Developmental paediatric anaesthetic pharmacology

Tom G Hansen

Abstract

Safe and effective drug therapy in neonates, infants and children require detailed knowledge about the ontogeny of drug disposition and action as well how these interact with genetics and co-morbidity of children. Recent advances in developmental pharmacology in children follow the increased understanding of the impact of growth and development on drug disposition (ADME: absorption, distribution, metabolism and excretion). Numerous approaches have been used to determine optimal dosing of drugs in children, none of which are perfect. Human growth is a non-linear process and age-related changes in body composition and organ function are dynamic and often discordant during infancy. Major gaps of knowledge remain regarding the ontogeny of drug metabolizing enzymes and transporting proteins, and the paucity of pharmacodynamic and pharmacogenetic data in the paediatric population remains overwhelming.

Keywords Drug metabolizing enzymes; ontogeny; paediatric pharmacology; pharmacodynamics; pharmacogenetics; pharmacokinetics

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Learning objectives

After reading this article, you should be able to:

- appreciate the challenges presented when delivering age-appropriate dosing of drugs in children of all ages
- explain the impact of age and growth on drug disposition in children
- explain the developmental changes in absorption, distribution, metabolism and elimination of drugs in children, and that developmental changes in pharmacodynamics and pharmacogentics as well as co-morbidity may be important too

Introduction

Rapid growth, differentiation and maturation characterize the first years of human life. The birth weight increases by 50% in the first 6 weeks of life, doubles in the first 3–4 months and triples at the end of infancy. Body length increases by 50% and body surface area doubles during infancy while caloric expenditure increases by fourfold. These developmental changes have a huge impact on the children's response to medications, requiring age-appropriate adjustment in dose of drugs. Approaches to ensure optimal dosing of drugs in children include allometric scaling and physiologically based clearance scaling models to estimate paediatric paediatric pharmacokinetic parameters (e.g. clearance and volume) in the absence of comprehensive age-specific data.[1–4] The allometric approach generally assumes that there are predictable relationships between mass and function or structure in the paediatric population, but does not account for growth and developmental changes in body composition and organ function during infancy.[1,4] Population pharmacokinetics (PK) and pharmacodynamics (PD) have taught us that covariates contributing to variability are crucial. Allometric scaling only accounts for size and does not attempt to explain other covariates (e.g. age, genomics, disease states and drug interaction) that are known to have effects on function and structure that are not related to mass. Extrapolation for individuals based solely on PK parameters estimated using allometry may be flawed due these covariate effects.[4]

Changes in body composition are most prominent in neonates and infants: the body fat content in neonates is lower (10%) and the body water content (80–90%) is markedly higher compared to observations in infants (60–65% and 15–20%, respectively) and adults (60% and 20–25%, respectively)[5] (Figure 1). This affects the distribution volume of both lipophilic and hydrophilic drugs. All phase I (e.g. cytochromes) and phase II (e.g. glucuronidation) metabolic processes mature in an iso-enzyme-specific pattern, while renal function (glomerular filtration rate and tubular absorption and excretion) also display age-dependent capacity. Further variability in PK and PD of drugs during infancy will be influenced by other, non-ontogeny-related covariates (e.g. hypothermia, co-administration of drugs, genetic polymorphisms and various disease states).

Pharmacokinetics

Pharmacokinetics describes the processes involved when a drug is administered to the body, it comprises: absorption, distribution, metabolism and elimination (ADME).[1–3]

Absorption

Drugs administered extravascularly must overcome chemical, physical, mechanical and biological barriers in order to be absorbed. Developmental changes in absorptive surfaces such as the gastrointestinal tract, skin or pulmonary tree can influence the absorption rate and bioavailability of a drug. The oral route is the primary means for drug administration. Changes in intraluminal pH, biliary function, gastric emptying time and intestinal motility all influence drug absorption. The stomach's pH is roughly neutral at birth, within 48 hours it decreases approximately to pH 3, returns to neutral over the subsequent 24 hours where it remains for the following 10 days. Then it decreases slowly but steadily to adult pH values at around 2 years of age. Similarly, the intestinal transit time is prolonged in neonates compared to older children and adults, but reduced in infants due to differences in motility. Immature biliary function in neonates may influence absorption of lipophilic drugs due to a reduction in the solubility effect of the bile. Thus in neonates, difficulties related to variability in absorption are often compensated for by using the intravenous route of administration.[1,2,6]

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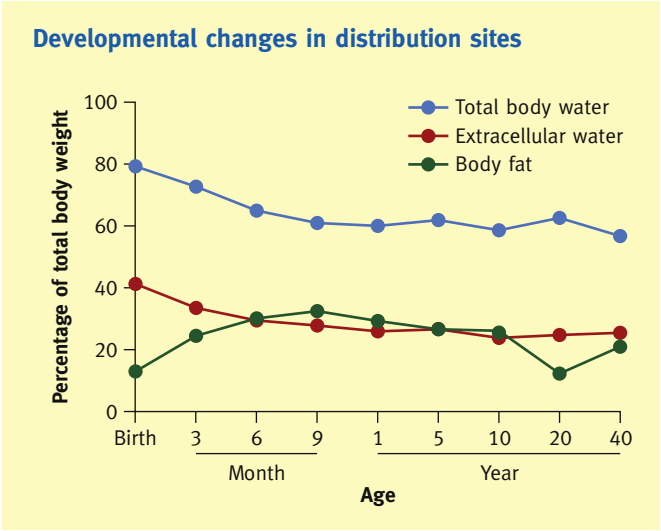

Figure 1 Developmental changes of total body water, extracellular water and body fat relative to body weight, which influence the apparent volume of distribution for drugs. Infants in the first 6 months of life have markedly expanded total body water and extracellular water, here expressed as a percentage of total body weight, as compared with older infants and adults. From: Kearns GL et al. N Engl J Med 2003; 349:1157–67.

