Neonatal pharmacology

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Abstract

The neonatal period represents a time of rapid growth and development. As a consequence, significant pharmacokinetic and pharmacodynamic changes occur. In addition, size, age, physiological changes, pathological processes and genomics all contribute to between patient variability that should be considered when trying to predict the action and disposition of drugs in the neonate. The problem is compounded by a relative paucity of research and data on many aspects of neonatal pharmacology. These issues pose significant challenges to the clinician to deliver safe and effective drug therapy to these vulnerable patients. Recent developments have attempted to redress this balance; many steps have been taken to increase the number of paediatric drug research programs and the traditional challenges to research in children and neonates are being addressed by legislative authorities, pharmaceutical companies, clinicians and the academic community. These research issues are discussed along with the basic science of neonatal pharmacology and new developments in the past few years.

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 in delivering appropriate dosing regimes in neonates, including appreciation of the non-linear relationship between metabolic processes and size of child
- 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).

Traditional barriers to research in neonates (and older children)

In 1968, Dr Harry Shirkey (Chair of the American Academy of Pediatrics Committee on Drugs) described how children were being systematically excluded from studies intending to establish safety and efficacy of new drugs. He coined the term 'therapeutic orphans' to emphasize the lack of adequate prescribing information for drugs in children.[1,2] Despite this assertion, studies for the next 30 years showed consistently that approximately 80% of prescription medicines approved and labelled for adults contained no paediatric safety or prescribing information and a disclaimer regarding use in children. As a result, there has been routine and widespread 'off-label' use of medications in infants and children in the absence of adequate safety, efficacy, and dosing information. This goes hand in hand with the risk of adverse outcomes due to under-dosing, over-dosing, or unanticipated adverse events unique to children and not predicted from experience in adults.[2]

A number of reasons have been cited for this void of information in childhood therapeutics:

Ethical constraints and Medico-legal issues

These principles concerning research on patients unable to give consent differ from the adult population. Generally it is not considered ethical for a parent to give consent to non-therapeutic research where the risk is more than a minor 'increase over minimal'. However, a significant body of literature has documented that a child being treated under protocol in a well-designed, carefully conducted study with appropriate institutional review board oversight, (generally) has a better outcome than comparable patients receiving 'standard care'. One could infer from this that it is more ethical to treat a child as a participant in a clinical trial rather than with 'off-label' treatment in which the child is an experiment of $N = 1$ without collection of data.[2]

Technical and logistic difficulties

- Difficulty in obtaining parental consent; particularly where there is some increased discomfort or risk and no direct benefit to the child.
- Recruiting adequate numbers of patients with the same pathology at a similar stage of growth and development is difficult.
- Small neonates can only tolerate a certain volume of blood to be taken for testing; sparse sampling methods, microsampling and more sensitive analytical methods have recently helped to circumvent this problem.
- It is often difficult to determine clinical endpoints (e.g. analgesic effect).[3]

Economics of drug development in children

There is a small market for most drugs in the paediatric age group. Financial incentives and legislative changes have been introduced to address this.

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 (Table 1). Enteral absorption is variable in the neonate due to a number of factors:

- Enteral absorption
  - ***Extent of drug absorption*** – the primary mechanism for drug absorption is passive diffusion of un-ionized molecules through lipophilic membranes. Therefore the pH at the site of absorption influences the extent of absorption. Neonates *are* able to produce gastric acid. At birth, the gastric pH is between 6 and 8; however, this falls rapidly within a few hours. Premature neonates

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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.

Table 1

born at 25 weeks postmenstrual age produce H−K−ATPase, and the expression increases with gestational age.[4] 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 more able to cross lipid membranes. Changes in the bile-salt pool can alter the solubilization and absorption of lipophilic drugs or formulations.

- ***Rate of drug absorption*** − the irregular and unpredictable peristaltic activity of the upper gastrointestinal tract contributes to a variable rate of drug absorption in the neonate.[5] If gastric emptying is slowed, the drug is delayed in reaching the small intestine from where it is absorbed. The peak serum drug concentration will also be reduced.[4] Slow gastric emptying is associated with: low gestational and postnatal age; type of feed (increased calorie density and long-chain fatty acids); and disease states (e.g. pyloric stenosis, congestive cardiac failure). Human milk and low-calorie feed quicken gastric emptying.

- Non-enteral absorption
  - Transdermal absorption in neonates is variable because of an incompletely formed stratum corneum and immature vasomotor control. The increased surface area-to-weight ratio must be taken into account and can be responsible for a higher drug exposure than intended compared with a similar dose per kg in an adult.[4] 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.

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 and tissue concentrations of water soluble drugs (e.g. aminoglycosides, neuromuscular blocking drugs) a higher dose per kg often needs to be administered in the neonate.

Body tissue composition: neonates have a smaller proportion of weight in the form of fat and muscle compared with adults (Figure 2). In the neonate, drugs that rely on redistribution to fat and muscle such as thiopentone or propofol will have prolonged and higher plasma concentrations. Opposing pharmacokinetic factors frequently need to be balanced when evaluating drug dosage in neonates. For example, water-soluble non-depolarizing neuromuscular blockers (e.g. atracurium) will have a higher extracellular volume of distribution, which may suggest that a higher dose per kg is required. However, the reduced acetylcholine released from the motor nerves reduces the concentration of non-depolarizing neuromuscular blocker required at the neuromuscular junction. Practically a similar dose per kg is therefore given to neonates as adults.[6]

Protein binding: neonates have reduced albumin and total protein concentrations. The quality of drug-protein binding also appears to be reduced. Lower protein binding in premature and term neonates compared to older children results in greater free-drug concentration and hence greater drug effect. This effect is clinically more pronounced with highly protein-bound drugs.[5] Examples of acidic drugs binding albumin include diazepam, thiopental and phenytoin. Basic drugs tend to bind alpha1-acid glycoprotein (AAG), which will also have reduced binding in the neonate (e.g. lidocaine and alfentanil). Neonatal jaundice is common in the premature neonate; bilirubin competes with some drugs (e.g. phenytoin) for protein binding, which can result in either further increased free drug concentration or increased free bilirubin. The latter would increase the risk of kernicterus.[7]

Blood−brain barrier: there are specific transport systems selectively expressed in the barrier endothelial cell membranes that mediate the transport of nutrients into the CNS and of toxic metabolites out of the CNS. Small molecules access fetal and neonatal brains more readily than they do adult brains.