

# Medication Dosage in Overweight and Obese Children

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Approximately 31.8% of U.S. children ages 2 to 19 years are considered overweight or 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 for lipophilic medications. Conversely, the Vd of hydrophilic medications may be increased or decreased due to increased lean body mass, blood volume, and decrease 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 Advocacy Group recommends that weight-based dosing should be used in patients ages < 18 years who are < 40 kg; weight-based dosing should be used in patients ≥ 40 kg, unless, unless the recommended adult dose for the specific indication is exceeded; clinicians should use pharmacokinetic analysis for adjusting medications in overweight/obese children; and research efforts continue to evaluate dosing of medications in obese/overweight children.

**ABBREVIATIONS** BMI, body mass index; PPAG, Pediatric Pharmacy Advocacy Group; 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

Following a dramatic increase during the past four decades, rates of overweight and obese American children have leveled off since 2010.<sup>1</sup> At present, approximately 31.8% of U.S. children ages 2 to 19 years are considered overweight or obese.<sup>1</sup> Reports from the hospital setting have shown similar epidemiology for pediatric patients.<sup>2-4</sup> This epidemic creates significant challenges to medication dosage (primarily weight based [mg/kg]) and predicting pharmacokinetics (lack of data) in pediatric patients.

Pediatric patients are classified as overweight or obese based on 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 ages 2 to 20 years by both the Centers for Disease Control and Prevention (CDC) and the Institute of Medicine.<sup>5,6</sup> Additionally, the CDC has published sex-specific BMI-for-age growth charts that can be used to determine a child's BMI percentile. The CDC considers children between the 5<sup>th</sup> and 85<sup>th</sup> percentiles to be at a "healthy weight." Both the CDC and the American Academy of Pediatrics classify children with a BMI between the 85<sup>th</sup> and 95<sup>th</sup> percentiles as "overweight," and those with a BMI > 95<sup>th</sup> percentile as "obese."<sup>7</sup>

## The Issue

Obese individuals possess a higher body proportion of fat and generally have a larger volume of distribution (Vd) for lipophilic medications due to distribution of these drugs into adipose tissue. Conversely, the Vd of hydrophilic medications will be altered (i.e., increased or decreased) in these individuals due to increased lean body mass, blood volume, and decreased total body water percentage.<sup>8-10</sup> Obesity may affect loading dose, dosage interval, plasma half-life, and time to reach steady-state concentration for various medications.<sup>8,10,11</sup>

Individuals with obesity also may have alterations in metabolism and elimination. It is hypothesized that obese patients have decreased hepatic clearance secondary to fatty infiltrates of the liver.<sup>11</sup> Obesity may increase both phase I and II reactions; however, the effect on renal clearance remains unknown.<sup>9,11</sup> It has been noted that kidney size increases with elevations in total body weight (TBW), resulting in increased glomerular filtration rate, potentially requiring more frequent dosage of renally eliminated medications to obtain therapeutic concentrations.<sup>8,9,11,12</sup>

Patient Vd and clearance are vital for determining a medication dose. For obese children, TBW should be used to describe Vd and lean body weight to describe clearance.<sup>9,10,13</sup> Additionally, drug solubility and the

need for loading or maintenance dosage should be reviewed because these factors are important for determining appropriate weight/size descriptors (i.e., TBW, ideal body weight, adjusted body weight, body surface area) to calculate the final dose.<sup>10,14,15</sup> In obese children requiring loading doses, for hydrophilic medications, use ideal body weight; for lipophilic medications, use TBW; for partially lipophilic medications, use adjusted body weight.<sup>10,15</sup> Lean body weight should be used for maintenance doses because it is most closely related to lean body mass.<sup>9,10,15</sup> Several studies have evaluated equations to estimate lean body mass in children and adolescents;<sup>16-19</sup> however, more research is needed to support their use. As with chemotherapeutic agents, body surface area may also be considered as an effective body size descriptor for maintenance doses in children ages 1 month to 14 years using the Mostellar equation.<sup>10</sup>

There are limited examples of altered pharmacokinetic changes of medications in obese children within the literature. Vancomycin has been the most extensively studied with respect to dosage strategies in pediatric obesity. Data suggest dosage regimens be based on TBW, although obese patients may require more vigilant serum-level monitoring.<sup>20-23</sup> Pediatric studies have also recommended aminoglycoside dosage be based on either TBW or adjusted body weight.<sup>15,24,25</sup> Kendrick et al<sup>14</sup> provide further dosage guidance in pediatric overweight and obese patients in an extensive review.

## Medication Error

The relative lack of standardized dosage regimens for children, coupled with unknowns related to obesity, is a cause for concern for potential medication errors.<sup>26,27</sup> Weight-based (mg/kg) and body surface area–based (mg/m<sup>2</sup>) dosages are the most common approaches used in determining drug dosage.<sup>28-31</sup> Specific determinates of pediatric to adult dosage conversions do not exist, which may lead to the potential for overdose situations. For example, an 8-year-old weighing 90 kg who is prescribed 100 mg/kg/day of ceftriaxone would receive a 9-g dose, which exceeds the maximum recommended dose of 4 g/day.<sup>30</sup> Conversely, early conversion to adult dosage may lead to subtherapeutic dosage. For example, an 8-year-old, 90-kg patient who is given the maximum adult recommended dosage of 1500 mg/day (16 mg/kg/day) of ciprofloxacin would receive a dosage that is below the recommended 20 mg/kg/day in pediatric patients.<sup>30</sup>

Incorrect dosage is the most commonly reported error in children.<sup>32,33</sup> To avoid errors, the American Academy of Pediatrics requests each prescriber ensure that the patient's weight is appropriate for weight-based regimens, and that the dose does not exceed the recommended adult dose.<sup>26</sup> Unfortunately, data are lacking regarding maximum doses for specific medications,

which poses a challenge for clinicians in optimizing medication therapy in obese/overweight children. Human intervention, applied judgment, dose-range limits, and education should all be applied to limit the incidence of dosage errors in obese pediatric patients.

## Recommendations

The Pediatric Pharmacy Advocacy Group (PPAG) continues to support the following discussion points that may be useful in determining empiric medication dosage in overweight/obese children based on weight-based dosage schemes:

- Weight-based dosing should be used in patients ages < 18 years who are < 40 kg;
- For children who are ≥ 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 dosage regimens is needed in order to avoid exceeding the recommended maximum adult dose;
- Clinicians should consider pharmacokinetic analysis for adjusting medications whenever possible in overweight/obese children to ensure the most effective and safe regimen.

The prevalence of overweight/obese children has reached an epidemic level in the United States.

Weight-based dosing is the most common scheme in determining medication dosage in children. The PPAG acknowledges that although studies continue to examine dosing strategies in obese children, overall limited data are available in this population. The PPAG continues to support research efforts to evaluate therapeutic agents in obese/overweight children.

## ARTICLE INFORMATION

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