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Review article

Principles of pharmacotherapy in pediatric patients: fundamental pharmacological and pharmacokinetic knowledge and its applicability

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ABSTRACT

This review article offers a comprehensive overview of the fundamental principles underpinning the management of pharmacotherapy in pediatric patients. Recognizing the distinct pharmacological and pharmacokinetic attributes of children is imperative for the safe and efficacious administration of drugs. By exploring critical concepts encompassing drug absorption, distribution, metabolism, and excretion within pediatric populations, healthcare providers can inform decisions when prescribing medications for children across all the age groups. Additionally, the implementation of pharmacokinetic/pharmacodynamic (PK/PD) principles in clinical practice assumes paramount importance in tailoring drug regimens to suit individual pediatric patients, thereby optimizing therapeutic outcomes and mitigating the potential for adverse events. As the landscape of pediatric pharmacotherapy research continues to advance, it is essential for healthcare professionals to remain up to date with the latest developments to ensure the provision of optimal care for this vulnerable patient demographic.

Keywords: pharmacotherapy, pharmacological, pharmacokinetic, pediatric

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Introduction

Each stage of human development is characterized by distinct physiological and pharmacological attributes. For instance, infants developing children, adults may experience pregnancy and lactation, and eventually transition into old age. These transitions are accompanied by changes in pharmacokinetics and pharmacodynamics, which generally tend to increase in magnitude from infancy to childhood and from childhood to adolescence and adulthood, followed by stability or a decline in old age. However, it is crucial to note that these pharmacological changes in humans do not progress linearly from lower to higher, as evidenced by the truth that, "Children are not miniature adults" and "Elderly individuals are not adults reverting to childhood".[1-2]

In the practice in pharmacotherapy, pharmacists must consider two key factors: "Pediatric pharmacokinetics and pharmacodynamics (PK/PD)" and "PK/PD of the drugs intended to use in children". Upon examination, it becomes apparent that, in general, pediatric PK/PD values are lower than those in adults, except for gastrointestinal (GI) surface area and skin permeability. Therefore, caution must be exercised when administering drugs to children, especially in cases where adverse drug reactions are not uncommon, as depicted in Fig.1.[2-5]

These evidences[2-5] provide insights into the differences in pharmacokinetic parameters between children and elderly individuals when compared to adults. From Table 1, it is noteworthy that there are variations in the terminology used to describe different age groups of children across various references or sources utilized. It is essential to ascertain the specific age range implied by these terms before establishing associations with various pieces of information, such as patient pharmacokinetic data (both theoretical and empirical) and drug pharmacokinetics. Consequently, it is imperative to cross-verify data from multiple sources before determining the actual dosing regimens for individual patients. Another noteworthy practical consideration relates to the size of medication packaging for children, often specified according to age. However, dosing recommendations from various drug references typically advise calculations based on body weight.[6] Consequently, it is crucial not to administer the drug to children solely based on packaging information without careful consideration. It is imperative to consistently weigh the child before determining the dosing regimen. Moreover, one must evaluate whether the child has normal body weight, is significantly underweight, or obese. Furthermore, it is essential to assess patient-specific pharmacokinetic and pharmacodynamic data in conjunction with drug-specific information before proceeding. From the content, it becomes evident that several considerations must be considered before pediatric patient management, particularly when administering any medication. These considerations can be broadly categorized into two major aspects: 1) pharmacokinetic and pharmacodynamic parameters "within the body of a child" and 2) pharmacokinetic and pharmacodynamic parameters of the drug intended for use in children.

This comprehensive review article systematically explores key aspects of pediatric pharmacology and pharmacokinetics. The introduction points out the importance of bridging theoretical knowledge with practical application in the context of pediatric pharmacotherapy. Delving into pharmacological foundations, the review elucidates age-related variations in drug responses, focusing on physiological and pharmacological factors influencing efficacy and safety in pediatric populations. The subsequent exploration of pharmacokinetic considerations addresses the impact of developmental factors on drug absorption, distribution, metabolism, and excretion. The practical applications section emphasizes dosing calculations and adjustments, emphasizing the necessity of individualized and age-appropriate strategies in prescribing medications for pediatric patients. Real-world examples of complex drug calculations in pediatric

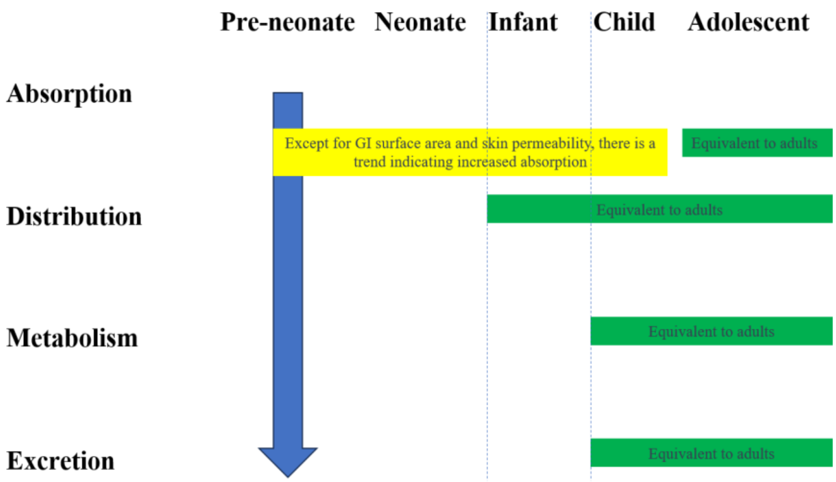

Fig. 1. An overview of changes in pediatric pharmacokinetics and pharmacodynamics in comparison to adults.

