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CHALLENGES OF PEDIATRIC PHARMACOTHERAPY: A NARRATIVE REVIEW OF PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENETICS

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ABSTRACT

Pediatrics pharmacotherapy requires tailored approaches due to age-related physiological differences that significantly affect drug pharmacokinetics and pharmacodynamics. The review explores key challenges in pediatric drug therapy, including formulation difficulties, the impact of obesity on dosing. The review also discusses the factors affecting pediatric pharmacotherapy and related diseases. By synthesizing recent findings from the articles published between 2015-2024, this review highlights the importance of advancing pediatric pharmacotherapy collaborative efforts among clinicians, researchers and regulatory bodies to ensure safe and effective treatment outcomes.

KEYWORD: Obesity, Pediatric pharmacotherapy, Pharmacokinetics, Pharmacodynamics.

INTRODUCTION

Pediatric pharmacotherapy demands meticulous attention and a nuanced understanding of the specific variations in drug responses among young and pediatric patients. Pediatric pharmacotherapy poses a significant challenge. Developmental, anatomical, and genetic changes during growth and development affect pediatric pharmacotherapy. While infectious diseases represent the most frequent pediatric pharmacotherapy, other indications include allergic diseases treated long-term, neurological disorders, and cancer, for which a suitable substitute is unavailable.

Over the past few years, there has been increasing recognition of the need to deal with these challenges holistically. Clinicians, researchers, and policymakers are increasingly focusing on optimizing pediatric drug management, evidence-based practice, and interprofessional collaboration.

The pediatric population may be subdivided, in line with the "International Council for Harmonization" (ICH) topic E11 (CPMP/ICH/2711/99) and the ICH E11(R1), as preterm newborn infants (from birth date up to expected date of birth plus 27 days), term and post-term newborn infants (between 0 to 27 days of age), infants and toddlers (between 28 days and 23 months), children (between the ages of 2 and 11 years old), and adolescents (with age brackets from 12 to 16–18 years old, varying by region) (figure 1).

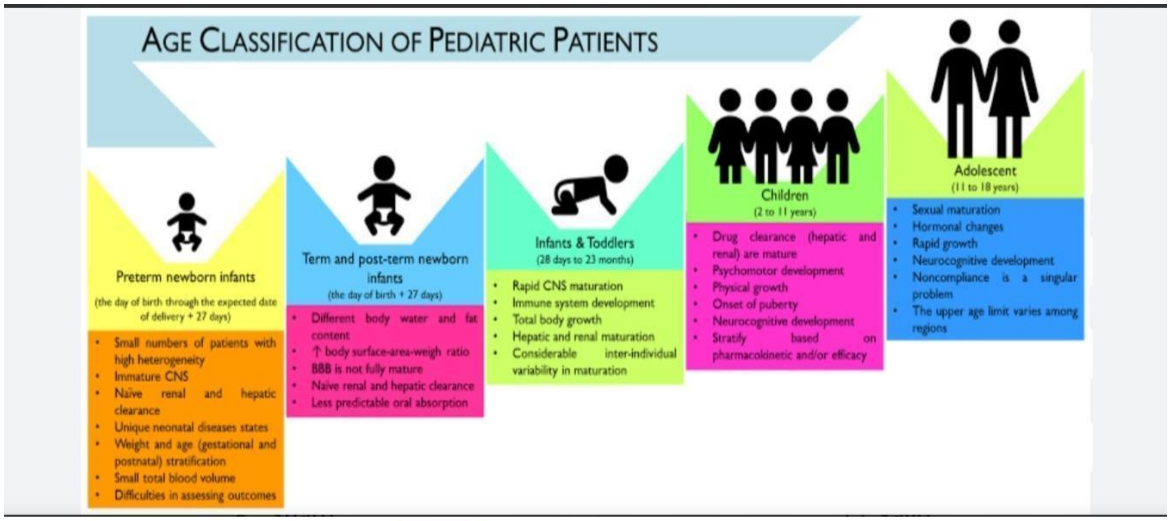

Figure 1.

