Section I Introduction

Chapter 1

Anatomical and physiological issues affecting anaesthesia in neonates and young children

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Introduction

Age is an important risk factor in anaesthesia, and the risks of anaesthesia are greater in neonates and infants, even in expert hands. There are important physiological and anatomical differences between neonates, young children and adults that influence anaesthesia techniques, and there are rapid changes that occur in the transition from fetal to neonatal life, and also during the first few months and years of life. This chapter will consider some of the differences in anatomy and physiology that affect neonates and young children during growth and development, and the clinical implications of these differences. The premature and ex-premature infant will be considered in more detail in Chapter 9.

The development of the respiratory system

The development of the lung starts early in the period of organogenesis; the lung buds with lobar structure are present by 6 weeks gestation and the structure of the bronchial tree is laid down by 16 weeks. The respiratory acinus consists of the respiratory bronchiole, alveolar ducts and alveolar sacs and starts to form by 24 weeks. The thin-walled terminal respiratory saccules appear by 24 weeks at the same time as complex pulmonary capillary networks start to develop. The respiratory saccules are lined by type I pneumocytes, which form the gas-exchanging surface, and type II pneumocytes, which produce pulmonary surfactant.

Surfactant is present in type II pneumocytes by 26 weeks and is secreted into the lumen of the airway by 30 weeks. Surfactant is important as it lines the airways and reduces surface tension to prevent the alveoli collapsing after birth. Fetal plasma cortisol levels rise from 24 weeks, which is important for lung maturation as cortisol stimulates surfactant release, alveolar cell differentiation and resorption of lung fluid. True alveoli start to develop at 32 weeks. Babies who are born at less than 30 weeks gestation benefit from antenatal steroids to facilitate lung maturation, and exogenous surfactant to assist in aeration of the lung. Babies born before 24 weeks gestation are unlikely to be viable owing to extreme immaturity of the respiratory system.

A baby born after 37 weeks gestation is considered as full term; the lung structure is mature with a large internal surface area and thin-walled alveoli in close proximity to the pulmonary capillaries. Alveolar development continues after birth and continues until the age of 18 months; in fact, 85% of alveolar development occurs in the post-natal period. Bronchial smooth muscle increases from birth to adulthood, with a rapid increase in the first few weeks after birth. Growth of the lungs occurs by increase in length and diameter of the airways, and continues until the long bones fuse.

Cardiorespiratory adaptation at birth

During fetal life, the placenta is the main site of respiratory gas exchange. Oxygenated blood returns from the placenta to the inferior vena cava via the ductus venosus, and is preferentially channelled across the foramen ovale to the left atrium, thence to the ascending aorta, coronary vessels and the brain (see Figure 1.1). Pulmonary arterioles are tightly constricted owing to low levels of oxygen, nitric oxide and prostacyclin (PGI_2), and pulmonary vascular resistance (PVR) is high. As a consequence, only about 10% of the right ventricular output enters

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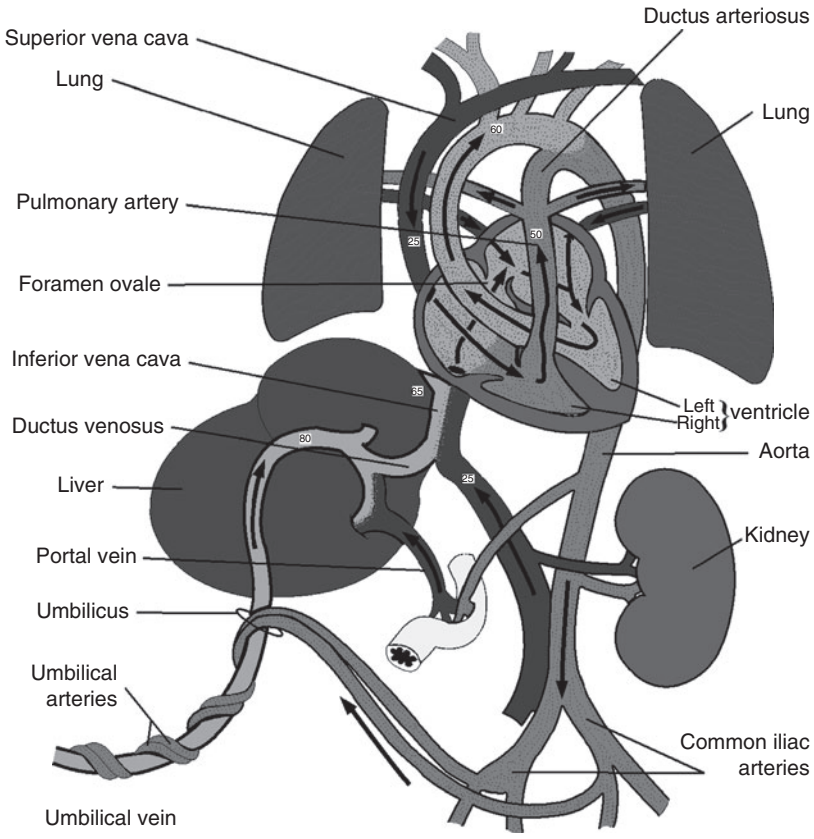

