Neonatal anaesthesia

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Introduction

Safe anaesthesia for neonates is based on understanding their unique physiology and response to medications so as best to provide analgesia and amnesia, depress stress responses, maintain cardiovascular stability, and return them to baseline status. Medications administered by any route have a similarly rapid uptake (alpha phase) followed by the slower elimination phase (beta phase) as adults. However, the duration of these phases is altered by changes in body composition, protein binding, and maturation of organ function.[1-11]

Pharmacologic considerations

The neonate looks "different" on the outside, but is also "different" on the inside. For example, total body water accounts for ~ 85% body weight in a premature infant, ~ 75% in a term infant and, in infants 6 months and older, the total body water only accounts for 60% of body weight (see Figure 1 and 2).[12] These differences in body composition have important implications for drug effect, loading dose, interval of dosing and drug metabolism.[2-4,12-16] A highly water soluble medication, for example, is rapidly redistributed in this large water compartment, necessitating a higher initial dose (mg/kg) compared with older patients. This effect will be relevant to, amongst other drugs, succinylcholine and many antibiotics.[17-21]

In addition, a premature infant has only ~ 18% of weight as muscle, a term infant ~ 30%, a 6-month-old ~ 40%, and most children > one year ~ 50%. If giving a medication that has its primary effect at the myoneural junction, one could postulate that a lower dose or a lower plasma level would be required to have a clinical effect compared to the other child; this has been demonstrated for most muscle relaxants.[17]

Total body fat content is also important. A premature infant has only ~ 4% body weight as fat; the term infant ~ 15%; the 6-month-old ~ 25%; and older children nearly 30%. If a drug redistributes into fat, then the volume of tissue into which that drug can be distributed varies by age. For example, the effect of thiopental is diminished through redistribution rather than metabolism. Prolonged sedation might result in neonates simply on the basis of them not having much fat tissue to redistribute into (Figure 3). In preterm infants, the only place where there is any fat is in the brain!

Figure 1: Body composition of preterm and term neonates and adults: intra- and extracellular fluids (%)

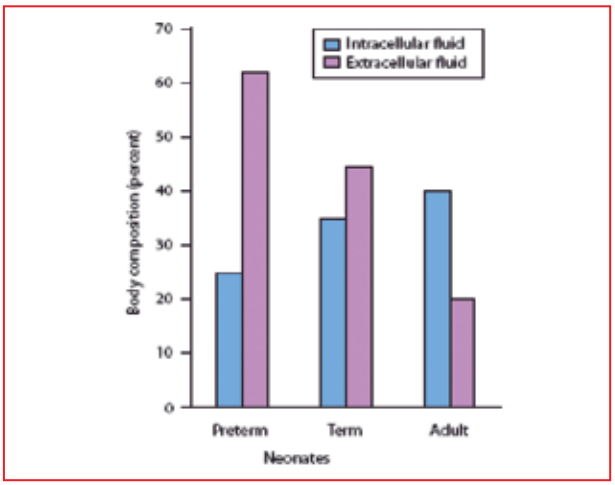

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Figure 2: Body composition of preterm and term neonates and adults: fat, muscle and water (%)

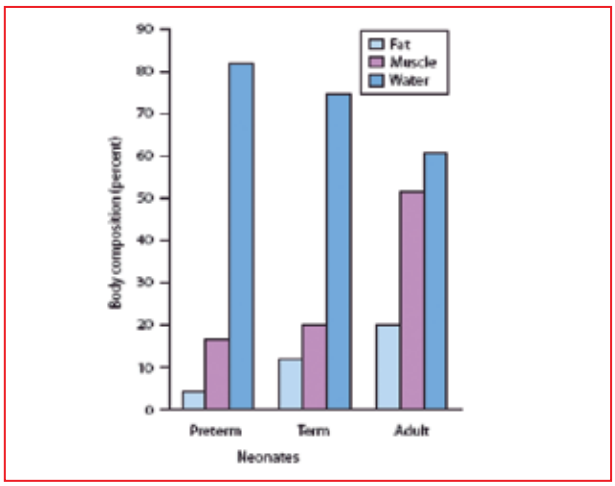

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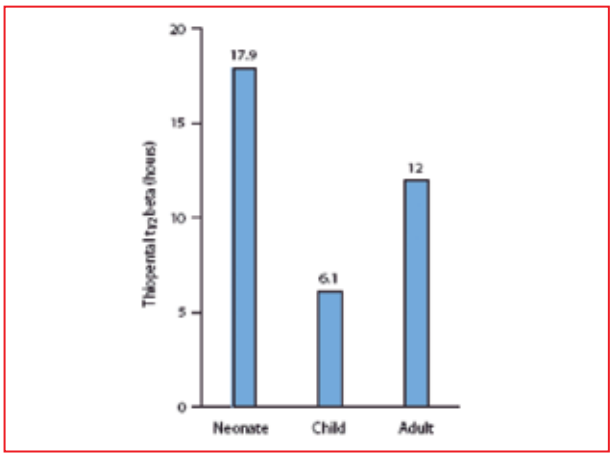
Figure 3: Length of elimination half-life (hours) of thiopental in the neonate, child and adult



