Drugs & Therapy Perspectives (2020) 36:341–346
https://doi.org/10.1007/s40267-020-00734-w

PRACTICAL ISSUES AND UPDATES

Dosage adjustment in obese children, even for common drugs, is largely unclear and a treat-to-effect approach may work best

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Published online: 25 May 2020

Abstract
Obesity in children, often accompanied by comorbidities, is increasingly common. For many frequently used paediatric drugs, information on dosage adjustment in obese children is lacking or absent. Scalars, such as total body weight, are not always helpful as obese children may weigh more than adults, but differ with regard to aspects of their anatomy and physiology, especially hepatic function. Further pharmacokinetic studies in obese children are urgently needed and, in the interim, close monitoring for therapeutic effect and toxicity is recommended.

Drug dosage in obese children a weighty challenge

Obesity in children and adolescents is a big problem, affecting at least 124 million children and carrying significant comorbidity [1]. Childhood obesity is defined by the World Health Organization (WHO) as having a body mass index (BMI, kg/m^2) above the 95th percentile of individuals the same age and sex in children aged 5–18 years inclusive, and above the 99th percentile in those aged up to 5 years [1]. Other organizations, such as the American Academy of Pediatrics [2], include "late adolescents" aged 18–21 years in the paediatric population. For simplicity, "children" and "paediatric" in this review refers to all paediatric age groups, including adolescents.

Although paediatric obesity is common, there are few pharmacokinetic or other studies on the best approach to use for drug dosage adjustment in this patient population [3]. Total body weight (TBW), the scalar most commonly used in the overall paediatric population, may be inappropriate for those who are obese. Their bodyweight (BW) may equate to or exceed that of adults, but aspects of their anatomy and physiology may differ [4–7]. The paucity of data results in inadequate or excessive drug levels in a huge percentage of obese children, with up to two-thirds being susceptible to either toxicity or treatment failure [3]. This article summarises current information on obesity-related dosage adjustment for commonly prescribed paediatric drugs, including those prescribed for obesity-related comorbidities, as reviewed by Kyler et al. [8].

Start with size, but be aware of pharmacokinetics

While paediatric dosage adjustments have traditionally been size-related, an all-round view that also considers patient physiology and drug physiochemical properties may be more clinically relevant [5]. Aside from TBW, proposed allometric or size-based measures include: normal fat mass scaled for volume, BW or body surface area (BSA); ideal BW (IBW); lean BW (LBW); and BMI or BSA alone [5].

Size-based measures are complicated by obese children's abnormal vertical growth. In childhood and/or puberty, overweight children grow taller than normal-weight peers [9], but by adulthood they are shorter or the same height [8]. Nomographs, which show relationships between ≥ 3 variables [4], or obesity-specific dose curves [8] may eventually provide better dose-adjustment models.

Size aside, obese children may display variations in pharmacokinetics and possibly even disease phenotypes relative to normal-weight children (Table 1) [10]. Drug absorption, distribution, metabolism and excretion all tend to differ between the two groups due to differing anatomy and physiology (Table 1) [7], but specifics are ill-defined, because of the limited physiological data for obese children (Table 1). Although more information is available for obese adults,

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Table 1 Physiological changes potentially affecting pharmacokinetics in obese children and adolescents

Changes in gastric emptying and intestinal motility that may affect absorption [8]
↑ splanchnic blood flow, including hepatic, that may affect absorption and V_d [11]
Changes in body composition: ↑ lean and total body mass, but ↓ lean:total body mass ratio that may affect V_d [12]
Change in fluid spaces: ↑ blood volume and cardiac output that may increase V_d [11]
Changes in drug binding for some drugs (e.g. propranolol and α_1 acid glycoprotein) that may ↑ V_d and affect metabolism [13], but no changes in drug binding changes for other drugs (e.g. phenytoin and albumin) [12, 13]
↑ activity of CYP2E1 and CYP2D6, but ↓ activity of CYP3A4 and CYP2C19, which may alter drug metabolism [14]
Renal hypertrophy and ↑ renal blood flow ↑ CL of some renally cleared drugs (e.g. vancomycin) [11, 15–17]
Hepatic hypertrophy (correlated with BSA) and ↑ hepatic blood flow, may ↑ CL of some hepatically cleared drugs [15, 17, 18]
Non-alcoholic fatty liver disease and associated inflammation may ↓ hepatic metabolism and CL [19, 20]

BSA body surface area, *CL* clearance, *CYP* cytochrome P450, *Vd* volume of distribution

such data can provide only a broad context regarding pharmacological changes, as physiology, hepatic function and other pharmacokinetic parameters differ between children and adults [8].