Figure 1.1 The fetal circulation. The numbers indicate oxygen saturation. From Murphy PJ. The fetal circulation. *Contin Educ Anaesth Crit Care Pain* 2005;5(4):107–112, with permission. See plate section for colour version.

the pulmonary circulation, and blood in the pulmonary artery is shunted across the ductus arteriosus to the descending aorta. Cardiorespiratory adaptation is the process whereby gas exchange is transferred from the placenta to the lungs and the fetal shunts close (foramen ovale, ductus arteriosus and ductus venosus).

In fetal life, the respiratory system is filled with liquid, and fetal breathing movements are present. Some lung fluid is squeezed out of the lungs during the second stage of labour, but most of the fluid is absorbed into the pulmonary lymphatics and capillaries when the first few breaths are taken. Sudden cooling and sensory inputs that increase central arousal act as the main stimuli for breathing. High negative pressures are generated initially, and active expiration during crying helps to distribute ventilation and facilitate clearance of lung fluid. Inflation breaths to clear lung fluid are an essential component of newborn resuscitation.

The foramen ovale

There is a marked fall in PVR associated with the mechanical changes that follow aeration of the lungs and the sudden increase in oxygen tension; pulmonary venous return is increased and the flap valve covering the foramen ovale closes, although the foramen ovale may remain 'probe patent' into adult life.

Ductus arteriosus

Patency of the ductus arteriosus is maintained *in utero* by low oxygen tension and the effect of prostaglandins. After birth, oxygen tension rises, and this causes the ductus arteriosus to constrict, a process that is usually complete by day 2 in healthy term infants, and by day 4 in most preterm babies. Anatomical closure of the ductus usually occurs by 2–3 weeks.

Patent ductus arteriosus (PDA) may be seen in up to 50% of babies with birth weight <800 g, with decreasing incidence as gestational age increases. PDA is due to persistently low oxygen tension or elevated prostaglandins, rather than abnormal ductal tissue per se. Pulmonary vascular resistance usually falls during the first few weeks of life, and the presence of a persisting PDA will lead to left to right shunting and increased pulmonary blood flow, with worsening respiratory distress and heart failure. Medical closure of the PDA may be attempted using prostaglandin synthetase inhibitors such as the NSAIDs ibuprofen or indomethacin. If unsuccessful, surgery may be required.

Continued ductal patency is essential in some congenital cardiac conditions, such as a duct dependent systemic circulation (e.g. hypoplastic left heart syndrome or critical coarctation) or duct dependent pulmonary circulation (e.g. pulmonary atresia with intact ventricular septum). Prostaglandin infusion may be required to keep the duct open until surgery can be performed.

Ductus venosus

The ductus venosus is a blood channel through the embryonic liver from the left umbilical vein to the inferior vena cava (IVC). It closes functionally within hours of birth, and anatomical closure starts after the first few days. It may be used immediately after birth to provide access to the right atrium via an umbilical venous catheter.

Pulmonary vascular resistance

Pulmonary blood flow increases eight-fold after birth owing to dilation of pulmonary arterioles in the first few minutes after birth, followed by a slow fall in PVR over the next few weeks and months (see Figure 1.2). The early fall in PVR is due to vasodilation of pulmonary arterioles mediated by increased lung volumes and increased oxygen tension, nitric oxide and PGI_2 levels, with later changes due to involution of smooth muscle in the arteriolar walls.