Table 1. Pharmacokinetic changes in children across different age groups: theoretical insights vs. clinical applications.[2-5]

Process	Theoretical insights	Clinical applications
Absorption	Gastric pH undergoes significant changes from birth to 2-3 years of age in infants. Initially alkaline due to residual amniotic fluid and underdeveloped parietal cells, the pH gradually shifts towards acidity within the first 24 hours after birth, although it remains lower than that in adults. By the age of 2-3 years, the gastric pH reaches a level comparable to that of adults.	In pediatric patients, administering drugs necessitates careful consideration of factors such as the medication's chemical properties (acidic or basic) and the child's age. Infants (up to one year old) exhibit decreased absorption with weakly acidic drugs, whereas weakly basic drugs enhance absorption. By ages 2-3, absorption rates approach those seen in adults. Tailoring medication administration to developmental stages is crucial. Weakly acidic drugs like Phenobarbital and Aspirin may result in delayed onset in infants, while weakly basic drugs like Salbutamol (in aerosol form) may pose toxicity risks in 1-2-year-old due to increased absorption. Immature gastrointestinal systems in infants can lead to irregular drug absorption. Children aged 1-6 may experience reduced small intestine absorption, necessitating careful monitoring with specialized dosage forms. Different administration routes (rectal, intramuscular, transdermal) present unique considerations based on factors such as first-pass metabolism, muscle mass, skin characteristics, and respiratory capacity in infants. Prudent drug administration

Process	Theoretical insights	Clinical applications
		strategies in pediatric care are essential, emphasizing both efficacy and safety.
Distribution	In children, the body has a higher proportion of water compared to adults. Increased extracellular fluid expands the volume of drug distribution, particularly for drugs that primarily distribute in extracellular fluid, leading to decreased overall drug concentration with more fluid. To ensure drug presence within tissues or cells, larger doses may be needed. However, improper dosage management in this context can risk toxicity.	Before administering medication to children, it's crucial to determine the drug's preference for intracellular or extracellular water. Water-soluble drugs like gentamicin, linezolid, phenobarbital, and propofol may necessitate larger doses in children due to their limited adipose tissue and muscle mass, resulting in a potentially limited volume of distribution and an increased risk of toxicity. Monitoring drug efficacy and safety is essential. Children's immature blood-brain barrier increases the risk of drugs crossing into the brain, especially with medications affecting the nervous system. First-generation antihistamines, for example, may induce restlessness in children. Additionally, children have lower protein-binding capacity, leading to a higher level of free drug and an increased risk of toxicity with drugs that have high protein-binding affinity.
Metabolism	Children experience significantly lower drug metabolism through the liver compared to adults, as certain enzymes involved in drug metabolism are not fully functional in children. P450 cytochrome enzyme activity in children fluctuates, stabilizing during puberty. This variation can lead to reduced drug metabolism, increasing the risk of drug accumulation and potential toxicity.	Elevated liver enzyme activity accelerates drug breakdown, requiring larger-than-usual doses, sometimes surpassing those used in adults. Thus, medication dosing must be rigorously assessed, and consistent monitoring of adverse reactions, especially in children under 1 year, is crucial when dosages significantly exceed the standard.
Excretion	Children exhibit lower drug clearance than adults, leading to prolonged drug presence and an elevated risk of toxicity. Caution is necessary when interpreting laboratory values, especially for kidney drug clearance, as infants aged 0-3 months typically have lower renal clearance, which may not indicate permanent kidney dysfunction.	Kidney function calculations, utilizing formulas like the Schwartz equation, are crucial for adjusting drug dosages in children. Cross-referencing these calculations with reputable medical references or databases is essential for accurate drug dosing in pediatric patients.

cases illustrate the intricacies of clinical decision-making. Highlighting the pharmacist's pivotal role, the article concludes by emphasizing the integration of theoretical insights into practical considerations, showcasing the pharmacist's contribution to personalized dosing, vigilant monitoring, and patient education for optimal therapeutic outcomes in pediatric pharmacotherapy.

Drug dosing in children should be determined by considering PK/PD values and clinical application.

This review article aims to present an illustrative case example underscoring a fundamental practice essential for every pharmacist—performing critical thinking and data analysis before determining drug administration and dosage calculations, particularly for pediatric patients. The focal point of this case example is the calculation of paracetamol dosage for children.

Paracetamol (acetaminophen), an analgesic and antipyretic medication with a history spanning over a century, still possesses an incompletely understood mechanism of action. Recent studies suggest that it does not act as a selective COX inhibitor, unlike most NSAIDs. Instead, paracetamol inhibits cyclooxygenases at the peroxidase domain, not the typical cyclooxygenase domain. Additionally, its metabolites, including AM404, activate TRPV1 and cannabinoid 1 receptors,[7] contributing to its analgesic effect. Despite a well-established medical literature supporting its indications, efficacy, and safety profile, practical considerations such as taste, odor, ease of administration, and cost significantly influence consumer choice. Paracetamol is available in various forms like oral solutions, suspensions, concentrated drops, chewable tablets, and injections.[8]

In pediatric care, ensuring the appropriate dosage is crucial, recognizing that "children are not miniature adults" and their pharmacokinetics continually evolve with growth.[9] Two pivotal factors influencing pediatric pharmacokinetics are metabolism and excretion. Children's metabolism is a complex process, with complete processes occurring in those above three months of age. The risk of drug toxicity, especially with paracetamol metabolized by cytochrome P450 2E1 and 2D6, similar to adults in children aged three to five years, needs careful assessment.[9] Excretion processes fully develop in children aged six months and above, involving glomerular filtration and tubular secretion.

