

Management of apnoea and bradycardia in neonates

Eve Atkinson

Alan C Fenton

Abstract

Apnoea is common in the preterm infant, particularly those less than 30 weeks gestation. It results from a combination of central and obstructive factors in the otherwise well preterm infant but can also be a sign of underlying pathology: therefore the diagnosis of apnoea of prematurity is one of exclusion. Apnoea and associated bradycardia and hypoxaemia may require cardiovascular resuscitation and may be associated with long term adverse neurodevelopmental sequelae. A variety of physical and pharmacological treatments have been used with the aim of reducing the severity of episodes and ultimately improving long term outcomes. Caffeine is currently the drug of choice in the treatment of apnoea, supplemented in refractory cases by additional mechanical respiratory support. Long term follow up of affected infants within multi-centre trials is key to optimising management strategies.

Keywords apnoea; bradycardia; management; neonate; preterm

Introduction

Neonatal apnoea is a common problem particularly in the preterm population. The American Academy of Pediatrics defines apnoea as a pause in breathing for more than 20 seconds or shorter pauses that are also associated with desaturation, bradycardia, pallor or reduced tone. Severe episodes, associated with hypoxaemia and reduced cardiac output, may require resuscitation and have the potential to cause brain injury. Accurate diagnosis and management is important to ensure secondary causes are appropriately treated and the consequences of severe apnoea are minimised. Several treatment options, both pharmacological and non-pharmacological, are available to treat or potentially prevent apnoea. The aim of this review is to evaluate the evidence base for the use of these therapies in the neonatal population.

Definitions and diagnosis

Apnoea can be classified physiologically as central, obstructive or mixed. Central apnoea occurs when there is absence of respiratory drive. In obstructive apnoea the infant makes continued respiratory effort but airflow is restricted due to airway

Eve Atkinson MBBS MRCPCH is a Specialist Registrar at Newcastle Neonatal Service, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK.

Alan C Fenton MD MRCP is a Consultant Neonatologist at Newcastle Neonatal Service, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK.

collapse. If the obstruction persists CNS depression due to hypoxia and acidosis will result in mixed apnoea. For the majority of preterm infants a mixed picture is seen with both obstructive and central factors contributing with only 10% of preterm apnoea being due solely to airway obstruction.

Apnoea of prematurity (AOP) is a diagnosis of exclusion and therefore thorough examination and appropriate investigation is essential to diagnose and treat secondary causes (Table 1). The clinical picture will determine the extent of investigation but may include a septic screen, full blood count, chest X-ray, blood gas, serum electrolytes and glucose, EEG, pH testing and neurological imaging. Many of the conditions listed in Table 1 are associated with apnoea but this does not necessarily imply causation and care must be taken when attributing the cause of apnoea. For example gastro-oesophageal reflux is much more common in preterm infants and is often falsely attributed as a cause of apnoea but this may not always be the case.

The incidence of apnoea is significantly greater in preterm infants affecting just under 10% of infants born at 34–35 weeks, increasing to 50% of those born between 30–31 weeks with an even higher incidence in extremely preterm infants. Although the precise underlying mechanisms responsible for AOP have not been fully defined, physical differences and immature physiology are important contributors. A large occiput, hypotonic neck muscles and smaller airways increase the risk of upper airway obstruction and with reduced reserves the preterm infant is more likely to tire. Immaturity of the pathways involved in respiratory drive and exaggerated inhibitory responses are thought to be the main physiological pathways involved. Several neurotransmitters including GABA, adenosine, serotonin and endorphins are under scrutiny as are cytokines involved in prostaglandin E2 production.

It is hoped that by defining the exact pathways and chemicals involved in AOP, development of more specific therapies may become possible, thus reducing potential side effects of non-specific blockade of receptors such as the adenosine receptors targeted by methylxanthines.

