

Apnoea in premature infants and caffeine therapy

Apnoea is one of the most common clinical manifestations in preterm infants. Apnoea of prematurity (AOP) is thought to be due to immaturity of cardiorespiratory control, hence it gradually improves with advancing gestational age. Methylxanthines are the mainstay of pharmacological treatment and caffeine citrate is the most commonly used therapy in current practice. This group of drugs has been administered over the last four decades despite a lack of robust evidence to support use. However, a large randomised controlled trial has now addressed the efficacy and long-term safety of caffeine therapy in preterm infants. In this article, key aspects of the pathophysiology of AOP will be highlighted and available evidence on caffeine therapy summarised.

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Preterm newborn infants are vulnerable to a number of problems due to the immaturity of various organ systems. Apnoea of prematurity (AOP) is one such problem, thought to be due to immaturity of the cardiorespiratory centre. Although the underlying pathophysiological mechanism of AOP is not fully understood, there have been concerns that recurrent apnoeic episodes, particularly those accompanied by bradycardia, may cause adverse neurological outcomes. Several interventions have been used to alleviate apnoea in preterm infants – caffeine citrate is the most commonly used therapy.

Definition and classification

The definition of apnoea varies widely. The most widely accepted definition among clinicians is the cessation of breathing for more than 15 seconds, typically accompanied by bradycardia and oxygen desaturation. However, apnoea of shorter duration can also manifest with

bradycardia and desaturation, particularly in the most immature infants¹.

There are three types of apnoea²:

1. Central
2. Obstructive
3. Mixed

In central apnoea there is simultaneous cessation of airflow and respiratory effort due to a loss of motor output from the brainstem. Obstructive apnoea occurs when there is inspiratory effort, seen in the form of chest wall movement, but no obvious airflow. Preterm babies are at greater risk of obstructive apnoea compared to their term counterparts due to their relatively small airways, large occiput (back of the head) and hypotonic neck muscles. Central pauses along with airway obstruction result in mixed apnoea and it is not always easy to differentiate between central and obstructive apnoea, making it difficult to treat. Mixed apnoea is the most common type seen in preterm infants accounting for more than 50% of

Keywords

apnoea; prematurity; AOP; caffeine; long-term outcome

Key points

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1. Apnoea in preterm infants is most commonly due to immaturity of cardiorespiratory control.
2. Caffeine therapy is the most widely used pharmacological intervention and its efficacy and long-term safety have now been established by a large randomised controlled trial.
3. The exact mechanism of caffeine therapy is unknown but it is thought to work by blocking adenosine receptors.

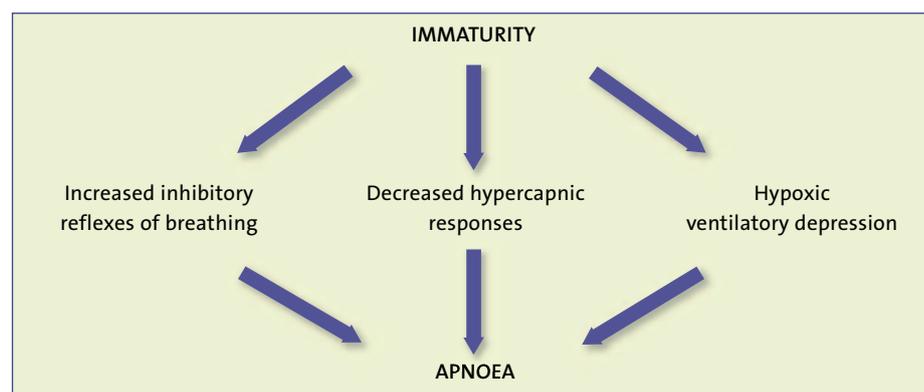


FIGURE 1 Pathophysiological mechanisms leading to AOP (adapted from Martin et al 2004³).

all apnoeas, whereas pure central or obstructive apnoeas are responsible for about 20% each³.