The PVR may remain high or increase during early neonatal life owing to asphyxia, hypoxia, sepsis, congenital diaphragmatic hernia and meconium aspiration. This results in shunting from right to left across the ductus arteriosus and severe hypoxaemia, so-called persistent pulmonary hypertension of the newborn (PPHN).

Infants who have congenital cardiac lesions associated with left to right shunting, such as unrestricted ventricular septal defect, usually become symptomatic during the first few weeks of life as PVR falls and pulmonary blood flow increases. If the child remains untreated and high pulmonary blood flow is sustained, pulmonary vascular remodelling occurs and the PVR rises. This reactive increase in PVR is the basis for subsequent flow reversal in Eisenmenger's syndrome.

Respiratory system in neonates and infants

Oxygen consumption in neonates is twice that in adults (6–8 ml kg^{-1} min^{-1} vs 3 ml kg^{-1} min^{-1}). The relatively high minute ventilation is achieved by increasing respiratory rate (30–40 min^{-1}) as the tidal volume is relatively fixed (7 ml kg^{-1}). Increased minute volume means that induction and emergence from inhalational anaesthesia is more rapid in infants compared with older children, and deep levels of anaesthesia may be obtained very quickly.

Neonates do not tolerate airway obstruction or pauses in ventilation and become hypoxic very quickly. Nasal resistance contributes one-third of pulmonary resistance, and a clear nasal airway is particularly important in small infants as they breathe predominantly through their noses. Hypoxia leads to profound bradycardia.

The airway is easily obstructed during anaesthesia. The tongue is relatively large, and the tongue and soft palate fall against the posterior pharyngeal wall. The occiput is prominent and encourages neck flexion. Airway patency is maintained by the action of pharyngeal dilators, but pharyngeal tone is lost on induction of anaesthesia. Airway obstruction may be improved by 'chin lift' and 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, so intubation in neonates is best achieved with a straight blade laryngoscope, possibly with a roll placed under the shoulders to overcome the effect of the large occiput. The larynx is conical in shape with the narrowest portion at the level of the cricoid cartilage. Uncuffed tracheal tubes are commonly used in neonates to avoid airway oedema and potential subglottic stenosis. Cuffed tracheal tubes are increasingly used in older children, especially in children with pulmonary disease requiring ventilation in

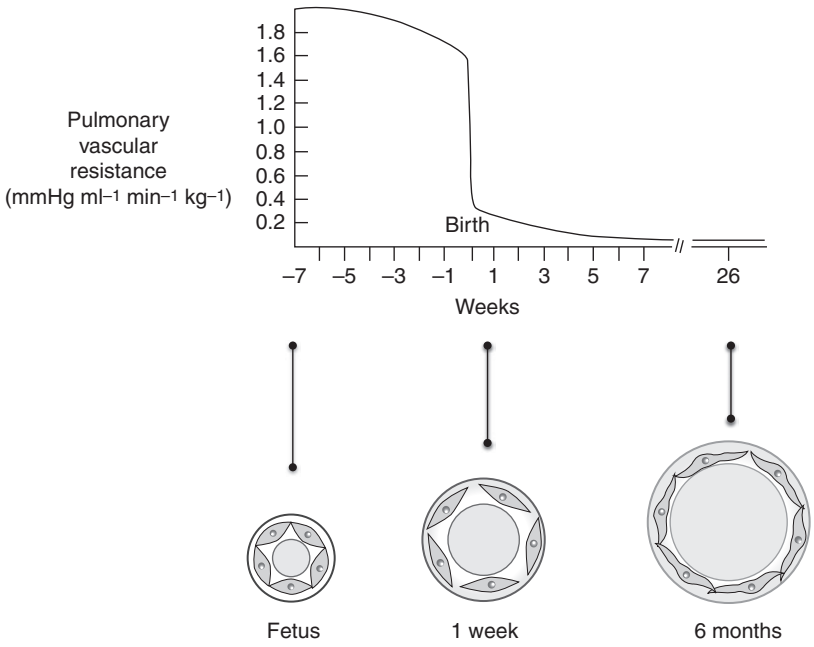

Figure 1.2 Structural changes in the pulmonary artery in the postnatal period and corresponding changes in pulmonary vascular resistance. Fetal pulmonary arteries have thick walls and a narrow lumen, with rounded densely packed smooth muscle cells (SMC). Within 1 week of life the SMC become thinner and spread around a larger lumen. By 6 months of age there is further decrease in the medial thickness of the vessel wall with reduced SMC density, and a larger lumen. (Adapted from Gao Y, Raj JU, *Physiol Rev* 2010;90:1291–1335, and Rudolph AM, *Congenital Diseases of the Heart*, Chicago: Year book, 1974.)

