Caffeine therapy for apnoea of prematurity: Pharmacological treatment

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ABSTRACT

Apnoea of prematurity is among the most commonly diagnosed conditions in the newborn intensive care unit and may prolong the hospital stay of some infants. Resolution of recurrent apnoea and episodes of bradycardia and the completion of an "apnoea-free" period are generally considered to be preconditions for the discharge of premature infants without a home cardiorespiratory monitor. Caffeine is one of the drugs most commonly prescribed for premature infants. It is a potent respiratory stimulant indicated primarily to reduce the incidence of episodes of apnoea associated with an immature central nervous system. It is also used frequently in these infants to facilitate weaning from mechanical ventilation. Caffeine is presently one of the 10 most frequently prescribed medications in neonatal intensive care for which extensive pharmacokinetic data are available, particularly in the preterm neonate. Although very similar in its actions to theophylline, caffeine has several advantages and has become the preferred methylxanthine in the treatment of apnoea. Its toxicity is lower and half-life is longer, and there is less need for therapeutic drug monitoring. Foetuses and newborns are exposed to caffeine via maternal intake of caffeine-containing foods and beverages. This widespread and extensive exposure to caffeine must be considered in the evaluation of the long-term effects of caffeine in the newborn and young infants. Despite the widespread use of caffeine for these indications, the evidence to support its use is based on the results of a few relatively small, short-term studies. Recently, there has been a resurgence of interest in this drug. Studies have reported some intriguing possibilities, such as the protective effect of caffeine on the brain and lungs. The main goal of this paper is to present a review of the pharmacokinetics of caffeine and its cellular effect on the physiology of newborns with apnoea.

Key words: Caffeine, apnoea, methylxanthines, prematurity

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Introduction

Neonatal apnoea is a common problem, particularly in the preterm population (Atkinson et al., 2009) and is the low-birthweight infants, with its incidence and severity most common and frequently recurring problem in very increasing at lower gestational ages (Bauer et al., 2001). On most occasions, apnoea is an isolated event, but it can put the newborn's life at risk if not promptly diagnosed and adequately treated (Lopes, 2001). Apnoea of Prematurity (AOP) is found in 50 to 80% of preterm infants at less than 30 weeks of gestation, and its incidence is even higher in extremely preterm infants. AOP is almost universal in infants who weigh <1000 g at birth (Finer et al., 2006). The literature defines clinically significant apnoea in infants as breathing pauses that last for >20 s or <20 s, but with bradycardia or oxygen desaturation (McCallum et al., 2007). This definition may vary depending on geographic location or the infant's symptomatology. Moreover, there is no consensus as to the duration of apnoeas that should be considered pathological, nor any agreement regarding the degree of change in oxygen saturation or severity of bradycardia that would constitute an important apnoea event (Finer et al., 2006). In exceptional cases, severe apnoea affects full-term newborn infants and animals (Olmos-Hernández et al., 2008; Orozco-Gregorio et al., 2008, 2010), but it is less common in newborns with birthweight >2.5 kg (Vohr, 2000).

The methylxanthines amynophylline, theophylline and caffeine are commonly used for treatment and prophylaxis of apnoea in preterm infants, as they decrease the frequency of apnoea and the need for mechanical ventilation during the first seven days of therapy (Schmidt, 2005; Orozco-Gregorio et al., 2010). Caffeine has several advantages over theophylline and is considered to be the most benign of the methylxanthines due to its wide therapeutic index (Ergenekon et al., 2001), its higher therapeutic ratio, its more reliable enteral absorption and its longer half-life (Hoecker et al., 2002). Caffeine is a competitive adenosine receptor antagonist that exerts most of its effects by blocking the regulatory effects of adenosine that decrease cell excitability (Jacobson et al., 2006). Nevertheless, blocking this type of receptors by caffeine might go so far as to present some adverse effects, since adenosine preserves brain ATP levels and protects brain cells during experimental hypoxia and ischemia in a variety of animal models (Schmidt et al., 2006). However, to achieve a better comprehension of the effects of therapy with caffeine on the premature newborn with apnoea, it is important to gain a more detailed understanding of the mechanisms of action of this drug. The objective of this paper is to present a review of the pharmacokinetics of caffeine and the cellular effect of caffeine on the physiology of newborns with apnoea, its collateral effects, the drug's toxicity and possible protective effects on the brain and lung.

