Caffeine

Newborn use only

2020

<table>
<tr><td>Alert</td><td>Caution with dosing: Caffeine citrate 2 mg = caffeine base 1 mg</td></tr>
<tr><td>Indication</td><td>1. Treatment of apnoea of prematurity.
2. Weaning from mechanical ventilation.
3. Prevention of post-operative apnoea.</td></tr>
<tr><td>Action</td><td>Competitive inhibition of the actions of adenosine at cell surface receptors.
Enhancement of respiratory effort and regularisation of breathing patterns through stimulation of central inspiratory drive and increased sensitivity of chemoreceptors to carbon dioxide.
Increase in respiratory centre output, smooth muscle relaxation and cardiac output.
Improvement in the contractility of the diaphragm and hence increasing the force of contraction and decreasing muscular fatigue.</td></tr>
<tr><td>Drug type</td><td>Central nervous system stimulant, respiratory stimulant.</td></tr>
<tr><td>Trade name</td><td>Cafnea (caffeine citrate), Auspman (Caffeine base)</td></tr>
<tr><td>Presentation</td><td>Caffeine citrate IV 40 mg/2 mL vial
Caffeine citrate oral 25 mg/5 mL solution
Caffeine base IV 50 mg/5 mL ampoule
Caffeine base oral 10 mg/mL solution</td></tr>
<tr><td>Dose</td><td><u>Caffeine citrate</u>

<table>
<tr><th></th><th>Loading dose</th><th>Maintenance dose
24 hours after loading dose</th><th>Post-Op apnoea
(single dose)</th></tr>
<tr><td>IV</td><td>20 mg/kg</td><td>10 mg/kg (range 5−20mg/kg) daily</td><td>10 mg/kg</td></tr>
<tr><td>Oral</td><td>20 mg/kg</td><td>10 mg/kg (range 5−20mg/kg) daily</td><td>10 mg/kg</td></tr>
</table>
Maintenance dose may be increased or decreased as per the clinical need.

<u>Caffeine base</u>

<table>
<tr><th></th><th>Loading dose</th><th>Maintenance dose
24 hours after loading dose</th><th>Post-Op apnoea
(single dose)</th></tr>
<tr><td>IV</td><td>10 mg/kg</td><td>5 mg/kg (range 2.5−10 mg/kg) daily</td><td>5 mg/kg</td></tr>
<tr><td>Oral</td><td>10 mg/kg</td><td>5 mg/kg (range 2.5−10 mg/kg) daily</td><td>5 mg/kg</td></tr>
</table>
Maintenance dose may be increased or decreased as per the clinical need.</td></tr>
<tr><td>Dose adjustment
Therapeutic hypothermia
ECMO
Renal impairment

Hepatic impairment</td><td>
Safety not demonstrated.
Not applicable
Current evidence is not enough to specify dose adjustment, but caution required in the context of renal impairment as caffeine is 86% renally excreted. Consider therapeutic drug monitoring.
No information.</td></tr>
<tr><td>Maximum dose</td><td>Loading dose: caffeine citrate in trials varied between 20 and 80 mg/kg.

Maintenance dose caffeine citrate in trials varied between 3 and 20 mg/kg/day. [1]</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV
Oral</td></tr>
<tr><td>Preparation</td><td><u>ORAL SOLUTION</u>
No dilution is required.

<u>IV INFUSION</u>
<u>Caffeine citrate</u>
Draw up 2 mL (40 mg) of caffeine citrate and add 3 mL sodium chloride 0.9% or glucose 5% to make a final volume of 5 mL with a concentration of 8 mg/mL.
<u>Caffeine base</u></td></tr>
</table>

