Management of apnoea and bradycardia in neonates

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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 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 impedence pneumograpy, respiratory inductance plethysmography, end tidal CO_2 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

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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, CO_2 sensitivity and diagphragmatic 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, dysrythmias, 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.