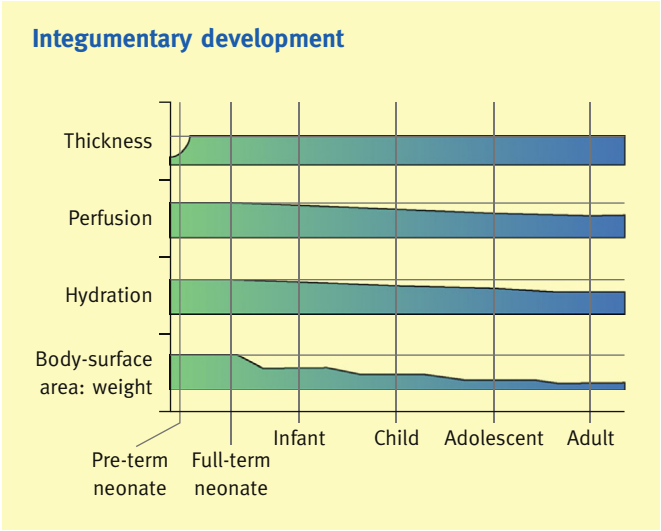

Figure 2 This figure shows age dependence in the thickness, extent of perfusion, and extent of hydration of the skin and the relative size of the skin surface area (reflected by the ratio of body surface area to body weight). Although skin thickness is similar in infants and adults, the extent of perfusion and hydration diminishes from infancy to adulthood. From: Kearns GL et al. N Engl J Med 2003; 349:1157–67.

In addition, developmental differences in the activity of intestinal drug metabolizing enzymes and efflux transporters (e.g. efflux transporter P-glycoprotein) may also contribute to inter-individual variability in bioavailability. Few studies have investigated the effects of developmental changes in absorptive function in children. Absorption of oral paracetamol has been shown to be significantly lower the first days of life.[7] A specific neonatal feature is greater absorption following cutaneous application due to a proportionally higher body surface area and a more permeable skin.[1,2] The extent of cutaneous absorption of (lipophilic) compounds depends on skin hydration, the absorptive surface area (relative to body weight) and the thickness of the stratum corneum (Figure 2). Percutaneous absorption in premature infants is inversely related to gestational age, with permeability rates 100 to 1000 times greater before 30 weeks of gestation compared to term neonates, and only a 3 to 4 times increased permeability beyond 32 weeks.[1,2] There is some evidence that the increased permeability in preterm infants is short-lived lasting only 2 weeks postnatally, even in the most immature infants. Topical use of the local anaesthetics cream EMLA® for pain relief may lead to methaemoglobinaemia in neonates due to a higher systemic absorption and an increased susceptibility of foetal haemoglobin to prilocaine.

Distribution

Following absorption or direct administration the drug distributes to various body compartments, tissues or cells. Distribution of drugs depends on drug physicochemical properties (i.e. molecular weight, ionization and lipophilicity), as well as host related factors such as, drug transporters, blood and tissue protein binding, tissue pH, cardiac output and regional and local blood flow. Age-related changes in drug distribution are mainly associated with developmental changes in body composition, concentration of and affinity to plasma and tissue proteins. In very immature and preterm infants the total body water is high (85–90% of body weight), while the fat content is low (10–15%); total body water declines gradually to 55–60% in adulthood. In neonates the extracellular water content is approximately 45% of body weight whereas in adults it is only 20%[1,2,5] (see Figure 1). Higher initial bolus doses (mg/kg) of water soluble drugs, which distribute into these compartments, are required to achieve similar plasma concentrations in neonates compared to older children and adults. Examples of water soluble drugs are aminoglycosides and suxamethonium which have a significantly higher volume of distribution in neonates compared to older children and adults.[1–3] The effect of age on the distribution of lipophilic drugs in children is less clear. It appears that during infancy the total body fat content increases steadily and this may have an impact on the volume of distribution of those drugs (e.g. propofol). This is also the clinical impression with this drug. Notably, in preterm and immediate term neonates propofol should be dosed with caution partly due to a lower fat content (and possible reduced plasma protein binding to albumin) in these babies.

Clearance also determines the concentration–time profile of drugs, and both clearance (CL) and volume (Vd) contribute to the elimination half-life ($t_{1/2} = \log 2 \times Vd/Cl$).[1,2] If CL and Vd are changing independently during infancy, the half-life may be the same in neonates as an adults, despite reduced clearance in neonates.

The amount of circulating plasma proteins (primarily albumin and α1-acid glycoprotein, AAG) influences drug distribution. Plasma proteins are large molecules and as such they do not leave the vascular space. Thus, the effect of increasing plasma protein binding of drugs is that it will decrease the volume of distribution. It is only the free and unbound portion of the drug