Incidence

The incidence of apnoea in preterm infants is hard to determine and various rates have been quoted. It can be present in up to 80% of neonates born at less than 30 weeks' gestation⁴. AOP usually resolves by 37 weeks' postmenstrual age but may persist for several weeks beyond term, especially in infants born before 28 weeks' gestation.

Pathophysiology

Immaturity of the cardiorespiratory centre plays a major role in pathogenesis. The frequency and severity of AOP is dependent upon the cardiorespiratory reflexes in response to hypoxia and hypercapnia. The hypersensitivity of the premature brain to inhibitory neurotransmitters, eg gamma-aminobutyric acid (GABA) and adenosine, and the up-regulation of GABA receptors in response to hypercapnia, hypoxia and signals from the upper airway, are significant factors in AOP (**FIGURE 1**). Furthermore, in preterm infants of less than 30 weeks' gestation there is poor myelination of the immature brainstem and a reduced number of synaptic connections and dendritic arborisation⁵.

In preterm infants, the respiratory response to an increase in carbon dioxide is impaired qualitatively and quantitatively compared to term babies or adults². With hypoxia, preterm babies exhibit an initial rise and then a decrease in breathing termed hypoxic ventilatory depression. The exact mechanism of this respiratory depression is not understood. Various postulations include a decrease in the partial pressure of arterial carbon dioxide due to initial hyperventilation and a reduced cerebral flow or neurotransmitter-mediated hypoxic central depression. Irrespective of aetiology, the low functional residual capacity and high metabolic rate in preterm babies puts them at risk of hypoxia following apnoea.

Another suggested mechanism involves stimulation of the laryngeal mucosa by mechanical or chemical stimuli – the laryngeal chemoreflex. This reflex-induced inhibition of breathing, which is mediated by the superior laryngeal nerve, also seems to improve with increasing gestational age. There is a complex relationship between

Infection	Systemic or localised
Gastrointestinal	Gastro-oesophageal reflux (GOR), necrotising enterocolitis (NEC), abdominal distension
Central nervous system	Intracranial haemorrhage, seizures
Cardiac	Patent ductus arteriosus (PDA), heart failure
Metabolic	Electrolyte imbalances, hypoglycaemia, hypocalcaemia, acidosis
Respiratory	Upper airway obstruction, bronchopulmonary dysplasia (BPD)
Drug therapies	Opioids, prostaglandin (PGE1), magnesium, general anaesthesia
Other	Anaemia

TABLE 1 Conditions associated with (but not necessarily causative of) increased prevalence of apnoea in the preterm infant.

the chest wall muscles, diaphragm and upper airway muscles that is responsible for opening of the airways and larynx during inspiration. However, this system is also responsible for glottic closure in response to laryngeal stimulation. One study found the larynx was closed in some central apnoeic episodes⁶.

In summary, AOP is mainly a consequence of immaturity of the regulation of breathing, an immature response to hypoxia and hypercapnia and an exaggerated response to stimulation of the upper airway (**FIGURE 1**).

Associated conditions

There are several conditions that render premature babies more vulnerable to increased frequency and severity of apnoea (**TABLE 1**)⁷ and these should be individually considered and excluded to guide clinical management.

It was noted nearly a century ago that frequency and severity of AOP worsen during and after feeding. Various mechanisms have been postulated about the relationship between feeding (bottle or gavage) and AOP. The hypothesis of stomach distension (with feeding) causing disturbed diaphragmatic function was put forward in 1936. It is now clear from several studies that some babies with bronchopulmonary dysplasia (BPD) become markedly hypoxic immediately after feeding⁸. Significant hypoxemic episodes may also be noted during gavage feeding and have been associated with a reduction in minute ventilation, activation of the laryngeal chemoreflex, gastro-oesophageal reflux (GOR), diaphragmatic fatigue or a combination of these factors. A reduced lung volume and increased effort of breathing may be the cause of hypoxia

after feeding due to the resulting stomach distension. One study showed no significant difference in frequency of apnoea or bradycardia with different feeding methods⁹.

