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Product Labeling of Drugs Commonly Administered to Children and Adults with Obesity

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Abstract

Obesity is a major public health problem that can affect drug disposition and dosing, particularly in vulnerable pediatric populations. Despite potentially detrimental consequences from inappropriately dosed drugs in children with obesity, drug product labels largely fail to include dosing or guidance specific to this population. Failure to include this information results in an increased incidence of adverse events, and concerns from treating physicians regarding their ability to provide appropriate care for children with obesity. Using data from the National Institute of Child Health and Human Development-funded Pediatric Trials Network (PTN), we explore possible ways to improve drug labeling in children with obesity. In order to improve health outcomes of children with obesity, carefully designed and executed PK trials and comprehensive PK analysis strategies are needed. Early collaboration with the Food and Drug Administration may be helpful in developing studies and analyses that are most beneficial for child health. This collaboration is particularly important for drugs that treat potentially life-threatening diseases, where inclusion of PK and dosing on the drug label is vital. We hope that increasing the body of knowledge on drug dosing in children with obesity will open the door to regulatory guidance based on extrapolation or population-specific PK studies, similar to other currently-recognized special populations. Given the magnitude of the pediatric obesity pandemic, recognition as a special population will offer substantial public health value.

Keywords: Pharmacokinetic data; Obese children; Drug dosing; FDA; EMA

Abbreviations: BMI: Body Mass Index; CDC: Centers for Disease Control; CER2: Comparative Effectiveness Research Through Collaborative Electronic Reporting; EMA: European Medicines Agency; FDA: Food and Drug Administration; PCORnet: National Patient-Centered Clinical Research Network; PK: Pharmacokinetic; PTN: Pediatric Trials Network; US: United States; WHO; World Health Organization; EMA: European Medicines Agency

Introduction

According to the World Health Organization (WHO), childhood obesity is "one of the most serious public health challenges of the 21st century" [1]. In the United States (U.S.), >12.7 million (17%) children ages 2-19 years of age are obese as determined by a body mass index (BMI) ≥ 95th percentile on the Centers for Disease Control and Prevention (CDC) BMI-for-age growth charts with some metropolitan areas estimating a prevalence of up to 30% [2,3]. Such pervasiveness indicates the need to routinely consider obesity in all matters involving child health. One of the possible side effects of obesity can be altered drug disposition. Observed changes in drug disposition include: increased total body water and lipids from adipose tissue, resulting in increased volume of distribution; increased serum concentrations of alpha-1-acid glycoprotein and lipoproteins, resulting in increased protein binding and altered drug elimination; increased or decreased hepatic metabolism of drugs and increased renal clearance of drugs eliminated by glomerular filtration (Figure 1) [4-7]. When a child with obesity receives a drug dosed for a child with a normal BMI, altered disposition can render a drug ineffective or toxic. In turn, ineffective or toxic drugs can result in adverse patient outcomes, including death [8,9]. Despite potentially detrimental consequences from inappropriately-dosed drugs in children with obesity, drug product labels largely fail to include dosing or guidance specific to this population [10-12]. Administration of drugs that lack pediatric dosing information in product labels has been associated with inappropriate dosing, increased incidence of adverse events, and concerns from treating physicians regarding inability to provide appropriate care [13-15]. For children with obesity and their medical providers, issues associated with incomplete product labels are only further exacerbated by limited availability of pediatric formulations that optimize drug concentrations in manageable palatable volumes for children with obesity. Such issues can contribute to under-dosing and drug non-compliance, resulting in especially dire consequences for children administered drugs to treat life-threatening or life-altering diseases such as epilepsy. Multiple phenomena explain the lack of product labeling to guide dosing in children with obesity, including limited existence of the following factors: 1) pharmacokinetic (PK) data collected from children with obesity to inform dosing; 2) knowledge of complex analysis methods necessary to evaluate PK in children; 3) product labeling specific to adults with obesity or children without obesity; and 4) lack of Food and Drug Administration (FDA) or European Medicines Agency (EMA) guidance for the conduct of drug trials in children with obesity. In this manuscript, we expand on the existing barriers to product labeling in children with obesity and offer potential solutions based on the experience of the Pediatric Trials Network (PTN), which is a National Institute of Child Health and Human Development-funded research network conducting off-patent therapeutic trials for regulatory labeling in children. We propose two strategic avenues to increase drug labeling in children with obesity: the first uses the concept of extrapolation, which leverages data from adults with obesity or children without obesity; the second uses PK data from children with obesity to supplement existing pediatric indications.