intensive care where a leak from an uncuffed tracheal tube may compromise ventilation. Care should be taken to avoid overinflation of the cuff, and the cuff pressure should be monitored ($<20\,cmH_2O$).

The trachea is short in absolute terms, and it is easy to cause endobronchial intubation. The position of the tracheal tube should always be checked by auscultation. The airways are narrow and are easily blocked by oedema or secretions. According to Poiseuille's law, airway resistance is proportional to viscosity and inversely proportional to the fourth power of the radius of the airway:

$$R = 8\,nl/\pi r^4$$

where R = resistance
n = viscosity
l = the length of the airway
r = the radius of the airway

Airway oedema that causes a small reduction in airway diameter in an infant results in a disproportionately large increase in airway resistance. Nebulised adrenaline (which reduces airway oedema) and heliox (which reduces airway resistance) may be useful in an emergency situation.

The thoracic cavity in neonates is round rather than dorso-ventrally flattened as in the adult. The cartilaginous ribs are soft and elastic and horizontally placed, so the 'bucket handle' action of the ribs that increases thoracic volume in adults does not occur. The lungs are very compliant, the chest wall is elastic and distending pressures on the lung are low. Closing volume occurs within tidal breathing in neonates and it is common to see intercostal and subcostal recession if lung compliance is reduced (e.g. infection or cardiac failure) (see Figure 1.3). Chest wall stability increases by about 1 year of age. Intercostal and subcostal recession in an older child is an ominous sign indicating severe lung disease.

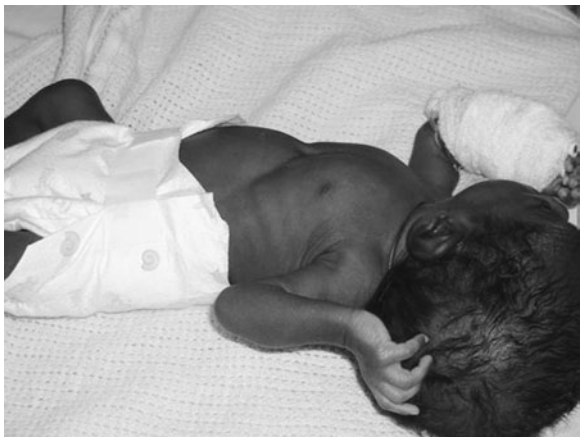

Figure 1.3 Subcostal and intercostal recession in an infant. Picture taken at Great Ormond Street Hospital (GOSH) with permission.

The diaphragm is the predominant respiratory muscle in neonates, but it is less efficient than in adults as it is relatively horizontal rather than dome shaped. Neonates are prone to respiratory failure as they have a lower proportion of fatigue resistant type 1 muscle fibres in the diaphragm. Gastric insufflation is common after facemask ventilation and may result in abdominal distension and splinting of the diaphragm. A nasogastric tube should be passed to relieve abdominal distension as this will improve respiratory function and reduce the risk of aspiration.

Infants have little respiratory reserve, and apparatus dead space and resistance should be kept to a minimum to reduce the work of breathing. Infants should not be left to breathe spontaneously through a tracheal tube, and ventilation under anaesthesia should be assisted. Application of continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP) increases lung volumes, reduces the work of breathing and should be employed during anaesthesia to improve gas exchange and prevent atelectasis. Neonates should be intubated for all except the briefest of procedures and positive pressure ventilation should be used.

Control of ventilation

The control of ventilation is immature at birth. Neonates are at risk from post-operative apnoeas, especially if born prematurely, anaemic, cold or exposed to opioids.

Fetal breathing is detected from 14 weeks gestation, and increases with gestational age. The fetus responds to increased maternal hypercapnia by an increase in respiratory rate, and to hypoxia by a reduction in respiratory rate.

