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Medication Dosing for Children With Overweight and Obesity

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Approximately 14.7 million US children aged 2 to 19 years are obese. This creates significant challenges to dosing medications that are primarily weight based (mg/kg) and in predicting pharmacokinetics parameters in pediatric patients. Obese individuals generally have a larger volume of distribution (Vd) for lipophilic medications. Conversely, the Vd of hydrophilic medications may be increased or decreased owing to increased lean body mass, blood volume, and decreased percentage of total body water. They may also experience decreased hepatic clearance secondary to fatty infiltrates of the liver. Hence, obesity may affect loading dose, dosage interval, plasma half-life, and time to reach steady-state concentration for various medications. Weight-based dosing is also a cause for potential medication errors. This position statement of the Pediatric Pharmacy Association recommends that weight-based dosing should be used in patients ages <18 years who weigh <40 kg; weight-based dosing should be used in patients ≥40 kg, unless the recommended adult dose for the specific indication is exceeded; clinicians should use pharmacokinetic analysis for adjusting medications in children diagnosed with overweight and obesity; and research efforts continue to evaluate dosing of medications in children diagnosed with overweight and obesity.

ABBREVIATIONS AAP, American Academy of Pediatrics; ABW, adjusted body weight; BMI, body mass index; BSA, body surface area; CDC, Centers for Disease Control and Prevention; IBW, ideal body weight; PPA, Pediatric Pharmacy Association; TBW, total body weight; Vd, volume of distribution

KEYWORDS drug dosage calculations; drug therapy; obese; overweight; pediatrics; pharmacokinetics; therapeutic drug monitoring

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Background

Prevalence data from 1999 to 2018 show a significant increase in obesity and severe obesity in American children.[1] During this time, rates of obesity and severe obesity rose from 14.7% to 19.2% and 3.9% to 6.1%, respectively. According to the Centers for Disease Control and Prevention (CDC), in 2020, 14.7 million (19.7%) American children and adolescents had obesity, with the highest rates in 6 to 11 year olds (20.7%) and 12 to 19 year olds (22.2%).[2] Approximately 13% of 2 to 5 year olds were found to be obese. There was a higher prevalence of obesity and severe obesity in Hispanic children and non-Hispanic Black children than in non-Hispanic White counterparts (26.9% and 24.2% vs 16.1% for obesity, respectively; 9.1% and 10.2% vs 4.3% for severe obesity, respectively).[1] This continuing epidemic creates significant challenges for medication dosing, as dosing in pediatrics is primarily weight based and our understanding of changes to drug disposition in pediatric patients with obesity is not well studied.

Pediatric patients have traditionally been classified as overweight or obese on the basis of body mass index (BMI) percentile, or their BMI in relation to other children of the same age and sex. Reference standards for BMI percentile have been established for children 2 to 20 years of age by both the CDC and the Institute of Medicine.[3,4] Additionally, the CDC has published biological sex–specific BMI-for-age growth charts that can be used to determine a child's BMI percentile. The CDC considers children between the 5th and 85th percentiles to be within the healthy range. Both the CDC and the American Academy of Pediatrics (AAP) classify children with a BMI between the 85th and 95th percentiles as "overweight," those with a BMI ≥95th percentile as "obese," and those with a BMI ≥120% of the 95th percentile or an overall BMI ≥35 kg/m^2 as "severe obesity."[5] The 2023 AAP obesity guidelines have further expanded the definitions: Class 1 obesity: >100% to <120% of the 95th percentile or BMI >30 kg/m^2 to <35 kg/m^2; Class 2 obesity: ≥120% to <140% of the 95th percentile or BMI ≥35 kg/m^2 to <40 kg/m^2; and Class 3 obesity: ≥140% of the 95th percentile or ≥40 kg/m^2, whichever is lower based on age and sex.[6] Using BMI as the sole assessment for obesity has become controversial and in 2023, the American Medical Association proposed that additional elements be factored when

determining body fat in patients.[7] These include, but are not limited to, waist circumference, body composition, and relative fat mass.[7]

Description of the Issue

Individuals with obesity possess a higher body fat proportion and generally have a higher Vd for lipophilic medications owing to distribution into adipose tissue. Conversely, Vd of hydrophilic medications will be altered (e.g., increased or decreased) in these individuals owing to increased lean body mass, increased blood volume, and decreased total body water percentage.[8–10] Obesity may affect loading dose, dosing interval, plasma half-life, and time to reach steady-state concentration for various medications.[8,10,11]

Individuals with obesity also may have varying alterations in metabolism. It has been hypothesized that patients with obesity have decreased hepatic clearance secondary to fatty infiltrates of the liver.[11] It has also been noted that obesity may cause an increase in phase I and II reactions. Individuals with obesity may also have varying alterations in elimination and the effect on renal clearance remains unknown.[9,11] There is no consensus on the most reliable renal function marker to use in children and adolescents with obesity.[12] For example, it has been theorized that cystatin C could be a better early marker than serum creatinine in determination of renal impairment in children with obesity.[12] Additionally, it has been noted that kidney size increases with elevations in total body weight (TBW), resulting in an increased glomerular filtration rate, potentially requiring more frequent dosing of renally eliminated medications to obtain therapeutic concentrations.[8,9,11–13]