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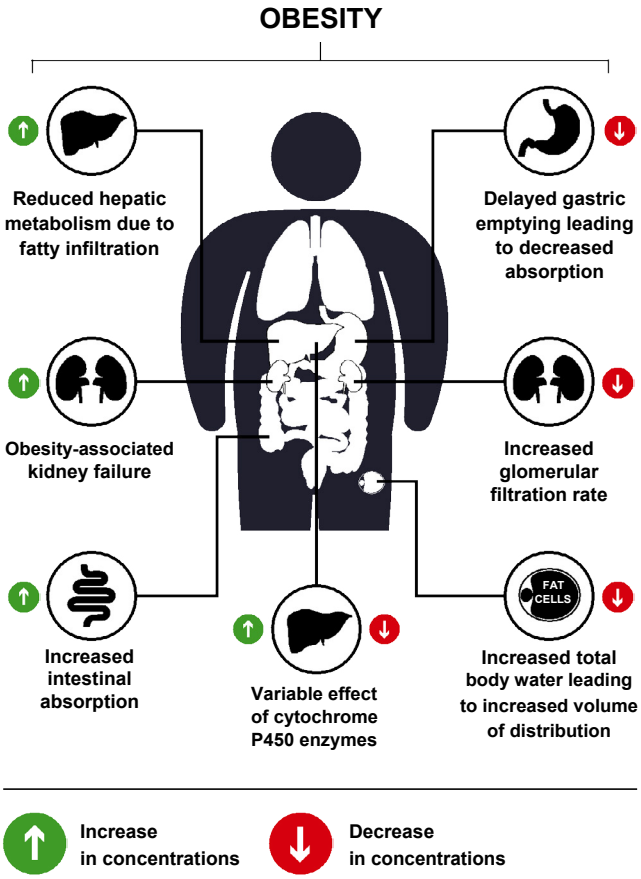

Figure 1: Obesity-associated Effects on various bodily functions.

Lack of PK Data in Children with Obesity to Inform Dosing

PK trials in children with obesity are clearly needed to inform dosing in this population. The conduct of pediatric PK trials is difficult due to limited numbers of eligible children, low parental consent rates, limited available blood volume in children compared to adults, and difficulties obtaining timed blood samples [16]. These issues of trial conduct are true for most pediatric clinical trials, but are often more complex in children with obesity [10,11]. Potential roadblocks to trial conduct in children with obesity largely relate to participant enrollment barriers. First, although childhood obesity is widespread, urban residence and associated low income and educational attainment are important risk factors; these same factors have also been associated with lower access to healthcare and lower willingness or ability to participate in clinical trials [17,18]. Second, obesity is stigmatized, so parents often misperceive a child's actual weight; consequently, parents may be unwilling to allow children to participate in clinical trials specific to obese populations [19]. Furthermore, revealing an obesity diagnosis during the process of informed consent could result in psychological distress. These challenges require proactive organization and consideration when designing much-needed PK trials. Collaboration with clinical sites that have active research or intervention programs on childhood obesity could be beneficial. Integrating PK trials in the context of existing programs increases the likelihood of enrollment and enables an adequate number of samples per participant to be collected. Additionally, integration improves the likelihood that an investigator will be more sensitive to the psychological morbidity associated with an obesity diagnosis. As a complimentary approach, investigators should engage parents and child obesity advocacy groups to identify best practices for sensitivity and communication regarding issues such as informed consent.

