(less than 37 weeks of gestation) can exhibit periodic breathing with pathological apnoea (apnoea of prematurity); this usually resolves as the infant approaches term and the neurological systems controlling ventilation mature.[1,2]

The management of neonatal apnoea for which no underlying disorder can be found may involve supportive measures such as cardiorespiratory monitoring;[1] continuous positive airways pressure and drug therapy may be required.[3]

The methylxanthines, aminophylline, theophylline, and caffeine, reduce the frequency of apnoea and the need for mechanical ventilation in preterm infants during the first seven days of therapy.[4] In preterm infants given intermittent positive airway pressure, prophylactic methylxanthine treatment increases the chances of successful extubation within one week.[5] There is evidence to suggest that this benefit might be more helpful in infants of extremely low birth-weight extubated in the first week. High doses of caffeine, 20 mg/kg daily, have been used around the time of extubation in neonates born at less than 30 weeks of gestation. Short term benefits were noted,[6] and no evidence of harm in the first year of life. Caffeine has also been reported to reduce the incidence of bronchopulmonary dysplasia in infants with very low birth-weight,[3] so that positive airways pressure could be stopped earlier in infants given caffeine compared with those given placebo. A later evaluation of these infants found that caffeine therapy improved the rate of survival without neurodevelopmental disability at 18 to 21 months.[7] The incidence of cerebral palsy and cognitive delay were also reduced. Earlier stopping of positive airway pressure in the infants assigned to caffeine explained almost half of the beneficial long-term effect of caffeine, but further studies are required to ascertain other potential mechanisms of action. Caffeine has a wider therapeutic index, fewer peripheral adverse effects than theophylline, and a longer half-life enabling once-daily dosage, and is therefore preferred.[4,8] Caffeine is given as the citrate salt. It is well absorbed when given orally; intravenous treatment is rarely necessary. For details of doses, see Administration in Children, above. The *BNFC* considers appropriate serum concentrations in neonatal apnoea to be 8 to 12 micrograms/mL for theophylline and 10 to 20 micrograms/mL for caffeine. Higher caffeine concentrations of 25 to 35 micrograms/mL may sometimes be required. Previous treatment with theophylline, infants born to mothers who consumed caffeine before delivery, infants showing signs of toxicity, or infants who require higher doses will require monitoring of plasma caffeine concentrations; however, routine monitoring of plasma concentrations is not always considered necessary.[9] During the first year of life, the elimination half-life of both caffeine and theophylline decreases significantly as the infant matures; regular monitoring of serum concentrations and constant dosage adjustments are therefore required if therapy is prolonged.[1]

For details of the adverse effects on the cardiovascular system associated with caffeine during treatment of neonatal apnoea, see Effects on the Cardiovascular System, above.

Use of doxapram may be considered for apnoea that does not respond to xanthine therapy.[1,2,10] It is reported to be similar in effect to the methylxanthines, and may also be of benefit as an addition to xanthine therapy.[11,12] Doxapram is poorly absorbed orally and adverse effects such as hypertension, CNS stimulation, and heart block have been reported.[13]

1. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
2. Ruggins NR. Pathophysiology of apnoea in preterm infants. *Arch Dis Child* 1991; **66:** 70–73.
3. Schmidt B, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354:** 2112–21.
4. Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 19/03/08).
5. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for extubation in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 19/03/08).
6. Steer P, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F499–F503.
7. Schmidt B, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; **357:** 1893–1902.
8. Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 19/03/08).
9. Natarajan G, *et al.* Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007; **119:** 936–40.
10. Hascoet J-M, *et al.* Risks and benefits of therapies for apnoea in premature infants. *Drug Safety* 2000; **23:** 363–79.
11. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
12. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
13. Henderson-Smart DJ, Steer P. Doxapram versus methylxanthine for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Obesity. A 1999 review[1] of non-prescription weight loss supplements concluded that controlled studies have not shown fat loss in overweight individuals using caffeine without an energy-restricted diet. A later study[2] examined a herbal combination product, containing amongst its active ingredients caffeine (from kola nut) and ephedrine (from ephedra), in the treatment of overweight and obesity without other lifestyle modifications. Some beneficial effects on body-weight were reported after 12 weeks of treatment compared with placebo; however, although no serious adverse effects were seen in the healthy subjects enrolled in this study, the herbal product used contained relatively low amounts of active ingredients compared with preparations used in other similar studies. The FDA has since banned the sale of dietary supplements containing ephedra as they present an unreasonable risk to health (see Ephedra, p.1558), and concerns have been raised about potential additive stimulant effects of preparations containing both caffeine and ephedrine, see Sympathomimetics under Interactions, above.

