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Perspective

Pharmacokinetics of Commonly Used Pediatrics Antiepileptic Drugs: Age-Related Variations

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DESCRIPTION

Epilepsy remains one of the most prevalent neurological disorders in childhood, affecting approximately 0.5–1% of Pediatrics populations worldwide. The pharmacological management of Pediatrics epilepsy relies heavily on AntiEpileptic Drugs (AEDs) to control seizures and improve quality of life. However, the PharmacoKinetics (PK) of AEDs in children differ markedly from adults due to age-related physiological changes. Understanding these variations is essential for optimizing dosing regimens, minimizing adverse effects and ensuring therapeutic efficacy. The Pediatrics population is heterogeneous, encompassing neonates, infants, toddlers, school-age children and adolescents. Each age group exhibits distinct maturational changes in organ function, body composition, enzyme activity and protein binding, all of which influence drug absorption, distribution, metabolism and elimination. Consequently, AED pharmacokinetics cannot be extrapolated simply from adult data, requiring dedicated Pediatrics studies and age-appropriate dosing strategies.

Absorption of AEDs in children may be influenced by gastrointestinal maturation. For example, gastric pH is higher in neonates, which can alter solubility and bioavailability of certain drugs. The delayed gastric emptying time and immature bile salt secretion also affect drug dissolution and absorption. These factors can variably impact drugs such as valproic acid and phenobarbital, whose bioavailability is important for seizure control. Distribution volume changes with age as body water content is higher in neonates (up to 80%) compared to adults (about 60%), while fat composition varies. Hydrophilic drugs like levetiracetam may have a larger volume of distribution in younger children, potentially necessitating higher per kilogram dosing. Conversely, highly lipophilic drugs may distribute differently in infants, altering therapeutic plasma concentrations.

Metabolism is perhaps the most significant factor driving PK variability. The liver's enzymatic capacity evolves throughout childhood. Phase I enzymes, including cytochrome P450 isoforms, show immature activity in neonates but can surpass adult levels during early childhood before normalizing in adolescence. This developmental pattern affects drugs metabolized by these enzymes carbamazepine and phenytoin are classic examples with nonlinear metabolism subject to age-dependent clearance. Phase II conjugation enzymes, such as glucuronosyltransferases, also mature over the first year of life, influencing drugs like valproic acid. Reduced metabolism in neonates may lead to drug accumulation and toxicity if adult dosing is used. In contrast, toddlers and pre-schoolers often have enhanced metabolic rates, requiring dose adjustments upwards to maintain therapeutic levels.

Renal elimination, critical for drugs such as levetiracetam and topiramate, is another key variable. Glomerular Filtration Rate (GFR), tubular secretion and reabsorption mature gradually during infancy. Neonates and young infants typically have reduced clearance, which increases with age. Failure to account for these changes can result in suboptimal drug levels or adverse effects. Therapeutic Drug Monitoring (TDM) remains a valuable tool in Pediatrics epilepsy management, enabling dose individualization based on measured plasma concentrations and clinical response. However, interpreting TDM results requires an understanding of age-related PK changes to avoid misjudging drug exposure.

Recent pharmacokinetic-pharmacodynamics (PK-PD) modelling studies in high-income countries have improved dosing guidelines for many AEDs. For instance, population PK models for levetiracetam now incorporate age, weight and renal function, allowing clinicians to tailor doses more precisely across Pediatrics age groups. Similarly, dosing nomograms for valproic acid and carbamazepine account for developmental enzymatic activity to minimize toxicity risks. Despite advancements, challenges remain. Pediatrics clinical trials for AEDs often face ethical and practical hurdles, limiting comprehensive PK data in the youngest patients. Off-label use is common and standardized dosing recommendations are not always available for newer AEDs. Additionally, genetic polymorphisms influencing metabolism (e.g., CYP2C9 variants affecting phenytoin clearance) add complexity to dosing decisions.

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Furthermore, comorbidities and concomitant medications in Pediatrics patients can modify AED pharmacokinetics. For example, enzyme-inducing drugs like phenobarbital can alter metabolism of other AEDs, necessitating vigilant monitoring and dose adjustments. Nutritional status, organ dysfunction and developmental delays also impact drug handling and response. To address these complexities, integrating pharmacogenomics and advanced PK-PD modelling into clinical practice holds promise. Personalized medicine approaches could refine dosing based on individual metabolic capacity, age and genetic profile. Electronic health records with embedded dosing algorithms may assist clinicians in real-time dose optimization.

CONCLUSION

Age-related variations in the pharmacokinetics of commonly used Pediatrics antiepileptic drugs profoundly influence therapeutic outcomes. Understanding these changes in absorption, distribution, metabolism and elimination is critical for safe and effective seizure management in children. High-income countries have made significant strides in characterizing these variations and developing evidence-based dosing guidelines. However, gaps remain, particularly in the youngest and most vulnerable Pediatrics populations. Future efforts should focus on expanding Pediatrics-specific pharmacokinetic research, integrating pharmacogenomics data and enhancing clinical decision support tools to individualize AED therapy. Through a comprehensive and nuanced approach that accounts for developmental physiology, clinicians can optimize antiepileptic drug regimens, reducing adverse effects and improving seizure control, ultimately enhancing the quality of life for children living with epilepsy.