Complexity of PK Analysis Methods

Characterizing PK across the pediatric age and disease continuum is difficult but complicated further by obesity in children [20]. For example, the most appropriate definition of obesity for pediatric PK analysis remains controversial. In the U.S., obesity is generally defined as a BMI $\geq 95^{th}$ percentile according to age and sex classification; however, for PK evaluation, body composition (including proportions of body fat) may be a more specific determinant of drug disposition than body size alone. Data regarding the adequacy of BMI as a measure of excess body fat are mixed. Some sources cite good correlation (r=0.78-0.88) of BMI with skinfold thickness, bioelectrical impedance, densitometry, and dual energy x-ray absorptiometry (i.e., the gold standard measurement) [21-23]. Other studies suggest that a combination of factors such as BMI and waist circumference more accurately predict adiposity; measures such as waist-to-hip or waist-to-height ratio may better correlate with clinical outcomes than BMI [24,25]. To date, these anthropometric measures have undergone limited evaluation in relation to pediatric drug PK [23]. Calculated size descriptors (e.g., total body weight, lean body mass, ideal body weight, fat-free mass) are most frequently used in PK analyses of obesity; these descriptors have yielded variable results with regard to drug exposures in children with obesity compared to controls (Table 1) [11]. Partly because of issues of variability, not only for obesity, but also for pediatric PK modeling in general, some have advocated for a more standardized approach to the base PK model prior to consideration of factors such as obesity. Such an approach would combine allometric weight scaling and a sigmoid function to account for organ maturation and related changes in clearance across the pediatric age continuum. Regardless of which approach is chosen, PK analyses in children with obesity are complex, and are most often successful when performed by groups with extensive expertise in the most complex PK modeling techniques [26-32]. Based on our experience, PK analyses in children with obesity should incorporate various definitions of obesity and analysis methods. We recently investigated the PK of a single dose of intravenous pantoprazole administered to children and adolescents 6 to <18 years of age with a BMI $\geq 95^{th}$ percentile for age and sex according to CDC criteria, and a confirmed diagnosis of gastrointestinal reflux disease [32]. We collected timed PK samples, gathered waist-to-hip ratios, and assembled resting energy expenditures. We developed a population PK model, evaluating total body weight, lean body mass, free fat mass, and nonfat mass as covariates, and explored relationships between PK parameters and other markers of adiposity. Using these methods, we identified that in children with obesity by BMI (compared to those without), pantoprazole clearance and volume of distribution were significantly lower, whereas systemic exposure was significantly higher. Consequently, we recommended dosing based on lean body weight [32]. We have taken similar approaches to PK analyses of clindamycin and methadone in children with obesity. For clindamycin, we identified total body weight dosing as sufficient for children with and without obesity receiving treatment for skin and soft tissue infections [26]. For methadone, clearance was markedly reduced for children with obesity compared to those of normal weight; however, similar dosing resulted in a therapeutic range of concentrations for both lean and total body weight in children with and without obesity (NCT01945736) [33-46].

Drug	Dosed Per	Body Weight Measurement	Exposure in Obesity
Antimicrobials			
Clindamycin [26]	kg	TBM	Therapeutic
Tobramycin [27]	kg	ABM	Therapeutic
Cefazolin [27]	kg	ABM	Therapeutic
Gentamicin [28]	kg	ABM	Therapeutic
Vancomycin [29-31]	kg	TBM TBM	Subtherapeutic [29,31] Therapeutic [30]
Other			
Pantoprazole [32]	kg	TBM	Supratherapeutic
Methadone*	kg	TBM	Therapeutic
Mercaptopurine [33]	m^2	TBM	Subtherapeutic
Teniposide [34]	kg	TBM	Therapeutic
Methotrexate [34]	m^2	TBM	Therapeutic
Cytarabine [34]	m^2	TBM	Therapeutic
Theophylline [35]	kg	TBM	Not available
Busulfan [36]	kg	TBM	Supratherapeutic
Divalproex sodium [37]	kg	TBM ABM	Supratherapeutic Therapeutic
Doxorubicin [38,39]	kg [24] m^2 [35]	TBM ABM	Therapeutic
Etoposide [34,39]	m^2; m^2	TBM; ABM	Therapeutic
Cyclosporine [40]	kg	ABM	Therapeutic
Propofol [40]	kg	ABM	Therapeutic
Acetaminophen [41]	Fixed dose	n/a	Therapeutic
Carbamazepine [42,43]	Fixed dose	n/a	Therapeutic [43]
Valproic acid [43]	Fixed dose	n/a	Therapeutic

ABM, adjusted body mass; *LBM*, lean body mass; *TBM*, total body mass
* Methadone is a PTN product, but not yet published.

Table 1: Body Weight Measurement and Effect on Drug Exposure in Children.