Patient Vd and clearance are vital for determining a medication dose. For children with obesity, TBW should be used to describe Vd and lean body weight to describe clearance.[9,10,14] Additionally, drug solubility and the need for loading or maintenance dosing should be reviewed because these factors are important for determining appropriate weight/size descriptors (e.g., TBW, ideal body weight [IBW], adjusted body weight [ABW], body surface area [BSA]) to calculate the final dose.[10,15,16] No universally accepted method used for size descriptors exists, thus it may be beneficial for institutions to agree on specific equations for clinical practice.[10] Consensus also has not been reached on the optimal size descriptors to use for loading and maintenance dosing, although studies have recommended that children with obesity requiring loading doses for hydrophilic medications use IBW; for lipophilic medications, use TBW; for partially lipophilic medications, use adjusted body weight (ABW).[10,16] Lean body weight or BSA should be used for maintenance doses because it is most closely related to lean body mass.[9,10,16] Several studies have evaluated equations to estimate lean body mass in children and adolescents; however, more research is needed to support their use.[17–20] As with chemotherapeutic agents, BSA may also be considered as an effective body size descriptor for maintenance doses in children 1 month to 14 years of age, using the Mosteller equation.[10]

Despite knowledge of altered pharmacokinetics in obesity, limited examples of specific recommendations regarding dosing for children with obesity exist in the published literature. Vancomycin has been the most extensively studied with respect to dosing strategies in pediatric obesity. Data suggest dosing regimens be based on TBW, although patients with obesity may require more vigilant serum concentration monitoring.[21–25] Smit and colleagues[21] recently proposed a novel dosing guideline for children with varying degrees of obesity and renal function, using population-based kinetics with TBW and creatinine clearance predicting vancomycin clearance. Findings provide additional information on the Infectious Diseases Society of America recommendations by detailing dose reductions for those with renal impairment in both obese and nonobese individuals. Pediatric studies have also recommended aminoglycoside dosing be based on either TBW or ABW.[16,26,27] Opiates may vary depending on drug solubility. Recommendations for fentanyl suggest ABW with a cofactor of 0.25 as weight-based dosing may accumulate owing to lipophilicity and reduced clearance, although IBW-based dosing is recommended for hydrophilic morphine.[16,28] A cofactor is recommended by the 25% increase in lean body mass in patients diagnosed as obese compared with nonobese unless otherwise specified by additional data.[16] Low-molecular-weight heparin is another example of ABW recommendations with a cofactor of 0.4.[16] A comprehensive review found supratherapeutic concentrations in pediatric patients with obesity when using TBW, thus dose adjustment and following anti-factor Xa concentrations should be used.[29] Kendrick and colleagues[15] provide further dosing guidance in pediatric overweight and obese patients in an extensive review.

Medication Error Potential Resulting From Weight-Based Dosing

The relative lack of standardized dosing regimens for children, coupled with unknowns related to obesity, is a cause for concern for potential medication errors.[30,31] Weight-based (mg/kg) and BSA-based (mg/m^2) dosing are the most common approaches in pediatric patients.[32–35] Specific determinates of pediatric to adult dosing conversions do not exist, which may lead to potential for overdose situations (e.g., 100 mg/kg/day dosing of ceftriaxone for 8 year old weighing 90 kg; patient would receive 9-g dose [exceeding 4 g/day max]).[34] Conversely, early conversion to adult dosing may lead to subtherapeutic dosing (e.g., 1500 mg/day max dose of ciprofloxacin for 8-year-old,

90-kg patient; dose = 16 mg/kg/day, below 20 mg/kg/day suggested dose).

Incorrect dosing is the most commonly reported error in children.[36,37] To avoid errors, the AAP requests each prescriber ensure the patient's weight is appropriate for weight-based regimens, and that dosing does not exceed the recommended adult dose.[30] For example, it is important to consider the appropriateness of weight-based dosing and maximum dosing recommendations for over-the-counter products such as acetaminophen. Underdosing could lead to uncontrolled pain/fever reduction, while overdosing could lead to toxicity. Childhood pharmacokinetic data of acetaminophen are lacking in overweight and obesity and there is not clear guidance on dosing for pediatric patients with obesity.[38] It has been reported in adults with obesity that the clearance of acetaminophen is increased, so this topic needs to be studied further in children with obesity.[38] If clearance is increased, then higher doses may be needed for pain/fever control. Unfortunately, data are lacking regarding maximum doses for specific medications, which poses a challenge for clinicians in optimizing medication therapy in children diagnosed as overweight and obese. Human intervention, applied judgment, dose-range limits, and education should all be applied to limit the incidence of dosing errors in obese pediatric patients.

Recommendations

The Pediatric Pharmacy Association (PPA) continues to support the following discussion points that may be useful in determining empiric medication dosing in children diagnosed with overweight and obesity, based on weight-based dosing schemes:

- Weight-based dosing should be used in patients <18 years of age who weigh <40 kg;
- For children who weigh ≥40 kg, weight-based dosing should be used, unless the patient's dose or dose per day exceeds the recommended adult dose for the specific indication; familiarity with adult dosing regimens is needed to avoid exceeding recommended maximum adult dose;
- Clinicians should consider therapeutic drug monitoring and/or pharmacokinetic analysis for adjusting medications whenever possible in children diagnosed as overweight and obesity to ensure the most effective and safe regimen.

Prevalence of children classified as overweight or obese has reached an epidemic level in the United States. Weight-based dosing is the most common scheme in determining medication dosing in children. PPA acknowledges that although studies continue to examine dosing strategies in obese children, overall, limited data are available on medication dosing for this population. PPA continues to support research efforts to evaluate therapeutic agents for children who are overweight or obese.

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