Neonates also respond to hypercapnia by increased respiratory rate, as in older children and adults. The response to hypoxia remains immature and results in a brief increase in ventilation followed by a fall in respiratory rate, or in premature neonates, by the baby becoming apnoeic. This apnoeic response to hypoxia may be due to persistence of the fetal response to hypoxia into neonatal life. In term infants this biphasic response disappears by 2 weeks of age, but maturation of respiratory control may be delayed in premature infants.

Anaesthetic agents depress ventilation in a dose dependent manner. Term neonates are probably at risk of post-operative apnoea after routine minor surgery (avoiding opioids) up to 1 month of age. Premature neonates are at low risk of post-operative apnoeas after 60 weeks postconceptional age; for a baby born at 28 weeks, this is when they are 8 months chronological age (5 months corrected age). Regional anaesthesia without sedation (e.g. spinal anaesthesia for hernia repair) may reduce the risk of post-operative apnoeas.

Cardiovascular system in neonates and infants

There is a period of ventricular remodelling after birth. *In utero*, the right ventricle dominates as it pumps 65% of the cardiac output and the left ventricle is relatively quiescent. After birth, the left ventricle becomes the dominant ventricle and supports the systemic circulation. The systemic vascular resistance increases after birth and the left ventricular wall thickness increases markedly during infancy, with a more modest increase in the right ventricular wall thickness. The newborn heart contains about half the myocytes present in the adult heart, and remodelling occurs by an increase in number, size and complexity of myocytes with age. The heart is relatively globular in the neonate, and the right ventricle is the same volume as the left. The right ventricle increases in volume relative to the left and reaches the adult volume ratio of 2:1 by 2 years of age. Left ventricular remodelling occurs as a consequence of increased systemic vascular resistance. Babies who have transposition of the great arteries and in whom the arterial switch operation is delayed beyond a few months may become inoperable, as the left ventricle is pumping into the pulmonary circulation where the PVR is low, and left ventricular remodelling does not occur.

Tissue oxygen delivery is achieved by a relatively high cardiac output ($300\,ml\,kg^{-1}\,min^{-1}$ vs $60–80\,ml\,kg^{-1}\,min^{-1}$ in adults) and high heart rate. There is limited cardiac reserve. The cardiac output is rate dependent, and the heart rate should be maintained in the normal range for age. The Frank–Starling relationship regulates cardiac output as in adults, but the ability to increase stroke volume is limited. Neonates can increase cardiac output with careful volume loading (bolus of 5–10 ml kg^{-1}), but they do not tolerate volume overload. Afterload is a major determinant of cardiac output, and the neonatal heart is very sensitive to increases in systemic or pulmonary vascular resistance.

Innervation of the heart is functionally immature at birth, and sympathetic tone dominates, resulting in high contractility and high resting heart rate. Parasympathetic tone increases with age, but vagally mediated cardiac reflexes are well developed in infancy.

Neonates are sensitive to the negative inotropic effects of anaesthetic agents. Atropine may counteract the reduction in cardiac output seen with volatile agents and will protect against vagally mediated reflexes, especially those associated with intubation. It is useful as premedication, although no longer used routinely.

Oxygen transport to the tissues

Oxygen transport by haemoglobin is characterised by changes in the oxygen dissociation curve and described by the P_{50}, the partial pressure of oxygen at which haemoglobin is 50% saturated.

At birth, fetal haemoglobin (HbF) forms 70–80% of total haemoglobin – it is suited to the hypoxic conditions found during fetal life but provides relatively poor tissue oxygenation after birth (low P_{50}). This is compensated for by a relatively high haemoglobin concentration.

Adult haemoglobin (HbA_2) production increases from birth, being the dominant haemoglobin by the first few months of life. It is very efficient at tissue oxygen delivery (high P_{50}), and tissue oxygen delivery increases during infancy to levels higher than found in adults, probably reflecting increased levels of 2,3-diphosphoglycerate (2,3 DPG) during a period of rapid growth (see Figure 1.4).