Limited Drug Product Labeling for Adults with Obesity

Despite the prevalence of obesity nearing 30% among adults and known associations between obesity and diseases that require lifelong drug administration, a review of multiple FDA labels suggests that obesity-specific information is also lacking in adult drug labels [47]. This omission is significant because drug labeling in children often depends on that in adults to establish initial dosing [48]. Although labeling of drug products for adults with obesity has not been a major focus for drug manufacturers and likely contributes to absence of label information for children with obesity, some dosing data in adults is available. Academic investigators have evaluated PK in obese adults for multiple drug products, including carbamazepine, midazolam, inhaled anesthetics, ibuprofen, phenytoin, diazepam, voriconazole, amiodarone, lorazepam, ciprofloxacin and propofol among others [42,49-58]. Unfortunately, publication of drug dosing recommendations in obese adults without regulatory submission for labeling has not consistently translated into improved clinical practice and optimal patient outcomes. In a recent study of more than 18,000 adults presenting to an emergency department for antibiotic therapy, obesity was a significant risk factor for antibiotic treatment failure [59]. Furthermore, multiple antibiotics evaluated in this study and drug products evaluated in other studies do not have physicochemical properties traditionally considered predictive of altered drug disposition in the setting of obesity (e.g., lipophilicity) [11,59,60]. These findings underscore two important messages: first, additional PK studies are needed to evaluate the effect of obesity on the dosing of many more drug products; and second, wide dissemination of available dosing information through drug labeling and publications is paramount to change clinical practice and improve patient outcomes.

Lack of an Existing Regulatory Paradigm for Drug Labeling in Obesity

A fourth contributor to the lack of widely-disseminated guidance on dosing in obese populations is the absence of existing regulatory guidance for PK evaluation and drug labeling specific to adults or children with obesity. Multiple considerations should guide the regulatory strategy for increasing pediatric product labels. Specifically, whether explicit PK analysis methods or definitions of obesity are necessary for inclusion in pediatric product labels needs to be determined. Whether or not safety outcomes are necessary for inclusion of PK data in pediatric labels and what outcomes are required needs to be evaluated. Such evaluation should consider the availability of multiple curated sources of both inpatient and outpatient real-world pediatric data, including the National Patient-Centered Clinical Research Network (PCORnet) and the Comparative Effectiveness Research Through Collaborative Electronic Reporting (CER2) data registries [61,62]. Requirements to collect safety data are consistent with FDA- and EMA-endorsed regulatory pathways of extrapolation in which efficacy data from obese adults or children without obesity could be used to reduce the burden of proof for pediatric labeling [63]. In addition, legislative mandates and incentives through the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act encourage using extrapolation to promote the examination of drug products in children after studying these products in adults [63]. Certainly, this strategy has been important for pediatric drug labeling, resulting in a substantial increase in new or expanded pediatric indications compared to no extrapolation [63]. To date, extrapolation has not been identified as an official regulatory pathway to update pediatric labeling with obesity-specific information. Rather, recent collaboration between the PTN and FDA has suggested more

Renal Impairment			Obesity		
Drug	**Drug Elimination Pathway**	**Magnitude of Altered PK Compared to Subjects without Renal Impairment**	**Drug**	**Physicochemical Characteristics**	**Magnitude of Altered PK Compared to Subjects without Obesity**
Paliperidone	Renal	AUC 1.5X (mild impairment); 4.8X (severe impairment) [66]	**Busulfan**	Highly lipophilic; 32% protein bound; hepatic metabolism by conjugation with glutathione [67]	Clearance 0.82X of subjects without obesity [36]
Duloxetine	Hepatic metabolism (CYP1A2, CYP2D6)	Cmax and AUC 2.0X in end-stage renal disease [66]	**Divalproex Sodium**	Moderately lipophilic; pKa 5.14; Concentration-dependent protein binding (81-90%); hepatic metabolism by glucuronidation and mitochondrial β-oxidation [67]	Usual dosing results in 1.56X drug exposure [37]
Telithromycin	Hepatic metabolism (CYP3A4 and cytochrome P450 independent)	Cmax 1.4X; AUC 1.9X in severe impairment [66]	**Acetaminophen**	Moderately lipophilic; 25% protein binding; hepatic and gut glucuronidation; sulfation; and oxidation by CYP2E1 [67]	83% decrease in volume of distribution [41]
Rosuvastatin	OATP1B1 transport; minimal CYP2C9 metabolism	Plasma concentrations 3X in end-stage renal disease [66]	**Ciprofloxacin**	Moderately lipophilic; 20-40% protein bound; 15% hepatic metabolized; renal clearance [67,68]	1.23X steady state volume of distribution [57]
PK, pharmacokinetic					