	Draw up 2 mL caffeine base (20 mg) and add 8 mL sodium chloride 0.9% or glucose 5% to make a final volume of 10 mL with a concentration of 2 mg/mL.
Administration	IV: Infuse • loading dose over at least 30 minutes • maintenance over 10 minutes. ORAL: Solution may be administered without feeds, however consider giving with feeds to reduce gastric irritation.
Monitoring	Heart rate, number and severity of apnoea episodes and assess for agitation. Consider withholding dose if HR > 180 bpm. Cardiorespiratory monitoring should continue for at least 5-7 days after the cessation of caffeine treatment for apnoea. Therapeutic drug monitoring is usually not necessary. [2] Trough concentrations may be taken one hour before the next dose is due but should only be done if using high doses or toxicity is suspected. Monitoring of serum drug concentration should be determined on approximately day 5 of therapy. Standard caffeine dosing of a 20 mg/kg load followed by 5 mg/kg once daily results in serum concentrations of 5–20 mg/L (26-103 micromol/L). Supratherapeutic levels 20-60 mg/L (103 – 308 micromol/L) offer potential increased effect. Levels >60 mg/L (>308 micromol/L) are considered the toxic range. [3]
Contraindications	Contraindicated in infants with hypersensitivity to methylxanthines or citrate.
Precautions	Use with caution in infants with impaired renal or hepatic function, seizure disorders, cardiovascular disease or congenital heart disease.
Drug interactions	Fluconazole and verapamil may decrease caffeine elimination. Phenytoin may increase caffeine elimination. Caffeine antagonises the effects of benzodiazepines. Other methylxanthines (theophylline, aminophylline) should not be used concomitantly.
Adverse reactions	Arrhythmia (ventricular), flushing, tachycardia, vasodilatation, functional cardiac symptoms. Increased left ventricular output & increased stroke volume, hypotension. Agitation, irritability, restlessness, sleep disturbances, seizures (with toxic doses). May relax the lower oesophageal sphincter & increase gastric acid secretion leading to increased episodes of gastro-oesophageal reflux, gastritis, vomiting. Urticaria, alterations in serum glucose, diuresis, tachypnoea.
Compatibility	Fluids: Glucose 5%, Glucose 10%, Glucose 50% and sodium chloride 0.9%. Y-site: Dopamine, fentanyl, heparin, amino acid solutions and fat emulsions.
Incompatibility	Fluids: No information. Y-site: Aciclovir, frusemide, glyceryl trinitrate and ibuprofen lysine.
Stability	Caffeine citrate: Discard unused portion. Caffeine base: IV − discard unused portion. Oral solution − store at room temperature.
Storage	Store below 30 °C
Excipients	Cafnea Injection and oral solution contain citric acid monohydrate and sodium citrate. The injection contains no preservatives. Auspman caffeine oral solution – glycerol, potassium sorbate, hydrochloric acid.
Special comments	Half-life in neonates: 72−96 hours (range 40−230 hours decreasing with advancing corrected gestational age). [4, 5] Time to peak serum concentration: Within 30 minutes to 2 hours in oral administration. Caffeine may not reach subtherapeutic levels until 11 to 12 days post cessation [6].
Evidence	**Weaning from mechanical ventilation.** In a subgroup analysis of the CAP 2016 trial [7], use of caffeine citrate (20mg/kg loading dose followed by 5 mg/kg maintenance) versus placebo for extubation of preterm infants born 500 to 1250g found a reduction in PDA ligation (717 infants; RR 0.32 [95%CI 0.20, 0.52]), PMA at last oxygen therapy (666 infants; MD -1.5 [-2.25, -0.75] days), PMA at last endotracheal tube (668 infants; MD -0.90 [-1.42, -0.38] weeks), PMA at last positive pressure ventilation (667 infants; MD -1.10 [-1.64, -0.56] weeks) and bronchopulmonary dysplasia at

term age (672 infants; RR 0.81 [0.70, 0.93]). Caffeine was associated with a reduction cerebral palsy (644 infants; RR 0.54 [0.32, 0.92]) and death or major disability by 18-21 months (676 infants; RR 0.85 [0.73, 0.99]) [8]. At age 11 years the caffeine-treated children had better respiratory function and reduced risk of motor impairment [9].

Prevention of apnea in preterm infants

In two trials including 104 preterm infants comparing caffeine versus placebo for prevention of apnea reported no significant difference in apnoea, bradycardia, hypoxaemic episodes, use of IPPV or side effects. Meta-analysis found no significant difference in use of IPPV or tachycardia. [10] In a subgroup analysis of the CAP 2006 trial [7], infants treated with prophylactic caffeine had a reduction in PDA (453 infants; RR 0.41, 95%CI 0.20, 0.84) and PMA at last positive pressure ventilation (432 infants; MD -1.00, 95%CI -1.62, -0.38 weeks]. There was no reported difference in PMA at last oxygen therapy, PMA at last endotracheal tube, bronchopulmonary dysplasia (437 infants; RR 0.83, 95%CI 0.67, 1.05), cognitive delay (396 infants; RR 1.08, 95%CI 0.83, 1.40), cerebral palsy (415 infants; RR 1.03, 95%CI 0.43, 2.49) or death or major disability (423 infants; RR 1.00, 95%CI 0.80, 1.24).

Higher versus lower dosage caffeine

Several systematic reviews [1, 11, 12] have assessed the effects of higher (loading dose >20 mg/kg and maintenance >10 mg/kg/day) versus lower dose caffeine citrate in preterm infants. Loading and maintenance caffeine citrate doses varied in trials between 20 and 80 mg/kg/day and 3 and 20 mg/kg/day, respectively.[1] In the largest review, 13 RCTs reporting 1515 infants compared low-dose 5-10 mg/kg daily versus high-dose group (10-20 mg/kg daily) caffeine citrate. The high-dose group had a lower extubation failure rate (RR: 0.5, 95%CI: 0.35 to 0.71, P=0.0001), frequency of apnea (MD: -1.55, 95%CI: -2.72 to -0.39, P=0.009), apnea duration (MD: -4.85, 95%CI: -8.29 to -1.40, P=0.006), and incidence of bronchopulmonary dysplasia (RR: 0.79, 95%CI: 0.68 to 0.91, P=0.002), but higher incidence of tachycardia (RR: 2.02, 5%CI: 1.30 to 3.12, P=0.002). There were no significant group differences in other adverse events including in-hospital death (P>0.05). [12] Higher maintenance doses of caffeine citrate was more effective and safer than low maintenance doses for treatment of premature apnea, despite a higher incidence of tachycardia. [LOE I GOR C]

Prevention of post-operative apnoea.