Coupled with a relatively high cardiac output, tissue oxygen delivery is extremely efficient in infants compared with adults. These factors affect the triggers for transfusion or the haemoglobin level at which a child should be considered significantly anaemic (see Table 1.1). A useful formula for transfusion is:

- 4 ml kg^{-1} packed cells raises the Hb by 1 g dl^{-1}
- 8ml kg^{-1} whole blood raises the Hb by 1 g dl^{-1}

Table 1.1 Haemoglobin requirements for equivalent tissue oxygen delivery

	P_{50} (mm Hg)	Haemoglobin required for equivalent tissue oxygen delivery (g dl^{-1})		
Neonate <2 months	24	17.6	14.7	11.7
Infant >6 months	30	9.8	8.2	6.5
Adult	27	12	10	8

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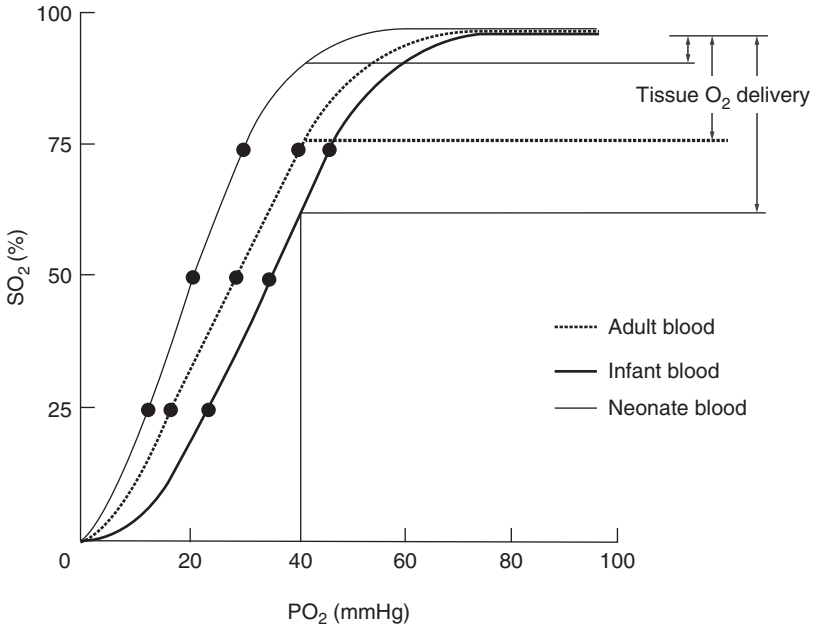

Figure 1.4 Oxygen–haemoglobin dissociation curves in infants and neonates. PO_2 = partial oxygen pressure; SO_2 = oxygen saturation. (Reproduced with permission from: Motoyama and Finer (2011) Respiratory physiology in infants and children. In Smith PJ, ed., *Smith's Anaesthesia for Infants and Children*. 8th edition. Elsevier Health Sciences. 2011, p. 62.)

Development of the kidney and changes with birth

Nephrogenesis begins at 5 weeks of gestation and is completed at 35 weeks. The main function of the fetal kidney is the production of amniotic fluid, which is in turn important for development of the fetal lung. Renal abnormalities *in utero* are associated with oligohydramnios and pulmonary hypoplasia. The full compliment of nephrons is present at birth, and maturation of the kidney is by increasing length and complexity of the tubules. The placenta performs the excretory functions of the fetus so at birth the urea and electrolytes in the neonate are similar to those of the mother, but fall within the first few days of life. Premature babies have impaired renal function in infancy, and may be hypertensive in later life. Glomerular filtration rate (GFR) is low after birth, but in normal children, reaches adult indexed values by 2 years of age.

The neonate does not take in very much fluid in the first few days of life during the time that lactation is established. Levels of antidiuretic hormone (ADH) are high so urine output is low and body water is conserved. A brisk diuresis occurs in the first few days of life as ADH levels fall and cardiorespiratory adaptation occurs, which results in increased pulmonary venous return and the release of atrial natriuretic hormone. Fluids should be restricted until the post-natal diuresis has occurred; excessive fluids may promote PDA, particularly in premature infants.

Sodium is retained in the first few days of life as the GFR is low, the mean arterial pressure is low, and the renin–angiotensin–aldosterone system is active and promotes the reabsorption of sodium in the collecting duct. Sodium is usually withheld in the first few days of life, but is added to maintenance fluids after the post-natal diuresis has occurred. The premature neonate has impaired tubular reabsorption of sodium and limited sodium retention, so frequently requires sodium supplements to avoid hyponatremia.

