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

Stevie Rowe, MD[a], **David Siegel, MD**[b], and **Daniel K. Benjamin Jr., MD, PhD, MPH**[a,c] **on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Administrative Core Committee**[*]

[a]Department of Pediatrics, Duke University, Durham, North Carolina [b]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda Maryland [c]Duke Clinical Research Institute, Durham, North Carolina

Abstract

Purpose—Approximately 1 out of 6 children in the United States is obese. This has important implications for drug dosing and safety, as pharmacokinetic (PK) changes are known to occur in obesity due to altered body composition and physiology. Inappropriate drug dosing can limit therapeutic efficacy and increase drug-related toxicity for obese children. Few systematic reviews examining PK and drug dosing in obese children have been performed.

Methods—We identified 25 acute 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. For each study population, we first reviewed a drug's Food and Drug Administration (FDA) label, followed by 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, by mouth, and inhaled). If sufficient PK data were not available by age/route of administration, a data gap was identified.

Corresponding author: Daniel K. Benjamin, Jr., MD, PhD, MPH, Kiser-Arena Professor of Pediatrics, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC 27710; phone: (919) 668-8295; Danny.Benjamin@dm.duke.edu.

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CONFLICTS OF INTEREST

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

Implications—Insufficient information exists to guide dosing in obese children for any of the acute 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 of acute care medications in obese children should be prioritized.

Keywords

obesity; children; pharmacokinetics; acute care

Introduction

Childhood obesity has reached epidemic proportions in the United States [1–3]. Approximately 1 out of 6 American 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 physiology: 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 volume of distribution (Vd), clearance (CL), and drug absorption [17–19], resulting in important implications for drug dosing and safety in obese children.

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

Few systematic reviews examining the PK and drug dosing in obese children have been performed [20, 23, 24], and all have concluded that more information is needed to safely and effectively dose obese children. We aimed to identify drugs used in pediatric emergency care and to determine which have been adequately studied or labeled for use in obese children.

Methods

We identified 25 acute care drugs from the Strategic National Stockpile (SNS) [25] and Acute Care Supportive Drugs List [26]. The SNS is a national repository of medicine and

medical supplies managed by the Centers for Disease Control and Prevention for use in public health emergencies. An Acute Care Supportive Drugs List is managed by the Chemical Hazards Emergency Medical Management website for use by healthcare professionals in the setting of a mass-casualty incident. We identified acute care drugs for review based on 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 a second reviewer with the necessary expertise in data management, PK, 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. Based on 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.

Next, 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 [e.g. population PK, non-compartmental analysis]).

Lastly, we reviewed all collected data for each drug separately in the following subpopulations: obese children ages 2–7 years; obese children ages 8–12 years; obese children ages 13–18 years; non-obese children ages 2–7 years; non-obese children ages 8–12 years; non-obese children ages 13–18 years; and obese adults (>18). When applicable, we further stratified drugs by route of administration (intramuscular [IM], intravenous [IV], by mouth [PO], and, rarely, inhaled [INH]). We considered data in each category sufficient for current dosing recommendations if PK parameters (Vd, CL, and half-life) were known and derived from data in at least 6 subjects in a defined age group. A data gap was identified if no PK parameters were identified or there were <6 subjects in a defined age group.

Results

The results of our FDA label review for all 25 acute care drugs in each of the 3 study populations are summarized in Table 1. Of the 25 drugs, only acyclovir and gentamicin had dosing information for obese children in the FDA label. The label for acyclovir recommends dosing obese children based on ideal body weight (IBW). The label for gentamicin recommends dosing obese children based on lean body mass (LBM). Categorization of the

acute care drugs based on dosing and indication information provided is summarized in Table 2.

