Caffeine Citrate

Brand names	Cafcit, generic
Medication error potential	Use caution in calculation of dose and selection of formulation. The dose of caffeine base is 50% the dose of caffeine citrate. Do not interchange the caffeine citrate salt for the caffeine sodium benzoate salt formulation.
Contraindications and warnings	**Contraindications:** Documented hypersensitivity to caffeine or any of its components.[1] Do not interchange the caffeine citrate salt with the caffeine sodium benzoate formulation since the latter contains benzyl alcohol. The sodium benzoate product is contraindicated in neonates due to potentially fatal toxicities associated with gasping syndrome. (See Appendix C.) **Warnings:** Although no direct relationship has been established, necrotizing enterocolitis has been reported in newborns receiving caffeine.[1] (See Rare Adverse Effects in the Comments section.) Use cautiously in patients with a history of a peptic ulcer, impaired renal or hepatic function, seizure disorders, or cardiovascular disease. Avoid in those with symptomatic cardiac arrhythmias.[1]
Infusion-related cautions	None reported
Dosage	Prior to initiation of caffeine citrate, baseline serum caffeine concentrations should be measured in infants previously treated with theophylline and in infants born to mothers who consumed caffeine prior to delivery.[1] The dose of caffeine base is 50% the dose of caffeine citrate (i.e., 20 mg of caffeine citrate is equivalent to 10 mg of caffeine base).[1] **Apnea of prematurity**[1-5] **Loading dose:** 20 mg/kg with a range of 10–40 mg/kg (as caffeine citrate) over 30 minutes. May repeat 20 mg/kg to a total cummulative dose of 80 mg/kg. **Maintenance dose:** 5–8 mg/kg (as caffeine citrate) q 24 hr given over 10 minutes. Begin maintenance dose 24 hours after loading dose.[6,7] 2006 infants (500–1250 g) were randomly assigned to receive either caffeine or placebo for apnea of prematurity. Treatment was continued until it was no longer required. Caffeine improved the rate of survival without causing neurodevelopmental disability at 18–21 months in infants with very low birth weight.[10] **Facilitate extubation** **Loading dose:** 20 mg/kg (as caffeine citrate) 24 hours prior to planned extubation. Should be given over 30 minutes. Doses as large as 80 mg/kg have been given.[6] **Maintenance dose:** 10–30 mg/kg, given over 10 minutes q 24 hr (as caffeine citrate). Begin maintenance dose 24 hours after loading dose.[6] In one report, neonates who received a loading dose of 80 mg/kg followed by 20 mg/kg/day resulted in a lower rate of extubation failure compared to those who received a loading dose of 20 mg/kg followed by 5 mg/kg/day.[6] One study measured diaphragmatic activity in 30 preterm infants 30 minutes before (baseline) to 3 hours after administration a loading dose of 10 mg/kg IV of caffeine base. Caffeine produced a rapid and sustained increase in diaphragmatic activity and tidal volume in preterm infants. Caffeine treatment results in a rapid and sustained increase in diaphragmatic activity and tidal volume in preterm infants.[17] **Treatment of postsedation paradoxical hyperactivity:** 63% of patients treated with 20 mg/kg (maximum of 200 mg) of caffeine citrate for postsedation paradoxical hyperactivity showed a positive effect and returned to baseline behavioral status after an average of 33 minutes (p <0.01 compared to control group).[8]

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Dosage adjustment in organ dysfunction	In neonates, approximately 86% of the drug is excreted unchanged in the urine, with the remainder metabolized by CYP1A2. Neonates with renal/hepatic dysfunction or those suffering from birth asphyxia should be monitored closely.[1] There are no recommendations for dosage adjustment in patients with renal impairment.[9]
Maximum dosage	Maximum loading dose of 20 mg/kg to a cummulative dose of 80 mg/kg. Maintenance dose of 30 mg/kg have been used.[6,7,10]
Additives	None
Suitable diluents	D5W, D10W, D5W¼NS[11]
Maximum concentration	20 mg/mL (as citrate) (commercially available)[1]
Preparation and delivery	*Parenteral products should be visually inspected for particulate matter and discoloration before use. Refer to appropriate references for more information on compatibility with other drugs and solutions; compatibility following Y-site delivery, and suggested storage and extended stability.*[11] **Stability:** Intact vials should be stored at room temperature.[11] Single-use vials do not contain preservative and should be discarded after use. There was <4% loss of caffeine citrate over a 60-day period when caffeine citrate (10 mg/mL) was stored at room temperature and under refrigeration at 4°C after repackaging in glass and plastic syringes (Becton-Dickinson).[11] Caffeine citrate is stable for 24 hours at room temperature when diluted to 10 mg/mL with D5W, D50W, Aminosyn 8.5%, dopamine 0.6 mg/mL, calcium gluconate 10%, heparin sodium 1 unit/mL, or fentanyl citrate 10 mcg/mL.[11] **Compatibility:** Compatible with TPN (2 in 1)[11]
IV push	Not recommended
Intermittent infusion	Loading dose should be given over 30 minutes.[1,2,4] The maintenance dose is usually infused over 10–15 minutes[1,4]; however, it has been infused over 3 minutes.[5]
Continuous infusion	No reports
Other routes of administration	None reported
Comments	**Rare adverse events:** During a randomized, double-blind, placebo-controlled trial, six cases of necrotizing enterocolitis were identified among 85 neonates studied (caffeine = 46, placebo = 39). Caffeine citrate loading dose of 20 mg/kg followed by 5 mg/kg/day orally or intravenously, or placebo, was given to patients for up to 10 days. Four neonates receiving caffeine citrate and two receiving placebo developed necrotizing enterocolitis.[4] Caffeine is known to increase metabolic rate and oxygen consumption and may contribute to growth failure.[5] **Monitoring:** Assess for signs/symptoms of necrotizing enterocolitis. Using standard dosage guidelines, a predicted concentration-time curve can be easily generated and routine monitoring of serum concentrations during treatment is probably not necessary unless a clinical problem arises.[2,13,14] If serum concentrations are monitored, the desired serum trough concentration ranges from 5–20 mg/L. Concentrations above 20 mg/L may be associated with toxicity and concentrations >50 mg/L are considered toxic.[1] **Drug interactions:** Consult appropriate resources for dosing recommendations before combining any drug with caffeine citrate. Caffeine is a substrate of CYP1A2.[1] It is an inhibitor of CYP1A2 and 3A4 (moderate). Because preterm neonates may conversion caffeine to theophylline concurrent administration of caffeine and theophylline is not recommended.[1]