Physiochemical drug properties, such as lipophilicity, suggest another possible path to optimal drug dosages [8]. In theory, highly lipophilic drugs have a higher volume of distribution (V_d) in obesity, suggesting that higher dosages, especially initially, are needed. However, while this seems logical, inconsistent relationships between lipophilicity and V_d have been observed, with factors such as unpredictable sequestering in, and release from, adipose tissue potentially affecting the correlation [7, 17, 19]. The pharmacokinetic profiles of hydrophilic drugs in obese individulals also require clarification [19].

Adjust dosages cautiously then monitor carefully

Clear guidelines on dosage adjustments in obese children are lacking, but pharmacokinetic studies and analyses in this patient population provide pointers to dosage adjustment for some commonly used drugs (Table 2). Studies to date focus on the in-hospital acute or intensive care setting, as well as on drugs with a narrow therapeutic index and serious potential toxicity [21]. As no paediatric data are yet available for many commonly used drugs, some adult information is included in Table 2; such data should be considered with caution and not just simply extrapolated to children. As information is sparse or uncertain, clinicians need to carefully monitor obese children's responses to treatment, and watch for signs of toxicity [8].

Use available data in common comorbidities

Obese children and adolescents are prone to the metabolic and cardiovascular disorders frequently seen in obese adults and, therefore, may require medications usually prescribed to adults. Information on appropriate dosage adjustment for these drugs is also scant [8]. Available information regarding some of the drugs commonly used to treat comorbid conditions in obese children suggests the following:

- *Metformin* Consider increasing dosages in line with increased TBW and LBW to compensate for increased clearance and perhaps V_d [51, 52]. Of note, metformin acts as a substrate for OCT1, a hepatic uptake transporter that increases in obese patients, potentially leading to interactions between metformin and other OCT1 drug substrates (e.g. cimetidine, tramadol).
- *Calcium channel blockers* May need to increase dosages if clinically required, possibly due to secondary increases in V_d [53, 54].
- *ACE inhibitors and ARBs* Do not adjust dosage unless clinically required, as both classes of antihypertensives appeared equally effective at standard dosages in a study in three obese and three non-obese paediatric patients with renal disease [53].
- *β-blockers* Do not adjust dosage to allow for an increase in Vd on the basis of lipophilia unless clinically appropriate, as these antihypertensives may preferentially target lean body tissue [8].
- *Statins* Systemic exposure to statins is not simply a function of BMI, as two- to fivefold increases in exposure to pravastatin were observed due to genetic variations in some obese children's hepatic uptake [55, 56].
- *Proton pump inhibitors (PPIs)* The treatment of GORD is a particular concern, as GORD is six times more common in obese children than in non-obese children, and the use of PPIs is associated with infections, osteopenia and other adverse drug events in children [57]. Base the dosage of pantoprazole on LBW to avoid systemic overexposure, as total CYP2C19-mediated clearance of the PPI from plasma may be reduced [58–60].

Table 2 Evidence underlying suggested dosage adjustments for selected drugs used in the treatment of obese children and adolescents