Incidence & monitoring

Changes in heart rate, respiratory rate, oxygen saturation and respiratory effort aid in the identification and management of apnoea. Quantifying the severity of episodes can be difficult but data monitoring and recording may help in assessment of apnoea severity in addition to clinical observation, thus aiding diagnosis and helping to monitor treatment outcomes. The limitations of monitoring devices must be taken into account. For example an apnoea mattress will not alarm in obstructive apnoea if the infant continues to make respiratory effort and it is acknowledged that the use of home apnoea monitors has not reduced the incidence of SIDS. Other monitoring devices including impedance pneumography, respiratory inductance plethysmography, end tidal CO₂ monitoring and thermistor beads provide additional measures but are usually confined to the research setting.

Management

Severe episodes leading to prolonged hypoxia and bradycardia may require cardiovascular resuscitation. Identification and appropriate treatment of contributing factors is essential in all

Secondary associations/causes of apnoea

Infection (bacterial and viral)	Sepsis, meningitis, NEC
Neurological	Intracranial haemorrhage Seizures Asphyxia Congenital malformations
Respiratory/Cardiovascular	Hypoxaemia, RDS, pneumonia aspiration PDA Hypovolaemia, hypotension Heart failure
Haematological	Anaemia
Gastrointestinal	GORD Abdominal distension
Drugs (infant and maternal)	Opiates Magnesium Prostaglandins Consider drug withdrawal
Acute/chronic pain	
Airway malformation	
Head/body position	
Metabolic	Hypoglycaemia Hypocalcaemia Hypothyroidism Hyponatraemia

Table 1

cases of neonatal apnoea. Additional respiratory support, physical and pharmacological treatments may also be required. The aim of therapy is to reduce the severity of hypoxaemia and ultimately prevent adverse neurological outcome. It is therefore important to ensure that short term gains are free from long term adverse effects. Ideally long term follow up of adequately powered RCTs of available treatments would help to determine the effectiveness of the many therapies available. Teasing out the effects of apnoea from other 'prematurity associated factors' is also challenging. The mainstays of therapies available are both pharmacological and non-pharmacological each with varying amounts of evidence to support their use.

Pharmacological treatments

Methylxanthines Methylxanthines have been used as a treatment for neonatal apnoea since the early 1970s. Their effectiveness in increasing minute ventilation, CO₂ sensitivity and diaphragmatic breathing, whilst reducing periodic breathing and hypoxic episodes is well documented. Caffeine is now one of the most commonly used drugs in neonatal care. The effectiveness of caffeine was demonstrated by a small number of studies and as a result few RCTs have taken place. A Cochrane review including 5 small studies (192 infants) demonstrated a significant decrease in apnoea and the need for IPPV in the first 2–7 days of life in those infants receiving caffeine compared to placebo or no treatment, with a second review demonstrating equal efficacy when compared to theophylline. The much wider therapeutic

index, once daily dosing, reduced side effect profile, increased CSF penetration and equal efficacy has favoured the use of caffeine over theophylline or aminophylline.

The mechanism of action of methylxanthines as a respiratory stimulant is still to be elucidated but it is generally accepted that non-specific inhibition of A1 and A2a adenosine receptors is a key effect. These receptors are found throughout the body therefore concerns that non-specific blockade may have unwanted side effects has been raised. Short term side effects of caffeine include a 20% increase in metabolic demand, diuresis, tachycardia, dysrhythmias, feed intolerance, reduced weight gain and rarely seizures. In the long term worries over potential adverse neurodevelopmental outcomes and other neonatal morbidities such as necrotising enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, reduced growth and behavioural problems led to the Caffeine for Apnoea of Prematurity (CAP) trial. Over 2000 infants weighing 500–1250 g at birth were randomised to caffeine or placebo. In addition to short term benefits of reduced apnoea and a reduction in ventilatory support, follow up at 18–21 months has also shown a reduction in death or survival with neurodisability and a reduced incidence of cerebral palsy and cognitive delay in those who received caffeine. Further follow up is planned at 5 years. In the interim these results are very encouraging and provide some reassurance that improved short term outcomes are not at the expense of long term adverse effects.

Doxapram Doxapram is a potent respiratory stimulant that has been shown to increase minute volume by increasing respiratory rate in adults. The response is dose related with effects at lower levels mediated by the carotid bodies and those at higher levels mediated by the brainstem. Use in neonatal apnoea has been documented, particularly when treatment with caffeine has failed.