These findings are consistent with data from medical guideline databases such as MICROMEDEX™,[10] which generally recommend paracetamol use from infancy onwards. However, it is crucial to calculate the appropriate dosage based on the child's weight and monitor for medication-related adverse effects, especially in children under the age of three to five years. MICROMEDEX™, for instance, suggests that the effective paracetamol dosage for pediatric patients can range from 10 to 15 mg/kg per dose, with a maximum daily dose of 75 mg/kg for infants and less than 100 mg/kg or 1,625 mg/day for young children.[10] These recommendations align with the drug database, which suggests determining the appropriate paracetamol dosage based on the child's weight and age. Another essential consideration is the choice of medication form and calculating the volume to administer appropriately based on the child's age.

Research indicates that the preferred dosage form varies among different age groups of children. For example, infants up to one year old may benefit from concentrated liquid drops, children aged two to six years may use concentrated liquid drops or thick liquid suspensions, and children aged six and above can take tablets.[11, 12] Therefore, when calculating paracetamol dosages, it is essential to consider the concentration of the available product. For instance, a one-year-old child weighing 10 kg may require 1 ml of paracetamol with a concentration of 80 mg/0.8 ml, while a three-year-old weighing

16 kg may need 5 ml of paracetamol with a concentration of 160 mg/5 ml, or one teaspoon.

Referring to Table 1, a comprehensive grasp of pediatric pharmacokinetics entails discerning the dynamic alterations in absorption, distribution, metabolism, and excretion within the pediatric demographic. During the initial stages, infants undergo a notable transition in gastric pH, shifting from an alkaline state at birth to an acidic milieu by the age of 2-3 years, thereby influencing drug absorption. As pediatric patients mature, absorption rates gradually converge with those observed in adults, necessitating a judicious approach to medication administration that accommodates both drug characteristics and developmental stages. The elevated proportion of water in pediatric populations significantly influences drug distribution, demanding meticulous dosage management to mitigate the risk of toxicity. The incompletely functional liver enzymes in children contribute to diminished drug metabolism, potentially resulting in accumulation and heightened toxicity risks, particularly in those under 1 year of age. Additionally, the diminished drug clearance in children underscores the critical need for tailored drug dosages, the interpretation of renal clearance values with regard to age-related fluctuations, and the utilization of formulas such as the Schwartz equation. Informed decision-making in pediatric drug therapy mandates consulting reputable references.

Conforming to Fig.1, the pediatric population undergoes dynamic physiological shifts that exert substantial impacts on drug absorption, distribution, metabolism, and excretion. These nuanced alterations necessitate a sophisticated and thoughtful approach to medication management in pediatric patients. Moreover, age-related variances in drug responses, receptor sensitivity, and immune function introduce distinctive considerations in pharmacodynamics, emphasizing the necessity of customizing therapeutic strategies on an individualized basis. Figure 1 functions as a tool to augment healthcare providers' comprehension of the inherent complexities in pediatric pharmacology, thereby facilitating evidence-based decision-making and ultimately improving patient care outcomes.

To exemplify concerns in pediatric drug utilization, Table 2 delineates pharmacokinetic (PK) and pharmacodynamic (PD) considerations. This serves as an illustrative reference to highlight the intricate interplay of factors influencing pediatric drug therapy, further emphasizing the need for meticulous attention and individualized approaches in clinical practice.

Conclusion

In conclusion, this review article has provided an overview of the fundamental principles of pharmacotherapy management in pediatric patients. Understanding the unique pharmacological and pharmacokinetic aspects of children is paramount for safe and effective drug administration. By delving into key concepts such as drug absorption, distribution, metabolism, and excretion in pediatric populations, healthcare practitioners can make informed decisions when prescribing medications for children of all ages. Furthermore, the application of PK/ PD principles in clinical practice is crucial for tailoring drug regimens to individual pediatric patients, optimizing therapeutic outcomes, and minimizing the risk of adverse events. As research in pediatric pharmacotherapy continues to evolve, healthcare professionals should stay abreast of the latest developments to ensure the best possible care for this vulnerable patient population.

Conflicts of Interest

The authors declare no conflict of interest.

Table 2 Concerns in pediatric drug use: an example in pharmacokinetics (PK) and pharmacodynamics (PD) considerations