Concepts and types of apnoea

Apnoea is a serious condition, especially when the respiratory pauses are being longer. It is frequently associated with decreases in heart rate below 80 beats per minute (Rigatto, 1986, 1988) and may be complicated Orozco-Gregorio et al. 565 by cyanosis, pallor, hypotonia, or bradycardia (Miller et al., 1997). Prolonged apnoea may lead to hypoxaemia and reflex bradycardia, and may increase the risk of ventricular haemorrhage, hydrocephalus and abnormal neurological development during the first year of life (McCallum et al., 2007). However, the definition of apnoea based on respiratory movements alone is incomplete, because even during active respiratory movements there may be an obstruction of the upper airways and a cessation of gas exchange (Lopes, 2001). Most authors agree that episodes of any duration followed by bradycardia and/or cyanosis are considered pathological (Harthorn, 1974; Martha et al., 1992; Lopes, 2001). Rigatto (1992) indicates that the duration of the respiratory pauses is not an adequate indicator of the severity of the condition. For this reason, cardiac frequency must be considered as the main indicator.

Apnoea of prematurity is among the most commonly diagnosed conditions in neonatal intensive care units, and may prolong the hospital stay of some infants. Resolution of recurrent apnoea and bradycardia episodes and the completion of an "apnoea-free" period are generally considered to be preconditions for the discharge of premature infants without a home cardiorespiratory monitor. The evaluation and management of premature infants who suffer from persistent apneic and/or bradycardic events after they are otherwise ready for discharge to the home remain controversial, and practice varies considerably among neonatologists (Bancalari, 2006).

Apnoea of the newborn can be classified according to the absence or presence of breathing efforts during the period of no airflow (Rigatto, 1992):

(1) Central apnoea. This is the total cessation of respiratory movements and the consequent cessation of airflow in the upper airways due to a lack of diaphragmatic activity (McNamara et al., 2004).

(2) Obstructive apnoea. This is the cessation of airflow in the upper airways in the presence of active respiratory movements (Lopes, 2001).

(3) Mixed apnoea. This is an episode of central apnoea followed by an obstructive episode (respiratory movements without airflow in the airways), or an obstructive episode followed by central apnoea (Lopes, 2001).

In most cases, apnoea is an isolated event, but one that can put the newborn's life at risk if not promptly diagnosed and adequately treated (Lopes, 2001). Immaturity and/or depression of the central respiratory drive to the muscles of respiration have been recognized as key factors in the pathogenesis of apnoea of prematurity. Vulnerability of the ventral surface of the medulla and adjacent areas in the brainstem to inhibitory mechanisms is the likely explanation for why apneic episodes occur in prematurely born infants. This vulnerability I nvolves diverse clinical and pathological events (Martin et al., 1986; Martin et al, 2005). Inhibitory events that affect the central respiratory generator and initiate apnoea, such as hypoxia, hyperthermia and adenosine secretion (Lagercrantz, 1995) in preterm infants and animals (especially genetically altered mice) have enhanced our understanding of the molecular and biochemical events leading to maturation of the central respiratory generator in preterm infants. Bradycardia observed during apnoea may be due to chemoreceptorinduced inhibition of the heart rate, in the absence of ventilatory effort (Martha et al., 1992). In extremely preterm infants, the paucity of quiet sleep, together with an extremely pliable rib cage, make paradoxical chestwall movements almost a constant phenomenon. Paradoxical chest movements may predispose the baby to apnoea by decreasing functional residual capacity and limiting oxygenation (Martin et al., 1979).

Although scientists cannot yet say whether AOP causes a clinically important effect on outcomes and is harmful, providing no treatment when an infant stops breathing in the neonatal intensive care unit is not an option. The immediate and irresistible urge to respond to apnoea is based partly on the uncertainty about exactly what causes the apneic episode and whether the unknown causative factor might also harm the brain or other systems and produce a long-term effect on neurodevelopment (National Institutes of Health Consensus Development Conference on Infant Apnoea and Home Monitoring, 1987).

