Review Article

Gaps in Drug Dosing for Obese Children: A Systematic Review of Commonly Prescribed Emergency Care Medications

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ABSTRACT

Purpose: Approximately 1 of 6 children in the United States is obese. This has important implications for drug dosing and safety because pharmacokinetic (PK) changes are known to occur in obesity due to altered body composition and physiologic mechanisms. Inappropriate drug dosing in an emergency setting can limit therapeutic efficacy and increase drug-related toxic effects for obese children. Few systematic reviews examining PK properties and drug dosing in obese children have been performed.

Methods: We identified 25 emergency care drugs from the Strategic National Stockpile and Acute Care Supportive Drugs List and performed a systematic review for each drug in 3 study populations: obese children (2–18 years of age), normal weight children, and obese adults (aged >18 years). For each study population, we first reviewed a drug's Food and Drug Administration label and then performed a systematic literature review. From the literature, we extracted drug PK data, biochemical properties, and dosing information. We then reviewed data in 3 age subpopulations (2–7 years, 8–12 years, and 13–18 years) for obese and normal weight children and by route of drug administration (intramuscular, intravenous, oral, and inhaled). If sufficient PK data were not available by age and route of administration, a data gap was identified.

Findings: Only 2 of 25 emergency care drugs (8%) contained dosing information on the Food and Drug Administration label for obese children and adults compared with 22 of 25 (88%) for normal weight children. We found no sufficient PK data in the literature for any of the emergency care drugs in obese children. Sufficient PK data were found for 7 of 25 emergency care drugs (28%) in normal weight children and 3 of 25 (12%) in obese adults.

Implications: Insufficient information exists to guide dosing in obese children for any of the emergency care drugs reviewed. This knowledge gap is alarming, given the known PK changes that occur in the setting of obesity. Future clinical trials examining the PK properties of emergency care medications in obese children should be prioritized. (*Clin Ther.* 2015;37:1924–1932)

Key words: obesity, children, pharmacokinetics, emergency care.

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INTRODUCTION

Childhood obesity has reached epidemic proportions in the United States. [1-3] Approximately 1 of 6 US children or adolescents has a body mass index for age and sex >95th percentile and is considered obese.[2] Since 1980, the prevalence of childhood obesity has nearly tripled.[3] Obese children require more frequent and more complex medical interventions given their increased rate and severity of multiple disease states.[4-9]

Obesity changes body composition and physiologic mechanisms: obese persons have increases in lean body mass,[10] fat mass,[11] and proportion of extracellular water to total body water.[12] Obesity also increases blood volume,[13] cardiac output,[14] and renal blood flow.[15,16] These changes can alter pharmacokinetic (PK) parameters, such as V_d, clearance (CL), and drug absorption,[17-19] resulting in important implications for drug dosing and tolerability in obese children.

Dosing obese individuals using traditional body size measurements or drug physiochemical profiles is unreliable.[20] Reduced survival in obese children after cardiopulmonary resuscitation may be a result of these suboptimal dosing strategies.[21] Conversely, inappropriately high drug dosing for obese children could result in significant toxic effects. Dosing epinephrine by total weight during a cardiac arrest in an obese child, for example, could result in an overdose given its linear PK properties.[22]

Few systematic reviews examining PK properties and drug dosing in obese children have been performed,[20,23,24] and all have concluded that more information is needed to effectively dose obese children. In an emergency setting, many commonly used drugs administered by weight may be dosed inaccurately resulting in therapeutic failure or significant toxicity, and possibly death. We aimed to determine which drugs used in pediatric emergency care have been adequately studied or labeled for use in obese children.

METHODS

We identified 25 emergency care drugs from the Strategic National Stockpile[25] and Acute Care Supportive Drugs List.[26] The Strategic National Stockpile is a national repository of medicine and medical supplies managed by the Centers for Disease Control and Prevention for use in public health emergencies. The Acute Care Supportive Drugs List is managed by the Chemical Hazards Emergency Medical Management website for use by health care professionals in the setting of a mass-casualty incident. We identified emergency care drugs for review on the basis of their frequency of use and potential indication for children in a national emergency.

We performed a systematic review of available data for each drug. Each step of the review process was performed by one reviewer and verified by another reviewer with the necessary expertise in data management, PK analysis, drug development, and regulatory affairs.

First, we reviewed each drug's Food and Drug Administration (FDA) label for dosing and indication information for 3 study populations: obese children (2–18 years of age), normal weight children, and obese adults (aged >18 years). On the basis of the findings from this review, each drug was sorted into one of the following categories: (1) dosing information and indication in study population provided on label, (2) dosing recommendation without indication in study population provided on label, or (3) neither dosing recommendation nor indication in study population provided on label.

Second, we conducted a systematic literature review for each drug in the 3 study populations. We selected peer-reviewed articles from PubMed and Embase using a uniform search strategy defined in collaboration with librarians at Duke University Medical Center Library and the National Library of Medicine. We included the following search terms: *pharmacokinetics, pharmacodynamics, medication, dosing, dose, dosage, overweight, obesity,* and *obese*. From the literature, we extracted drug PK data, biochemical properties, and dosing information, as well as basic study characteristics (sample size, number of PK samples per patient, and analysis type [eg, population PK properties, noncompartmental analysis]).

Third, we reviewed all collected data for each drug separately in the following subpopulations: obese children aged 2 to 7 years, obese children aged 8 to 12 years, obese children aged 13 to 18 years, nonobese children aged 2 to 7 years, nonobese children aged 8 to 12 years, nonobese children aged 13 to 18 years, and obese adults (aged >18 years). When applicable, we further stratified drugs by route of administration (intramuscular, intravenous, oral, and, rarely, inhaled). We considered data in each category sufficient for current dosing recommendations if PK parameters (V_d, CL, and half-life) were known and derived from data in at least 6 individuals in a defined age group. A data gap was identified if no PK parameters were identified or there were <6 individuals in a defined age group.