Babies obtain their calories from a liquid diet, and have an immature urinary concentrating ability so they produce relatively large volumes of dilute urine that is isotonic with plasma (300 mOsmol kg^{-1}). They are therefore prone to dehydration if they are starved for excessive periods of time, and renal failure is common in sick infants. The renal tubular system and concentrating abilities mature over the first few months of life, and infants are able to produce concentrated urine (1200–1400 mOsmol kg^{-1}) and withstand fluid deprivation by 1 year of age.

Hepatic function and drug handling

Children have been described as 'therapeutic orphans' in that many drugs, especially new drugs, have not been studied in this age group; we can hope that this will be rectified in future. The liver in the newborn infant contains 20% of the hepatocytes found in adults and continues to grow until early adulthood. The liver is the principal site of drug metabolism, some evidence of which can be found in fetal life, albeit at low levels.

Phase I processes (metabolic, e.g. the cytochrome P-450 system) are significantly reduced at birth whilst phase II processes (conjugation) may be well developed (sulfation) or limited (glucuronidation). Paracetamol is excreted by sulfation in the neonate and glucuronidation 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. Plasma protein binding is reduced in neonates and infants (low levels of α1-acid glycoprotein), and drugs that are plasma protein bound (such as local anaesthetics) may demonstrate increased toxicity.

Infants have reduced hepatic stores of glycogen and immature gluconeogenic enzyme systems. They have a high metabolic rate so they are susceptible to hypoglycaemia following starvation. Blood sugar should be measured routinely during surgery. An isotonic solution containing glucose should be used if the child has been hypoglycaemic or receiving parenteral nutrition pre-operatively

Coagulation

Development of the coagulation system starts *in utero* and continues until about 6 months of age. Vitamin K dependent factors are 70% of adult values at birth, and all newborn infants require vitamin

K prophylaxis to prevent haemorrhagic disease of the newborn. Platelets are present in normal numbers at birth, and reach adult reactivity at 2 weeks of age. Coagulation screening tests are prolonged in normal infants up to the age of 6 months, which is reflected in values for the normal ranges.

Temperature control

Thermoregulation in the neonate is limited and easily overwhelmed by environmental conditions. 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 reduces heat loss by vasoconstriction and increases heat production through brown fat metabolism (non-shivering thermogenesis), although this is at the expense of increased oxygen consumption. Brown fat metabolism is inhibited by volatile agents. The preterm baby is particularly vulnerable to cooling as the immature skin is thin and allows major heat and evaporative fluid losses. Premature infants should have minimal handling and exposure to avoid excessive heat loss. Surgery is frequently performed in the neonatal unit for this reason.

Central nervous system, nociception and the stress response

The brain forms 10–15% of body weight at birth, but only 2% of body weight by the age of 8 years. The brain is reliant on glucose for metabolism but the child is also able to utilise ketones under normal conditions. The cerebral metabolic requirement for oxygen ($CMRO_2$) is higher in young children owing to the demands of growth.

Autoregulation of cerebral blood flow is present in the newborn period. The lower limit for cerebral autoregulation in neonates is not known, but is thought to be around a cerebral perfusion pressure of 30 mmHg. The appropriate mean arterial blood pressure for premature neonates is 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 30 mmHg by 3 days.

Developmental aspects of pain

Neonates, including premature neonates, show well-developed responses to painful stimuli. Indeed, the fetus shows a stress response (and behavioural changes) to nociceptive stimulation from 18–20 weeks gestation, which can be attenuated by the administration of fentanyl. It has long been known that attenuation of the stress response to surgery improves post-operative morbidity and mortality.

The neonatal period is characterised by marked sensitivity to sensory stimuli of all types, with low thresholds of response to mechanical and noxious stimulation. The nociceptive responses of neonates are significantly different from those of adults; at birth, a noxious stimulus (e.g. heel prick) will elicit an exaggerated movement of the whole body and movement of all four limbs.

The process of maturation of the nociceptive system is complex and involves interactions between the peripheral and central nervous systems, changes in receptor, ion channel and neurotransmitter expression and the effects of neurotrophins. Experimental evidence has shown widespread, functional opioid receptors in the spinal cord of newborn animals (rather than located to lamina I and II of the spinal cord as in adult life). It appears that there is a great deal of neuronal fine-tuning during early neonatal life, which may be influenced by the activity of endogenous opioids. There is a question about the long-term effects of exposure to exogenous morphine in neonates at this time of neuronal plasticity. Conversely, early pain experiences may result in sensitisation and may also have long-term effects, possibly through developmental changes in sensitivity to nociceptive stimuli.