Although GOR has been considered extensively in the literature, its role as a causative factor in apnoea remains unsubstantiated. Many studies have shown no temporal relationship between apnoea and GOR¹⁰⁻¹². It is difficult to prove GOR by pH monitoring, as most reflux at this age is non-acidic. Similarly, disagreement exists regarding the role of anaemia in the development of apnoea.

Outcomes related to AOP

The causal relationship between AOP and poor neurodevelopmental outcome is difficult to prove and attempts to look at prognostic risk that may be imposed by AOP have conflicting results. Some small case-control or cohort studies show no evidence of a detrimental effect^{13,14}, while other similar studies report associations between AOP and neurological impairments, cerebral palsy and behavioural difficulties in later life¹⁵⁻¹⁷. Interpreting the findings of these studies is difficult because of an inability to accurately quantify AOP, lack of a control group when using various therapeutic interventions, existing co-morbidities (eg intraventricular-periventricular haemorrhage, periventricular leukomalacia) and various confounding factors including socioeconomic status and the level of parental education.

Treatment

Most AOP episodes are self-limiting and require no specific treatment; however any

associated condition should be considered and treated accordingly (**TABLE 1**). There is no consensus on when apnoea should be treated or what frequency or severity of apnoea is acceptable. The main objectives of treatment are to reduce severe hypoxic episodes by improving the respiratory drive and reducing the work of breathing with the ultimate aim of preventing long-term neurological consequences. The choice of treatment could be non-pharmacological or pharmacological.

Non-pharmacological interventions

Non-pharmacological interventions include prone positioning¹⁸, nursing in a thermoneutral environment, kinaesthetic/physical stimulation¹⁹, appropriate placement of feeding tubes, kangaroo care, oxygen delivery via nasal cannulae and, in the more severe cases, continuous positive airway pressure (CPAP) or mechanical ventilation. Nasal CPAP only helps mixed or obstructive apnoea, with negligible effect on central apnoea. Its beneficial effect is thought to be due to splinting of the upper airway with positive pressure throughout the respiratory cycle. The preventative role of olfactory stimulation, kangaroo care, an orogastric or transpyloric feeding tube (rather than nasogastric) remains unclear.

Pharmacological interventions

Several groups of drugs, including methylxanthines, doxapram, acetazolamide, primidone and carnitine, have been used in the management of AOP. Subsequent discussion will be limited to methylxanthines and in particular, caffeine citrate.

The methylxanthines have been widely used over the last four decades for prophylaxis and treatment of AOP; the use of caffeine in AOP was first reported in 1977²⁰. These drugs are central nervous system (CNS) stimulants and act by increasing respiratory drive. The widespread use of methylxanthines was based entirely on reports of short-term outcomes and, until recently, there were no data on long-term effects, including the safety of this therapy. Several Cochrane Library systematic reviews have now been published supporting the use of methylxanthines.

Caffeine

Various characteristics make caffeine (1,3,7-trimethylxanthine) the drug of

choice over other methylxanthines, namely: a wider therapeutic window (no need for blood level monitoring), a longer half-life (once daily dosing), fewer side-effects and better cerebrospinal fluid (CSF) penetration. Caffeine is available for intravenous (IV) or oral use. Various dosing schedules are in practice although a loading dose of 20mg/kg of caffeine citrate, followed by 5mg/kg/day as a single daily maintenance dose, is most widely used. One multi-centre randomised controlled trial (RCT) has shown that the use of a higher loading dose (80mg/kg) followed by a higher maintenance dose (20mg/kg/day) significantly reduced extubation failure in preterm infants of less than 30 weeks' gestation²¹, although the long-term safety of this regimen has not been established. In one other study, the use of higher doses was shown to be more effective in prevention of AOP but was associated with impairment of cerebral and intestinal blood flow velocity²².