- **Pharmacokinetics of drugs**

Understanding of pediatric pharmacotherapy

In depth understanding of pediatric pharmacokinetics is essential for efficacious and safe drug therapy. Physiological and anatomical differences in children critically affect drug excretion, metabolism, distribution, and absorption.[1] To successfully overcome challenges due to performing pharmacokinetic evaluations in pediatric groups, novel measures such as different sampling methods and population-based models are needed.

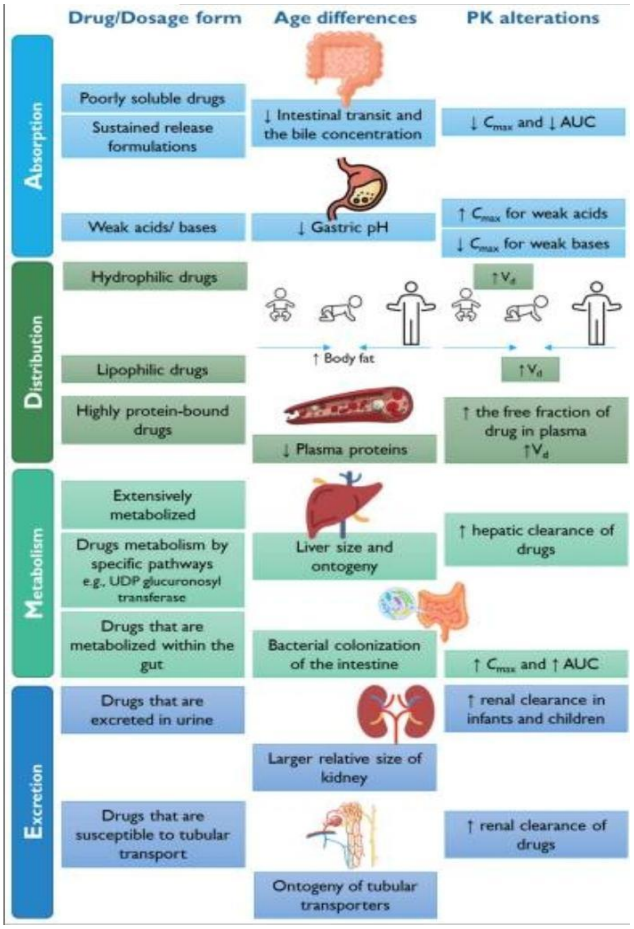

Figure 2.

ABSORPTION

Gastrointestinal tract is influenced by two factors: pH-dependent passive diffusion and gastric emptying time. Compared to adults and older children, preterm newborns exhibit a remarkable diversity of both phenomena. A term infant's gastric pH ranges from 6 to 8 at delivery, but within 24 hours, it drops to 1 to 3.[2] However, because of their undeveloped acid secretion, preterm newborns have a high gastric pH.[3]

Increased gastric pH in premature children can explain lower serum levels of a weak acid like phenobarbital[8] and higher serum levels of acid-labile medications like penicillin,[8] ampicillin,[8] and nafcillin.[8] medication bioavailability variability in preterm newborns is poorly understood due to a lack of comprehensive data for comparing blood concentration–time profiles after oral versus IV medication treatment. Although little is known about how age-related developmental changes affect children's drug absorption, studies using drugs (like digoxin and phenobarbital) and nutrients (like arabinose and xylose) have suggested that both passive and active transport mechanisms are probably established by the time a child is 4

months old.[8] The development and function of intestinal drug-metabolizing enzymes and the efflux transporter P-glycoprotein, as well as their impact on drug absorption and bioavailability in infants and children, are poorly understood.

Studies have shown that preterm newborns have sluggish gastric emptying.[9] Therefore, because premature babies have a longer time of contact with the gastrointestinal mucosa, medications with restricted adult absorption may be absorbed optimally in these babies.

