Drug Dosing in Obese Children

Challenges and Evidence-Based Strategies

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KEYWORDS

• Pharmacokinetics • Pharmacodynamics • Obese children • Model-informed doing • Prediction in pharmacology

KEY POINTS

- Pathophysiologic alterations associated with obesity can predict changes in the pharmacokinetics and pharmacodynamics of drugs, but drug-specific properties, disease progression, and other comorbidities also need to be considered.
- Appropriate weight-based descriptors serve as important factors for estimating critical pharmacokinetic parameters as part of dose calculations.
- Future research should focus on pediatric population pharmacokinetic/pharmacodynamic studies to allow evidence-based dosing in obese children.

INTRODUCTION

The incidence of overweight and obesity is rising at an alarming rate around the world. Within the United States, the prevalence of obesity increased from less than 15% in the 1990s to more than 36% in 2010 according to the data obtained from the US Centers for Disease Control and Prevention (CDC). An estimated 1.1 billion individuals will be obese worldwide by 2030 if the current trend persists.[1] In 2013, the American Medical Association officially redefined obesity as a disease.

Disclosure Statement: None of the authors declared a conflict of interest.
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Pediatr Clin N Am 64 (2017) 1417–1438
http://dx.doi.org/10.1016/j.pcl.2017.08.011 **pediatric.theclinics.com**

Obesity is associated with a variety of pathophysiologic changes and has an etiology that encompasses behavioral and genetic factors. Childhood obesity often continues into adulthood, because it is greatly impacted by environment and habit. Obesity in children is commonly defined as a body mass index (BMI) above the 95th percentile of specific age and sex according to CDC growth charts. This classification differs slightly from the current definition by the World Health Organization, which states a BMI of greater or equal than 2 times the standard deviation of the average BMI for age and sex (equal to approximately the 97th percentile in the CDC charts). Per the 2014 CDC update, 1 in 6 children and adolescents in the United States is obese.

In recent years, specific pediatric drug information has been progressively implemented in drug labels under the initiatives of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. In 2012, the US Food and Drug Administration launched the New Pediatric Labeling Information Database, which simplifies the search of drugs with pediatric information based on trade and generic name or indication. At present, there are 684 drug labels with pediatric study data available, which include 619 labels of small molecule drugs and 65 of biologics.

Currently, US Food and Drug Administration labels lack information for appropriate use in obese children or obese patients in general. This is in part due to a limited number of obese children participating in clinical studies, and the lack of demand for inclusion of obese subjects in clinical trials, except for studies specifically addressing obesity related indications. However, owing to the high incidence of childhood obesity, it is increasingly common for clinicians to face important treatment and dosing decisions for this population.[2] The absence of studies or surveillance data in obese subjects not only impedes the ability of clinicians to appropriately dose, but also compromises the safety and efficacy of drug administration in this growing population.

Obesity is a complex, multifactorial disease that can be either primary or secondary. Besides the alteration in body composition, obesity-associated underlying conditions are causing changes in drug disposition and clinical responses, which compromise pharmacologic treatment in many diseases.[3–5] In this article, we discuss how the drug pharmacokinetics (PK) and disease-specific response to therapy are modified by obesity. In addition, evaluation and suggestions for the dosing of drugs in obese pediatric subjects including current evidence-based dosing strategies, are being discussed.

OBESITY AND CHANGES IN DRUG DISPOSITION

Obesity-Induced Physiologic and Pathologic Changes

Prominent changes as part of obesity are disproportional body weight gain with a significantly increased ratio of fat to lean body mass. These changes are highly and positively correlated with BMI.[6] Obesity is accompanied by numerous physiologic and pathologic alterations, such as increased cardiac output and circulating blood volume, reduced tissue perfusion, and altered liver and kidney function.[7–9] These changes are likely to influence drug disposition and pharmacologic effects. **Table 1** summarizes the potential effects of obesity related changes in body composition and physiology on drug PK and pharmacodynamics (PD). Changes in drug disposition can be characterized by a number of PK parameters, such as bioavailability (F), total body clearance (CL), volume of distribution (V_d), and absorption rate (K_a). These PK parameters, together with the maximum or peak (C_{max}) and minimum or predose trough concentrations (C_{trough}) and the area under the concentration-time curve characterize the extent and duration of drug exposure, and provide an indication whether obese patients are underexposed or overexposed compared with nonobese patients.