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Another factor is maturity of hepatic function. Newborns are capable of conjugating and glucuronidating most medications, but the rate of metabolism is generally delayed compared to the older child or adult.[3,4,20,22-31] The half-life of thiopental is ~18 hours in a term newborn, ~7 hours in a child 4 - 10 years of age, and 10 hours in the adult. Thus, in addition to having less fat for the thiopental to redistribute into, there is a markedly prolonged beta elimination phase due to immaturity of hepatic metabolism. Alterations in hepatic blood flow (altered drug delivery to the liver) significantly affect pharmacokinetics. Procedures that increase intra-abdominal pressure such as, for example, omphalocoele repair, will decrease hepatic blood flow and markedly delay drug metabolism; a single dose of fentanyl can maintain constant plasma values up to 16 hours.[32-34]

Maturity of renal function also markedly alters a drug's half-life.[35-39] There is a very rapid maturation of renal function in the first months of life (Figure 4). In preterm infants, the glomerular filtration rate (ml/minute/1.73 m^2 surface area) is only ~ 25, in the term infant ~ 35, by two weeks of age it has doubled to ~ 60, by 6 months it is ~ 80, and at 1 year it is equivalent to an adult. Thus, drugs that are excreted by the kidneys (e.g. antibiotics) are given at less frequent intervals in the premature compared to the term newborn, and at less frequent intervals in the term newborn compared to older children. For example, gentamicin has a half-life of ~ 8½ hours in the preterm infant, six hours at 1 week of age, four hours at 2 weeks, and two hours in adults (Figure 5).[40-42]

In addition to these maturational factors in body composition, renal and hepatic functions, differences in protein binding and competitive drug binding with bilirubin in jaundiced infants may also alter metabolism and pharmacodynamics.[43-48] As infants mature, there are marked changes in both total protein and albumin values (Figure 6).[49-53] These differences alter the amount of protein bound drug which affects the amount of free drug available to cross biologic membranes. Neonates might be particularly vulnerable to drug effects simply because of reduced protein binding. If a drug has low protein binding, then this effect is minimal, e.g. for ampicillin the change from 90% unbound drug to 92% unbound in the presence of hyperbilirubinaemia is

Figure 4: Glomerular filtration rate at 1 day, 5 days, 3 months, 6 months, 1 year, and 2 years, and in the adult

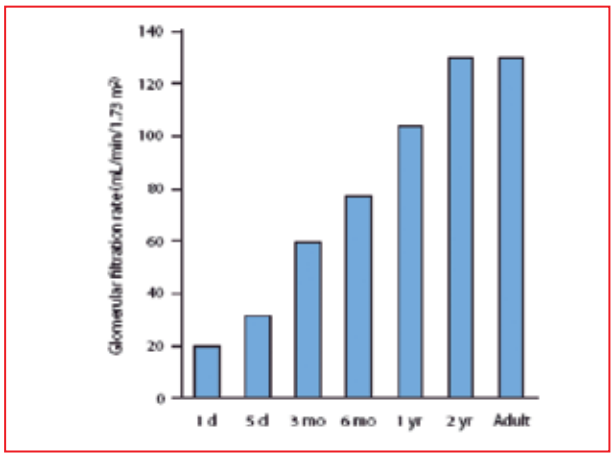

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Figure 5: Length of elimination half-life (hours) of gentamicim and ampicillin in the preterm and term neonate, and adult