DISTRIBUTION

The physicochemical properties of the drug (pKa, molecular weight, and partition coefficient) as well as physiological variables unique to each patient control drug distribution. The drug's physicochemical properties don't change, but different patient populations tend to have different physiological responses. Extracellular and total body water, drug-protein binding in plasma, and the existence of clinical diseases that change physiological function are a few important patient-specific aspects. According to estimates, the percentage of total body water as a percentage of total body weight is 60% in adults, 78% in full-term infants, 85% in preterm infants, and 94% in fetuses.[10] preterm infants' extracellular fluid volume differs greatly from that of older children and adults; in preterm newborns, it can make up 50% of body weight, whereas in 4- to 6-month-old infants, it can make up 35%, in 1-year-old children, 25%, and in adults, 19%.[11] Gentamicin distribution volumes of 0.48 L/kg in neonates and 0.20 L/kg in adults are in agreement with this.[12] Studies have shown that the distribution volume of tobramycin is highest in the most preterm neonates and decreases as the infant's birth weight and gestational age grow.[13]

Because of decreased plasma protein content, decreased protein binding capacity, decreased protein affinity for drug binding, and competition for some of the binding sites by endogenous chemicals like bilirubin, protein binding of medicines is decreased in newborn neonates. Neonates have significantly lower plasma protein binding of medications such phenobarbital, salicylates, and phenytoin than adults do.[14] Drugs' apparent volumes of distribution may increase if their plasma protein binding is decreased. Therefore, to achieve a therapeutic blood concentration of medications such as phenobarbital[15] and phenytoin, a higher loading dose is required in preterm newborns than in older children and adults.[16]

It is necessary to take into account the consequences of increasing concentrations of free or unbound medications in serum and tissues. The amount of free medicines in the body has a

direct correlation with its pharmacological and harmful effects. Drug displacement from binding sites or decreases in plasma protein binding can both directly or indirectly cause rising quantities of free medicines. There is evidence of increased kernicterus mortality in neonates as a result of sulfisoxazole's displacement of bilirubin from albumin and other blood proteins.[17] However, an increase in the concentration of free drug may also improve its clearance because the kidneys cannot eliminate drugs attached to plasma proteins.[18] Neonates have substantially less body fat than adults, which could have an impact on medication therapy. Infants' distribution of several highly lipid-soluble medications is lower than that of adults'. Diazepam's apparent volume of distribution ranged from 2.2 to 2.6 L/kg in adults and from 1.4 to 1.8 L/kg in newborns.[19] Mothers breastfeeding their children has become more common in recent years. As a result, some medications that are given to babies through breast milk may cause problems. Bromocriptine, cyclophosphamide, cyclosporine, doxorubicin, ergotamine, lithium, methotrexate, phenindione, codeine, and all drugs of abuse (such as amphetamine, cocaine, heroin, marijuana, and phencyclidine [PCP]) should not be given to nursing mothers, according to the American Academy of Pediatrics (AAP). During lactation, use of nuclear medications must be temporarily stopped.[27] Keep in mind that there is little data to support these recommendations. Long-term use of other drugs by the mother may also be detrimental to the baby. For example, some breastfeeding infants have experienced adverse effects with acebutolol, aspirin, atenolol, clemastine, phenobarbital, primidone, sulfasalazine, and 5-aminosalicylic acid.[20] During pregnancy and nursing, the mother must abstain from all drug usage unless the advantages outweigh the hazards.

METABOLISM

Infants' drug metabolism is slower than that of children or older adults. Premature newborns have notable variations in the maturation of several metabolic pathways. For instance, babies have a well-developed sulfation pathway but an underdeveloped glucuronidation system.[21] although acetaminophen glucuronidation is less effective in newborns than in adults, the sulfation route partially replaces it. Reduced metabolism of chloramphenicol by glucuronyl transferases to the inactive glucuronide metabolite is the cause of the devastating gray baby syndrome in newborns caused by chloramphenicol.[22] As seen by the rise in clearance with age up to one year, this metabolic pathway appears to be age dependent[23] and may require several months to a year to mature.[27]

Because preterm newborns are unable to properly metabolize morphine to its 6-glucuronide metabolite, which is 20 times more strong than morphine, more blood morphine is required to be effective in these patients than in adults.[27] The fact that morphine clearance quadruples between 27 and 40 weeks of postconceptional age somewhat offsets this.

