the need for mechanical ventilation

Dosing

Caffeine citrate is a once-a-day therapy administered intravenously or orally, with a loading dose of 10 to 20 mg/kg and a daily maintenance dosage of 5 to 10 mg/kg.

Caffeine citrate has a very long half-life. The half-life ranges from 52 to 101 hours for patients between 30 and 33 weeks gestation.

Initiation of caffeine treatment in the first 3 days after birth and the use of higher maintenance doses may have incremental beneficial effects on later outcomes.

The necessary duration of treatment with a methylxanthine is highly variable.

In general, the lower the gestational age at birth, the later the apnea of prematurity-related symptoms resolve, with the most prematurely born infants sometimes displaying apnea of prematurity related symptoms beyond term-equivalent age.

By 33 to 36 weeks of PMA, however, most overt apnea related symptoms have resolved, and methylxanthine therapy is routinely discontinued.

After cessation of therapy, continuous monitor an infant for a variable period of time (3 to 8 days) during drug “washout” is important before concluding that the infant is ready for discharge.

This is important when weaning and discontinuing caffeine therapy, because it may take a week or more to return to subtherapeutic serum caffeine levels that will allow clinicians to observe the true resolution of apnea of prematurity without pharmacological therapy.

Infants with recurrent clinical symptoms of bradycardia or cyanosis related to AOP may require the reinstitution of medical treatment.

There is no known minimum gestational age at birth for treatment. Treatment usually begins within the first postnatal week and is typically discontinued following the resolution of clinically apparent AOP related symptoms.

Caffeine base dose is 50% of the caffeine citrate dose.

Doses are identical for parenteral and oral administration

Side effects of methylxanthines

The side effects of methylxanthines result from an increased metabolic rate and catecholamine stimulation, leading potentially to a transient slowing of growth, tachycardia, arrhythmias, irritability, crying, feeding intolerance, and seizures.

These side effects, which are only evident when methylxanthine therapy reaches toxic levels, are rarely seen with caffeine because caffeine has a wide therapeutic margin.

There are reports of an increased risk of necrotizing enterocolitis (NEC) with methylxanthine use in premature infants, which have not been substantiated for caffeine.

The increased oxygen consumption has the potential to decrease weight gain in the short term, but it is not substantial in the long term

What are the Benefits of Caffeine Therapy in Infants Born Preterm?

Established Benefits of caffeine citrate are:

- It treats apnoea of prematurity.
- It facilitates extubation and shortens the duration of intubation.
- Shortens duration of positive pressure ventilation and supplemental oxygen use.
- Reduces the incidence of bronchopulmonary dysplasia.
- Decreases need for treatment of patent ductus arteriosus.
- Reduces the severity of retinopathy of prematurity.
- Improves motor function and visual perception at a 5-year follow-up.

Possible Benefits are;

- Prevents intermittent hypoxia associated with apnoea of prematurity-related symptoms.
- Prevents postoperative apnea in preterm infants undergoing general anesthesia.
- Prevents apnea associated with viral bronchiolitis in young infants.
- Induces an anti-inflammatory cytokine profile.