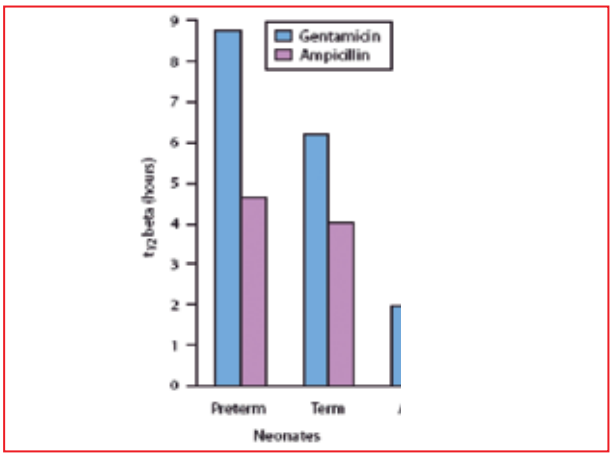

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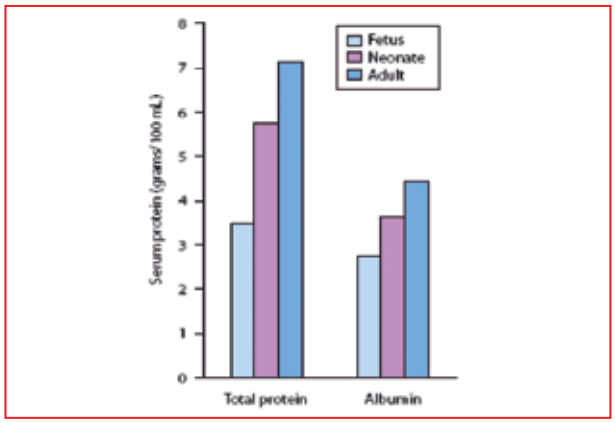
Figure 6: Serum protein concentrations (total protein and albumin) in the foetus, neonante and adult



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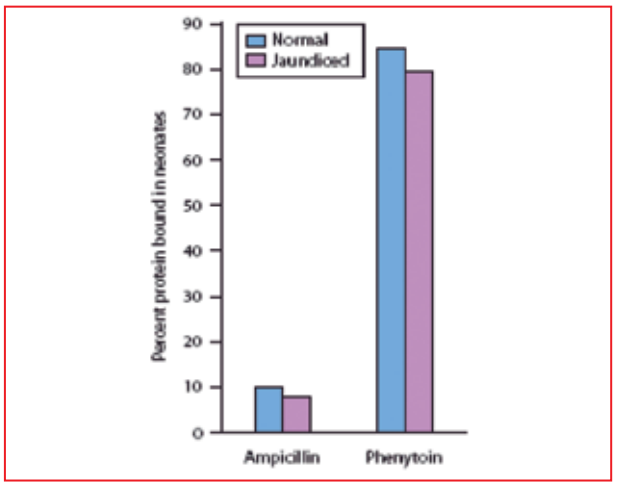
insignificant (Figure 7). However, if a drug is highly protein bound and that drug also competes with bilirubin, then the jaundiced infant may have a marked increase in free drug levels and therefore increased response (In Figure 7, unbound diphenylhydantoin nearly doubles).

Figure 7: Percent protein bound drug (ampicillin and phenytoin) in normal and jaundiced neonates



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Another issue is maturation of the central nervous system (CNS) and blood brain barrier. For medications with high fat solubility, the blood brain barrier does not make a significant difference, but it will for medications that have low fat solubility, since fat solubility determines a drug's ability to cross cell membranes.[54] If one compares the fat solubility of fentanyl vs. morphine, one finds that fentanyl is so fat soluble (nearly 2 000 000 times greater than morphine!) that there virtually is no blood brain barrier effect.[55] Whereas with morphine, which has a low fat solubility, a proportionally higher amount of morphine would cross into the brain of a newborn compared to an older child, simply because of the immaturity of the blood brain barrier.[56] Studies have shown that the peak pharmacodynamic effects of benzodiazepines are also directly proportional to fat solubility; the peak EEG effect of diazepam is **nearly three times faster** than that of midazolam.[57,58] A common misconception is the reverse, i.e. because midazolam is shorter acting it must enter the CNS more rapidly.

Perhaps the least understood, but most important, difference is the neonate's response to inhalation anesthetic agents. We still do no know why the minimum alveolar concentration (MAC) is higher compared with older children. The rate of rise of inhalation agent depends upon the combination of delivery of drug to and removal from the lungs.[59] A steady state exists once the alveolar and the inspired concentrations (F_A/F_I) equilibrate; this equilibrium is more rapid in children.[60]

Delivery of drug to the lungs is affected by inspired concentration, minute ventilation, and the ratio of minute ventilation to functional residual capacity, whereas uptake is related to cardiac output, tissue/blood solubility and alveolar to venous partial pressure gradient. In neonates, the greater cardiac output increases the equilibration of F_A/F_I because of the high distribution to vessel rich groups (~ 18% neonate vs. ~ 8% adult). The rate of increase of F_A/F_I of inhalation anaesthetics varies inversely with the solubility in blood: nitrous oxide > desflurane > sevoflurane > isoflurane > enflurane > halothane > methoxyflurane.[59,61] Another factor is the tissue/gas solubilities of the inhalation anaesthetics, which is about half that of adults.[62] This reduced tissue solubility decreases the time for partial pressure equilibration. Thus F_A/F_I equilibrates more rapidly in neonates and infants compared with adults.[60,63]