1. Egger G, *et al.* The effectiveness of popular, non-prescription weight loss supplements. *Med J Aust* 1999; **171:** 604–8.
2. Coffey CS, *et al.* A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. *Int J Obes Relat Metab Disord* 2004; **28:** 1411–19.

Orthostatic hypotension. Caffeine has been of benefit in the treatment of orthostatic hypotension (p.1530) due to autonomic failure in some patients, especially for postprandial hypotension.[1-3] However, efficacy has only been shown in mild cases and it is usually ineffective in severe cases.[4]

1. Onrot J, *et al.* Hemodynamic and humoral effects of caffeine in autonomic failure. *N Engl J Med* 1985; **313:** 549–54.
2. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with dihydroergotamine and caffeine. *Ann Intern Med* 1986; **105:** 168–73.
3. Tonkin AL. Postural hypotension. *Med J Aust* 1995; **162:** 436–8.
4. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; **35:** 124–32.

Pain. Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics but is of debatable benefit (see under Choice of Analgesic, p.2). Some investigators have failed to show that caffeine offers any benefit[1,2] but others have shown that the adjuvant use of caffeine can increase analgesic activity.[3-8] A meta-analysis of 10 studies comparing paracetamol plus caffeine with paracetamol alone in women with postpartum uterine cramp found any benefit of the combination to be minimal.[9] A literature review[10] concluded that there was some evidence that caffeine may be useful as an analgesic adjuvant in relieving headache, but that the dose may need to be at least 65 mg and that these higher doses increase the risk of nervousness and dizziness. Evidence for the effects of caffeine in other types of pain, such as postpartum, postoperative, dental, rheumatic, and cancer pain, was inconclusive.

In the UK it is generally recommended that caffeine-containing analgesic preparations should not be used not only because of doubts about caffeine enhancing the analgesic effect but because it can add to gastrointestinal adverse effects and in large doses can itself cause headache.

Whether caffeine enhances the gastrointestinal absorption of ergotamine in preparations for the relief of migraine is not clear.

1. Winter L, *et al.* A double-blind, comparative evaluation of acetaminophen, caffeine, and the combination of acetaminophen and caffeine in outpatients with post-operative oral surgery pain. *Curr Ther Res* 1983; **33:** 115–22.
2. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.
3. Laska EM, *et al.* Caffeine as an analgesic adjuvant. *JAMA* 1984; **251:** 1711–18.
4. Rubin A, Winter L. A double-blind randomized study of an aspirin/caffeine combination versus acetaminophen/aspirin combination versus acetaminophen versus placebo in patients with moderate to severe post-partum pain. *J Int Med Res* 1984; **12:** 338–45.
5. Schachtel BP, *et al.* Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* 1991; **151:** 733–7.
6. Migliardi JR, *et al.* Caffeine as an analgesic adjuvant in tension headache. *Clin Pharmacol Ther* 1994; **56:** 576–86.
7. Kraetsch HG, *et al.* Analgesic effects of propyphenazone in comparison to its combination with caffeine. *Eur J Clin Pharmacol* 1996; **49:** 377–82.
8. Diener HC, *et al.* The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; **25:** 776–87.
9. Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain—a meta-analysis. *J Clin Pharm Ther* 1996; **21:** 261–82.
10. Zhang W-Y. A benefit-risk assessment of caffeine as an analgesic adjuvant. *Drug Safety* 2001; **24:** 1127–42.

POST-DURAL PUNCTURE HEADACHE. Intravenous caffeine sodium benzoate may relieve post-dural puncture headache (p.1851) that persists despite conservative therapy.

Psoriasis. The efficacy of a 10% formulation of topical caffeine in the treatment of psoriasis has been investigated in a group of 39 patients with stable plaque psoriasis.[1] Improvements were seen at each 2-week follow-up stage, but the difference only became significant after 8 weeks. The only adverse effect noted during the study was mild itching, reported by 2 of the caffeine recipients.

