Use of Medicines in Children: Pharmacological and Practical Issues

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Abstract

Pediatric patients have very different pharmacokinetic and pharmacodynamic profiles compared to adults. A number of anatomical and physiological factors determine the pharmacokinetic profile of a drug. Differences in physiology in pediatric populations compared with adults can influence the concentration of drug within the plasma or tissue. When considering medication for a child or adolescent, one should be cautious about extrapolating from adult studies or practices. Always remember, children are not small adults. Children tend to have higher rates of metabolism and elimination than adults. As a result, children generally require higher weight-adjusted doses of most medications to achieve similar blood levels as adults. As pharmacokinetics is hard to predict in children, and thus a 'start low and go slow' approach is important. This review details key pharmacological and practical considerations which a healthcare professional should be aware of to understand consequences of drug use and dose adjustments in infants and children.

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Introduction

It was more than 100 years ago, Dr. Abraham Jacob, the father of American pediatrics, had then recognized the importance and need for age-appropriate pharmacotherapy when he wrote, "Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but, has its own independent range and horizon" (1,2). Apart from the varied difference in the physiology according to age and development, and the divergent pharmacological responses to the drugs between children and adults, there are concerns over lack of adequate safety and efficacy data, ethical issues with pediatric clinical trials and lack of adequate drug formulations (3, 4). In this review article, we will discuss all these issues and concerns regarding drug use in pediatric population.

There are many differences between children and adults that varies according to the age and developmental stage. Pediatric patients not only differ from the adults but they also differ among themselves as a preterm neonate differs from a 16 year old adolescent in terms of developmental biology and pharmacology (4). Any classification of the pediatric population into age categories is to some extent arbitrary, but it may provide a basis for determining the difference in response to therapy. For the purpose of this review, the World Health Organization (WHO) classification has been used as mentioned below:

Preterm newborn infants	Born before 37 weeks of gestation
Term newborn infants	Birth to 30 days
Infants and toddlers	1 month to 2 years
Young child	2 to 6 years
Child	6 to 12 years
Adolescents	12 to 18 years

Physiological and pharmacokinetic differences in pediatric population

Neonates differ in terms of immaturity of the renal and hepatic clearance mechanisms, protein binding and displacement characteristics (particularly bilirubin), penetration of drugs into the central nervous system (CNS), and diseases unique to their age group (e.g., respiratory distress syndrome of the newborn, primary pulmonary hypertension, necrotizing enterocolitis etc.).

The maturational changes from the newborn period to adolescence results in a striking effect on drug disposition. For example, absorption, distribution, metabolism, and excretion in neonates are different from adults because of age specific changes in body composition, function, and/or age-specific patterns of development of phase I and II metabolizing enzymes and renal function. Most drugs are administered orally to children (2, 4). Clinically important developmental changes in the gastrointestinal tract that may affect oral absorption of medicines occur predominantly during

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the newborn period, infancy and early childhood. These changes affect gastric acidity, gastric emptying time, gut motility, gut surface area, gastrointestinal drug-metabolizing enzymes and transporters, secretion of bile acids and pancreatic lipases, first-pass metabolism, enterohepatic recirculation, bacterial colonization of the gut, diet at different ages and diurnal variations. Changes in the intraluminal pH in different segments of the gastrointestinal tract can directly affect both the stability and the degree of ionization of a drug, thus influencing the relative amount of drug available for absorption. During the neonatal period, intragastric pH is relatively elevated (greater than 4) consequent to reductions in both basal acid output and the total volume of gastric secretions. Thus, oral administration of acid-labile compounds produces greater bioavailability in neonates than in older infants and children. In contrast, drugs that are weak acids, such as phenobarbital, may require larger oral doses in the very young in order to achieve therapeutic plasma levels (5-8). Newborn have a much higher extracellular fluid volume than any other pediatric population or adults. Preterm babies have a higher extra-cellular fluid volume than full-term infants, older infants or adults. Total body water is also much greater in neonates. On the other hand, fat content is lower in premature babies than in full-term neonates and infants. As medicines are distributed between extracellular water and depot fat based on their lipid/ water partition coefficient, these changes in body composition can influence the distribution of a drug in various compartments of the body (6-9).

