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NEONATAL ANAESTHESIA 1: PHYSIOLOGY ANAESTHESIA TUTORIAL OF THE WEEK 65

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Self assessment

Please answer the following questions prior to reading the tutorial

1. Explain why atropine is useful for premedication or on induction in neonates.
2. What are the normal values for heart rate, respiratory rate and blood pressure in a neonate?
3. What are the consequences of a patent arterial duct? (PDA); is a PDA always a bad thing?
3. Explain why you should support the ventilation in a neonate?
4. When is it safe to discharge a baby home on the day of surgery?
6. What happens if babies get cold?
7. What are the principles of fluid administration in neonates?

Introduction

Age is an important risk factor in anaesthesia. The risks of anaesthesia are greater in neonates and infants, even in expert hands. In order to reduce these risks, surgeons and anaesthetists should only undertake work that they have been trained to do and that they have continuing experience of. The full range of facilities for the perioperative care of children should be available.

This article will consider the physiology of the neonate and the premature infant and the implications for clinical practice.

Physiology of the neonate

Definitions

- Infant: child less than 1 year of age
- Full term neonate: born between 37-40 weeks and aged less than 1 month
- Premature neonate: child born before 37 weeks gestation
- Extreme preterm neonate: child born less than 28 weeks gestation
- Postconceptional age: gestational age + postnatal age.

Respiratory function

- Development of the lung starts early in embryonic life, pulmonary surfactant is produced at 24-26 weeks; alveolar development begins at 32 weeks and is complete by 18 months of age. Extreme prems require pulmonary surfactant

and CPAP or IPPV after delivery for survival and are susceptible to bronchopulmonary dysplasia and later chronic lung disease.

- The newborn lung is small in relation to body size, tidal volumes small in absolute terms (7 ml/kg), the respiratory rate is high (30-40 breaths per minute) and there is little respiratory reserve. The deadspace and resistance of the breathing circuit should be kept to a minimum in infants who are breathing spontaneously, to minimise the work of breathing.
- The tongue is relatively large, the occiput prominent so the head tips forward and the airway is easily obstructed. Airway patency is best maintained by chin lift, avoiding compression of the floor of the mouth, possibly with the use of an oropharyngeal airway.
- The epiglottis is long and straight and tends to flop back over the laryngeal inlet which is high and anterior; intubation is best achieved with a straight blade laryngoscope.
- The larynx is conical in shape, the narrowest portion at the level of the cricoid cartilage. Uncuffed tracheal tubes are commonly used in neonates to avoid airway oedema, also later subglottic stenosis.
- The trachea is short and endobronchial intubation is not uncommon. The position of the tracheal tube should always be checked by auscultation.
- The airways are narrow and are easily blocked by oedema or secretions. A clear nasal airway is important in a small infant postoperatively as they breathe predominantly through their noses whilst feeding.
- Lung compliance is high and the ribs soft and elastic; chest wall compliance is higher compared with adults. Chest wall stability increases by about 1 year of life. The distending pressures on the lung are low and the newborn infant is prone to lung collapse, especially under general anaesthesia. The diaphragm is the predominant respiratory muscle in neonates but is more easily fatigable than in adults. Ventilation under anaesthesia should be at least assisted and infants should not be left to breathe spontaneously through a tracheal tube. CPAP or PEEP should be employed to avoid atelectasis.
- Gastric distension is common after facemask ventilation and will splint the diaphragm, compromise respiration and increase the possibility of aspiration. A nasogastric tube should be passed to relieve gastric distension.
- Anaesthetic agents depress the pharyngeal dilator muscles leading to upper airway obstruction. Neonates should be intubated for all except the briefest of procedures and positive pressure ventilation should be used.

Oxygen transport

- Neonates have a high metabolic requirement for oxygen (6-8 ml/kg/min vs 4-6 ml/kg/min in adults).
- Tissue oxygen delivery is achieved by a relatively high cardiac output (300ml/kg/min vs 60-80 ml/kg/min in adults), high heart rate (120-180 beats per min) and respiratory rate (30-40 breaths per min); neonates do not tolerate bradycardia or interruption in ventilation for any length of time and become hypoxic very readily. Hypoxia may lead to profound bradycardia.