The numbers of subjects for which PK data are available for each age/route of administration are provided in Table 3. We found no sufficient PK data for any of the acute care drugs in obese children. We found sufficient PK data for 7/25 (28%) acute care drugs in normal weight children: IV ceftazidime ages 2–12 years; PO ciprofloxacin ages 2–18 years and IV ciprofloxacin ages 13–18 years; IM gentamicin ages 2–18 years; IV and PO levofloxacin ages 2–12 years; IV amphotericin ages 2–7 years; PO acyclovir ages 2–7 years; and PO oseltamivir ages 2–18 years. We found sufficient PK data for 3/25 (12%) acute care drugs in obese adults: IV ceftazidime, IV levofloxacin, and PO oseltamivir.

Discussion

The lack of sufficient data to guide acute care drug dosing in obese children is alarming. Federal legislation and the FDA require that drugs be tested for safety and efficacy. Before most drugs are approved for clinical use, they must be tested in the specified population, at the specified dose, and for a specified amount of time. Clinical, ethical, and logistical challenges have prevented the testing of many drugs in children. This has led to the common use of “off-label” or unauthorized drugs in children [22–28], which has been associated with an increased incidence in adverse drug reactions [29, 30]. The Best Pharmaceuticals for Children Act, established in 2002 and most recently renewed in 2012, provides mechanisms for studying on- and off-patent drugs in children and has established a program for pediatric drug development through the National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Despite this legislation, obese children remain largely understudied.

Given the prevalence of childhood obesity, the paucity of PK data in this population is concerning. A systematic review of PK studies in obese children was conducted in 2014 and found only 20 studies (21 drugs) over a course of 40 years [23]. While many showed important obesity-related changes in PK, they were limited by small sample sizes, and many of the drugs were not commonly prescribed agents. A review in 2010 found only 10 drugs with available PK data in obese children and concluded that extrapolation from adult data could be made if the effects of a child’s growth and development on PK parameters were considered [31]. However, simple extrapolation from adult studies has been shown to be inaccurate when attempting to predict CL and other PK parameters in children due to maturational differences surrounding enzyme expression and activity, as well as drug elimination and metabolizing pathways [32].

PK alterations occur in the setting of obesity secondary to changes in body composition and physiology. Obese children have increases in lean body mass [10], fat-free mass/fat mass/mineral [11, 27], extracellular water proportion [12], and increased drug-metabolizing enzymatic activity [28]. In adults, obesity has also been shown to increase blood volume [12], cardiac output [13], and renal blood flow [14, 15]. Although increased cardiac output and alterations in enterohepatic circulation have been shown to increase drug absorption in

obesity [29], other studies suggest that absorption is not significantly altered in the setting of obesity. [19].

The principle PK parameter altered in obesity is Vd [30–32], which is determined by the physiochemical properties of a drug, such as lipophilicity and protein binding [30]. Studies have shown that hydrophilic compounds should be dosed according to IBW, given their relatively small Vd [33–35]. This can be explained by the premise that hydrophilic compounds are expected to remain in the intravascular space and bind less to adipose tissue, making their Vd lower and potentially placing children at risk for overdose. In contrast, there is an expected affinity of lipophilic compounds to adipose tissue, making their Vd higher and potentially necessitating increased dosing. This relationship between a drug's lipophilicity and its distribution to adipose tissue has not been shown to be consistent with certain highly lipophilic drugs. For example, a study found that β-blockers bind with greater affinity to lean tissue rather than adipose tissue [36]. Overall, lipophilic compounds seem to display much greater PK variability in obese subjects and should not be dosed with only physicochemical properties in mind [36, 37]. Altered metabolic activity can occur as result of fatty infiltration of the liver in obese individuals [33], although this has been difficult to study [19]. Also, the increased size, perfusion, and glomerular filtration [17] of the kidneys seen in obesity may alter renal elimination [16].

Body size measurements have been used in the absence of dosing recommendations in obese children. Unlike their normal weight counterparts who are typically dosed by kg of TBW, other measurements such as IBW, LBM, and body surface area have been used to better correlate with Vd and CL to achieve a more accurate and desired exposure [30]. However, a study evaluating the PK of antimicrobials in obese children concluded that traditional body size measures used for drug dosing in obese children do not account for potential changes in CL mechanisms, such as drug-metabolizing enzyme activity and renal function [20].