There are significant differences in the eliminating capacities of neonates, infants and children. In general, the more premature the infant the poorer the hepatic metabolizing and renal excreting capacity. For medicines that are entirely eliminated through kidney, the greater the prematurity, the less able are the kidneys to excrete them and therefore the longer their half-life. Age specific pharmacokinetic changes and their effect on drug levels can be understood from the table given below (10-16):

Table 1. Changes in pharmacokinetic parameters in pediatric population and their consequences.

	Developmental change	PK consequence	Drugs affected	Examples
Absorption	↓ Intestinal transit time	↓C_{max} and ↓AUC	Poorly soluble	Theophylline
	↑ gastric pH	↑Cmax	Acid labile	Penicillin
		↓ Cmax	Weak Acids	Phenytoin
Distribution	Body composition	↔Vd (neonates have relatively reduced fat whereas infants have relatively increased fat compared with adults; extracellular water is relatively higher in neonates compared with preschool children)	Lipophilic drugs: ↓V_d in neonates and ↑V_d in infants compared with adults	Diazepam
			Hydrophilic drugs: ↑V_d in infants compared with neonates	Aminoglycosides (e.g. gentamycin)
Metabolism	Relative larger size of liver	↑hepatic clearance	Those extensively metabolized	Theophylline, caffeine, carbamazepine and valproic acid
Elimination	Larger relative size of kidney	↑renal clearance in infants and preschool children	Those excreted unchanged in urine	Levetiracetam, cimetidine and cetirizine

Finding the Right dose for children

So far, empirical scaling from adults to children continues to be the prevailing method for dose selection in children, with adjustment for body weight as the most commonly used approach. The most rampant practice is dividing the adult dose by a fixed (scaling) factor, presuming that the appropriate efficacy/safety profile can be achieved (17). Such an approach has some serious disadvantages like the risk of toxicity due to lack of understanding of the ontogeny of metabolic pathways in neonates and toddlers, or poor efficacy due to suboptimal dosing. Most common methods for dose selection in pediatric patient are based on age, weight and body surface area which does not take into account the developmental changes. The dose of a drug for children is often calculated from the adult dose according to the age or body surface area (17-20). Most commonly used methods are

$$\text{Child dose} = \frac{\text{Age}}{\text{Age}+12} \text{ X Adult dose.....Young' s formula}$$

$$\text{Child dose} = \frac{\text{Age}}{\text{Age}+12} \text{ X Adult dose.....Dilling' s formula}$$

$$\text{Child dose} = \text{Weight (kg)} \times \frac{\text{Adult dose}}{70} \text{ .... Clark' s formula}$$

$$\text{Child dose} = \frac{\text{BSA}(m^2)}{1.7} \text{ x Adult dose}$$

The pharmacokinetics parameter does not vary proportionally with weight or body surface area and it is understandable that the inference of a linear relationship between body size and drug exposure or response is not always plausible as size itself may not be a surrogate for developmental growth (18, 19).

Presently, a more reliable way to establish how dose relates to body weight is through the use of nonlinear relationships, such as allometric scaling, where P is the parameter of interest, WT the bodyweight of the individual child and x the allometric exponent (17).

$$P_{child} = P_{adul}t.(WT/70)^{x}$$

Different examples show that this approach yields the most accurate results in terms of exposure in children. Besides allometric scaling, a more mechanistic approach is lacking for pediatric dosing recommendation that can counter the empiricism in current clinical practice. Such an approach must identify which physiological factors alter pharmacokinetics and how these (might) differ across the pediatric population(s), without relying on a priori assumptions about the correlation between pharmacokinetic parameters and demographic covariates. In addition, ontogeny (the development and maturation of metabolic pathways) which is proven to have considerable effects on drug elimination and the enzymatic maturation (i.e. metabolic capacity) is completely unrelated to body weight, and as such does not follow developmental growth (20,21). For the above mentioned reasons, physiologically based scaling approach described as scaling for function has been proposed and dosing requirements are derived primarily from a model-based analysis of pharmacokinetic or pharmacokinetic–pharmacodynamic data.

