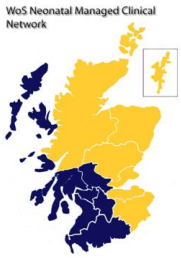
MCN for Neonatology

West of Scotland

Neonatal Guideline



Apnoea of Prematurity

Introduction

An apnoea is defined as a pause in breathing for 20 seconds or longer or a shorter pause accompanied by bradycardia (<100 beats per minute), cyanosis, or pallor[1]

Apnoeas can be central in origin (cessation of breathing effort), obstructive (blockage of airflow at pharyngeal level) or mixed

Apnoeas can be caused by:

- **Apnoea of prematurity (<35weeks)**: The most common cause of apnoea, attributable to the immaturity of the respiratory centre in the brain.
- **Airway obstruction**: Position not neutral, obstruction with secretions/vomit
- **Infections**: Sepsis, necrotising enterocolitis, meningitis
- **Cardiovascular**: Anaemia, hypotension, cardiac failure
- **Pain**: Acute and chronic
- **Central nervous system**: Intraventricular haemorrhage, seizures, hypoxic injury, raised intra cranial pressure, neuromuscular disorders, brainstem infarction or anomalies, birth trauma, congenital malformations, central hypoventilation, syndromic
- **Respiratory**: Infection, lesions causing airway obstruction, respiratory distress syndrome, hypoxia, malformations of chest, phrenic nerve paralysis, pulmonary haemorrhage, aspiration
- **Gastrointestinal**: Intestinal perforation, gastro oesophageal reflux, abdominal distension
- **Metabolic**: Hypoglycaemia, electrolyte disturbance, metabolic conditions, hypothermia
- **Drugs**: Maternal drugs, opiates, prostin, high levels of phenobarbitone, chloral hydrate or other sedatives, general anaesthetic.
- **Immunisations**

It is therefore important that in babies with new onset apnoeas a full clinical review and examination is performed before commencing any treatment for apnoea of prematurity.

Apnoea of prematurity is extremely common in preterm neonates. Previous studies have shown that treatment of AoP has lead to improved survival rates without neurodisability at 5 years of age. The aim of this guideline is to provide a streamlined approach to the assessment and management of a neonate with suspected AoP

Current studies suggest that the incidence of AoP is inversely proportional to age, with 100% of infants born <28 weeks developing AoP as defined above. 85% of babies born at 30 weeks gestation developed AoP, which reduced to 20% at 34 weeks. The natural history of AoP is that the more severe episodes resolve first, with isolated bradycardias last to resolve. However persistent events beyond 40 weeks cGA are more common in babies born less than 28 weeks cGA with several studies suggesting on going apnoeas were occurring post 40 weeks cGA in up to 22% of babies born with a gestational age of 23-28 weeks.

Treatment Options

Caffeine Citrate – PLEASE NOTE ALL CAFFEINE PRESCIPTIONS IN NHS GGC NEONATAL UNITS MUST BE PRESCRIBED AS CAFFEINE CITRATE

Methylxanthines are among the most commonly used medications in preterm infants. They have been used for the treatment of AoP over the past 40 years. Caffeine citrate has now largely replaced theophylline and aminophylline for treatment of AoP because of its wider therapeutic index and longer half-life that allows once daily administration.

Caffeine citrate acts as a selective adenosine antagonist at the A2a receptors and a non-selective adenosine antagonist at A1 receptor. Through this action it modulates many neurotransmitters and can also lead to increased levels of bronchodilation.

Moreover, caffeine citrate enhances peripheral chemoreceptors activity; therefore it can terminate apnoea and initiate normal breathing. Caffeine citrate may also have an anti-inflammatory action in the immature lung. The benefits of caffeine citrate therapy on respiratory functions increase the success of early nasal-continuous positive airway pressure (CPAP) therapy, facilitate earlier weaning from mechanical ventilation, and reduce ventilator-induced lung injury.

Current evidence suggests that caffeine citrate should be given initially as a loading dose followed by a maintenance dose as per local drug formulary. Current evidence suggests that these doses of caffeine citrate may reduce neurodevelopmental impairment at 5 years of age. Moreover a recent update from the CAP trial has found that at aged 11, patients in the treatment group had improved visuomotor, visuospatial and visuoperceptual abilities without any difference in intelligence or behaviour

Caffeine citrate should be commenced in all babies under 30 weeks gestation and should be **administered within 2 hours after birth** for apnoea prophylaxis regardless of level of respiratory support**.** The most studied maintenance doses are 5mg/kg and 10 mg/kg with some evidence to suggest that the higher dose confers additional benefits, particularly in the most immature neonates. **We therefore recommend commencing 10mg/kg maintenance dose 24 hours after loading dose as per NHS GGC Neonatal Formulary.** Other studies have looked at higher doses >10mg/kg maintenance still but there is insufficient evidence to recommend these currently. **If babies are at risk of requiring Less Invasive Surfactant Administration (LISA) then the loading dose should be given within 1 hour of birth**.