There are however only a small number of studies in neonates. A Cochrane review found only one small trial of 21 infants carried out in 1990. Although fewer treatment failures were seen after 48 hours in those who received doxapram the result was not significant and the cross-over design of the study also prevented evaluation after 48 hours in the placebo group. No long term outcomes were measured and the authors conclude that there is insufficient data to evaluate the precision of the results or potential adverse effects; they suggest further studies are required to determine the role of doxapram in clinical practice.

Several other studies have highlighted side effects including hypertension, seizures and GI disturbance with one study also reporting second-degree heart block in 3 infants that resolved following discontinuation of doxapram. A decrease in maximal cerebral blood flow velocity has also been demonstrated and the oral preparation is poorly absorbed and tolerated. A small number of studies have also reported adverse neurodevelopmental outcomes. One group of 40 infants treated with doxapram were found to have a lower mental developmental index at 18 months than controls. Confounding effects of possible underlying cerebral dysfunction cannot be ruled out and there was no comparison with frequency, duration and severity of apnoea. Studies in rats under ischaemic conditions have shown increased white matter damage with the use of doxapram.

As a result of the adverse side effect profile and lack of long term data doxapram is not recommended as routine therapy for AOP.

Other pharmacological treatments Several other pharmacological therapies have been suggested as possible therapies for apnoea including: acetazolamine, primidone, carnitine and methylsulphate diphemanyl. However there are very limited data on short term outcomes and virtually no information on long term effects of these therapies.

Elucidation of the precise mechanisms responsible for apnoea, including the influences of associated factors will help to refine and target existing therapies or perhaps enable development of new therapies in the future. Identification of susceptibility perhaps in terms of increased genetic load may further target specific treatments to those who may benefit most. In all cases these pharmacological agents will need to be evaluated for both short and long term outcomes.

Non-pharmacological treatments

Environmental factors Several environmental factors have been assessed in relation to AOP including sleep position, temperature, physical stimulation and even exposure to different aromas. The 'back to sleep' campaign and subsequent reduction in SIDS has highlighted the importance of the supine position in reducing SIDS. However for the preterm infant monitored and cared for on the neonatal unit the prone sleeping position is recommended as this can improve oxygenation and ventilation, reduce energy expenditure in respiration and also reduce regurgitation and gastric aspiration. A Cochrane review of short term outcomes in 206 infants from 11 trials examined the effect of body position in infants receiving mechanical ventilation. There was an improvement in oxygenation with prone positioning, but there was no evidence that this was associated with sustained and clinically relevant outcomes. It is important that parents understand the need to change to the supine position to reduce the risk of SIDS on resolution of apnoea when planning for home.

Appropriate head and neck positioning may help to combat some of the contributing factors of obstructive apnoea and a tilted cot position of 15° has also been shown to reduce episodes of hypoxia. Humidification of warm gas may help and some have argued that a thermoneutral or even slightly lower temperature may help. Kangaroo care improves parent-infant contact but no definite reduction in apnoea has been demonstrated and in one small study bradycardia and hypoxaemia were in fact increased. The authors suggested this may be due to increased temperature or neck flexion. Inhalation of low concentrations of CO₂ (0.5%–1.5%) has also been suggested as has the use of a pleasant odour known to modulate the infants respiratory rate. The numbers in both studies were small and thus it is difficult to advocate their use in management of AOP at this time.

Stimulation Stimulation is often used to terminate an episode of apnoea and bradycardia. With this in mind several rocking, pulsating and moving mattresses/beds have been devised with the aim of treating or preventing neonatal apnoea. A Cochrane review of 3 small trials aimed to assess the effectiveness of kinaesthetic stimulation in the treatment of apnoea. Two of the three trials did demonstrate a 25% reduction in episodes, although numbers were small (49 infants), the devices differed and long

term effects were not assessed. In light of these limitations the authors conclude that at present there is insufficient evidence to recommend these devices as a treatment for neonatal apnoea. A further review also demonstrated theophylline to be significantly more effective in AOP treatment than an oscillating water bed, although study numbers were also small. More recently mechanosensory stimulation using a vibrating (30–60 Hz) mattress has been demonstrated to reduce inter-breath interval variance by around 50% with no adverse effect on infant movement, sleep state or EEG. Habituation may become problematic, study numbers were also small and long term outcomes are also required.