Concerns in pediatric drug use	Details
Antibiotics[13]	**Drug:** Amoxicillin for pediatric bacterial infections **PK/PD concerns:** Age-related variability: neonates and infants exhibit altered drug absorption due to factors like gastric pH variations and incomplete enzyme development. Developmental changes: pediatric patients undergo physiological changes affecting drug distribution within the body. **Theory mentioned:** Gastrointestinal absorption: fluctuating gastric pH in neonates and limited enzyme functionality impact amoxicillin metabolism. Developmental changes in PK: consideration of body composition and organ maturation influencing drug distribution and clearance. **Practical use:** Individualized dosage determinants: consideration of age and weight for personalized dosing calculations. Renal function considerations: close monitoring for potential toxicity due to immature renal function. Continuous monitoring: regular assessment of efficacy and adverse effects, with dosage adjustments based on observed responses. Adapting dosage regimens: recognizing the need for age-appropriate dosing strategies to ensure efficacy and safety in pediatric antibiotic therapy. **Example:** In a practical scenario involving a 9-month-old pediatric patient with a bacterial infection, the physician navigates the complexities of amoxicillin dosage calculation. Considering the patient's age (9 months) and weight (9.5 kg), an initial dose of 12 mg is determined using a formula that accounts for developmental and weight factors. After the caregiver reports symptomatic improvement, the pediatrician, aware of the dynamic nature of pediatric pharmacokinetics, reassesses the patient due to a weight change to 10 kg. The dosage is recalculated, resulting in an adjusted dose of 120 mg.
Anticonvulsants[14]	**Drug:** Levetiracetam in pediatric epilepsy management **PK/PD concerns:** Age-related variability: pediatric patients may manifest diverse pharmacokinetic and pharmacodynamic responses to levetiracetam due to age-related factors, impacting drug absorption, distribution, metabolism, and excretion. Physiological changes: early developmental stages introduce differences in drug absorption related to gastric pH variations and the maturation of drug-metabolizing enzymes. **Theory mentioned:** Gastric pH and enzyme maturation: children, particularly in early developmental stages, may experience variations in drug absorption due to fluctuating gastric pH and the ongoing maturation of drug-metabolizing enzymes, influencing levetiracetam's pharmacokinetics. **Practical use:** Individualized dosage determinants: prescribing levetiracetam in pediatric epilepsy patients necessitates a meticulous assessment of age, weight, and developmental status for personalized dosing calculations.

Concerns in pediatric drug use	Details
	Dosage adjustments: recognition of age-related variations in drug metabolism and clearance demands periodic adjustments to optimize therapeutic outcomes. Continuous monitoring: vigilant observation for drug efficacy and potential side effects, including changes in behavior or cognitive function, is paramount in pediatric patients. Balancing act: striking the delicate balance between achieving seizure control and minimizing adverse effects requires a nuanced understanding of the immature physiology of children and its impact on drug responses. **Example:** In a clinical scenario, a 7-year-old pediatric patient with epilepsy, weighing 22 kg, is prescribed levetiracetam. The initial dose calculation involves adjusting for age (1.0) and weight (20 mg/kg), resulting in an initial dose of 440 mg. However, after a month, the patient experiences behavioral changes, necessitating a reassessment. Considering the age-related variations in drug metabolism and clearance, the pediatrician recalculates the dosage based on the patient's weight, now 23 kg, resulting in an adjusted dose of 460 mg.
A nonsteroidal anti-inflammatory drug (NSAID)[15]	**Drug:** Ibuprofen in pediatric pain and fever management **PK/PD concerns:** Multifactorial variability: pediatric patients exhibit diverse pharmacokinetic and pharmacodynamic responses to ibuprofen, influenced by age, weight, and developmental stage. Physiological factors: age-related differences impact drug absorption, distribution, metabolism, and excretion, contributing to variations in ibuprofen's effectiveness and safety. **Theory mentioned:** Gastric pH and enzyme maturation: children may demonstrate distinctive drug absorption patterns due to variations in gastric pH and the ongoing maturation of drug-metabolizing enzymes, posing implications for ibuprofen's pharmacokinetics. **Practical use:** Age and weight-based dosage determinants: prescribing ibuprofen in pediatric patients involves a meticulous assessment of age and weight, necessitating tailored dosage calculations for individualized therapy. Adjustments for physiology: acknowledging the higher water content and limited enzyme functionality in children guides necessary adjustments in ibuprofen doses to ensure therapeutic effects without compromising safety. Comprehensive monitoring: vigilant monitoring for potential side effects, particularly related to gastrointestinal and renal functions, is paramount to identify and manage adverse reactions promptly. Risk awareness: recognizing the potential for increased adverse effects, such as gastrointestinal bleeding, in specific age groups underscores the importance of risk-stratified dosing for safe and effective use. **Example:** A 5-year-old pediatric patient weighing 18 kg presents with a fever, and the physician considers ibuprofen for relief. Initial dosage calculation involves adjusting for age (0.9) and weight (10 mg/kg), resulting in an initial dose of 162 mg. However, due to the child's history of gastrointestinal sensitivity, the physician decides to further adjust the dose downward to 150 mg to