Mechanism of action

Although the exact mechanism of action of caffeine is unknown, it is considered to work by non-specific blockage of subtypes of adenosine receptors². It has been suggested that the blockage of A1 and A2A adenosine receptors on GABAergic neurons diminishes respiratory inhibition¹. The resulting physiological effects, including improved respiratory muscle function, generalised CNS stimulation and increased chemoreceptor responsiveness to carbon dioxide, are responsible for a reduction in apnoeic episodes. Caffeine is a non-selective adenosine receptor antagonist and, as it is suggested that adenosine is neuroprotective during ischaemia²³, concerns have been raised about the long-term safety of caffeine therapy.

Caffeine for Apnoea of Prematurity (CAP) trial

The Caffeine for Apnoea of Prematurity (CAP) trial was conducted between 1999 and 2004 in nine countries across four continents as a global collaboration to address the concerns relating to the long-term safety and efficacy of this commonly used therapy. This multi-centre RCT enrolled >2,000 infants with birth weights between 500 and 1250 grams. Infants received either caffeine citrate (20mg/kg loading dose followed by 5-10mg/kg/day maintenance) or equivalent volumes of

placebo. This is the largest trial to date using the combined rate of mortality and neurodevelopmental disability in survivors at corrected age of 18 months as primary outcomes. The trial also addressed the effect of caffeine on neonatal morbidities and other clinically important secondary outcomes²⁴.

Caffeine therapy significantly reduced the risk of BPD: 36% in the caffeine group vs. 47% in the placebo group (OR 0.63; 95% CI: 0.52-0.76; p<0.001). Supplemental oxygen therapy, CPAP and mechanical ventilation were discontinued one week earlier with the use of caffeine compared to the placebo. Unexpectedly, there was also a significant reduction in the risk of persistent PDA requiring pharmacological or surgical closure in the caffeine treated group. There was a temporary reduction in weight gain during the first three weeks of caffeine therapy, but no adverse effect on growth at the time of hospital discharge. The CAP trial also provides the reassurance that caffeine therapy does not increase the risk of NEC or ultrasonographic evidence of brain injury. Adequate data for an analysis of primary outcomes were available for 93% of the subjects and the high quality follow-up data of the CAP trial showed that caffeine therapy improves the rate of survival without neurodevelopmental disability at corrected age of 18 months (death or disability 40.2% in caffeine group vs. 46.2% in placebo group; OR 0.77; 95% CI: 0.64-0.93; p=0.008). Caffeine therapy also reduced the incidence of cerebral palsy (4.4% vs. 7.3%; p=0.009) and cognitive delay (33.8% vs. 38.3%; p=0.04)²⁵. The *post-hoc* analysis to explore the likely mechanisms why caffeine therapy resulted in better outcome suggested that earlier discontinuation of positive airway pressure in infants who received caffeine was the most important variable. This mechanism was supported by further analysis of subgroups in the CAP trial which showed that infants receiving CPAP or mechanical ventilation appeared to have gained more benefit from caffeine therapy, compared with infants who were not requiring any positive airway pressure support²⁶.

Follow-up information at five years of age for 1,932 participants in the original CAP study was published more recently. Adequate data for the main outcome were available for 85% of participants and show that neonatal caffeine therapy is no longer associated with a significant improvement

in the rate of survival without disability in children when assessed at five years. Similarly the rates of death, motor impairment, behavioural problems, deafness and blindness do not differ significantly between the two groups²⁷. Nevertheless, absence of any adverse effects at five years of age in children who were randomly assigned to receive caffeine is reassuring with regard to concerns about long-term detrimental effect of neonatal caffeine therapy.

Summary

AOP continues to be a concern in neonatal units although the understanding of the various mechanisms responsible for this clinical entity has improved over the last few decades. Several non-pharmacological and pharmacological interventions have been used to treat AOP but caffeine therapy is the only intervention that is widely studied and supported by strong evidence.

The CAP trial is a good example of using the 'gold standard', the RCT, to examine the benefits and long-term safety of a commonly used therapy.

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