A clinically important issue for neonates (with a MAC for halothane of 0,87%, and a MAC of sevoflurane of ~ 3%) is that the currently available vaporisers deliver more MAC multiples of halothane than sevoflurane. Excessive concentrations of sevoflurane cannot be administered, because the large MAC values more than offset reduced solubilities. Thus the cardiovascular safety profile of sevoflurane appears to be far better than halothane (Table I).[64] However, cardiac arrest may occur with both agents with the onset of controlled respirations which forces more drug into the lungs.[64] Once respirations are controlled, the inspired concentration must be dramatically reduced to avoid cardiac depression.

Table I: MAC multiples for a neonate allowed by current vaporisers

Agent	Maximum vaporiser output (%)	MAC (%)	Maximum possible MAC multiples
Halothane	5	0,87	5,75
Isoflurane	5	1,20	4,20
Sevoflurane	8	9,16	1,96
Desflurane	18	3,30	2,42

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General considerations

Neonatal anaesthetic care begins with a careful pre-operative evaluation, including maternal history (medications, drug use, diabetes, etc) and birth history (small, appropriate, or large for gestational age, birth trauma, meconium, respiratory status, focused airway examination, current medications, laboratory data, congenital anomalies, echo cardiogram, etc).

Review and understand the surgical issues (how urgent, elective or emergent, who is the surgeon and what are his/her skills), as well as venous access, arterial, central venous, peripherally-inserted central catheter (PICC) and umbilical lines, and will you be able to use these in the operating room (OR)? Do they provide adequate access for rapid transfusion?

The next problem is how to safely transport to the OR. You will need a transport monitor with adequate battery time, secure airway (retape the endotracheal tube (ETT) to your satisfaction), and an appropriately sized laryngoscope, ETT, stylet, mask, and oral airway.

Also, ensure an adequate oxygen supply, and a Mapleson-D or Ambu bag). Also, there must be adequate battery time for infusion pumps; (make sure the nurses set the limits to extend well beyond the anticipated operating time to avoid nuisance alarms), and bring emergency drugs (atropine, epinephrine, muscle relaxant).

The mnemonic **SOAPME** particularly applies in preparing the OR:

- **S**uction;
- **O**xygen;
- **A**irway (intact circuit, appropriate size bag, age- and size-appropriate ETT, laryngoscope);
- **P**harmacology (drugs drawn up in appropriately sized syringes, or diluted in appropriate concentrations with the air ejected from the syringe, appropriate intravenous (IV) solutions (ensure $D_{10}W$ already mounted on an infusion pump), vasopressors;
- **M**onitors (arterial line, central venous pressure); and
- **E**quipment (adequate pumps plugged in, blood warmer, Bair Hugger, etc).

Change the IV line to an OR IV line to facilitate drug administration and check baseline oxygen saturation, blood pressure and heart rate. In the neonate still at risk for opening and closing of a patent ductus arteriosus (PDA), right hand and foot pulse oximetry will help to monitor for this eventuality.

The appropriate anaesthetic prescription is based upon underlying medical and surgical conditions, cardiac function, potential for blood loss, need for post-operative mechanical ventilation, pain management, and neurological function.

Most premature infants will arrive in the OR already intubated, so a very gentle inhalational or intravenous induction can occur. Recall that if respirations are controlled (the usual and safest method of ventilation in preterms), then the inspired concentration of sevoflurane should be very low (0,5 - 1%) initially, and then titrated as tolerated. Controlled ventilation without regard for the inspired anaesthetic concentration will, and has, resulted in cardiac arrest.[65] If an intravenous induction is preferred, the selection of propofol, ketamine or etomidate is based upon cardiovascular stability. If the infant is not intubated and has a known difficult airway, then an awake sedated approach is indicated. The need to maintain spontaneous respirations is emphasised. One approach is to allow the infant to inhale nebulised lidocaine, followed by viscous lidocaine applied to a laryngeal mask airway (LMA). This allows securing of the airway in preparation for a fibre-optic intubation through the LMA. Very small doses of midazolam (0,025 – 0,05 mg/kg, or 25 to 50 µg/kg) and/or fentanyl (0,25 – 0,5 µg/kg) may be titrated to effect.

