

**Use**

Caffeine reduces apnoea and speeds extubation, so decreasing the time very preterm babies spend ventilated and in supplemental oxygen. Use also seems to decrease the number of survivors with disability.

**Pharmacology**

Caffeine citrate is a general stimulant which increases metabolic rate, central chemoreceptor sensitivity to CO<sub>2</sub>, and inspiratory drive. It crosses the placenta easily, and an intake of more than 300 mg a day (equivalent to 8 cups of tea or 3 cups of strong coffee) probably increases in the risk of miscarriage and stillbirth (see web commentary). The amount in the breast milk of mothers on a normal diet is of no clinical significance, even though the neonatal half life (60–140 hours) is 16 times as long as it is in adults. Caffeine is well absorbed by mouth, and IV treatment is seldom necessary. It is mostly excreted, unchanged, in the urine in the first month of life, but clearance rises and approaches the rate found in adults in infants over 4 months old. Use marginally reduces weight gain for a few weeks, but it can reduce the number needing surgery for retinopathy of prematurity (ROP), and use does not increase the risk of necrotising enterocolitis. Benefit is most marked in the ventilator dependent baby started on treatment within 3 days of birth. Tachycardia and agitation are the first signs of toxicity, while a ten fold overdose can cause hyperglycaemia, hypertonia and heart failure.

**Managing neonatal apnoea**

Caffeine is now preferred to theophylline (q.v.) when managing apnoea, once sepsis, hypoglycaemia, subtle seizures and respiratory exhaustion have been excluded, but medication is no substitute for a sensible nursing strategy. While simple bradycardia can be detected with an ECG monitor and central apnoea with a trans-thoracic impedance or other movement monitor, a pulse oximeter picks up what really matters – clinically significant spells of hypoxaemia. A prone (face-down) posture, or a left lateral position, may help but there is very little evidence for the long held view that it is reflux of milk back into the lower oesophagus that commonly triggers apnoea, and all babies are best nursed supine (on their backs) after discharge even if this leaves them marginally more oxygen dependent. Neither does bolus feeding cause more apnoea than continuous feeding. Constant positive airway pressure (CPAP) may help, (and a similar nasal devise can also be used to provide ventilatory support). So too may doxapram (q.v.), but stimulants seldom help when obstructive apnoea is due to reflex glottic closure, or sleep-associated pharyngeal hypotonia, and caffeine can make reflux worse. Serious apnoea is commonest in the very preterm baby, becomes more troublesome a few days after birth and is uncommon in babies with a postconceptional age of more than 33 weeks, so treatment can usually be stopped two weeks before discharge and any monitor removed a week after treatment ceases. Developmental delay is commoner when serious apnoea persists longer than this.

**Drug equivalence**

There is only 1 mg of caffeine in 2 mg of caffeine citrate. Most neonatologists worldwide have, for the last 25 years, quoted the amount of caffeine citrate used when prescribing or writing about this drug, but the UK drug regulator has now said that prescribers should state the amount of caffeine base to be given. This advice now makes it essential to always specify either the amount caffeine **citrate** to be given (as has been traditional and recommended by this book for the last 15 years) or, to avoid confusion, the amount of caffeine **base** required.

**Treatment**

**Neonatal apnoea:** Give a loading dose of 20 mg/kg of caffeine *citrate* IV or by mouth, followed by a maintenance dose of 5 mg/kg (or very occasionally 10 mg/kg) IV or by mouth once every 24 hours.

**Later apnoea:** In the few babies who merit treatment at a postconceptional age of more than 52 weeks it is sometimes necessary to give a maintenance dose of 5 mg/kg of caffeine *citrate* four times a day.

**Facilitating extubation:** The dose used to control neonatal apnoea (see above) will usually suffice. A higher loading dose of 80 mg/kg IV followed by 20 mg/kg once a day may further speed tracheal extubation in a few babies of less than 30 weeks gestation, but it often causes quite significant tachycardia (170–190 bpm).

**Blood levels**

Measurement seldom influences management. While the usual target plasma level is 10–20 mg/l, a few babies respond better to a level of 25–35 mg/l. Signs of toxicity only occur when the level exceeds 50 mg/l (1 mg/l = 5.14 µmol/l). Samples do not need to be collected at any set time.

**Supply**

**IV products:** Two commercial products designed mainly for IV use, but also marketed for oral use, are available. Each 3 ml (20 mg/ml) vial in America costs \$15, and each 1 ml (10 mg/ml) ampoule in the UK costs £5. Do not give IM, and do not freeze. The UK product label highlights the amount of caffeine **base** present.

**Oral products:** Many centres in America, and some in the UK, continue to make a more easily used (and cheaper) sugar-free preparation ‘in house’ with a one year shelf life that is useable for a month once opened.

**References**

See also the relevant Cochrane reviews ©

Steer P, Flenady V, Shearman A, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child* 2004;**89**:F499–503. [RCT]

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Schmidt B, Roberts RS, Davis P, *et al.* The long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;**357**:1893–1902. [RCT] (See also 1967–8.)