Pharmacodynamic variability in pediatric population

Children are more vulnerable to the long term effects of the drugs not only because of the physiological immaturity but also because the developing brain may be affected during the period of neuropsychiatric development. A clinical review of developmental neuropharmacology deliberated about the effects of childhood psychotropic drug exposure setting forth that the "adult system assimilates the drug only temporarily" whereas the "drug harbors into the developing brain by producing permanent modification of the system" so that the "juvenile brain reprograms its developmental pathway as if the drug was part of its local environment." It is, therefore, theorized by neuroscientists that "chronic exposure to commonly used therapeutic agents during a sensitive period of development can either prevent or exacerbate symptoms later in life. For example, long term use of phenobarbital in children is associated with a decrease in IQ even after discontinuation of the drug. Gabapentin use in children is associated with behavioral changes consisting of intensification of baseline behaviors as well as new behavioral problems like tantrums, aggression directed towards others, hyperactivity, and defiance. Use of selective serotonin inhibitors in children has been linked to increased suicidality (22, 23).

As treatment is administered at a time of rapid brain development, there is a need to evaluate the possible impact, either favorable or detrimental, of antipsychotic medications on cognition and other aspects of brain maturation at various ages and duration of exposure. Only very limited data are currently available about cognitive functioning during antipsychotic treatment in children (24, 25). In addition to identify the effects of medications on physical, mental, and sexual development, it is also necessary to determine if such effects are either partially or fully reversible.

Safety of drugs in children

Drug handling also vary substantially with age and developmental stage. Children are more vulnerable to the adverse effects of the drugs because of the immaturity of the physiological system. Medicine targets, such as receptors, transporters and channels, are certainly also subjected to developmental processes (as are metabolizing enzymes). For example, earlier development of opioid receptors specifically in the medulla and pons, where respiratory and cardiovascular centers are located, than in other parts of the brain, is consistent with a clinically observed higher incidence of opioid-related respiratory depression and bradycardia associated with insufficient analgesia in newborns who receive opioids. There are several well-documented examples of increased drug sensitivity or toxicity in young children. For example, acute dystonic reactions or seizures in young children have been reported after exposure to the dopamine 2-antagonists metoclopramide and prochlorperazine as antiemetics, hyperpyrexic reactions to anticholinergic drugs such as atropine and scopolamine in infants and young children have been documented, and an increased risk of sudden cardiac arrest has been noted in infants with supraventricular tachyarrhythmias treated with verapamil. Ignorance or lack of knowledge of these differences in pediatric pharmacotherapy has led to various medicine-related tragedies in the past. Most of them occurred in early life, during the neonatal period: e.g. sulfonamides causing kernicterus (severe brain damage related to neonatal hyperbilirubinaemia) and chloramphenicol causing grey baby syndrome (cardiovascular collapse) in the newborn. These tragedies resulted in regulations requiring extensive and thorough premarketing studies of the drugs (26-27).

Lack of safety and efficacy information: need for regulatory workup

Most of the drugs prescribed to the children are without safety and efficacy data in children. Once a medicine is approved and is available in the market it is prescribed to children on the basis of adult data. More commonly, the drugs prescribed in children are off-label. They are not largely unsafe but the level of clinical evidence of safety and effectiveness is less as compared to the adults. These problems have arisen due to the ethical issues of including children in clinical trials and lack of incentives to the pharmaceutical companies to promote studies in children. But these issues are being addressed by the new regulatory changes in the western countries where incentives are given for conducting pediatric clinical trials and for age appropriate formulations. Despite about 27% of the world's population being children, pediatric trials constitute only 16.7% of the total number of trials registered on the WHO portal. To address this problem, the current U.S. regulatory framework includes:

• The Best Pharmaceuticals for Children Act (BPCA), that provides incentives for drug companies to conduct (after FDA Written Request) pediatric studies by granting additional six months of marketing exclusivity.

• The Pediatric Research Equity Act (PREA) that requires drug companies to study their products in children under certain circumstances. When pediatric studies are required, they must be conducted with the same drug and for the same use for which they were approved in adults.

Apart from the new regulations, there are two novel clinical trial tools which offer the possibility of improving the field of pharmacokinetic trials in children: multiple-drug assays and dried blood spot sampling (DBS) which reduce the necessity of the traditional high volume multiple blood samples. These changes will come a long way to ensure the availability of safe and effective medicines (27-31).

