Neonatal pharmacology

Brian J Anderson

Abstract

Neonatal anaesthesia dosing needs to be based on physiological characteristics of the newborn, pharmacokinetic knowledge, pharmacodynamic considerations and the adverse effects profile. Disease processes and treatments in this group are distinct from adults. Immaturity of enzyme, anatomical and physiological systems cause extensive variability of drug disposition and drug response in neonates. This is further compounded by pharmacogenomic influences. Postmenstrual age is a reasonable measure for maturation of clearance pathways. The neonatal response to drugs is altered and monitoring of effect that guides adult drug use is limited. While neuromuscular monitoring is robust, few other clinically applicable tools are available to provide pharmacodynamic effect feedback. Tools that assess depth of anaesthesia, sedation and pain in neonates have potential to improve effectiveness and safety.

Keywords Drugs; neonatal; off-label; paediatric; pharmacodynamics; pharmacokinetics; pharmacology; therapeutic orphan

Royal College of Anaesthetists CPD Matrix: 1A02

Learning objectives

After reading this article, you should be able to:

- précis the challenges facing the clinician delivering dosing regimens in neonates, including appreciation of the non-linear relationship between metabolic processes and size in children
- explain how growth and development in the neonate affects drug disposition (with examples)
- provide an overview of the recent developments in neonatal pharmacology (with immediate relevance to the anaesthetist)

Not all neonates are the same

Neonates are a heterogeneous group of children from birth up to the age of 28 days of life. The word 'neonate' also includes former preterm neonates. Postmenstrual age (PMA) may range from extreme preterm birth at 22 weeks up to 50 weeks PMA while weight may range from less than 0.5 kg to over 5 kg; an entire order of magnitude. Age, size, co-morbidity, co-administration of drugs and genetic polymorphisms contribute to the extensive between-individual pharmacokinetic (PK) and pharmacodynamic (PD) variability.

Neonates became 'therapeutic orphans' after misuse of drugs such as chloramphenicol and thalidomide in this population. Ethical constraints and medicolegal issues surrounding consent and risk in non-therapeutic research limited drug study participation. Technical issues such as blood sampling and amount for assay made PK studies difficult. Recruitment of adequate numbers of neonates with similar pathology at the same stage of growth and development was difficult. Clinical endpoints were often poorly defined. Adverse drug effects may not become apparent until later life. Further, the market for most drugs in children is small in comparison to that in adults.

Many of these research obstacles have been dismantled. Financial incentives and legislative changes have been introduced to encourage drug labelling in children. Microsampling, more sensitive analytical methods, pooling of data from multiple institutions and better computer programmes have enabled greater understanding of PK and PD.

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Neonatal pharmacokinetics

Absorption

Physicochemical and patient factors influence the ability of a drug to translocate from its site of administration to the bloodstream and site of action (Box 1).

Enteral absorption: enteral absorption when drugs are given orally is slower in neonates and infants. Gastric emptying and intestinal motility are delayed and may not mature until 6–8 months. This results in an increased time to peak concentration as well as decreased peak concentration compared to older children. Slow gastric emptying is also associated with type of feed (increased calorie density and long-chain fatty acids); and disease states (e.g. pyloric stenosis, congestive cardiac failure, duodenal atresia). Human milk and low-calorie feed quicken gastric emptying. Co-administration of drugs (e.g. opioids) can slow gastro-oesophageal motility.

The volume and pH of gastric secretion after birth is variable; gastric and duodenal content influences the ability of a drug to dissolve and alters the ratio of ionized to un-ionized particles. A low pH environment will render acidic drugs with a low pK more un-ionized and better able to cross lipid membranes. Changes in the bile-salt pool can alter the solubilization and absorption of lipophilic drugs or formulations.

Non-enteral absorption: transdermal absorption in neonates is variable because of an incompletely formed stratum corneum and immature vasomotor control. Neonates have a tendency to form methaemoglobin because they have reduced methaemoglobin reductase activity and fetal haemoglobin is more readily oxidized compared to adult haemoglobin. This, combined with increased percutaneous absorption resulted in reluctance to use repeat lidocaine–prilocaine cream in this age group. Similarly, cutaneous application of iodine antiseptics can result in transient hypothyroidism. Rectal administration is associated with variable plasma concentrations; factors such as variable lower gastrointestinal motility and depth of insertion may affect bioavailability. Absorption via the upper rectal veins undergoes first-pass metabolism, whereas the inferior and middle rectal veins bypass the hepatic first-pass effect and drain directly into the inferior vena cava. Rectal administration (e.g. thiopentone, methohexitone) is speedier for neonates undergoing cardiac catheter study or radiological sedation. However, the between-individual absorption and relative bioavailability variability

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Some factors affecting drug absorption relating to neonates

Physicochemical factors

Drug formulation

- Disintegration of tablets or solid phase
- Dissolution of drug in gastric or intestinal fluid
- Release from sustained-release preparations