In babies at 30 -37 weeks gestation with recurrent episodes of apnoea an assessment should be made for other potential causes of apnoea and caffeine citrate should be commenced for recurrent episodes of apnoea which are felt to be secondary to apnoea of prematurity. Babies at 30-37 weeks who are requiring ventilation or are post surgical procedures may also benefit from caffeine citrate as these babies are at increased risk of apnoeic episodes.

There are no clinical trials to support decisions about when to discontinue caffeine citrate therapy in preterm infants. However, because AoP is not common past 34 weeks gestation, caffeine citrate therapy should be continued until preterm infants are at least 33 weeks cGA and free of any apnoea episodes for at least 3 days. Ideally caffeine citrate should be stopped 7 days prior to discharge as this is felt to be the maximum amount of time required for the

drug to completely clear the body. However discretion can be used by the senior clinician if it is felt that this may potentially delay discharge in an otherwise well baby with no apnoeic episodes for > 3days.

Gastro oesophageal Reflux Disease (GORD)

Although there is little evidence to support a link between GORD and AoP, it is accepted that preterm infants are at more risk of developing GORD. This may in turn lead to episodes of desaturation and apnoea. However, as the link between AOP and GORD is not based on strong evidence, empirical treatment of GORD is discouraged, particularly with H2 receptor antagonists as they increase the risk of NEC. If there is felt to be a strong association between feeds and AoP in an individual patient then appropriate investigation should be undertaken to determine if reflux is causal (pH / Impedence study). If so then feeding thickeners should be tried initially and H2 receptor antagonists reserved for those with significant GORD unresponsive to thickening of the feeds

Blood Transfusion

A number of studies have previously looked at the link between apnoea of prematurity and anaemia. Whilst most of these studies concluded that anaemia may increase the likelihood of apnoea of prematurity and blood transfusions may result in a short term reduction in apnoeas, there is currently no data to indicate that blood transfusions will lead to long term reductions in apnoea. Therefore infants suspected of having anaemia should be investigated and treated as per WoS guidance on blood transfusion in the neonate.

Nasal CPAP

Premature infants with ongoing episodes of apnoea despite optimal caffeine citrate therapy and no other underlying causes may also benefit from a period of nasal CPAP. Nasal CPAP (NCPAP) pressures of 4-6 in conjunction with caffeine citrate therapy have been shown to reduce the frequency and severity of apnoeic episodes in premature infants. Humidified high-flow nasal cannula or nasal intermittent positive-pressure ventilation may be acceptable substitutes for NCPAP. However, larger studies that specifically examine the advantages and disadvantages of nasal intermittent positive-pressure ventilation and high-flow nasal cannula versus conventional NCPAP on the incidence and severity of recurrent apnoea are currently lacking and very much required.

Monitoring for AoP

Indications for apnoea monitoring:

- Infants <34 weeks, regardless of saturation monitoring or not
- Infants receiving caffeine citrate therapy
- Infants receiving their first set of immunisations and for 48hr after
- Infants receiving morphine sulphate or other sedation
- Infants with known syndromes or anomalies predisposing to apnoea (central or obstructive)
- Unwell/unstable infants
- Infants on prostaglandin infusions
- At the discretion of senior nursing and medical staff

There is currently a lack of evidence to suggest the optimum time to discontinue monitoring for a neonate prior to discharge. This has led to a wide variation in practice regarding the cessation of monitoring for any episodes of apnoea. However, given changes in the management of late preterm infants, babies > 34 weeks cGA who have been free of apnoeas for 3 consecutive days whilst off caffeine citrate may have all forms of monitoring

discontinued. An apnoea alarm may be continued if the baby has had a procedure performed (e.g. ROP, immunisations etc) but must be discontinued at least 48 hours prior to discharge. Babies ready for rooming in should have their apnoea monitors removed.

There is currently no evidence to suggest the routine use of home monitoring using an apnoea alarm. Indeed this may cause unnecessary parental anxiety. All parents with premature infants on SCBU should be offered a discharge discussion with nursing staff regarding sleeping and feeding and resuscitation training if appropriate.

If it is felt that an apnoea alarm may be required for a particular patient prior to discharge then **this must be discussed with the discharging or named neonatal Consultant for the patient**.

References

1) Eichenwald E et al, Apnea of Prematurity, Pediatrics, Vol 137, Number 1, January 2016 https://pediatrics.aappublications.org/content/pediatrics/early/2015/11/30/peds.2015-3757.full.pdf
2) https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Apnoea_Neonatal/
3) https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Observation_and_Continuous_Monitoring/#Continuous Monitoring

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