Concerns in pediatric drug use	Details
	minimize potential side effects. Regular monitoring over the next 24 hours reveals a reduction in fever without adverse effects.
1st generation antihistamines[16]	**Drug:** Diphenhydramine in pediatric allergic reactions management **PK/PD concerns:** Age-related variability: pediatric patients exhibit diverse pharmacokinetic and pharmacodynamic responses to diphenhydramine, influenced by age-related factors such as metabolism, clearance, and receptor sensitivity. Metabolism and clearance: variations in liver enzyme activity contribute to differences in drug metabolism, impacting the duration of action and clearance of diphenhydramine. Receptor sensitivity: age-related changes may influence receptor sensitivity, affecting the effectiveness of diphenhydramine in managing allergic symptoms. **Theory mentioned:** Liver enzyme activity: children may demonstrate different rates of drug metabolism due to variations in liver enzyme activity, influencing the pharmacokinetics of diphenhydramine. Receptor sensitivity changes: age-related alterations in receptor sensitivity may impact the therapeutic efficacy and duration of action of antihistamines. **Practical use:** Age, weight, and metabolism-based dosage determinants: prescribing diphenhydramine in pediatric patients involves a detailed assessment of age, weight, and potential variations in drug metabolism, necessitating personalized dosage calculations for optimal therapeutic outcomes. Individualized adjustments: recognition of age-related variability prompts adjustments in dosage to achieve the desired antihistaminic effect while mitigating risks of over-sedation or adverse reactions. Central nervous system effects: heightened vigilance is essential due to the immature blood-brain barrier in children, emphasizing the need for careful monitoring of antihistamines that may cause central nervous system effects, such as drowsiness. Paradoxical reactions: understanding potential paradoxical reactions, where antihistamines may cause increased restlessness in some children, is crucial for safe and effective use. **Example:** A 4-year-old pediatric patient weighing 16 kg presents severe allergic reactions. The initial diphenhydramine dosage calculation involves adjusting for age (0.8) and weight (2 mg/kg), resulting in an initial dose of 25.6 mg. However, due to the child's history of rapid drug metabolism, a pharmacogenomic analysis is performed, revealing a genetic polymorphism affecting liver enzyme activity. Based on this information, the dosage is further adjusted downward to 20 mg to account for the potential for accelerated metabolism. Continuous monitoring over the next 12 hours shows effective symptom relief without adverse effects.
2nd generation antihistamine[17]	**Drug:** Cetirizine in pediatric allergic conditions management **PK/PD concerns:** Age-related variability: pediatric patients present diverse pharmacokinetic and pharmacodynamic responses to cetirizine, influenced by age-related factors such as metabolism, clearance, and receptor sensitivity.

Concerns in pediatric drug use	Details
	Metabolism and clearance: variations in liver enzyme activity contribute to differences in cetirizine metabolism, impacting duration of action and clearance. Receptor sensitivity: age-related changes may influence receptor sensitivity, affecting the effectiveness of cetirizine as an antihistamine. **Theory mentioned:** Liver enzyme activity: children may demonstrate different rates of cetirizine metabolism due to variations in liver enzyme activity, influencing pharmacokinetics. Receptor sensitivity changes: age-related alterations in receptor sensitivity may impact the therapeutic efficacy and duration of action of cetirizine. **Practical use:** Age and weight-based dosage determinants: prescribing cetirizine in pediatric patients necessitates a detailed assessment of age and weight for personalized dosage calculations. Individualized adjustments: adjustments in dosage are necessary to achieve the desired antihistaminic effect without inducing sedation or other adverse reactions, considering age-related variability. Central nervous system effects: heightened vigilance is essential due to the immature blood-brain barrier in children, emphasizing the need for careful monitoring of potential central nervous system effects, despite cetirizine being a second-generation antihistamine designed to be less sedating. Understanding unique PK/PD profile: healthcare providers must comprehend the unique pharmacokinetic and pharmacodynamic profile of cetirizine in children and tailor the dosing regimen accordingly. **Example:** A 6-year-old pediatric patient weighing 22 kg is diagnosed with severe allergic rhinitis. The initial cetirizine dosage calculation involves adjusting for age (1.2) and weight (1 mg/kg), resulting in an initial dose of 26.4 mg. However, a pre-existing medical condition affecting liver enzyme activity is identified through comprehensive genomic testing. Based on the genetic findings, the dosage is further adjusted downward to 18 mg to account for the potential impact on cetirizine metabolism. Continuous monitoring over the next 24 hours reveals effective symptom relief without adverse effects, demonstrating the intricacies of integrating pharmacogenomics into pediatric antihistamine therapy for precise, personalized care in complex clinical scenarios.
Intranasal corticosteroids[18]	**Drug:** Fluticasone propionate in pediatric allergic rhinitis management **PK/PD concerns:** Nasal physiology variability: pediatric patients exhibit diverse pharmacokinetic and pharmacodynamic responses to fluticasone propionate, influenced by age-related factors such as nasal physiology, impacting deposition and absorption. Metabolic variations: variations in metabolic rates may affect systemic exposure to fluticasone propionate, introducing potential variability in drug response. **Theory mentioned:** Nasal anatomy and physiology: children may present differences in nasal anatomy and physiology, influencing the deposition and absorption of intranasal corticosteroids like fluticasone propionate.

Concerns in pediatric drug use	Details
	Metabolic rate variability: variations in metabolic rates among pediatric patients may contribute to differences in systemic exposure to fluticasone propionate. **Practical use:** Age, weight, and nasal development-based dosage determinants: prescribing fluticasone propionate in pediatric patients requires a comprehensive assessment of age, weight, and nasal development to tailor dosage calculations for individualized therapy. Local therapeutic effects: adjustments in dosage are essential to achieve optimal local therapeutic effects while minimizing systemic absorption and potential systemic side effects. Systemic monitoring: vigilant monitoring for signs of systemic corticosteroid effects, such as growth suppression or adrenal suppression, is crucial in the pediatric population. Tailoring therapy: emphasizes the necessity of tailoring intranasal corticosteroid therapy to individual pediatric patients, considering both local and systemic effects, and underscores the importance of vigilant monitoring for optimal therapeutic outcomes. **Example:** A 10-year-old pediatric patient, weighing 30 kg, is diagnosed with severe allergic rhinitis. The initial fluticasone propionate dosage calculation involves adjusting for age (1.5) and weight (100 µg per day), resulting in an initial dose of 150 µg. However, further evaluation reveals a unique nasal anatomy, affecting drug deposition. Advanced imaging and computational modeling are utilized to assess nasal airflow patterns, and the dosage is adjusted upward to 200 µg to ensure optimal deposition in the affected nasal regions. Continuous monitoring over the next several weeks reveals effective local symptom relief without signs of systemic corticosteroid effects.
Topical skin drugs[19]	**Drug:** Topical hydrocortisone and neomycin combination cream in pediatric dermatitis **PK/PD concerns:** Pediatric variability: pediatric patients may demonstrate diverse pharmacokinetic and pharmacodynamic responses to hydrocortisone and neomycin, influenced by age, skin integrity, and potential systemic absorption. Skin permeability and integrity: differences in skin permeability and integrity among children may impact the absorption of both corticosteroids and antibiotics. Immature immune system: the immature immune system in pediatric patients may influence the local and systemic response to hydrocortisone and neomycin. **Theory mentioned:** Skin factors: children may present differences in skin permeability and integrity, impacting the absorption of corticosteroids and antibiotics in topical formulations. Immune system development: the immature immune system in pediatric patients may influence the local and systemic response to hydrocortisone and neomycin. **Practical use:**