Newborns also have reduced oxidative drug metabolism, including that of theophylline, phenobarbital, and phenytoin. However, phenobarbital and phenytoin have a quicker rate of metabolism than theophylline, which may be due to the usage of distinct cytochrome P450 (CYP) isozymes. While theophylline clearance takes a few months to fully develop, phenytoin clearance by CYP2C9 and, to a lesser extent, CYP2C19, surpasses adult levels by two weeks of age.[14] It is necessary to address two additional points about CYP1A2's metabolism of theophylline in youngsters. First, compared to older children and adults, significant levels of theophylline's active metabolite caffeine are present in premature infants receiving treatment for apnea.[26] Second, compared to newborns and adults, children aged 1 to 9 have a higher theophylline clearance. As a result, compared to adults, children with asthma typically require far higher weight-based theophylline dosages.[27]

Premature newborns require lower daily dosages of medications including theophylline, phenobarbital, phenytoin, and diazepam due to their decreased metabolism. Even after controlling for total body weight, prepubertal children had significantly higher clearance of unbound S-warfarin, a CYP2C9 substrate, than pubertal children and adults. [27] Finally, after girls reach Tanner stage II (early puberty) and boys reach Tanner stages IV and V (late puberty), the demethylated caffeine clearance drops to adult levels. [27] In some circumstances, pharmacogenetics and pharmacogenomics information are currently being applied to patient care. Thiopurine S-methyltransferase (TPMT) metabolizes 6-Mercaptopurine (6-MP), a drug commonly used in children with leukemia.

The three variants in the TPMT gene (*2, 3A, and 3C) are mostly responsible for the hereditary deficit, an autosomal recessive condition that affects 6% to 11% of patients. To achieve survival rates equivalent to those receiving full dosages without TPMT deficiency, heterozygotic children need to have the 6-MP dose reduced by around 50%, and homozygous children for one of the mutant alleles need to have the dose reduced by about 90%. As a result, TPMT screening is recommended to identify people whose genes suggest TPMT deficiency and who would benefit from a dose reduction to prevent toxicity.[30]

EXCRETION

The kidneys often eliminate drugs and their metabolites. In mature newborns, the glomerular filtration rate (GFR) is approximately 2 to 4 mL/min per 1.73 m2 (0.02-0.04 mL/s/m2), but in preterm infants, it can be as low as 0.6 to 0.8 mL/min per 1.73 m2 (0.006-0.008 mL/s/m2). Renal excretion is caused by glomerular filtration, tubular secretion, and tubular reabsorption. After birth, these mechanisms might not fully develop for a few weeks, a year, or longer.

According to research on infants, as gestational age increases, so does the amount of tobramycin cleared in the first week of postnatal life.[13] Additionally, there was a direct correlation between postnatal age and aminoglycoside clearance in infants born within a month.[24] Consequently, during the first week of life, preterm newborns require a lower daily dosage of kidney-excreting medications; after that, the amount must be raised.

Premature neonates may have higher sodium succinate or chloramphenicol concentrations due to impaired renal elimination. This concentration may account for the increased bioavailability of the active chloramphenicol in preterm newborns as compared to older children, even though chloramphenicol sodium succinate is inactive.[23] These findings suggest that, in addition to enhanced chloramphenicol bioavailability in preterm newborns, dose-dependent toxicity may result from a poorly formed glucuronidation pathway.

Pharmacodynamics

Blood and plasma samples can be used to quantify pharmacodynamics including drug absorption, distribution, metabolism, and elimination. Pharmacodynamics also encompasses the physiological and biological effects of the drug and is not always synonymous with pharmacokinetics. It is impossible to ignore how children's pharmacokinetics and pharmacodynamics interact with sensible dosage. Pharmacokinetic analysis measures the drug concentrations over time using biological samples. Endpoint measurements used in the pharmacodynamic analysis need to be verified in children.