There is a similar lack of evidence for kinaesthetic stimulation as a prophylactic therapy for AOP. A meta-analysis of 3 trials of 154 found no significant reduction in the incidence of apnoea or the need for mechanical ventilation and only one study looked at possible adverse effects.

Respiratory support A number of infants will require additional respiratory support. The intensity and duration of support required will vary and must be assessed and reassessed on an individual basis. In general the aim is to use the minimum support required to prevent hypoxia and bradycardia. The ability to identify when an infant is 'ready' for extubation would reduce the number of reintubations. A number of factors will influence this decision and as yet there is no 'one formula fits all' solution. An array of strategies are available to aid weaning and provide support following extubation and these must be tailored to each infant.

Nasal cannulae oxygen A trial of 40 preterm infants comparing nasal cannulae oxygen (max 2.5 L/min) with nasal continuous positive airway pressure (nCPAP) 6 cm H₂O concluded that high flow nasal cannulae oxygen was just as effective as nCPAP. The authors comment that airflow escape may reduce effectiveness if the infant mouth breathes although they also state that this also occurs with nCPAP, albeit to a lesser extent.

Continuous positive airway pressure For infants with an obstructive or mixed apnoea continuous positive airway pressure (CPAP) may reduce apnoea by increasing pharyngeal pressure thereby reducing the likelihood of upper airway collapse leading to obstruction. There is an increase in FRC and thus oxygenation. 'Stimulation' from the device itself may also contribute to the effect.

One early study demonstrated theophylline to be more effective than nCPAP in the treatment of apnoea and bradycardia with 5/18 infants needing IPPV compared to 12/14 given nCPAP. However pressures used were low (2–3 cm H₂O) increasing to 4–5 cm H₂O if ineffective and 13/14 of the CPAP group had perinatal complications. It was difficult to compare the two treatments long term as many infants received both treatments at some point. Adverse outcome including death and severe disability was increased in those requiring IPPV. Since these early trials meta-analysis has demonstrated that the use of nasal CPAP following extubation reduces extubation failure. Possible side effects of CPAP include: pneumothorax, nasal trauma, barotrauma and bowel distension, so as with all therapies treatment duration should be constantly reviewed and weaned where possible.

Non invasive positive pressure ventilation Non invasive positive pressure ventilation (NIPPV) is increasingly being used in neonatal care. The optimum inspiratory and expiratory

pressures and times and weaning strategies are yet to be determined but there is some evidence that it may be effective in the management of neonatal apnoea. Two randomised controlled trials have compared the use of NIPPV and nCPAP in treating neonatal apnoea. Both trials are relatively small (20 and 34 infants) and the results conflicting. A meta-analysis of 3 trials using synchronised NIPPV demonstrated clinical and statistically significant benefit of NIPPV compared to nCPAP. Although rates of GI perforation were not increased as in earlier studies, it was suggested that larger studies are required including assessment of long term outcomes.

Conventional ventilation For those infants who do not respond to non-invasive forms of ventilation or pharmacological therapies invasive ventilation may be required. Trigger synchronized ventilation using minimal peak inspiratory pressures should be used.

Prophylactic therapies

Several of the above therapies have been used to try and prevent AOP in at-risk preterm infants but their effectiveness is difficult to determine due to the lack of large randomised controlled trials. A meta-analysis of studies using caffeine prophylactically identified only 104 infants, concluding that there were insufficient data to recommend use in this setting. A more recent review of post-operative apnoea risk suggested that infants with a post-conceptual age of less than 46 weeks should be monitored for at least 12 hours post-op and IV caffeine can reduce that the risk of apnoea in former preterm infants. A meta-analysis of two small trials (85 infants) of prophylactic doxapram to assist extubation found no significant difference in outcome compared to placebo with a trend towards increased side effects in the doxapram group. A small number of studies have also looked at carnitine supplementation prophylactically but no recommendations can be made for its use as treatment or prophylaxis.