1. Vali A, *et al.* Evaluation of the efficacy of topical caffeine in the treatment of psoriasis vulgaris. *J Dermatol Treat* 2005; **16:** 234–7.

Preparations

BP 2008: Aspirin and Caffeine Tablets; Caffeine Citrate Injection; Caffeine Citrate Oral Solution;
USP 31: Acetaminophen and Caffeine Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Caffeine and Sodium Benzoate Injection; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Guarana; Percutafeine; ***Austria:*** Coffekapton; ***Braz.:*** Percutafeine†; ***Canad.:*** Wake-Up Tablets; ***Chile:*** Asafen Nueva Formula†; Jaquedryl; ***Cz.:*** Kinedryl; ***Fin.:*** Cofi-Tabs; ***Fr.:*** Percutafeine; ***Ger.:*** Percoffedrinol N†; ***Gr.:*** Cafcit; ***Irl.:*** Pro-Plus; ***Mex.:*** Ifa Kafen†; Kafen†; ***Pol.:*** Kofex; ***Port.:*** Bioregime SlimKit†; ***Rus.:*** Vasobral (Вазобрал); ***Spain:*** Durvitan; ***UK:*** Pro-Plus; ***USA:*** Cafcit; Caffedrine; Enerjets; Keep Alert; Lucidex; NoDoz; Stay Alert; Vivarin.

Multi-ingredient: numerous preparations are listed in Part 3.

Choline Theophyllinate *(BAN, rINN)*

Choline, Théophyllinate de; Cholini Theophyllinas; Koliiniteofyllinaatti; Kolinteofyllinat; Oxtriphylline; Teofilinato de colina; Theophylline Cholinate.

Холина Теофиллинат

$C_{12}H_{21}N_5O_3$ = 283.3.
CAS — 4499-40-5.
ATC — R03DA02.
ATC Vet — QR03DA02.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.
BP 2008 (Choline Theophyllinate). A white crystalline powder, odourless or with a faint amine-like odour. It contains between 41.9% and 43.6% of choline and between 61.7% and 65.5% of theophylline, each calculated with reference to the dried substance. Very soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. Store at a temperature not exceeding 25°. Protect from light.
USP 31 (Oxtriphylline). A white crystalline powder, having an amine-like odour. It contains not less than 61.7% and not more than 65.5% of anhydrous theophylline. Soluble 1 in 1 of water; freely soluble in alcohol; very slightly soluble in chloroform. A 1% solution in water has a pH of about 10.3. Store in airtight containers.

Profile
Choline theophyllinate is a theophylline salt that liberates theophylline (p.1140) in the body; choline theophyllinate 1.57 mg is equivalent in theophylline content to about 1 mg of anhydrous theophylline. It is used as a bronchodilator for reversible airways obstruction. The usual oral maintenance dose for adults is 800 mg daily, in 4 divided doses. The daily dose should be adjusted according to clinical response and serum-theophylline concentrations (see Uses and Administration of Theophylline, p.1146). For details of doses in children see Administration in children, below.

Administration in children. Choline theophyllinate can be given to children in oral doses of 10 to 20 mg/kg daily, in 3 or 4 divided doses.

Preparations
BP 2008: Choline Theophyllinate Tablets;
USP 31: Oxtriphylline Delayed-release Tablets; Oxtriphylline Extended-release Tablets; Oxtriphylline Oral Solution; Oxtriphylline Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Brondecon Elixir; ***Canad.:*** Choledyl; ***Ger.:*** Euspirax†; ***Gr.:*** Choledyl; ***Swed.:*** Teovent; ***USA:*** Choledyl†.

Multi-ingredient: ***Austral.:*** Brondecon Expectorant; ***Canad.:*** Choledyl Expectorant; ***NZ:*** Broncelix; Brondecon; Pharmacycare Cough Expectorant†; ***Port.:*** Vitasma†.

Cilomilast *(USAN, rINN)*

Cilomilastum; SB-207499. *cis*-4-Cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexanecarboxylic acid.

Циломиласт

$C_{20}H_{25}NO_4$ = 343.4.
CAS — 153259-65-5.