Long-term effects of early exposure to anaesthetic agents

Recent work has investigated the effects of exposure of the developing brain to drugs that block NMDA receptors or potentiate GABA receptors in animal models. All anaesthetic drugs commonly used in paediatric practice (midazolam, propofol, barbiturates, all volatile agents, ketamine and etomidate) are found to cause dose dependent neuronal apoptosis with deficits in hippocampal synaptic function and persistent memory/learning impairments in these

animal models. The relevance to clinical practice is unclear at present. Surgery without effective anaesthesia and pain relief would be inhumane and would also have significant adverse effects. It would seem sensible to avoid surgery during infancy unless it is necessary, to avoid multiple agents and, if possible, to limit duration of anaesthesia to less than 2 hours.

Key points

- Early neonatal life is a time of rapid development and adaptation that makes the neonate particularly vulnerable during surgery.
- Neonates and infants are prone to airway obstruction and respiratory failure; respiration should be supported with CPAP as a minimum during anaesthesia, with positive pressure ventilation for all except minor procedures.
- Neonates and infants have limited cardiac reserve, and deep anaesthesia should be avoided.
- Surgery should only be undertaken if necessary during infancy. Babies should be kept warm, should not be volume loaded or starved for excessive periods of time, and balanced anaesthesia should be used, with judicious use of opioids.

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Section I Introduction

Chapter 2

Pharmacological issues affecting anaesthesia in neonates and young children

George H. Meakin

Introduction

Paediatric patients, especially neonates and infants, differ from adults in the way they respond to drugs. These differences became apparent in the 1950s following a number of major adverse drug events including an increase in kernicterus in newborns treated with sulfonamides, and fatal cardiovascular collapse among infants treated with chloramphenicol. Research into these conditions showed that paediatric responses to drugs are determined by a large number of factors that change independently during growth and development.

The factors that determine paediatric responses to drugs can be divided into those affecting pharmacokinetics and those affecting pharmacodynamics. This chapter reviews these factors and describes how they affect the pharmacology of selected anaesthetic drugs in neonates and young children.

Factors affecting pharmacokinetics

- Absorption
- Distribution
- Elimination

The processes of absorption, distribution and elimination of drugs are influenced by a number of age-related factors. In general, absorption and distribution of drugs tend to be increased in neonates and infants compared with older subjects, while the capacity for elimination is often reduced. Thus, there is an increased risk of drug overdose and toxicity in the very young.

Absorption

Absorption refers to the translocation of a drug from its site of administration into the systemic circulation. Many anaesthetic drugs and adjuvants are administered by intravenous injection. Absorption by this route is rapid and complete. Absorption by other routes (e.g. intramuscular, inhalation) is usually faster in neonates and infants, and this contributes to a more rapid onset of therapeutic as well as adverse effects.

Distribution

Distribution refers to the transfer of a drug from the systemic circulation into the various body compartments, and is affected by:

- Cardiac output
- Protein binding
- Body water
- Blood–brain barrier

Cardiac output: At birth, weight-normalised resting cardiac output is around 200 ml kg^{-1} min^{-1}; thereafter it declines gradually to about 100 ml kg^{-1} min^{-1} by adolescence (Figure 2.1). The relatively high cardiac output in infants and young children translates into faster circulation times, so that drugs are distributed to and from their sites of action more rapidly.

Cardiac output varies with $(\text{body weight})^{3/4}$ because it depends on metabolic rate (see section on dosing below). However, when normalised for body weight, as in Figure 2.1, it declines exponentially in relation to $(\text{body weight})^{-1/4}$ (i.e. $\text{weight}^{(3/4-1)} = \text{weight}^{-1/4}$). The same exponential decline is evident for weight-normalised extracellular fluid (ECF) volume (Figure 2.3) and the per kilogram doses of many drugs in older infants and children (Figure 2.7).

Protein binding: Plasma protein binding limits the amount of drug that is available to diffuse into the extracellular space and interact with tissue receptors. In general, acidic drugs such as barbiturates bind to

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