Concerns in pediatric drug use	Details
	Age, skin involvement, and risk assessment: prescribing a hydrocortisone and neomycin combination cream in pediatric dermatitis necessitates a meticulous assessment of the child's age, the extent of skin involvement, and the risk of systemic absorption for personalized dosing calculations. Dosage and duration adjustments: adjustments in dosage and duration of use are crucial to minimize the potential for systemic side effects, especially with prolonged use, emphasizing the need for individualized therapeutic regimens. Monitoring for adverse effects: healthcare providers must closely monitor for signs of skin atrophy, local sensitization, and any signs of bacterial resistance to ensure optimal therapeutic outcomes. Systemic effects awareness: awareness of potential systemic effects related to corticosteroids is crucial, particularly in younger pediatric patients, highlighting the pharmacist's role in educating caregivers about the importance of proper application and monitoring. **Example:** A 3-year-old pediatric patient with extensive eczema, weighing 12 kg, is prescribed a hydrocortisone and neomycin combination cream. The initial dosage calculation involves adjusting for age (0.5) and weight (0.5 mg/kg hydrocortisone and 1 mg/kg neomycin), resulting in an initial dose of 3 mg hydrocortisone and 12 mg neomycin. However, after a week of application, the child's skin shows signs of over-sensitivity, prompting a reassessment. The pharmacist, collaborating with the healthcare team, recommends a reduction in both dosage and frequency, adjusting to 2 mg hydrocortisone and 8 mg neomycin to minimize adverse reactions while maintaining therapeutic efficacy. Continuous monitoring over the next month reveals improved skin integrity without signs of systemic absorption or bacterial resistance, showcasing the pharmacist's critical role in optimizing therapeutic outcomes in complex pediatric dermatologic cases.
Topical eyes drug[20]	**Drug:** Atropine eye drops in pediatric myopia control **PK/PD concerns:** Pediatric variability: pediatric patients may exhibit diverse pharmacokinetic and pharmacodynamic responses to atropine eye drops, influenced by age, ocular physiology, and potential systemic absorption. Ocular physiology: differences in ocular physiology among children may impact the absorption and local effects of atropine in the eyes. Systemic absorption: variations in systemic absorption may influence potential side effects beyond the ocular tissues. **Theory mentioned:** Ocular physiology differences: children may present differences in ocular physiology, affecting the absorption and local effects of atropine in the eyes. Systemic absorption variability: variations in systemic absorption may lead to varying systemic effects, potentially influencing side effects beyond the ocular tissues. **Practical use:** Age, degree of myopia, and systemic risk assessment: prescribing atropine eye drops for myopia control in pediatric patients requires a thorough assessment of the child's age, degree of myopia, and potential for systemic absorption for individualized dosing calculations.

Concerns in pediatric drug use	Details
	Dosage concentration adjustments: adjustments in dosage concentration may be necessary to balance the desired therapeutic effect with minimizing potential systemic side effects, emphasizing the need for personalized therapeutic regimens. Monitoring for ocular and systemic effects: crucial monitoring for ocular effects, such as changes in pupil size and accommodation, as well as systemic side effects like increased heart rate, is essential for optimal therapeutic outcomes. Communication with caregivers: healthcare providers must maintain close communication with parents or caregivers to ensure proper administration and adherence to the prescribed regimen, highlighting the pharmacist's role in patient education and support. **Example:** A 9-year-old pediatric patient with progressive myopia, undergoing atropine eye drop therapy, presents a complex case. The initial dosage calculation involves adjusting for age (1.2) and myopia degree (0.01%), resulting in an initial concentration of 0.012%. However, after a month of therapy, the child experiences significant systemic side effects, including an increase in heart rate. The pharmacist collaborated with the healthcare team to conduct a thorough pharmacogenomic analysis, revealing a genetic polymorphism affecting atropine metabolism. The dosage concentration is subsequently adjusted downward to 0.008%, leading to improved myopia control without systemic side effects.
Topical ears drug[21]	**Drug:** Otic corticosteroid drops (e.g., hydrocortisone) in pediatric otitis externa **PK/PD concerns:** Pediatric variability: pediatric patients may manifest diverse pharmacokinetic and pharmacodynamic responses to otic corticosteroid drops, influenced by age, ear anatomy, and potential systemic absorption. Ear anatomy and permeability: differences in ear anatomy and permeability among children may impact the absorption and local effects of corticosteroids in the ear canal. Systemic absorption: variations in systemic absorption may lead to varying systemic effects, potentially influencing side effects beyond the ear canal. **Theory mentioned:** Ear anatomy and permeability differences: children may present differences in ear anatomy and permeability, influencing the absorption and local effects of corticosteroids in the ear canal. Systemic absorption variability: variations in systemic absorption may lead to varying systemic effects, potentially influencing side effects beyond the ear canal. **Practical use:** Age, ear involvement, and systemic risk assessment: prescribing otic corticosteroid drops for pediatric otitis externa necessitates a comprehensive assessment of the child's age, the extent of ear canal involvement, and the potential for systemic absorption for individualized dosing calculations. Dosage and duration adjustments: adjustments in dosage and duration of use are essential to balance therapeutic effects with minimizing potential