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- Oxygen transport by haemoglobin shows developmental changes with time and is characterised by changes in the oxygen dissociation curve, described by the P_{50} , the partial pressure of oxygen at which haemoglobin is 50% saturated.
- At birth, foetal haemoglobin (HbF) forms 70-80% of total haemoglobin. Foetal haemoglobin delivers oxygen effectively to the tissues in the hypoxic conditions found during foetal life but tends to 'hold on' to oxygen in normal conditions after birth (the oxygen dissociation curve for foetal haemoglobin is shifted to the left). This is compensated for by a relatively high haemoglobin concentration at birth, from 13-20 g/dl, depending on the degree of placental transfusion, increasing the availability of oxygen to be delivered to the tissues.
- Adult haemoglobin, HbA₂ increases from birth, being the dominant haemoglobin by the first few months of life. It is very efficient at delivering oxygen to the tissues, even more so during infancy than adult life (the oxygen dissociation curve is shifted to the right during infancy). This is because there are higher levels of 2,3 diphosphoglycerate (2,3 DPG) during infancy which helps 'offload' oxygen to the tissues.
- Coupled with a relatively high cardiac output, tissue oxygen delivery is extremely efficient in infants compared to adults. These factors affect the triggers for transfusion or the haemoglobin level at which a child should be considered significantly anaemic. Equivalent haemoglobin concentrations for the same tissue oxygen delivery are 8g/dl, 6.5g/dl and 12g/dl for an adult, infant and neonate respectively. An infant tolerates anaemia fairly well, a neonate does not.
- If a child does require transfusion, they should be transfused if possible from one donor unit. A useful formula for transfusion is:
 - 4 ml/kg packed cells raises the Hb by 1g/dl
 - 8ml/kg whole blood raises the Hb by 1 g/dl

Control of ventilation

The control of ventilation is immature at birth and neonates are at risk from postoperative apnoeas, especially if born prematurely, anaemic or exposed to opiates.

- The ventilatory response to hypercapnia is blunted in the first few weeks of life.
- Neonates respond to hypoxia by a brief increase in ventilation followed by apnoea. The apnoeic response to hypoxia is probably due to respiratory muscle fatigue or upper airway obstruction.
- Control of respiration matures by three weeks of age in the term baby.
- Anaesthetic agents depress ventilation in a dose dependent manner.
- Term neonates are probably not at risk of postoperative apnoea after routine minor surgery (avoiding opiates) from 1 month of age (i.e. 44 weeks PCA)
- Premature neonates are at low risk of postoperative apnoeas after 60 weeks post conception.
- Regional anaesthesia, without sedation (e.g. spinal anaesthesia for hernia repair) may reduce the risk of postoperative apnoeas.

Cardiovascular function

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- The cardiac muscle is immature at birth.
- Heart rate is an important determinant of cardiac output and the heart rate should be maintained in the normal range (120-180 bpm, term neonate).
- The Frank-Starling relationship regulates cardiac output as in adults but is limited; neonates increase cardiac output with careful volume loading (fluid bolus 5-10ml/kg), but they do not tolerate fluid overload.
- Contractility in neonates is high due to high sympathetic tone, especially around the time of birth, and this also explains the high resting heart rate of neonates.
- Cholinergic innervation is well developed at birth and vagally mediated cardiac reflexes are obvious, even in premature infants. Hypoxia and laryngoscopy lead to profound bradycardia.
- Afterload is also a major determinant of cardiac output. The neonatal heart is exquisitely sensitive to increases in systemic or pulmonary vascular resistance which will reduce the cardiac output.
- The myocardium is dependent on extracellular calcium for contraction and ionised hypocalcaemia is poorly tolerated. Hypocalcaemia may occur after large volume blood or blood product transfusion or in a child who is septic.
- Neonates are more sensitive to the negative inotropic effects of anaesthetic agents than older children; the effect is more marked with halothane than isoflurane or sevoflurane. Avoid deep anaesthesia, especially ventilation with high concentrations of volatile agents
- Atropine may counteract the reduction in cardiac output seen with volatile agents and will protect against vagally mediated reflexes, especially those associated with laryngoscopy and intubation. It is useful as premedication, although no longer routinely used, but should always be drawn up ready.