Drug/drug class	Population of interest	Comments and suggestions for dosage calculations
Antimicrobials		
Azithromycin	Obese/non-obese children [22]	↑ BW associated with ↑ CL (details of obese population not reported)
Cefazolin	Obese children [23–25]	No difference in CL or Vd vs non-obese children, with TBW-based dosage
		Base dosage on TBW, although maximum safe total paediatric dose is unclear [8]
Ceftriaxone	Paediatric PK analysis [4]	Base dosage for all cefalosporins on TBW
Clindamycin	Obese children [26]	Base dosage on TBW, as for non-obese children (PK values are not predicted by lipophilicity)
Vancomycin	Obese children [27–32]	CL, Vd and PK profile not clearly different vs non-obese children [28–30]
		Obese pts may have ↑ trough concentrations when dosage is based on TBW, but within normal therapeutic range; clinical significance is unknown [27, 32]
		Base dosage on TBW [23, 31]
Analgesics/anaesthetics		
Acetaminophen (oral; 5 mg/kg; ≤ 325 mg)	Obese children with non-alcoholic fatty liver disease [33]	Drug concentrations did not significantly differ vs non-obese children
		Significant ↑ in plasma and urinary acetaminophen glucuronide metabolite, suggesting ↑ hepatic UGT activity; results consistent with those in adults [34–36]
		Do not adjust dosage in obese children [8]
Acetaminophen (IV)	Morbidly obese adults [35]	↓ concentrations → ↑ risk of treatment failure, but ↑ in hepatotoxic metabolites mediated by CYP2E1 ↑ risk of toxicity
Fentanyl	Obese adolescents [37]	Vd similar, but ↑ CL vs non-obese adolescents
		Base dosage on IBW [37] or LBW [38], as TBW ↑ risk of overdose in adults [39]
Ibuprofen	Obese adults [34]	↑ Vd and ↑ CL vs non-obese adults
Morphine sulfate	Obese adolescents [40], paediatric PK analysis [4]	Base dosage on IBW
Propofol	PK analysis in morbidly obese pts (all ages) [41]	Base maintenance dosage on TBW, as CL is most affected by TBW
	Obese children and adolescents [42]	Dose for anaesthetic induction was lower in obese pts than non–obese pts
		Unclear whether TBW or LBW is more appropriate [8]
Rocuronium	Obese adults [43, 44]	Base dosage on IBW (effect is prolonged when TBW is used) [44]
Benzodiazepines		
Midazolam	Obese adolescents [45, 46]	Markedly ↑ peripheral Vd vs standard population [46]
		↑ CL vs morbidly obese adults (possibly due to ↓ CYP3A activity in adults) [45]
		Consider ↑ loading dose when used in continual infusion [46]
Corticosteroids		
Prednisolone	Obese adults [47]	Poor oral absorption; ↑ apparent CL and ↓ efficacy vs non-obese adults
Asthma drugs		
Albuterol (single inhalation)	Black and Hispanic obese children/adolescents [10]	↑ objective/subjective treatment failure rates and ↑ need for inhaled corticosteroids or long-acting β_2 agonists vs non-obese children/adolescents
		Poorer results may have been influenced by obesity-related inflammation [10, 48]

Table 2 (continued)

Drug/drug class	Population of interest	Comments and suggestions for dosage calculations
Fluticasone	Morbidly obese adults [49]	Treatment failure with standard dosage twice as likely in the morbidly obese than in all other adult populations
Montelukast	Black and Hispanic children and adolescents [50]	Better response at 24 weeks in obese vs non-obese pts [50], perhaps secondary to a different asthma phenotype [10]
Anticoagulants		
Enoxaparin	Paediatric PK analysis [4]	Some evidence of need for ↑ dosage to achieve therapeutic concentrations
		Base dosage on TBW; treat to achieve anti-Xa 0.1–0.3 IU/mL

Adult studies included if paediatric studies are not available; direct extrapolation to paediatric population is not recommended

BW body weight, *IBW* ideal BW, *IV* intravenous, *LBW* lean BW, *PK* pharmacokinetic, *pt* patient, *TBW* total BW, *UGT* glucuronosyltransferase, *Vd* volume of distribution, ↓ decrease(d), ↑ increase(d), → leading to

Take home messages

- Be aware that obese children often require pharmacological treatment for comorbid conditions, such as T2D and hypertension.
- Realize that adjusting the dosage based on treatment effect may be the best option for many commonly prescribed drugs, as adjustment based on TBW, as for normal-weight children, is hampered by a lack of reliable data for most drugs.
- Recognize the urgent need for pharmacokinetic studies in obese children to provide clearer dosage adjustment guidelines.

Author contributions The article was written by employees of Adis International Ltd./Springer Nature and was adapted, in part, from Pediatric Drugs 2019;21(5):357–69 [8].

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Funding The preparation of this review was not supported by any external funding.

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