Table 2: Select Drugs with Altered PK Due to Obesity or Renal Impairment.

of a conditional approach. For drugs in which PK studies do not support a difference in dosing between children with and without obesity, supplemental data (including population-specific safety and efficacy data) may be necessary prior to negotiation of a label change. For drugs in which PK studies demonstrate a difference in dosing between children with and without obesity, negotiation of PK and dosing updates of the product label can be undertaken without supplemental safety and efficacy data. Considering the public health burden of obesity and the existing need to acquire data for hundreds of approved drug products, a standardized pathway to update product labels with obesity-specific data is important. Such a pathway could entail supplementation of an existing pediatric indication with PK data from children with obesity. This pathway is likely more efficient and equally effective as the extrapolation pathway, particularly for life-threatening or life-altering diseases for which appropriate drug dosing is vital. Supplementation of an existing pediatric indication with PK data from children with obesity could occur by designating obese persons as a special population. Precedent exists for issuing regulatory guidance to evaluate PK and dosing in special populations where PK could differ from normal physiologic state (i.e., renal impairment and hepatic dysfunction). For example, in 1998, following a marked increase in the proportion of U.S. adults with chronic kidney disease, the FDA issued draft guidance for conducting PK studies in patients with impaired renal function and representation of results in approved product labeling [64]. This original guidance recommended conduct of a PK study when the drug had a renal elimination pathway. In 2010, refined guidance recommended that PK studies be consistently conducted in persons with renal impairment, with the extent of the study being dependent upon a renal or non-renal elimination pathway [65]. Subsequently, positive, negative, or unknown results (in the event of an omitted PK study) are documented in the product label. Issuing regulatory guidance for patients with renal impairment has proven effective by increasing the number of PK studies conducted in this population. In a study evaluating the effects of the 1998 guidance, investigators identified a 15-point increase in the percentage of applications for new molecular entities submitted to the FDA that included renal impairment studies [66]. Categorizing children and adults with obesity as a special population could have the same effect. Notably, in many circumstances, the magnitude of obesity's impact on PK is similar to that observed with renal impairment, and the presence or magnitude of alteration is not always predictable based on drug elimination pathways or drug physicochemical characteristics (Table 2). Furthermore, the prevalence of adults (30%) and children (17%) with obesity in the U.S. exceeds the prevalence of chronic kidney disease (14-15%) [64,65]. Therefore, the potential public health impact of classifying obesity as a special population could be substantial, perhaps even more so than the impact observed with classifying renal impairment. Given the public health burden associated with obesity, establishing methods for product labeling and dissemination of information represents an urgent, unmet public health need. Continued, concerted efforts to improve pharmacotherapy in pediatric obesity provide unique opportunities for the field of pediatrics to pave the way in addressing the needs of children and adults with obesity.

Conclusion

Childhood obesity is a major public health burden with important implications for drug dosing. Similar to other special populations, children with obesity are at risk of drug under- or over-dosing. To reduce this risk and improve health outcomes, carefully designed and executed PK trials and comprehensive PK analysis strategies are needed. These strategies are best undertaken within the context of a collaborative network and with expertise from pediatric clinical pharmacologists experienced in obesity analyses. Since the FDA mandate regarding studies in children and adults with obesity is unclear, early collaboration with the FDA may be helpful in developing studies and analyses that are most beneficial for child health. This collaboration is particularly important for drugs that treat potentially life-threatening (e.g., epilepsy) diseases, where inclusion of PK and dosing on the drug label is vital, regardless of identified dosing and PK differences in children with and without obesity. Ultimately, we hope that increasing the body of knowledge on drug dosing in children with obesity will open the door to regulatory guidance based on extrapolation or population-specific PK studies, similar to other currently-recognized special populations. Given the magnitude of the pediatric obesity pandemic, recognition as a special population will offer substantial public health value.