Transitional circulation

- Cardiorespiratory adaptation at birth results in an increase in pulmonary blood flow and closure of the foetal shunts which allow the blood to bypass the lungs – the foramen ovale and ductus arteriosus.
- In utero the right and left hearts pump in parallel. There is a connection between the systemic and pulmonary circulation via the ductus arteriosus (pulmonary artery to the aorta) and the foramen ovale (right to left atrium). The pulmonary circulation has a high resistance and the right and left ventricular pressures are equal, even though the right ventricle ejects 66% of the combined ventricular output.
- When the umbilical cord is clamped and the low resistance placental circulation is lost, there is a sudden rise in systemic vascular resistance
- With the first breath and expansion of the lungs there is an increase in pH and increased oxygenation, the pulmonary vascular resistance decreases and pulmonary blood flow increases. The increased pulmonary venous return to the left atrium raises the left atrial pressure above the right and as a result the flap valve of the foramen ovale closes.
- The increase in left sided pressures and the fall in right pressures results in a decrease or reverse flow through the ductus arteriosus

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- The duct closes in response to oxygen, prostaglandins, bradykinin and acetylcholine. Anatomical closure by constriction occurs at 6hrs, complete occlusion usually occurs at 6 weeks of age.
- The pulmonary vascular resistance may increase in response to hypoxia, hypercarbia or acidosis. Severe pulmonary hypertension may ensue, with reopening of the foetal shunts, causing profound hypoxia and cardiovascular compromise.
- Persistent Pulmonary Hypertension of the Newborn (PPHN) is associated with congenital diaphragmatic hernia, meconium aspiration, asphyxia, hypoxia and sepsis. Management includes optimising oxygenation and ventilation, sedation, inotropic support, inhaled nitric oxide and high frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO) if available.
- Patent arterial duct (PDA) is seen in 50% of extreme premature infants. Shunting from the aorta to the pulmonary artery results in respiratory distress syndrome and is a risk factor for intraventricular haemorrhage and necrotising enterocolitis.
- Some congenital cardiac abnormalities may be dependent on a patent arterial duct. Collapse of the neonate will occur with closure of the duct, typically at one week of age. For example, duct dependent pulmonary circulation (pulmonary atresia) and duct dependent systemic circulation (critical coarctation of the aorta); prostaglandin infusion is required until definitive treatment is possible. The differential diagnosis of collapse in a neonate is sepsis.

Hepatic function and drug handling.

- The liver in the newborn contains 20% of the hepatocytes found in adults and continues to grow until early adulthood.
- The liver is the principle site of drug metabolism, some evidence of which can be found in foetal life, albeit at low levels.
- Phase I processes (metabolic, e.g. the cytochrome P450 system) are significantly reduced at birth whilst phase II processes (conjugation) may be well developed (sulfation) or limited (glucuronidation). Paracetamol is useful in neonates as it is excreted by sulfation (rather than glucuronidation as in adults).
- In general, drug effects are prolonged in neonates and drugs should be titrated to effect, given by bolus rather than infusion, or plasma levels monitored as appropriate.
- Maturation of enzymatic processes increases over the first few weeks of life and the half-life of drugs such as morphine reaches adult levels at 2 months of life. Neonates require significantly less morphine than older children, especially in the first week of life. Morphine should be given as a bolus dose of 10 mcg/kg; beware, the half-life may be up to 8 hours (double that of older children).
- Plasma protein binding is reduced in neonates (low levels of α 1-acid glycoprotein) and drugs that are plasma protein bound (such as local anaesthetics) may demonstrate increased toxicity in infants.

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- Neonates have reduced hepatic stores of glycogen and immature gluconeogenic enzyme systems. Coupled with a high metabolic rate, this makes them susceptible to hypoglycaemia following starvation. Neonates should not be starved excessively (breast milk feed 4 hours preoperatively, clear fluids 2 hours preoperatively), and if possible, blood sugar should be measured during surgery. Glucose should be added to the intraoperative fluids, for instance, add 25ml of 50% dextrose to 500ml of Ringers Lactate to give a solution of 2.5% dextrose in Ringers Lactate.

Renal function

- Nephrogenesis is completed at 36 weeks gestation and no further nephrons are produced (impaired nephrogenesis in premature infants has been related to hypertension in adult life). Further increase in renal mass is due to the growth of tubules.
- The glomerular filtration rate at term is low and reaches adult indexed values only at 2 years of age. Creatinine at birth reflects the mother's creatinine and falls to reflect renal function of the baby by 1 week of age.
- Tubular function matures over the first few months of life; infants usually produce urine that is isotonic to plasma, but if required, can concentrate their urine to achieve an osmolality of 500-700 mOsmol/kg H₂O. Adult values (urinary osmolality typically 1200-1400 mOsmol/kg H₂O) are reached by a year of age. Infants tolerate fluid restriction poorly and become dehydrated quickly.
- The neonate's limited renal function is appropriate to the period of rapid growth after birth – growth has been termed the 'third kidney'. However, in the postoperative (catabolic) infant, renal insufficiency may become apparent and the neonate does not handle fluid or sodium overload.