Molecular weight

pK/Proportion of drug in ionized/un-ionized form

Lipid solubility

Patient factors

General

- Surface area available for absorption

Gastrointestinal

- Gastric content and gastric emptying
- Gastric and duodenal pH
- Size of bile-salt pool
- Bacterial colonization of lower intestine
- Disease states (e.g. short-gut syndrome, biliary atresia)

Muscle

- Increased capillary density in neonatal muscle compared with adults increases absorption from muscles
- Reduced cardiac output states reduce absorption

Skin

- Blood supply
- Peripheral vasodilation
- Thickness of skin/stratum corneum
- Surface area

Rectal

- Rectal venous drainage site
- Neonatal absorption > older children

The patient factors are particularly relevant in neonates.

Box 1

may be more extensive compared to oral administration, making rectal administration less suitable for repeated administration.

Absorption by other routes (e.g. intramuscular, inhalation) is often faster in infants. Inhalational anaesthetic delivery is determined largely by alveolar ventilation and functional residual capacity (FRC). Neonates have increased alveolar ventilation and a smaller FRC compared to adults because of increased chest wall compliance. Consequently, pulmonary absorption is generally more rapid in neonates. The higher cardiac output and greater fraction of the cardiac output distributed to vessel rich tissues (i.e. a clearance factor) and the lower tissue/blood solubility (i.e. a volume factor) further contribute to the more rapid wash-in of inhalational anaesthetics in early life.

Disease characteristics further contribute to the variability in inhalational absorption. Induction of anaesthesia may be slowed by right-to-left shunting of blood in neonates suffering cyanotic congenital cardiac disease or intrapulmonary conditions. This slowing is greatest with the least soluble anaesthetics (e.g. nitrous oxide, sevoflurane). Left to right shunts usually have minimal impact on uptake unless cardiac output is decreased and peripheral perfusion is reduced. There will then be less anaesthetic uptake in the lung. Alveolar anaesthetic partial pressure may be observed to rise rapidly, but there will be a slower rise in tissue partial pressure and anaesthetic effect is delayed.

Distribution

Fluid distribution: the greatest change in body water compartments occurs in the first year of life (Figure 1). In premature and term neonates, the volume of distribution for water-soluble drugs is increased compared to older children. To achieve the required plasma concentrations of water soluble drugs (e.g., aminoglycosides, neuromuscular blocking drugs) a higher loading dose per kg needs to be administered in the neonate. Cerebrospinal fluid contributes a greater proportion of body composition, necessitating increased dose (per kg) of spinal local anaesthesia drug.

Body tissue composition: neonates have a smaller proportion of weight in the form of fat and muscle compared with adults (Figure 2). The percentage of body weight contributed by fat is 3% in a 1.5 kg premature neonate, 12% in a term neonate. Drugs that rely on redistribution to fat and muscle, such as thiopentone or propofol, will have prolonged and higher plasma concentrations.[1]

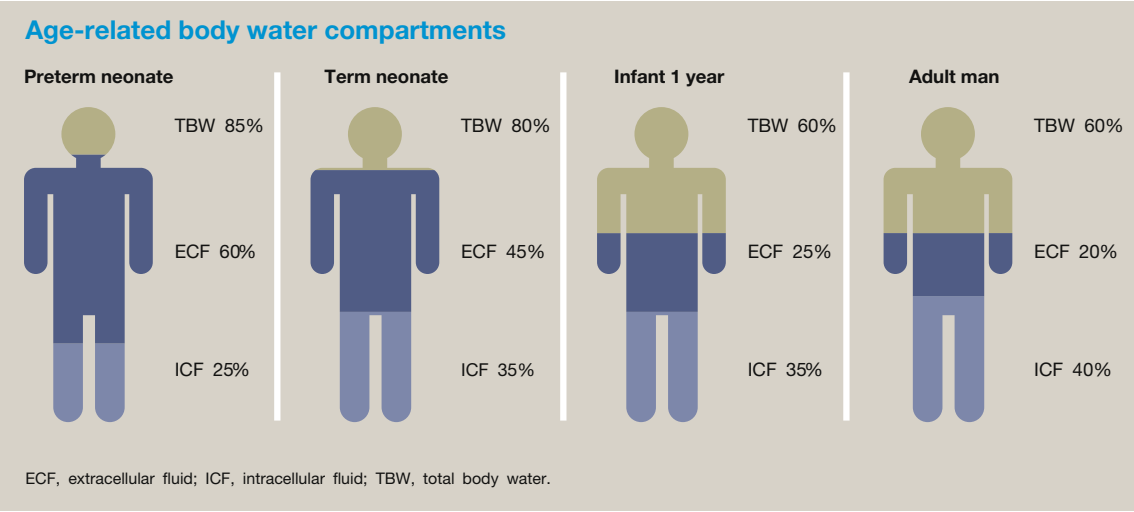

Figure 1

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