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Conflicts of Interest

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References

1. World Health Organization (WHO). Global strategy on diet, physical activity and health. Childhood overweight and obesity.
2. Centers for Disease Control and Prevention (CDC), Defining childhood obesity.
3. Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, et al. (2016) Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 through 2013-2014. JAMA 315: 2292-2299.
4. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, et al. (2005) Quantification of lean bodyweight. Clin Pharmacokinet 44: 1051-1065.
5. Benedek IH, Blouin RA, McNamara PJ (1984) Serum protein binding and the role of increased alpha 1-acid glycoprotein in moderately obese male subjects. Br J Clin Pharmacol 18: 941-946.
6. Blouin RA, Warren GW (1999) Pharmacokinetic considerations in obesity. J Pharm Sci 88: 1-7.
7. Bosma RJ, Krikken JA, Homan van der Heide JJ, de Jong PE, Navis GJ, et al. (2006) Obesity and renal hemodynamics. Contrib Nephrol 151: 184-202.
8. Gales BJ, Gales MA (1995) Death associated with inappropriate ketorolac dosing. Ann Pharmacother 29: 1299.
9. Bonnel RA, Villalba ML, Karwoski CB, Beitz J (2002) Deaths associated with inappropriate intravenous colchicine administration. J Emerg Med 22: 385-387.
10. Rowe S, Siegel D, Benjamin DK Jr. (2015) Best Pharmaceuticals for Children Act - Pediatric Trials Network Administrative Core Committee. Gaps in drug dosing for obese children: a systematic review of commonly prescribed emergency care medications. Clin Ther 37: 1924-1932.
11. Harskamp-van Ginkel MW, Hill KD, Becker KC, Testoni D, Cohen-Wolkowiez M, et al. (2015) Drug dosing and pharmacokinetics in children with obesity: a systematic review. JAMA Pediatr 169: 678-685.
12. Matson KL, Horton ER, Capino AC (2017) Advocacy Committee for the Pediatric Pharmacy Advocacy Group. Medication dosage in overweight and obese children. J Pediatr Pharmacol Ther 22: 81-83.
13. Zed PJ, Black KJ, Fitzpatrick EA, Ackroyd-Stolarz S, Murphy NG, et al. (2015) Medication-related emergency department visits in pediatrics: a prospective observational study. Pediatrics 135: 435-443.
14. Ufer M, Kimland E, Bergman U (2004) Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf 13: 147-152.
15. Healio.com. Pharmacology Consult. Predicting drug dosing in obese patients can be a challenge. Infectious Diseases in Children.
16. Laughon MM, Benjamin DK, Capparelli EV, Kearns GL, Berezny K, et al. (2011) Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol 4: 643-652.
17. Brophy S, Cooksey R, Gravenor MB, Mistry R, Thomas N, et al. (2009) Risk factors for childhood obesity at age 5: analysis of the Millennium Cohort Study. BMC Public Health 9: 467.
18. Unger JM, Gralow JR, Albain KS, Ramsey SD, Hershman DL, et al. (2016) Patient income level and cancer clinical trial participation: a prospective survey study. JAMA Oncol 2: 137-139.
19. Rietmeijer-Mentink M, Paulis WD, van Middelkoop M, Bindels PJ, van der Wouden JC, et al. (2013) Difference between parental perception and actual weight status of children: a systematic review. Matern Child Nutr 9: 3-22.
20. Anderson BJ, Holford NH (2009) Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet 24: 25-36.
21. Musaad SMA, Patterson T, Ericksen M, Lindsey M, Dietrich K, et al. (2009) Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant. J Allergy Clin Immunol 123: 1321-1327.e12.
22. US Preventive Services Task Force, Barton M (2010) Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. Pediatrics 125: 361-367.