Previously, drug LogP was considered an important determinant of drug distribution in obese patients [17], but it was recently found that PK alterations in obesity were not predicted by this or Biopharmaceutics Drug Disposition Classification System (BDDCS) [23]. The BDDCS takes into consideration both the extent of metabolism and solubility, and may help predict routes of elimination, the role of drug transporters in the gut and liver, and the transporter-enzyme interplay [38]. Although the analysis was limited by a small amount of PK data, it seems that Vd and CL in obese children are affected by other drug-specific factors such as metabolic pathways and routes of absorption and elimination [23].

The known alterations that occur in obese individuals have the potential to result in inappropriate drug dosing, which can limit therapeutic efficacy. For example, obese children who suffer a cardiac arrest are 25% more likely to die than are their non-obese counterparts. Although this increase in mortality is likely multifactorial [21], inappropriate dosing is likely to be an important component. Several examples include: 1) use of the Broselow tape has resulted in under-dosing of select drugs such as amiodarone [39]; 2) obese children had a decreased response to calcium channel blockers when provided similar mg/m2 dosing [40]; and 3) dosing based on actual weight for an obese patient during a cardiac arrest can also result in significant over-dosing (e.g., epinephrine) [22].

Obesity is a risk factor for antibiotic treatment failure (ATF) that may result from a "one size fits all" dosing strategy [41]. In a comprehensive PK review of antibiotic dosing in adults, it was found that modifications in Vd and CL generally result in less-than-optimal drug concentrations in the blood and tissue for the most commonly prescribed antibiotic classes and indications [42]. While extrapolation from adult studies has proven to be inaccurate for children [32], the PK changes known to occur in obese children make ATF a plausible and important consideration when dosing antibiotics.

Overall, we found significant data gaps for the majority of acute care drugs in our review, with obese children being the population most affected. None of the acute care drugs we chose has been adequately studied or labeled for appropriate use in obese children—a knowledge gap that is alarming and has important implications as obesity has reached epidemic proportions. Future clinical trials examining the PK of acute care medications in obese children should be prioritized.

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The Pediatric Trials Network Administrative Core Committee

Katherine Y. Berezny, Duke Clinical Research Institute, Durham, NC; Edmund Capparelli, University of California–San Diego, San Diego, CA; Michael Cohen-Wolkowiez, Duke Clinical Research Institute, Durham, NC; Gregory L. Kearns, Children's Mercy Hospital, Kansas City, MO; Matthew Laughon, University of North Carolina at Chapel Hill, Chapel Hill, NC; Andre Muelenaer, Virginia Tech Carilion School of Medicine, Roanoke, VA; T. Michael O'Shea, Wake Forest Baptist Medical Center, Winston Salem, NC; Ian M. Paul, Penn State College of Medicine, Hershey, PA; P. Brian Smith, Duke Clinical Research Institute Durham, NC; John van den Anker, George Washington University School of Medicine and Health, Washington, DC; Kelly Wade, Children's Hospital of Philadelphia, Philadelphia, PA; Thomas J. Walsh, Weill Cornell Medical College of Cornell University, New York, NY.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development: David Siegel, Perdita Taylor-Zapata, Anne Zajicek, Alice Pagan

The Emmes Corporation (Data Coordinating Center): Ravinder Anand, Gina Simone

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Table 1

FDA label review of priority drugs

Drug Class	Drug Name	Dosing			Indication		
		Obese Children	Normal Weight Children	Obese Adults	Obese Children	Normal Weight Children	Obese Adults
Antibiotic	Amoxicillin-clavulanate		x			x	
	Ceftazidime		x				
	Cidofovir					x	
	Ciprofloxacin		x			x	
	Gentamicin	x[a]	x	x[a]			
	Levofloxacin		x			x	
	Raxibacumab		x			x	
Antifungal	Amphotericin		x				
	Fluconazole		x			x	
Antiviral	Acyclovir	x[a]	x	x[a]		x	
	Oseltamivir		x			x	
	Probenacid		x				
	Rimantadine		x			x	
	Zanamivir		x			x	
Chemical	Sodium thiosulfate		x				
Radiation	Calcium diethylenetriamine pentaacetate		x				
	Neupogen						
	Prussian blue		x				
	Zinc diethylenetriamine pentaacetate		x				
Supportive	Calcium chloride		x			x	
	Diphenhydramine		x				
	Ipratropium		x			x	
	Magnesium sulfate		x			x	
	Oxycodone/acetaminophen						