Pharmacokinetics of caffeine

Methylxanthines appear to act primarily on brainstem respiratory structures, producing a central stimulatory effect (Miller et al., 1997). Of the methylxanthines, caffeine is widely used as a first-line drug therapy in apnoea of prematurity. Its pharmacologic effects in apnoea include stimulation of the medullary respiratory centre, increased sensitivity to carbon dioxide, and enhanced diaphragmatic contractility (Roberts, 1984). Peripheral chemoreceptors provide feedforward control of respiration, which can terminate apnoea and start normal breathing; it could be supposed that these receptors are an important target for caffeine action in premature neonates (Chardon et al., 2004).

In addition, caffeine is a competitive adenosine receptor antagonist (Daly et al., 1983; de Jong et al., 2000). There are three main subtypes of adenosine receptors, designated A1, A2, and A3. There is also evidence that the A2 subtype can be further subdivided into A2A and A2B (Feldman et al., 1997). Caffeine and adenosine have similar molecular structures and the former has the potential to occupy adenosine receptor sites (especially A1 and A2A), thereby blocking the regulatory effects of the latter. By antagonizing adenosine, which has generalized inhibitory functions, the effect of caffeine is broadly stimulatory (Biaggioni et al., 1991; Carter et al., 1995). In this way, and due to the properties of the endogenous modulator of intercellular signalling, adenosine decreases cell excitability (Fredholm, 1980) and, as a result, can produce respiratory depression (Miller et al., 1992), since some of its receptors (A1) mediate the inhibition of adenylate cyclase, whereas others (A2) can stimulate that same substance (Fredholm, 1980).

Schmidt et al. (2006) indicate that some of methylxanthines's side effects must be considered because they are inhibitors of the adenosine's receptors. Adenosine preserves brain ATP levels and protects brain cells during experimental hypoxia and ischemia in a variety of animal models. However, in later studies, these same investigators concluded that the use of an initial dose of 20 mg/kg caffeine citrate, followed by a daily maintenance dose of 5 mg/kg, significantly improved the rate of survival with no neurodevelopment disability at a corrected age of 18 to 21 months in premature infants with very low birthweights and apnoea.

A second mechanism of action of caffeine has been suggested, one that acts through the inhibition

of cyclical nucleotides phosphodiesterase (PDE). These enzymes catalyze the degradation of adenosine monophosphate (AMP) and cyclical guanosine monophosphate (GMP) up to the forms 5`-AMP and 5`-GMP, respectively. The inhibition of the aforementioned phosphodiesterases leads to the accumulation of AMP and cyclic GMP and, with this, the signalling transduction is intensified across the nervous routes in which they intervene. For this reason, the PDE can intensify the activity of endogenous neurotransmitters, as they send signs across cyclical nucleotide messengers (Undem et al., 2005) that perform extremely important functions, when we consider that during a process of asphyxia a depolarization of the neurons occurs, as well as a loss of spontaneous electrical activity, due to the transformation of the nicotinamide adenine dinucleotide (NAD) to NADH, a few seconds after the induction of the asphyxia, which causes an increase in the ionic permeability of the neuron membranes (Menkes, 1984). Nevertheless, the concentrations required to produce this effect are 20 to 50 times higher than those needed to block the adenosine receptors (Fredholm, 1980).

Caffeine (1, 3, 7-trimethylxanthine) is a biotransformation product of theophylline (1, 3-dimethylxanthine) in the human foetus. Liver explants, obtained from human foetuses with gestational ages of 12 to 20 weeks, were incubated with theophylline and produced caffeine and, in lesser amounts, 1, 3-dimethyluric acid and 3- methylxanthine. These findings suggest that the predominant pathway in theophylline metabolism in the foetus and newborn infant is the methylation reaction that produces caffeine. This may contribute to the neonate's exceedingly slow elimination of caffeine relative to t heophylline. Caffeine produced from theophylline may add to the pharmacologic effects of theophylline in newborn infants with apnoea (Aranda et al., 1979). The rate of metabolism of caffeine is variable, with half-lives ranging from 2 to 12 h in healthy adults. However, neonates eliminate caffeine very slowly, with half-lives averaging 100 h. which reflects a maturational deficit in hepatic biotransformation (Aranda et al., 1979; Benowitz, 1990; Donovan et al., 2001). Previous studies in Asiatic and Caucasian neonates estimated a clearance (CL) of 0.00628 L/h-1 (coefficient of variation = 17.5%) and volume of distribution (V) 0.96 L/kg (coefficient of variation = 20.3%) for both populations (Sung et al., 2002).

