Refresher Course: Neonatal anaesthesia

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 (%)
(Reproduced from: Coté, Lerman, Todres: A practice of anesthesia for infants and children. 4th Edition. 2009).

Figure 2: Body composition of preterm and term neonates and adults: fat, muscle and water (%)
(Reproduced from: Coté, Lerman, Todres: A practice of anesthesia for infants and children. 4th Edition. 2009).
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. 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.

Maturity of renal function also markedly alters a drug’s half-life. 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 m² 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).

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. As infants mature, there are marked changes in both total protein and albumin values (Figure 6). 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 hyperbilirubinemia is

(Reproduced from: Coté, Lerman, Todres: A practice of anesthesia for infants and children. 4th Edition. 2009).

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

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

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

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

(Reproduced from: Coté, Lerman, Todres: A practice of anesthesia for infants and children. 4th Edition. 2009).
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. 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. 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. Studies have shown that the peak pharmacodynamic effects of benzodiazepines are also directly proportional to fat solubility; the peak EEG effect of diazepam is faster than that of midazolam. 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. A steady state exists once the alveolar and inspired concentrations (\(F_{A}/F_{I}\)) equilibrate; this equilibrium is more rapid in children.

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 > enfurane > halothane > methoxyflurane. Another factor is the tissue/gas solubilities of the inhalation anaesthetics, which is about half that of adults. 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.

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). However, cardiac arrest may occur with both agents with the onset of controlled respirations which forces more drug into the lungs. 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 vapouriser 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                          |

(Reproduced from: Coté, Lerman, Todres: A practice of anesthesia for infants and children. 4th Edition. 2009).

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:

- Suction;
- Oxygen;
- Airway (intact circuit, appropriate size bag, age- and size-appropriate ETT, laryngoscope);
- Pharmacology (drugs drawn up in appropriately sized syringes, or diluted in appropriate intravenous (IV) solutions (ensure D„W already mounted on an infusion pump), vasopressors;
- Monitors (arterial line, central venous pressure); and
- Equipment (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 anesthetic 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 ventilation in preterms), then the inspired concentration of

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 induction 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 anesthesia 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.6-7 This is the only medication I am aware of that has a shorter half-life in neonates than adults!7-78 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

References:

1. Pacifici GM. Pharmacokinetics of antivirals in neonate. Early Hum Dev. 2005; 81: 773-83.
2. Besunder JH, Reed MD, Blumer JL. Principles of drug biodistribution in the neonate: A critical evaluation of the pharmacokinetic-pharmacodynamic interface, Part I. Clin.Pharmacokinet. 1988; 14: 189-216.
3. Besunder JH, Reed MD, Blumer JL. Principles of drug biodistribution in the neonate: A critical evaluation of the pharmacokinetic-pharmacodynamic interface, Part II. Clin.Pharmacokinet. 1988; 14: 263-86.
4. Levy G. Pharmacokinetics of fetal and neonatal exposure to drugs. Obstetrics and Gynecology 1981; 58: Suppl: 168-166.
5. Ward RM, Merin BL. Perinatal/neonatal pharmacology. Human Pharmacology: Molecular-to-Clinical, 3rd edition. Edited by Brody TM, Lerner J, Minneman KP. St Louis, Mosby-Year Book, 1998, pp 873-83.
6. Johnson TN. Modelling approaches to dose estimation in children. Br J Clin Pharmacol. 2005; 59: 663-9.
| Organ system | Characteristic 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 | Increased oxygen consumption            | Small airway collapse with each breath |
|             | 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/O₂ 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 |

7. de Hoog M, Muusen JW, van den Anker JN. New dosing strategies for antibacterial agents in the neonate. Semin-Fetal Neonatal Med. 2000; 10: 185-94.
8. Knaus SL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med. 2003; 349: 1157-67.
9. Lugho RA, Ward RA. Basic pharmacokinetic principles, Fetal and Neonatal Physiology, 3rd edition. Edited by Polin RA, Fox WW, Abman SH. Philadelphia, Harcourt Health Sciences, 2004, pp 190-7.
10. Ward RM, Lugho RA. Pharmacologic principles and practicalities, Avery’s Diseases of the Newborn, 8th edition. Edited by Tench MRH, Ballard RA, Gibson CA. Philadelphia, W.B. Saunders Company, 2005, pp 427-37.
11. Ward RM, Lugho RA. Drug therapy in the newborn, Avery’s Neonatology: Pathophysiology and Management of the Newborn, 6th edition. Edited by MacDonald MG, Sennin MM, Mulkert MD. Philadelphia, Lippincott Williams & Wilkins, 2005, pp 1027-56.
12. Fritzen-Hansen B. Body composition during growth. In: two measurements and biochemical data correlated to differential anatomical growth. Pediatrics 1971; 47: 169-81.
13. Morselli PL, Franci-Morselli R, Rossi L. Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. Clin Pharmacokinet. 1980; 5: 485-507.
14. Regeza A, Wilton JT. Clinical pharmacokinetics in infants and children. Clin Pharmacokinet. 1976; 1: 2-24.
15. Udskow S. Pediatric clinical pharmacology. A practical review. Am J Dis Child 1976; 19: 1025-32.
16. Jusko WJ. Pharmacokinetic principles in pediatric pharmacology. Pediatr Clin North Am. 1972; 19: 81-100.
17. Fisher DM, O’Keefe C, Staniski DR, et al. Pharmacokinetics and pharmacodynamics of d-tubocurarine in infants, children, and adults. Anesthesiology 1982; 57: 203-8.
18. Kaplan JM, McCracken GH, Jr. Horton LJ, et al. Pharmacologic studies in neonates given large dosages of ampicillin. J Pediatr. 1974; 84: 571-7.
19. Nickerson SC, Schreiner MS, Watcha MF. Preoperative preparation of the child for anesthesia. Am J Anaesth. 1996; 23: 157-62.
20. Aranda JL, Stier DS, Parsons WD, et al. Pharmacokinetic aspects of theophylline in premature newborns. N Engl J Med 1976; 295: 410-6.
21. McCracken GH, Jr. Pharmacological basis for antimicrobial therapy in newborn infants. Am J Dis Child 1974; 128: 407-19.
22. Koch-Weser J, Sellers EM. Binding of drugs to serum albumin (first of two parts). N Engl J Med 1976; 294: 311-6.