Drug Class	Drug Name	Dosing			Indication		
		Obese Children	Normal Weight Children	Obese Adults	Obese Children	Normal Weight Children	Obese Adults
	Promethazine		x			x	

[a] Gentamicin dosing is by lean body weight. Acyclovir dosing is by ideal body weight.

Table 2

Drug categories

	Obese Children	Normal Weight Children	Obese Adults
Dosing + indication	0/25	13/25 (52%)	0/25
Dosing	2/25 (8%)	9/25 (36%)	2/25 (8%)
Neither	23/25 (92%	2/25 (8%)	23/25 (92%)

Table 3

Acute care drug gaps

Drug Class	Drug Name	Route of Administration	Study Population						
			Obese Children			Normal Weight Children			Obese Adults
			2–7 years	8–12 years	13–18 years	2–7 years	8–12 years	13–18 years	>18 years
Antibiotic	Amoxicillin-clavulanate	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	0	0	0	0	0	0	0
	Ceftazidime	IM	0	0	0	0	0	0	0
		IV	0	0	0	16	13	0	49
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Cidofovir	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Ciprofloxacin	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	7	0
		PO	0	0	0	16	6	12	0
	Gentamicin	IM	0	0	0	92	24	20	0
		IV	0	0	0	N/A	N/A	N/A	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Levofloxacin	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	7	7	0	25
		PO	0	0	0	8	8	0	0
	Raxibacumab	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Antifungal	Amphotericin	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	7	0	0	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Fluconazole	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0

Drug Class	Drug Name	Route of Administration	Study Population						
			Obese Children			Normal Weight Children			Obese Adults
			2–7 years	8–12 years	13–18 years	2–7 years	8–12 years	13–18 years	>18 years
		PO	0	0	0	0	0	0	0
Antiviral	Acyclovir	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	0	0	0	16	0	0	0
	Oseltamivir	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	0	0	0	14	8	8	72
	Probenacid	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	0	0	0	0	0	0	0
	Rimantadine	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	0	0	0	0	0	0	0
	Zanamivir	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		INH	0	0	0	0	0	0	0
Chemical	Sodium thiosulfate	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Radiation	Calcium diethylenetriamine pentaacetate	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	0	0	0	0	0	0	0
	Neupogen	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Prussian blue	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Drug Class	Drug Name	Route of Administration	Study Population						
			Obese Children			Normal Weight Children			Obese Adults
			2–7 years	8–12 years	13–18 years	2–7 years	8–12 years	13–18 years	>18 years
		PO	0	0	0	0	0	0	0
	Zinc diethylenetriamine pentaacetate	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	0	0	0	0	0	0	0
Supportive	Calcium chloride	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	0	0	0	0	0	0	0
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	Diphenhydramine	IM	0	0	0	0	0	0	0
		IV	0	0	0	0	0	0	0
		PO	0	0	0	0	0	0	0
	Ipratropium	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		INH	0	0	0	0	0	0	0
	Magnesium sulfate	IM	0	0	0	0	0	0	0
		IV	0	0	0	0	0	0	0
		PO	0	0	0	0	0	0	0
	Oxycodone/acetaminophen	IM	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		IV	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PO	0	0	0	0	0	0	0
	Promethazine	IM	0	0	0	0	0	0	0
		IV	0	0	0	0	0	0	0
		PO	0	0	0	0	0	0	0

IM = intra-muscular; INH = inhaled; IV = intravenous; N/A = not applicable; PO = by mouth.