When caffeine is administered orally, it is absorbed rapidly and nearly completely from the gastrointestinal tract. Peak concentrations in plasma frequently occur in less than one hour (Donovan et al., 2001). The metabolism of caffeine depends on the activities of the hepatic enzymes that vary from one infant to another. The biotransformation of caffeine occurs in the liver via microsomal cytochrome P450 mono-oxygenases (CYP1A2) and via the soluble enzyme xanthine oxidase. CYP1A2 is localized in the mitochondria and in the smooth endoplasmic reticulum, and is the most important enzyme in the metabolism of the methylxanthines, such as caffeine and theophylline (Galli et al., 2002). Female neonates demonstrate a higher rate of caffeine metabolism than males. The predominant process of caffeine metabolism in the preterm infant is N7-demethylation, which matures at about 4 months of age. N3- and N7-demethylation increase exponentially with postnatal age, regardless of birthweight or gestational age (Cazeneuve et al., 1994; al-Alaiyan et al., 2001).

Neonatal apnoea and pharmacological treatment

Henderson-Smart et al. (2001) showed the results of five trials which involved a total of 192 preterm infants with apnoea and indicated that methylxanthine therapy leads to a reduction in apnoea and the use of intermittent positive pressure ventilation in the first two to seven days. Their conclusion was that methylxanthines are effective in reducing the number of apneic attacks and the use of mechanical ventilation in the two to seven days after commencing treatment.

Kuzemko and Paala (1973) an English paediatrician, together with his registrar in Peterborough, were the first to show, in 1973, that rectal aminophylline could reduce the incidence of neonatal apnoea. Dr. Kuzemko had been using aminophylline suppositories in the management of toddlers with severe episodic asthma, and had been able to show that using 10 to 20 mg/(kg/day) rectally was therapeutically useful, produced blood levels of 10 to 20 mg/ml, and did not generate any significant side effects. Faced with a baby with repeated apnoea in his nursery, he speculated that this might also be helpful in this infant because of its action on the respiratory centre. When the nursing staff found this to be successful, he encouraged the Peterborough clinicians to launch a prospective study of ten consecutive babies; the study that finally generated the first published paper three years later. Early replication of this study in three separate centres in America over the next couple of years led the paediatric pharmacologist Jacob Aranda and his

colleagues in Montreal to undertake a thorough study of the phamacokinetics of both theophlylline and caffeine in 1976. As a result, oral treatment with theophylline (or IV treatment with aminophylline) soon came into widespread use in North America, although it took more than a decade for the same strategy to become common in the United Kingdom. It took even longer for caffeine to become the more widely used product, largely because no commercial substance was available. A licensed product of the latter did eventually become commercially available in the USA in 2000, but its use to accelerate extubation in the very preterm baby still remains an "off label" use of this product (Neonatal formulary 5, web site, last up date, 2007).

Methylxanthines are thought to stimulate breathing efforts and have been used in clinical practice to reduce apnoea since the 1970's. Theophylline is the most potent of the methylxanthines extensively used to relax the bronchial muscle, making it effective as an asthma treatment (Gong et al., 1986). However, a review of the literature suggests that caffeine citrate may be the agent of choice for apnoea of prematurity (Bathia, 2000). Comparative clinical studies have demonstrated that caffeine is at least as effective as theophylline, has a longer half-life, is associated with fewer adverse eventsnd, in addition, is easier to administer. Caffeine stimulates the respiratory and central nervous systems more effectively and penetrates into the cerebrospinal fluid more readily than theophylline. One of the problems with theophylline is that treatment levels are very near toxic levels. Likewise, the drug causes other undesirable effects, such as upper digestive haemorrhages, increased diuresis, hyperglycemia, and hypercalciuria (Lopes, 2001). For this reasons, caffeine has several advantages over theophylline and is considered to be the most benign of the methylxanthines because of its wide therapeutic index (Ergenekon et al., 2001). Therefore, caffeine is widely used as first-line drug therapy in apnoea of prematurity (Natarajan et al., 2007).