23. Boeke CE, Oken E, Kleinman KP, Rifas-Shiman SL, Taveras EM, et al. (2013) Correlations among adiposity measures in school-aged children. BMC Pediatr 13: 99.
24. Aeberli I, Gut-Knabenhans M, Kusche-Ammann RS, Molinari L, Zimmermann MB, et al. (2013) A composite score combining waist circumference and body mass index more accurately predicts body fat percentage in 6- to 13-year-old children. Eur J Nutr 52: 247-253.
25. Khoury M, Manlhiot C, McCrindle BW (2013) Role of the waist/height ratio in the cardiometabolic risk assessment of children classified by body mass index. J Am Coll Cardiol 62: 742-751.
26. Smith MJ, Gonzalez D, Goldman JL, Yogev R, Sullivan JE, et al. (2017) Pharmacokinetics of clindamycin in obese and nonobese children. Antimicrob Agents Chemother 61: pii: e02014-16.
27. Koshida R, Nakashima E, Taniguchi N, Tsuji A, Benet LZ, et al. (1989) Prediction of the distribution volumes of cefazolin and tobramycin in obese children based on physiological pharmacokinetic concepts. Pharm Res 6: 486-491.
28. Choi JJ, Moffett BS, McDade EJ, Palazzi DL (2011) Altered gentamicin serum concentrations in obese pediatric patients. Pediatr Infect Dis J 30: 347-349.
29. Nassar L, Hadad S, Gefen A, Shachor-Meyouhas Y, Mashiach T, et al. (2012) Prospective evaluation of the dosing regimen of vancomycin in children of different weight categories. Curr Drug Saf 7: 375-381.
30. Miller M, Miller JL, Hagemann TM, Harrison D, Chavez-Bueno S, et al. (2011) Vancomycin dosage in overweight and obese children. Am J Health Syst Pharm 68: 2062-2068.
31. Moffett BS, Kim S, Edwards MS (2011)Vancomycin dosing in obese pediatric patients. Clin Pediatr (Phila) 50: 442-446.
32. Shakhnovich V, Smith PB, Guptill JT, James LP, Collier DN, et al. (2018) Obese children require lower doses of pantoprazole than nonobese peers to achieve equal systemic drug exposures. J Pediatr 193: 102-108.e1.
33. Zuccaro P, Guandalini S, Pacifici R, Pichini S, Di Martino L, et al. (1991) Fat body mass and pharmacokinetics of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. Ther Drug Monit 13: 37-41.
34. Hijiya N, Panetta JC, Zhou Y, Kyzer EP, Howard SC, et al. (2006) Body mass index does not influence pharmacokinetics or outcome of treatment in children with acute lymphoblastic leukemia. Blood 108: 3997-4002.
35. Yaffe SJ, Danish M (1978) Problems of drug administration in the pediatric patient. Drug Metab Rev 8: 303-318.
36. Browning B, Thormann K, Donaldson A, Halverson T, Shinkle M, et al. (2011) Busulfan dosing in children with BMIs ≥ 85% undergoing HSCT: a new optimal strategy. Biol Blood Marrow Transplant 17: 1383-1388.
37. Good CR, Feaster CS, Krecko VF (2001) Tolerability of oral loading of divalproex sodium in child psychiatry inpatients. J Child Adolesc Psychopharmacol 11: 53-57.
38. Thompson PA, Rosner GL, Matthay KK, Moore TB, Bomgaars LR, et al. (2009) Impact of body composition on pharmacokinetics of doxorubicin in children: a Glaser Pediatric Research Network study. Cancer Chemother Pharmacol 64: 243-251.
39. Ritzmo C, Soderhall S, Karlen J, Nygren H, Eksborg S, et al. (2007) Pharmacokinetics of doxorubicin and etoposide in a morbidly obese pediatric patient. Pediatr Hematol Oncol 24: 437-445.
40. Kasap B, Soylu A, Türkmen M, Kavukçu S, Bora S, et al. (2006) Effect of obesity and overweight on cyclosporine blood levels and renal functions in renal adolescent recipients. Transplant Proc 38: 463-465.
41. Barshop NJ, Capparelli EV, Sirlin CB, Schwimmer JB, Lavine JE, et al. (2011) Acetaminophen pharmacokinetics in children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr 52: 198-202.
42. Caraco Y, Zylber-Katz E, Berry EM, Levy M (1995) Carbamazepine pharmacokinetics in obese and lean subjects. Ann Pharmacother 29: 843-847.