Fluid and electrolyte balance

- The extracellular fluid compartment is expanded in neonates, with total body water representing 85% of body weight in premature babies, 75% of body weight in term babies, compared to 60% body weight in adults.
- The expanded extracellular fluid compartment results in an increased volume of distribution of commonly used drugs and increased dose requirements, despite increased sensitivity (muscle relaxants, intravenous induction agents).
- Contraction of the extracellular fluid compartment and weight loss in the first few days after birth is a normal physiological process, due in part to a diuresis induced by atrial natriuretic peptide (ANP) secondary to increased pulmonary blood flow and stretch of left atrial receptors. After this period of negative water and sodium balance, water and sodium requirements increase to match those of the growing infant.
- Fluids should therefore be restricted until the postnatal weight loss has occurred. Liberal fluid regimens in the first few days of life have been shown to be associated with worse outcomes in premature infants (increased patent ductus arteriosus, necrotising enterocolitis and death). Fluid requirements increase incrementally from day 1 of life (60ml/kg/day) to 150ml/kg/day at 1

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week of life (up to 180ml/kg/day in a premature neonate with high evaporative losses)

Temperature control

- Thermoregulation in the neonate is limited and babies become cold easily.
- Heat production is limited and there is a greater potential for heat loss (high body surface area to body weight ratio, increased thermal conductance, increased evaporative heat loss through the skin). The newborn infant is able to increase heat production through brown fat metabolism (non shivering thermogenesis, inhibited by volatile agents), however this is at the expense of increased oxygen consumption.
- Hypothermia is associated with hypoxia, impaired wound healing, prolonged coagulation with reduced platelet function, reduced drug metabolism, cerebral depression, myocardial depression, acidosis, decreased immunity, patient discomfort.
- The preterm baby is particularly vulnerable as the immature skin is thin and allows major heat (and evaporative fluid) losses.

Central nervous system, nociception and the stress response

- The lower limit for cerebral autoregulation in neonates is not known, but is thought to be around a cerebral perfusion pressure of 30 mmHg. Appropriate mean arterial blood pressures for extreme premature neonates are controversial but it is generally accepted that the mean arterial pressure equates to the gestational age of the child during the first day of life, rising to a minimum of 30mmHg by 3 days.
- Survival of extreme preterm infants has improved considerably in recent years, but this has been associated with high levels of disability. A major determinant of cerebral impairment is intraventricular haemorrhage (IVH) which usually occurs within the first few days of life. Steroids are thought to interfere with the development of the brain in the newborn and avoidance of postnatal dexamethasone is currently the single most important factor to improve neurological outcomes in premature infants.

Developmental aspects of pain

- Neonates, including premature neonates, show well developed responses to painful stimuli. The foetus shows a stress response (and behavioural changes) to painful stimulation from 18-20 weeks gestation, which can be attenuated by the administration of fentanyl. Attenuation of the stress response to surgery improves postoperative morbidity and mortality in neonates.
- There is a great deal of neuronal fine tuning of pain pathways during early neonatal life which may be influenced by the activity of endogenous opioids (and by implication, administered opioids).
- There is a question about the long term effects of exogenous morphine administration to neonates, also the long term effects of painful experiences in the neonatal period. Surgery should be avoided in neonates if possible. Pain in neonates should be treated using multimodal analgesia, but opiates should be used judiciously, for both pharmacokinetic (reduced drug metabolism) and pharmacodynamic reasons (increased opiate sensitivity).

Further reading:

An excellent account of all aspects of anaesthesia for children and neonates is to be found in the chapter by Simon Berg in the Oxford Handbook of Anaesthesia, Ed Allman K, Wilson I. 2nd edition 2006 Oxford University Press, Oxford.

Answers to questions

1. Explain why atropine is useful for premedication or on induction in neonates. Atropine is a muscarinic acetylcholine antagonist. It causes vagal blockade at the AV and sinus node in the heart and increases heart rate. A dose of 40 mcg/kg PO or 20 mcg/kg IM/IV is used to prevent reflex bradycardia, for instance from hypoxia, deep volatile anaesthesia or from reflex vagal stimulation with intubation/laryngoscopy. Bradycardia results in a marked fall in cardiac output. Atropine also dries secretions, including after ketamine anaesthesia; secretions might obstruct the airway or cause laryngospasm.