The therapeutic concentration range of caffeine in neonatal apnoea is 5 to 20 mg L-1. Recently, a higher target of 30 to 35 mg L-1 has been proposed (Lee et al., 2002). However, newborn infants with recurring apnoea require a more aggressive treatment (Lopes, 2001). Concha et al. (2007) reported that higher dosing regimens can increase the effectiveness of caffeine in treating apnoea of prematurity. In studies realized by Scanlon et al. (1992) a loading dose of 25 mg/kg caffeine was shown to improve apnoeas in 72% of treated preterm infants, whereas a loading dose of 12.5 mg/kg was effective in only 25%. Nevertheless, an overdose of caffeine can be dangerous with many side effects, such as tachycardia, agitation, and vomiting. Likewise, caffeine treatment in very low birthweight infants is associated with long-term metabolic stimulation that exceeds normal maturational changes. This may have implications for clinical practice, as feeding or environmental temperature need to be adjusted during this therapy (Bauer et al., 2001). Ergenekon et al. (2001) reported an accidental caffeine base overdose of 300 mg/kg by mouth in a 30-day-old (28-week preterm newborn). In this case, 90 min after administration of the drug, the patient exhibited agitation, irritability, tachycardia, tachypnoea, diuresis, electrolyte abnormalities, hyperglycaemia and metabolic acidosis. The baby was treated with i.v. fluids, sodium and potassium replacement, sodium bicarbonate, restricted glucose intake of 4 mg/kg/min-1 and IV insulin infusion for 12 h. After 96 h of caffeine exposure, both vital signs and laboratory tests were back to normal and the patient made a full recovery from this dangerous situation.

Salivary caffeine concentration monitoring is a satisfactory alternative to blood sampling across a wide range of caffeine doses used to treat apnoea, especially in very sick premature neonates. Caffeine citrate at 3, 15 or 30 mg/kg was administered once daily for 7 days in a randomized, parallel design to 59 newborn, premature infants with an initial loading dose of twice the maintenance dose. Serum and saliva samples (131 pairs) were collected and assayed by high-performance liquid chromatography for caffeine content. Measurable caffeine concentrations in serum ranged from 0.28 to 93.3 mg/L and in saliva from 0.35 to 91.5 mg/L. The mean ratio of the saliva-to-serum concentrations was 0.924. There was no significant difference in precision between the serum and salivary data. The mean serum caffeine concentration was 29.9 mg/L, and the mean salivary concentration was 27.7 mg/L, indicating a small negative bias for saliva versus serum monitoring (Lee et al., 1996).

Protective effect

Neuroprotection

Periventricular white matter injury (PWMI) is the major cause of cerebral palsy and cognitive impairment in prematurely born infants. PWMI is characterized by reductions in cerebral myelination and cerebrocortical volumes and is associated with secondary ventriculomegaly. Back et al. (2006) reported that after they treated C57-Bl6 mice reared

under hypoxic or normoxic conditions from postnatal days 3 (P3) to P12. The mice raised in hypoxia were maintained at 10.0 ± 0.3% O2. Lactating dams were provided *ad libitum* with water that did or did not contain caffeine (300 mg/L). Caffeine was supplied to the dams when pups were P2 (P0, day of birth). Caffeine levels were measured in the blood of pups. Hypomyelination was related to abnormal oligodendrocyte lineage progression and a reduction in the OL progenitor pool. Myelination was enhanced and ventriculomegaly reduced in hypoxia-exposed neonatal pups treated with caffeine from P3 to P12. These observations support that hypoxia inhibits oligodendrocyte maturation and that caffeine administration during early postnatal development may be useful in preventing PWMI.

Schmidt et al. (2007) studied 2006 infants with birthweights of 500 to 1250 g who received either caffeine or a placebo until therapy for apnoea of prematurity was no longer needed. Of the 937 infants assigned to caffeine for whom adequate data on the primary outcome were available, 377 (40.2%) died, or survived with some neurodevelopmental disability, as compared to 431 of the 932 infants (46.2%) assigned to placebo therapy for whom adequate data on the primary outcome were available (odds ratio adjusted for centre, 0.77; 95% confidence interval [CI], 0.64 to 0.93; P = 0.008). Treatment with caffeine as compared to the placebo reduced the incidence of cerebral palsy (4.4 vs.7.3%; adjusted odds ratio, 0.58; 95% CI, 0.39 to 0.87; P = 0.009) and cognitive delay (33.8 vs. 38.3%; adjusted odds ratio, 0.81; 95% CI, 0.66 to 0.99; P = 0.04). The authors concluded that caffeine therapy for apnoea of prematurity improves the rate of survival with no neurodevelopmental disability at 18 to 21 months in infants with very low birthweight. The overall frequency of retinopathy of prematurity did not differ significantly between the two groups, but a post hoc analysis showed that severe eye disease was less common in infants assigned to the caffeine group.