Prophylactic caffeine for prevention of postoperative apnea following general anaesthesia in preterm infants reduced postoperative apnoea/bradycardia (3 trials, 78 infants; RR 0.09 [0.02, 0.34] and postoperative oxygen desaturations (2 trials, 58 infants; RR 0.13 [0.03, 0.63].[13] Caffeine can be used to prevent postoperative apnea/bradycardia and episodes of oxygen desaturation in preterm infants at risk [14] undergoing general anaesthesia for surgery. [LOE I GOR B]

Safety

Systematic review of RCTs largely report caffeine to be safe and well tolerated in preterm infants with few side effects and improved clinical outcomes [15-17]. Caffeine has been reported to have fewer side effects including tachycardia than other methylxanthines [18]. Early lower dose caffeine compared to placebo was no associated with significant differences in tachycardia (3 trials, 156 infants; RR 4.0, 95%CI0.48, 33.5), bradycardia (2 trials, 102 infants; RR 0.36, 95%CI 0.01, 12.85) or hypoxaemia (2 trials, 102 infants: RR 0.59, 95%CI 2.02)[15].

Systematic reviews of higher versus lower dose caffeine also report higher dose caffeine was more effective than lower dose caffeine at reducing extubation failure [1, 11, 12] and apnea [1, 12], and may reduce the rate of BPD [12]. Higher dose caffeine is associated with higher incidence of tachycardia (RR: 2.02, 5%CI: 1.30 to 3.12, P=0.002) [12]. Despite the increased incidence of tachycardia, growth was not adversely affected in infants in the CAP trial assessed at 18 to 24 months [8]. A trial of caffeine versus aminophylline reported similar growth parameters at 18 to 24 months [19].

Although higher maintenance doses of up to 20 mg/kg/day may be even more effective] [11], it is recommended [20] this needs further testing in randomised trials as higher doses

	(80 mg/kg loading dose) were reported in a clinical trial to be associated with increased risk of cerebellar haemorrhage, hypertonicity and possibly seizure burden [21, 22], a concern not completely addressed by the reporting of a retrospective cohort which did not find an association [23, 24]. **Pharmacokinetics and pharmacodynamics** Caffeine has a long elimination half-life in preterm infants of 72–96 hours (range 40–230 hours) [4, 5], necessitating a loading dose to rapidly achieve therapeutic concentrations and allowing for once-daily dosing. In contrast, the half-life of caffeine in adults is 4–5 hours. Caffeine is metabolized in the liver by cytochrome P450 1A2 before rapid renal elimination of metabolites. This pathway is limited in preterm infants because of immaturity of hepatic enzyme system, therefore, most of a caffeine dose is eliminated unchanged in infancy, with 86 percent of the dose excreted in the urine at a slow rate. In contrast, only 1 percent of a caffeine dose is excreted unchanged by the kidneys in adults. The time to peak concentration from an oral dose is 30 minutes to two hours. The volume of distribution in infants is 0.8–0.9 L/kg.[3, 5] Loading doses of caffeine citrate produce relatively predictable serum concentrations. Caffeine citrate is 50 percent caffeine base; therefore, a loading dose of caffeine citrate 20 mg/kg produces a serum concentration of approximately 10 mg/L. Loading doses ranging from 6 to 60 mg/kg with daily maintenance doses ranging from 3 to 30 mg/kg examined in clinical trials and resulted in serum levels ranging from 6.7 to 59.9 mg/L. Standard caffeine dosing of a 20 mg/kg load followed by 5 mg/kg once daily results in serum concentrations of 5–20 mg/L. Supratherapeutic levels 20-60 mg/L offer potential increased therapeutic effect, whereas levels >60 mg/L are considered the toxic range.[3] Following cessation of caffeine at a mean postmenstrual age of 35 weeks, caffeine levels decreased from 13.3 ± 3.8 to 4.3 ± 2 mg/L (n = 50) at 24 and 168 hours respectively (P<0.01). The mean caffeine half-life was 87 ± 25 hours. Seven days after discontinuation of caffeine, 64% of the infants had pathologic apnea. Caffeine may not reach subtherapeutic levels until 11–12 days post cessation [6].
Practice 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). 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). [20] **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. Monitoring routine serum caffeine levels usually is not contributory to management. A trial off caffeine may be considered when an infant has been free of clinically significant apnea/bradycardia events off positive pressure for 5 to 7 days or at 33 to 34 weeks' PMA, whichever comes first. [2] However, caffeine may not reach subtherapeutic levels until 11-12 days post-cessation [6]. **Caffeine as a primary neuroprotectice agent for preterm infants:** By definition, neuroprotection is an effect that may result in salvage, recovery or regeneration of the nervous system, its cells, structure and function.[25] Routine use of caffeine as a neuroprotective agent in preterm infants (non-ventilated with no history of apneas) has not been proven.
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