2. What are the normal values for heart rate, respiratory rate and blood pressure in a term neonate?

Heart rate	120-180 beats per min
Respiratory rate	30-40 breaths per min
Mean arterial blood pressure	30-50 mmHg
Mean systolic BP	50-90 mmHg
Mean diastolic BP	25-60 mmHg

3. What are the consequences of a patent arterial duct? (PDA); is a PDA always a bad thing?

A PDA results in left to right shunting from the aorta to the pulmonary artery and increase in pulmonary blood flow. In the premature neonate this will result in cardiac failure. There is a low diastolic blood pressure which may cause gut hypoperfusion, resulting in necrotising enterocolitis, or intraventricular haemorrhage. In an older child, persistence of a PDA may cause mild cardiac failure presenting as frequent chest infections. If a child has a PDA for many years, this may eventually cause pulmonary hypertension and result in flow reversal across the duct (Eisenmenger circulation). There are a few conditions where patency of the arterial duct is required for survival: for instance, duct dependent systemic circulation in critical coarctation (blood flow to the lower body is from the pulmonary artery, via the duct), or duct dependent pulmonary circulation in pulmonary atresia (blood flow to the lungs is from the aorta, via the duct). Such children collapse about a week after birth as the duct closes and require a prostaglandin infusion to maintain the duct until a definitive procedure is undertaken (e.g. coarctation repair or a systemic to pulmonary artery shunt in pulmonary atresia, known as a modified Blalock Taussig shunt (mBT shunt)).

4. Explain why you should support the ventilation in a neonate?

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The neonate is prone to upper airway obstruction so anaesthesia is best managed by intubation. The work of breathing is high and breathing through the high resistance of a tracheal tube further adds to the work of breathing and the neonate will tire rapidly. The neonate is prone to atelectasis and small airway collapse as the ribs are soft and lack elastic recoil to maintain lung volumes. In addition, the diaphragm is the principle muscle of respiration and tires easily; abdominal distension will further interfere with diaphragmatic movement.

Neonates should therefore be intubated and ventilated for anaesthesia, using low pressure ventilation (<20cmH₂O), to achieve the appropriate small tidal volumes (7ml/kg), with the application of a small amount of PEEP (4cmH₂O). If the neonate is breathing spontaneously under volatile anaesthesia on a facemask, an oropharyngeal airway should be considered with the application of a small amount of CPAP (4cmH₂O). A neonate breathing spontaneously under ketamine anaesthesia should have the airway supported by a chin lift and supplemental oxygen administered.

5. When is it safe to discharge a baby home on the day of surgery?

Provided the baby has undergone minor uncomplicated surgery, without the use of opioids, is otherwise well, not anaemic, and the home circumstances are appropriate, a baby who was born at term can probably be discharged on the day of surgery when they are 1 month old. It is sensible for surgery to be performed in the morning to allow for observation in hospital during the day – any complications in the recovery room are a contraindication to discharge on the day of surgery.

A baby who was born prematurely may be discharged when they are 60 weeks post conception. For instance, if the baby was born at 30 weeks conception, it would be reasonable to discharge them on the day of surgery when they have a PCA of 60 weeks, that is, they are 7 1/2 months old, provided they are otherwise well. Babies younger than this should be observed in hospital overnight after surgery.

6. What happens if babies get cold?

If a baby becomes cold they may become hypoxic, may be slow to wake after surgery and may have increased bleeding and increased wound infections.

7. What are the principles of fluid administration in neonates?

Neonates have reduced renal function and produce dilute urine. They are unable to tolerate dehydration; similarly, they cannot handle a high fluid load or sodium load in the first few days of life. They undergo a diuresis after a few days of life. If a baby requires intravenous fluids from birth, they should be given as 10% dextrose in the following volumes. Sodium 3 mmol/kg/day and potassium 2 mmol/kg/day should be added after the postnatal diuresis or if the baby becomes hyponatraemic:

	Fluid volume (ml/kg/day)
Day 1	60
Day 2	90

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Day 3	120
Day 4	150
Day 5	150

A premature neonate may require an additional 30 ml/kg/day because of increased insensible fluid losses and may also require additional sodium supplements (4 mmol/kg/day).

Replacement fluids (ie during surgery or to correct hypovolaemia) should be given as isotonic fluid (0.9% saline or Ringers-Lactate/Hartmann's) or blood to maintain the haemoglobin at 10-12 g/dl. 50% dextrose 25ml may be added to 500ml of isotonic solution to give a 2.5% solution if the blood sugar is low. It is safer to administer fluids via a burette to avoid fluid overload. Postoperatively fluids should be restricted to 60% of maintenance (or remain at day 1-2 levels of restriction if the child undergoes early surgery).