Concerns in pediatric drug use	Details
	systemic side effects, emphasizing the need for personalized therapeutic regimens. Local and systemic monitoring: crucial monitoring for local reactions and any signs of systemic effects is essential for optimal therapeutic outcomes. Communication with parents or caregivers is vital to ensure proper administration and adherence to the prescribed regimen. Pharmacists' integration roles: pharmacists play a crucial role in advising on proper administration techniques, educating caregivers about potential side effects, and collaborating with healthcare providers to monitor for adverse reactions, showcasing their integral role in patient safety and optimal therapeutic outcomes. **Example:** A 7-year-old pediatric patient with severe otitis externa, weighing 25 kg, is prescribed otic hydrocortisone drops. The initial dosage calculation involves adjusting for age (1.1) and ear involvement (0.03%), resulting in an initial concentration of 0.033%. However, after two weeks, the child experiences local irritation and itching, prompting a reassessment. The pharmacist, collaborating with the healthcare team, recommends a lower concentration of 0.025% and a reduction in frequency. Continuous monitoring over the next month reveals improved ear canal integrity without signs of systemic absorption or adverse reactions.
Intravenous antibiotics[22]	**Drug:** Intravenous ampicillin in pediatric bacterial infections **PK/PD concerns:** Pediatric variability: pediatric patients may demonstrate diverse pharmacokinetic and pharmacodynamic responses to intravenous antibiotics, influenced by age, weight, and organ function. Distribution, metabolism, and renal function: differences in drug distribution, metabolism, and renal function among children may impact the absorption, distribution, and elimination of intravenous antibiotics. Age-related immune response: age-related variations in immune response can influence pharmacodynamic outcomes of intravenous antibiotics. **Theory mentioned:** Organ function variability: children may present differences in organ function, affecting the absorption, distribution, and elimination of intravenous antibiotics. Age-related immune response: variations in immune response based on age can influence the pharmacodynamic outcomes of intravenous antibiotics. **Practical use:** Age, weight, and renal function-based dosage determinants: prescribing intravenous ampicillin for pediatric infections demands a detailed assessment of the child's age, weight, and renal function for individualized dosing calculations. Dosage adjustments for therapeutic levels: adjustments in dosage may be necessary to achieve therapeutic antibiotic levels without risking toxicity, emphasizing the need for personalized therapeutic regimens. Monitoring for adverse reactions: crucial monitoring for adverse reactions, including renal impairment or allergic responses, is essential for optimal therapeutic outcomes. Consideration of infusion rates and drug clearance: healthcare providers must ensure accurate dosing, consider infusion rates, and account for

Concerns in pediatric drug use	Details
	potential changes in drug clearance in pediatric patients, showcasing the pharmacist's role in optimizing therapy. **Example:** A 3-month-old infant, weighing 5 kg, is diagnosed with a severe bacterial infection, and prescribed intravenous ampicillin. The initial dosage calculation involves adjusting for age (0.2), weight (40 mg/kg), and renal function, resulting in an initial dose of 40 mg every 12 hours. However, after two days, the infant exhibits signs of mild renal impairment. The pharmacist collaborates with the healthcare team to conduct frequent renal function tests and recommends a reduction in dosage to 30 mg every 12 hours, ensuring therapeutic levels while minimizing renal stress. Continuous monitoring over the next week reveals improved infection control without signs of renal toxicity, highlighting the pharmacist's critical role in optimizing therapeutic outcomes by addressing individual patient factors and ensuring safety in complex pediatric antibiotic therapy.
Inhaler[23]	**Drug:** Inhaled albuterol in pediatric asthma management **PK/PD concerns:** Pediatric variability: pediatric patients may exhibit diverse pharmacokinetic and pharmacodynamic responses to inhaled albuterol, influenced by age, lung development, and inhalation technique. Lung physiology and inhalation patterns: differences in lung physiology and inhalation patterns among children may impact the absorption and local effects of inhaled medications. Systemic absorption: variations in systemic absorption may lead to varying systemic effects, potentially influencing side effects beyond the respiratory system. **Theory mentioned:** Lung physiology differences: children may present differences in lung physiology, affecting the absorption and local effects of inhaled albuterol. Inhalation pattern variability: variations in inhalation patterns may influence the effectiveness of albuterol delivery to the lungs. **Practical use:** Age, lung function, and inhalation technique assessment: prescribing albuterol inhalers for pediatric asthma management necessitates a comprehensive assessment of the child's age, lung function, and ability to use the inhaler correctly for individualized dosing calculations. Dosage and inhalation technique adjustments: adjustments in dosage and inhalation technique may be necessary to ensure optimal bronchodilation without risking adverse effects, emphasizing the need for personalized therapeutic regimens. Patient and caregiver education: healthcare providers must educate both the child and parents or caregivers on proper inhaler use, emphasizing the importance of coordination between inhalation and actuation, showcasing the pharmacist's role in patient education. Regular monitoring and systemic effect assessment: crucial monitoring of lung function and assessing for signs of systemic effects, such as increased heart rate, is essential for optimal therapeutic outcomes, highlighting the pharmacist's role in ensuring safety and efficacy. **Example:**