If this degree of difficulty is anticipated, availability of another pair of skilled hands (a surgeon qualified to perform an emergency tracheotomy or another anesthesiologist familiar with paediatric patients) is an essential part of the anaesthetic plan. The disaster we are trying to avoid is “can’t ventilate, can’t intubate, can’t oxygenate”. An emergency means for transtracheal cricothyrotomy should be anticipated. Generally, a non-sedated attempt at intubation is to be avoided, because of the possible adverse haemodynamic responses that may increase the potential for CNS haemorrhage. However, if you are uncomfortable or unsure about sedation with midazolam or fentanyl, then no sedation is preferable to an adverse event as a result of poorly administered sedation. The most important consideration if you are unable to pass the tracheal tube, is that the infant is still exchanging air, maintaining saturations, and that you have not traumatised the airway. It is better to back off and let another take a try, than to persist and injure the airway or worse. A gaseous induction is not generally recommended, since all inhalation agents depress the heart long before they adequately depress airway reflexes, and because of the effects of inhalation agents on the airway: increased respiratory rate, decreased tidal volume, loss of intercostal muscle function (decreased functional residual capacity), and collapse of upper airway structures leading to upper airway obstruction (often relieved with 5 - 10 cm PEEP). If the infant has apparent normal airway anatomy, then a standard intravenous induction with muscle relaxant to facilitate intubation is indicated.

Monitoring must be appropriate for the procedure. If invasive arterial or central venous monitoring is indicated, these need to be placed either by the anesthesiologist or the surgeon. One should never feel pressed to move forward without adequate monitoring. Table II lists many of the differences between neonates and older children.

With the above considerations in mind, the choice for maintenance of anaesthesia is often a combination of short acting opioid, muscle relaxant, and low dose inhalation agent. Remifentanil, the metabolism of which is unaffected by renal or hepatic maturity, is gaining increased popularity due to the very favourable pharmacokinetics in infants.[66-70] This is the only medication I am aware of that has a shorter half-life in neonates than adults![71-78] If this technique is chosen, the dilution of the drug must be such that there is a measurable unit dose per minute and, generally, a starting dose of 0,1 – 0,15 µg/kg/minute is utilised. The safest means for administration is continuous infusion with a carrier, e.g. the maintenance IV fluid as the carrier, with a second IV line to be used for all other interventions such as other medications, blood, or third space losses. If this technique is used, there must be a transition to a longer acting opioid, or the placement of a nerve block or local infiltration, prior to emergence. Cisatracurium would be the ideal muscle relaxant for the same reason as remifentanil.[79]

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Table II: Differences between infants and older children: anaesthetic implications

Organ system	Characteristi c in infants (vs. older children)	Implications
Airway	Larger tongue	Difficult to control position
	Higher in neck	Difficult to visualise glottis
	Short, stubby epiglottis	Difficult to pick up epiglottis
	Angled vocal cord	Can make nasal intubation more difficult
	Narrow subglottic region	Reason why uncuffed tubes are often selected
	Decreased type II muscle fibres in diaphragm and intercostal muscles	Fatigue more easily
Cardiac	Fewer contractile elements (30% vs. 60%)	Easier to depress the heart with inhalation agents
	Reduced calcium regulation	More dependent on ionised calcium
	Less compliant ventricle	Limited Frank-Starling response
	Reduced systolic and diastolic function	Rate dependent cardiac output
	Reduced sympathetic development	Parasympathetic dominates
Lungs	Highly compliant airways	Dynamic airway collapse with or without airway obstruction
	FRC = closing volume	Small airway collapse with each breath
	Increased oxygen consumption	Rapid desaturation
	Immature rib structure	Minimal to no FRC
Kidneys	Immature renal function	Age related renal maturation and delayed drug excretion, particularly antibiotics
Liver	Immature enzyme systems	Delayed metabolism of some medications, e.g. thiopental, midazolam, opioids
	Reduced albumin and globulins	Altered drug binding to protein, more unbound drug
	Hyperbilirubinaemia	Drug displacement from protein binding by bilirubin
Hematopoietic	High foetal haemoglobin	Left shift of Haemoglobin/O_2 binding, but then slower release to tissues (need higher haemoglobin values)
Skin	Very thin skin	Increased loss of fluid and heat
Temperature regulation	Infant response	Non-shivering thermogenesis
Neurologic	Immature blood brain barrier, immature respiratory center	Sensitivity to sedating medications Prone to apnoea
Myoneural junction	Immature	Paralysis with lower blood concentrations

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