Pharmacogenetics

In order to customize drug treatment to each patient's needs, pharmacogenetics (PGx) investigates how genetic variation affects drug response. Pharmacogenetic testing has primarily been used in clinical settings to examine cases of toxic drug responses that cannot be explained. For instance, we documented an instance of azathioprine overexposure in a

neonate with a homozygous TPMT*3C genotype, which leads to the build-up of 6-TGN, azathioprine's active metabolite.[31]

The ultimate goal of pharmacogenetic testing is to use our knowledge of how genetic variation influences drug response and toxicity in a proactive manner, guiding precision therapeutic decisions, even though retrospective testing is still helpful in certain situations.

The Dutch Pharmacogenetics Working Group and the Clinical Pharmacogenetic Implementation Consortium have jointly released evidence-based recommendations for over 100 gene-drug combinations.[32]

Remarkably, 90–95% of people in various populations carry at least one actionable variant, and the frequency of these variants typically occurs at the population level.[33] Furthermore, an estimated ~25% of people have an actionable variant related to the medications they are taking, including antidepressants, anticoagulants, painkillers, and chemotherapy, which are among the commonly prescribed medications covered by the guidelines.[34] The PREPARE-study recently tested the clinical utility of a pre-emptive pharmacokinetic panel strategy.[35] 6944 patients who began treatment with one of the 39 medications for which the DPWG had an actionable recommendation were enrolled in the prospective study PREPARE.

According to the findings, a 30% decreased risk of clinically significant adverse drug reactions within the first 12 weeks following the start of treatment was achieved by using the 12-gene PGx panel test in advance in conjunction with DPWG guidelines. These data, when combined with other available evidence, offer a strong foundation for a wider clinical use of pre-emptive Pharmacogenetic testing.[36] Drugs with a narrow therapeutic index, a steady PK-PD relationship, and situations where response (or side effects) are unpredictable and trial-and-error time is limited are the ones where PGx testing is most likely to be clinically relevant. Therefore, PGx testing will be beneficial not only in clinical settings where it is already widely accepted, but also in the intensive care unit, where complex patients are receiving multiple medications at the same time.

Addressing formulation challenges

Developing age-appropriate dosage forms presents significant challenges for pediatric drug development. Pharmaceutical companies are encouraged by regulatory initiatives to carry out pediatric clinical studies that address formulation issues and guarantee therapeutic

equivalency.[37-39] To improve treatment adherence and efficacy, pediatric dosage forms must prioritize palatability, stability, therapeutic equivalency, and ease of administration.[40-44]

Emerging strategies

A promising method for maximizing drug exposure in pediatric populations is PBPK modelling.[45] Pharmacogenetic techniques, therapeutic drug monitoring, and customized dosing plans have enormous potential to improve therapeutic results and treatment accuracy.

CONCLUSION

Even though pediatric pharmacotherapy has advanced significantly, there are still a lot of unsolved concerns. Many significant medications have had their pharmacokinetics clarified, but their pharmacodynamics have not been thoroughly investigated. Likewise, for the majority of medications, the impact of illness states and patient attributes, including genetic status, has not been investigated. It is necessary to investigate how these factors affect the development of P-glycoprotein, other enzymes, and CYP isozymes (such as CYP3A4, CYP2D6, CYP1A2, CYP2C9, and CYP2C19) (see Chapters e5 and e6). Improved treatment for pediatric cancer may be possible with targeted precision medicine matched to molecular changes found by tumor profiling. In a similar vein, several treatments lack comparative safety and efficacy data.

Just preventing diarrhea and administering vaccinations might save millions of these lives every year. Nonetheless, many nations might not have the funds for immunizations. Black people in the US have an infant mortality rate that is almost twice as high as that of white people. Pregnancy-related deaths and morbidity from diseases like acquired immunodeficiency syndrome may be reduced by better prenatal care, educational initiatives, and abstinence from alcohol, tobacco, and illicit drugs. Lastly, attempts should be made to provide medication that is supported by evidence. When medications must be used outside of FDA-approved standards and indications, this can be challenging in juvenile populations. Institutions should provide recommendations for the use of expensive and high-risk medications as well as for the use of medications in particular conditions.

Although much needs to be learned about the optimization of therapy, it is encouraging to witness the continued growth of knowledge in this area that has improved the quality of life and survival from pharmacotherapy in pediatric patients.

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