Resolution and outcome of AOP

Age at resolution of apnoea varies. The largest study to date is the CHIME study (Collaborative Home Infant monitoring Evaluation). On the whole AOP resolved in most preterm infants by 37 weeks post-conceptual age, although for some infants the return to 'normal' term levels occurred at around 43–44 weeks.

Despite being a very common neonatal problem there are a paucity of data regarding long term outcomes. A small number of studies have attempted to address this question but there are several difficulties including small numbers of infants, lack of prospective trials, differing definitions and recording, relatively short term follow up and the difficulty of teasing out the effects of apnoea from other prematurity related factors. One study of 60 preterm infants at 2 year follow up showed no difference in outcome compared to age-related controls with another suggesting worse neurodevelopmental outcome infants with obstructive apnoea. A further study identified adverse neurological outcome in relation to several neonatal complications including apnoea, but this relationship was partly due to abnormal findings on cranial ultrasound. These studies have focused on outcomes in those infants with and without apnoea and tend to include the 'older' preterm infant. In a group of 175 preterm infants an association was demonstrated between the

number of days of apnoea and adverse neurological and developmental outcome at 3 years. The CHIME study also demonstrated a reduction in neurodevelopmental outcome at one year in term and preterm infants who were found to have 5+ cardiorespiratory events when monitored at home compared with infants who had no events, with mental developmental indices 5.6 points lower in term infants and 4.9 points lower in Preterm infants. The authors comment that it is not clear whether the documented events with apnoea and bradycardia are the cause or whether they are the result of a common underlying cause that also causes adverse neurodevelopment.

With a significant increase in survival of extremely preterm infants, trials will need to determine effects of differing severity of apnoea as almost all extremely preterm infants will suffer apnoea to some degree. One prospective study examined neurodevelopmental outcome at 13 months in 83 VLBW infants, 75 of whom had received methylxanthine treatment. Using an observational score including an assessment of severity it was found that a more prolonged course or a more severe course over the period 31 to 37 weeks PMA may be more useful predictors of later developmental delay. The total number of episodes and the highest score were less useful as they reflected the degree of prematurity which is known to be a good predictor of poor outcome in itself.

As many infants are already receiving treatment such as caffeine outcomes from the CAP trial will be more relevant than those looking at outcome of the natural untreated course of AOP. As many infants with severe AOP also receive additional treatments such as doxapram and choice of respiratory support increases more long term outcome trials will be necessary.

The majority of long term studies of AOP have focused on neurodevelopmental outcomes. Although the incidence of sleep disordered breathing is increased in children born preterm the long term respiratory outcomes in infants with AOP per se is not known.

Planning for discharge home

The half life and elimination time of caffeine varies but is around 5–7 days. It is therefore important that a period of observation following discontinuation of treatment is carried out to ensure that resolution is complete and that supine sleeping position is established. Rooming in can help in the transition to home and acquisition of basic life support skills by all those involved in infant care is very important.

The journey home including appropriate transport should be discussed. The use of car safety seats/cots for the transfer of infants is mandatory by law in many countries including the UK. Comparisons between different designs have shown little difference between different models. However episodes of apnoea and bradycardia may increase regardless of the model used so keeping the time spent in these devices to a minimum is advisable.

The use of home monitors is debated. There is no evidence that their use prevents SIDS and in fact most AOP resolves prior to the peak incidence of SIDS. A policy statement by the American Academy of Pediatrics highlights the huge investment of resources in home monitoring over several decades despite a lack of evidence that this reduces morbidity and mortality. They suggest that if used parents must understand that infants have died despite

monitoring and clear plans for review and discontinuation of monitoring should be agreed before the infant goes home.

Summary

The management of neonatal apnoea and bradycardia is a common problem faced by all neonatologists. Adequate resuscitation and identification and treatment of contributing factors is essential. Caffeine is the drug of choice in the treatment of apnoea and respiratory support should be provided where necessary using the minimum level of support required to reduce hypoxia and bradycardia. There is some evidence of the long term neurological impairment that may result from severe apnoea and bradycardia. Information from the CAP trial indicates that long term adverse neurological outcome may be reduced with caffeine treatment. Continued follow up will be extremely valuable in advising optimal management strategies as would similar trials of multiple drug therapies that are commonly used in some units with little knowledge on long term effects.