Concerns in pediatric drug use	Details
	An 8-year-old pediatric patient with severe asthma, weighing 30 kg, is prescribed an albuterol inhaler. The initial dosage calculation involves adjusting for age (1.2) and weight (2.5 mg/kg), resulting in an initial dose of 75 mg. However, after a week, the child experiences increased heart rate and minimal improvement in symptoms. The pharmacist collaborates with the healthcare team to assess inhalation technique and recommends a spacer device for improved drug delivery. The dosage is subsequently adjusted downward to 50 mg.

References

[1] Lim SY, Pettit RS. Pharmacokinetic considerations in pediatric pharmacotherapy. Am J Health Syst Pharm. 2019;76:1472-1480.

[2] Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. Br J Clin Pharmacol. 2015;79:395-404.

[3] Barker CIS, Standing JF, Kelly LE, Hanly Faught L, Needham AC, Rieder MJ, et al. Pharmacokinetic studies in children: recommendations for practice and research. Arch Dis Child. 2018;103:695-702.

[4] Lu H, Rosenbaum S. Developmental pharmacokinetics in pediatric populations. J Pediatr Pharmacol Ther. 2014;19:262-276.

[5] Wagner J, Abdel-Rahman SM. Pediatric pharmacokinetics. Pediatr Rev. 2013;34: 258-269.

[6] Pan SD, Zhu LL, Chen M, Xia P, Zhou Q. Weight-based dosing in medication use: what should we know? Patient Prefer Adherence. 2016;10:549-560.

[7] Jóźwiak- Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. Acta Pol Pharm. 2014; 71:11-23.

[8] Gerriets V, Anderson J, Nappe TM. Acetaminophen [Internet]. Treasure Island (FL): StatPearls Publishing; [Updated 2023 Jun 20, Cited 2023 Oct 10]. Available from: https://www.ncbi.nlm.nih.gov/books/ NBK482369/

[9] Holladay J, Winch P, Morse J, Anderson BJ, McKee CT, Rice-Weimer J, et al. Acetaminophen pharmacokinetics in infants and children with congenital heart disease. Paediatr Anaesth. 2023;33:46-51.

[10] Micromedex® (electronic version). Acetaminophen. Merative, Ann Arbor, Michigan, USA. Available at https://www.micromedexsolutions.com/micromedex2/librarian/CS/A0F0E7/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/9334F3/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/NDT/evidencexpert/PFActionId/evidencexpert.DoIntegratedSearch?SearchTerm=acetaminophen&UserSearchTerm=acetaminophen&SearchFilter=filterNone&navitem=searchALL (cited: Oct/ 3/2023)

[11] Abernethy DR, Burckart GJ. Pediatric dose selection. Clin Pharmacol Ther. 2010;87: 270-271.

[12] Lajoinie A, Henin E, Kassai B. Choisir la forme pharmaceutique orale la plus adaptée à l'enfant [Oral formulation of choice for children]. Arch Pediatr. 2015;22:877-885.

[13] Little P, Francis NA, Stuart B, O'Reilly G, Thompson N, Becque T, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care: ARTIC-PC RCT. Health Technol Assess. 2023;27:1-90.

[14] Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: a systematic review. PLoS One. 2016;11: e0149686.

[15] de Martino M, Chiarugi A, Boner A, Montini G, De' Angelis GL. Working towards an appropriate use of ibuprofen in children: an evidence-based appraisal. Drugs. 2017;77:1295-1311.

[16] Sicari V, Zabbo CP. Diphenhydramine [Internet]. Treasure Island (FL): StatPearls Publishing; [Updated 2023 Jul 10, Cited 2023 Oct 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526010/

[17] Zhou P, Jia Q, Wang Z, Zhao R, Zhou W. Cetirizine for the treatment of allergic diseases in children: a systematic review and meta-analysis. Front Pediatr. 2022;10:940213.

[18] Oliver AJ, Covar RA, Goldfrad CH, Klein RM, Pedersen SE, Sorkness CA, et al.

Randomized trial of once-daily fluticasone furoate in children with inadequately controlled asthma. J Pediatr. 2016;178:246-253.

[19] Dallo M, Patel K, Hebert AA. Topical antibiotic treatment in dermatology. Antibiotics (Basel). 2023;12(2):88.

[20] Verzhanskaya TY. Primenenie atropina dlia lecheniia progressiruiushcheĭ miopii u deteĭ i podrostkov [atropine use for progressive myopia in children and adolescents]. Vestn Oftalmol. 2017;133:89-98.

[21] Sandhu N, Thomson D, Stang A. In children with chronic suppurative otitis media, should one prescribe topical or systemic antibiotics? Paediatr Child Health. 2012;17: 385-386.

[22] Spurling GK, Doust J, Del Mar CB, Eriksson L. Antibiotics for bronchiolitis in children. Cochrane Database Syst Rev. 2011; 15:CD005189.

[23] Muchão FP, Souza JM, Torres HC, De Lalibera IB, de Souza AV, Rodrigues JC, et al. Albuterol via metered-dose inhaler in children: lower doses are effective, and higher doses are safe. Pediatr Pulmonol. 2016;51:1122.