Pediatric drug formulations: still an unmet need

Drug formulations used in pediatric pharmacotherapy should be adapted to children's needs to suit their age, size, physiologic condition, taste preferences and treatment requirements (32, 33). Such pediatric medicines are key to achieving safe and accurate dose administration, reducing the risk of medication errors, enhancing medication adherence, and improving therapeutic outcomes in children (32,34). The use of inadequate drug formulations in children may pose problems not seen in adults, such as difficulty in swallowing conventionally sized tablets, safety issues with certain excipients that are acceptable in adult formulations, and adherence problems with unpalatable medicines (34-37).

Historically, the failure to appreciate the developmental changes in children has led to many adverse outcomes in clinical practice. Examples include infant deaths from choking on albendazole tablets, the lethal use of benzyl alcohol or diethylene glycol in sulfanilamide elixirs, and electrolyte imbalances caused by high contents of sodium or potassium in parenteral formulations (33-39).

To prevent such tragedies and ensure adequate treatment of children of all ages, different routes of administration, dosage forms, and strengths are often needed for the same active substance. The selection for clinical use is influenced by the limitations of each dosage form. Oral solids are associated with the risk of choking or chewing and with limited dose flexibility, whereas palatability and dose uniformity may be challenging for liquid preparations.

Table 2. Some of the novel formulation specifically designed for pediatric patients. (39-46)

Dosage form	International non-proprietary name
Orodispersible films	Ondansetron
Chewable dispersible tablets	Lamotrigine
Multiparticulate sprinkles	Rabeprazole
Dispersible tablets	Isoniazid/Rifampicin
Chewable tablet	Atorvastatin

There has been a positive change towards making drug formulations appropriate for children. New regulations, additional funding opportunities, and innovative collaborative research initiatives have resulted in recent progress in the development of pediatric formulations. These advances include a paradigm shift toward oral solid formulations and a focus on novel preparations, including flexible, dispersible, and multi-particulate oral solid dosage forms. More such efforts shall be undertaken for making medicines safe and effective for children.

In addition to pharmacological issues, practical issues specifically related to drug use in children also needs to be addressed. For example, owing to lower esophageal sphincter tone, infants often regurgitate orally administered drugs. This changes the actually administered dose. Similarly, due to irregular bowel bladder habits, drug-food interaction are often difficult to control in children. These issues becomes more important because children depend totally upon their guardians for accurate drug administration and many such critical pharmacological and practical issues may go unaddressed owing to unawareness or reluctance.

The Ideal Children's Medicine

WHO states that "The ideal children's medicine is one that suits the age, physiological condition, and body weight of the child taking them and is available in a flexible solid oral dosage form that can be taken whole, dissolved in a variety of liquids, or sprinkled on foods, making it easier for children to take (47)". Differences in therapeutic approaches in children are wide, which implies the need for harmonization. A formulary is required which, in addition to providing the therapeutic function and dosage of the drug, can also be a source of up-to-date and evidence-based information for the most common clinical problems in and out of hospital. Close collaboration will ensure that really appropriate investigation plans can be produced; avoiding the egregious blunders that ensue when a protocol suited for adults is uncritically applied

to children (48). Pediatric dose selection was also not a scientific process till 2020, but dosing science is moving toward making this more of a structured process (49). Better pediatric dose selection methods exist through the application of classical PK-PD, population PK, and physiologically based PK models (50, 51). These models do not necessarily replace traditional dose-finding studies but complement and guide dosing decisions based on the additional information they provide.

Conclusion

There are many issues with the use of medicines in children. The concern about the adverse drug reactions in the vulnerable group, practical issues encountered like the lack of adequate formulations, safety and efficacy data for the children are some of the questions which need to be addressed within a time frame. All the stakeholders and regulatory authorities shall work hand in hand to make use of medicine safer in the most vulnerable group of the society. Availability of safe and properly labeled pediatric formulations, regular case audits, rational prescriptions, proper counseling of patients/ relatives about drug administration, monitoring of adverse effects, and pediatric drug clinical trials are the best possible interventions to offer appropriate medicines to children and prevent drug related mishaps.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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