Conflict of interest statement

Dr E Atkinson and Dr A Fenton have no financial or personal conflicts of interest to declare.

Funding body

Not applicable. ◆

FURTHER READING

- AAP. Consensus statement. national institutes of health consensus development conference of infantile apnea and home monitoring, sept 29 to Oct 1, 1986. *Pediatrics* 1987; **79**(2): 292–300.
- AAP. Policy statement. *Pediatrics* 2003; **111**(4): 914–7.
- Abu-Shaweesh JM. Maturation of respiratory reflex responses in the fetus and neonate. *Semin Neonatol* 2004; **9**(3): 169–80.
- Davis PG, Lemyre B, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev*; 2001 (3):CD003212.
- Finer NN, Barrington KJ, Hayes BJ, Hugh A. Obstructive, mixed, and central apnea in the neonate: physiologic correlates. *J Pediatr* 1992; **121**(6): 943–50.
- Henderson-Smart DJ. The effect of gestational age on the incidence and duration of recurrent apnoea in newborn babies. *Aust Paediatr J* 1981; **17**(4): 273–6.
- Henderson-Smart D, Steer PA. Doxapram treatment for apnea in preterm infants [update of Cochrane Database Syst Rev. 2001;(4):CD000074; PMID: 11687067]. *Cochrane Database Syst Rev*; 2004 (4):CD000074.
- Henderson-Smart DJ, Steer PA. Methylxanthine treatment for apnea in preterm infants [update of Cochrane Database Syst Rev. 2000;(2):

CD000140; PMID: 10796304]. *Cochrane Database Syst Rev*; 2001 (3): CD000140.

Henderson-Smart DJ, Osborn DA. Kinesthetic stimulation for preventing apnea in preterm infants [update of Cochrane Database Syst Rev. 2000;(2):CD000373; PMID: 10796201]. *Cochrane Database Syst Rev*; 2002 (2):CD000373.

Henderson-Smart DJ, Davis PG. Prophylactic doxapram for the prevention of morbidity and mortality in preterm infants undergoing endotracheal extubation. *Cochrane Database Syst Rev*; 2000 (3):CD001966.

Hunt CE, Corwin MJ, Baird T, et al. Cardiorespiratory events detected by home memory monitoring and one-year neurodevelopmental outcome. *J Pediatr* 2004; **145**(4): 465–71.

Martin RJ, Wilson CG, Abu-Shaweesh JM, Haxhiu MA. Role of inhibitory neurotransmitter interactions in the pathogenesis of neonatal apnea: implications for management. *Semin Perinatol* 2004; **28**(4): 273–8.

Millar D, Schmidt B. Controversies surrounding xanthine therapy. *Semin Neonatol* 2004; **9**(3): 239–44.

Osborn DA, Henderson-Smart D. Kinesthetic stimulation for treating apnea in preterm infants. *Cochrane Database Syst Rev*; 2000 (2): CD000499.

Osborn DA, Henderson-Smart D. Kinesthetic stimulation versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev*; 2000 (2):CD000502.

Pillekamp F, Hermann C, Keller T, von Gontard A, Kribs A, Roth B. Factors influencing apnea and bradycardia of prematurity - implications for neurodevelopment. *Neonatology* 2007; **91**(3): 155–61.

Ramanathan R, Corwin MJ, Hunt CE, et al. Cardiorespiratory events recorded on home monitors: comparison of healthy infants with those at increased risk for SIDS [see comment]. *JAMA* 2001; **285**(17): 2199–207.

Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure [see comment]. *Pediatrics* 2001; **107**(5): 1081–3.

Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity [see comment]. *N Engl J Med* 2007; **357**(19): 1893–902.

Steer PA, Henderson-Smart D. Caffeine versus theophylline for apnea in preterm infants. *Cochrane Database Syst Rev*; 2000 (2):CD000273.

Practice points

- Apnoea and associated bradycardia are common in the preterm infant, increasing with decreasing gestation
- Apnoea of prematurity (AOP) is a diagnosis of exclusion
- Caffeine is the drug of choice for AOP
- AOP refractory to caffeine may require additional respiratory support