Lungs

Caffeine increases the central respiratory drive, thereby improving oxygenation and ventilation and decreasing hypoxic episodes. In the large, randomized, controlled caffeine for apnoea of prematurity (CAP) trial, the rates of bronchopulmonary dysplasia (BPD), defined as an oxygen need at 36 weeks postconception age, were 36.3% in the caffeine group, and 46.9% in the placebo group; a statistically significant difference. This promising effect on the incidence of BPD has been attributed to the diuretic, respiratory stimulant, and anti-inflammatory effects of caffeine (Schmidt et al., 2006). One intriguing possibility is that the lung protective effect of caffeine reported by Schmidt (Schmidt et al., 2006) may relate to their finding that infants treated with caffeine had a decreased need for pharmacologic and surgical closure of the ductus arteriosus (Bancalari, 2006). There is evidence that the prolonged patency of the ductus arteriosus in preterm infants is associated with deterioration in lung function and an increased risk of bronchopulmonary dysplasia (Rojas et al., 1995; Gonzalez et al., 1996). After almost 40 years of searching unsuccessfully for effective strategies to prevent bronchopulmonary dysplasia, it would be a welcome surprise if a simple pharmacologic intervention proved to reduce its incidence. The findings of Schmidt et al. (2006) suggested the possibility that caffeine may have this effect, at least in infants who do not require prolonged intubation. However, neonatologists must not repeat the same mishap that occurred with the use of corticosteroids in preterm infants to prevent bronchopulmonary dysplasia, which resulted in worse long-term neurologic outcomes. The primary outcomes of the caffeine trial (that is, long-term outcomes) are still pending. Assessment of the long-term effects of caffeine is needed before this therapy can be routinely recommended to prevent bronchopulmonary dysplasia (Bancalari, 2006).

Potential adverse effects

Whether there are any countervailing adverse effects remains less well established. Caffeine is a mild diuretic and sustained use increases urinary calcium loss (Zanardo et al., 1995). We also know that methylxanthine use reduces early weight gain, presumably because of the drug's effect on the metabolic rate, but we also know now that this has no long term impact on later growth. Changes in gut blood flow and gastric emptying have been documented, but we now know that the reduction in splanchnic blood flow is not associated with any increased risk of necrotizing enterocolitis, as was once feared. A loading dose more than twice as high as the one recommended here causes a measurable fall in cerebral blood flow (Hoecker et al., 2002), but it is not known whether this is of any long-term significance. Caffeine is a direct myocardial stimulant and its use in the preterm infant causes an increase in ventricular output, stroke volume and mean arterial blood pressure (Walther et al., 1990); effects that were generally assumed to be beneficial rather than potentially adverse consequences of treatment.

In one important follow-up study (Davis et al., 2000), the incidence of cerebral palsy was higher in those babies who were treated with theophylline, but this just shows that the information provided by any observational study is never as reliable, or informative, as that provided by a controlled trial. In hindsight, now that the outcome of the CAP trial is known, it is clear that theophylline use was almost certainly not the cause of the cerebral palsy seen in this well conducted study (a conclusion the authors were careful not to draw). A much more likely explanation is that non-routine use was triggered in this study by some early manifestation of the problem that later developed into cerebral palsy.

Conclusion

Apnoea has long been recognized as a clinical problem in infants. Considerable investigative and clinical attention has been directed toward this condition. Although progress has been made and certain categories of apnoea have been delineated, aetiology remains unclear in many situations. Furthermore, the condition is common in certain populations, such as infants born prematurely. Theophylline is the most potent of the methylxanthines extensively used to relax the bronchial muscle, which makes it effective as an asthma treatment. However, a review of the literature suggests that caffeine citrate may be the agent of choice for apnoea of prematurity. Both methylxantines are potent respiratory stimulants and can reduce the incidence of apnoea episodes. One of the problems with theophylline is that treatment levels are very near toxic levels. Although very similar in its action to theophylline, caffeine has several advantages and has become the preferred methylxanthine in the treatment of apnoea. Its toxicity is lower and half-life longer and there is less need for therapeutic drug monitoring. It has been reported that caffeine may have some protective effects on the brain and lungs.

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