43. Suemaru K, Kawasaki H, Yasuhara K, Yao K, Furuno K, et al. (1998) Steady-state serum concentrations of carbamazepine and valproic acid in obese and lean patients with epilepsy. Acta Med Okayama 52: 139-142.

44. Anderson BJ, Holford NH (2017) What is the best size predictor for dose in the obese child? Paediatr Anaesth. 27: 1176-1184.

45. Germovsek E, Barker CIS, Sharland M, Standing JF (2019) Pharmacokinetic-pharmacodynamic modeling in pediatric drug development, and the importance of standardized scaling of clearance. Clin Pharmacokinet 58: 39-52.

46. Pharmacokinetics of Multiple Dose Methadone in Children Treated for Opiate Withdrawal (MTH01).

47. NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, and Treatment of Obesity in Adults (US). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. Bethesda, MD: National Heart Lung Blood Institute (1998).

48. DiMasi JA, Hansen RW, Grabowski HG (2003) The price of innovation: new estimates of drug development costs. J Health Econ 22: 151-185.

49. Greenblatt DJ, Abernethy DR, Locniskar A, Harmatz JS, Limjuco RA, et al. (1984) Effect of age, gender, and obesity on midazolam kinetics. Anesthesiology 61: 27-35.

50. Frink EJ Jr, Malan TP Jr, Brown EA, Morgan S, Brown BR Jr, et al. (1993) Plasma inorganic fluoride levels with sevoflurane anesthesia in morbidly obese and nonobese patients. Anesth Analg 76: 1333-1337.

51. Abernethy DR, Greenblatt DJ (1985) Ibuprofen disposition in obese individuals. Arthritis Rheum 28: 1117-1121.

52. Abernethy DR, Greenblatt DJ (1985) Phenytoin disposition in obesity. Determination of loading dose. Arch Neurol 42: 468-471.

53. Abernethy DR, Greenblatt DJ, Divoll M, Harmatz JS, Shader RI, et al. (1981) Alterations in drug distribution and clearance due to obesity. J Pharmacol Exp Ther 217: 681-685.

54. Pai MP, Lodise TP (2011) Steady-state plasma pharmacokinetics of oral voriconazole in obese adults. Antimicrob Agents Chemother 55: 2601-2605.

55. Fukuchi H, Nakashima M, Araki R, Komiya N, Hayano M, et al. (2009) Effect of obesity on serum amiodarone concentration in Japanese patients: population pharmacokinetic investigation by multiple trough screen analysis. J Clin Pharm Ther 34: 329-336.

56. Abernethy DR, Greenblatt DJ, Divoll M, Shader RI (1983) Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med 101: 873-880.

57. Allard S, Kinzig M, Boivin G, Sörgel F, Le Bel M, et al. (1993) Intravenous ciprofloxacin disposition in obesity. Clin Pharmacol Ther 54: 368-373.

58. Cortinez LI, Anderson BJ, Penna A, Olivares L, Muñoz HR, et al. (2010) Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth 105: 448-456.

59. Longo C, Bartlett G, Macgibbon B, Mayo N, Rosenberg E, et al. (2013) The effect of obesity on antibiotic treatment failure: a historical cohort study. Pharmacoepidemiol Drug Saf 22: 970-976.

60. Brill MJ, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN, et al. (2012) Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 51: 277-304.

61. Baer HJ, Cho I, Walmer RA, Bain PA, Bates DW, et al. (2013) Using electronic health records to address overweight and obesity: a systematic review. Am J Prev Med 45: 494-500.

62. McMahon AW, Dal Pan G (2018) Assessing drug safety in children - the role of real-world data. N Engl J Med 378: 2155-2157.

63. Dunne J, Rodriguez WJ, Murphy MD, Beasley BN, Burckart GJ, et al. (2011) Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 128: e1242-1249.

64. Food and Drug Administration (FDA). Guidance for industry: pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling.

65. Zhang Y, Zhang L, Abraham S, Apparaju S, Wu TC, et al. (2009) Assessment of the impact of renal impairment on systemic exposure of new molecular entities: evaluation of recent new drug applications. Clin Pharmacol Ther 85: 305-311.

66. https://www.drugbank.ca/drugs/DB00537

67. Kimura T, Sudo K, Kanzaki Y, Miki K, Takeichi Y, et al. (1994) Drug absorption from large intestine: physicochemical factors governing drug absorption. Biol Pharm Bull 17: 327-333.

68. Takacsnovak K, Jozan M, Hermecz I, Szasz G (1992) Lipophilicity of antibacterial fluoroquinolones. Int J Pharm 79: 89-96.