REVIEW ARTICLE

Pharmacological Prescription Dilemmas in Obese Children and Adolescents

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Abstract

Paediatric obesity is a serious public health concern. We daily face the need to medicate obese children, whether in the context of acute or chronic diseases. Prescribing in these patients becomes a real challenge as there are scarce specific recommendations available to optimise drug dosing. The main pharmacokinetic parameter which is altered in obesity is the volume of distribution, determined by the physiochemical properties of the drug, such as lipophilicity and protein binding. There is no single size descriptor that is undeniably better for dosing drugs in obese patients. We searched for the terms children, pharmacokinetic, obesity, overweight, body mass index, lean body weight, ideal body weight and specific drugs in the PubMed, Medline and Cochrane databases between 2006 and 2016. A chart to identify the most adequate body size descriptor for different types of drugs is proposed, providing foundations for safer drug dose calculation. There is an urgent need to raise awareness for prescription rationality and harmonising the current existing guidelines.

Keywords: Adolescent; Child; Body Weight; Drug Dosage Calculations; Paediatric Obesity; Pharmaceutical Preparations/administration & dosage; Pharmacokinetics

Introduction

A 14-year-old male adolescent, with a history of epilepsy, 140 kg in weight and 1.67 m in height, is transported by an ambulance to the emergency department with a generalised tonic-clonic seizure, which began at school and was controlled with rectal diazepam, administered on site, with remission. At triage, the patient suffered a new seizure which did not respond to intravenous administration of diazepam and, phenytoin was used. Phenytoin has a high bioavailability, 90% binds to albumin, and it is rapidly distributed, reaching the brain tissue in significant concentrations.[1,2] In obese patients, the volume of distribution (V_D) is higher compared to normal weight patients.[1] The appropriate impregnation dose of phenytoin is 20 mg/kg/dose, which could result, in this case, in a toxic dose if calculated using the total weight. Will the maximum possible administration dose of phenytoin be enough for this adolescent patient? What will be the most appropriate formula to calculate the optimal dose, i.e. the effective and simultaneously safe dose?

As paediatricians, we are increasingly faced with this problem on a daily basis and, although there is a significant body of research focused on paediatric obesity as a public health problem, studies on its effect on pharmacokinetics and pharmacodynamics of drugs most frequently used in children are scarce.[1-3] In this age group, body weight is the most used variable to determine the therapeutic dose to be administered, together with other patient-related factors, such as age and organ dysfunction. Over the last decade, we have witnessed significant developments in methods used to identify effective and safe doses of paediatric drugs. The traditional allometric approach, which assumes linearity between body size and drug exposure, has been ruled out in favour of integrated pharmacokinetic and pharmacodynamic models.[2,4] However, models including obese children are scarce and small-sized and, therefore, this special population is not consistently considered in the development of new drugs. Consequently, there is a lack of guidelines for calculating drug doses in obese children.[2,3,5]

We performed a review of literature on the pharmacological effect of physiological changes present in overweight and obesity, and we discuss potentially appropriate anthropometric measurements to be used for a therapeutic dose adjustment. Review articles or observational studies aimed at identifying or reviewing

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measurements and guidelines for the definition of the correct dose of different drugs in the obese paediatric population and principles regarding the effect of obesity on pharmacokinetics were considered eligible. This review focuses on concepts related to drug choice and dose in obese children especially drugs which are used the most in paediatric age. Medline and Cochrane databases were searched between 2006 and 2016, including the following keywords: children, pharmacokinetics, obesity, overweight, body mass index, lean body weight, ideal body weight and drug/medicine. In addition, references known to the authors were used. The most relevant articles were included by author consensus. Those articles were subject to a brief critical evaluation.

Twenty-four articles (11 clinical studies, 12 review articles and one case report) were selected, and their references, which may not have been selected in the initial electronic search, were analysed. It should also be noted that most references are related to review articles and guidelines of relevance for the specific population and, when necessary, information was derived from studies in adults.

What is the effect of obesity on the pharmacokinetics of a drug?

Pharmacokinetics studies the evolution over time in concentrations of drugs and their metabolites in different fluids and tissues, seeking to establish the mathematical relationships necessary for the development of appropriate interpretation models.

The effect of obesity on the pharmacokinetics of different drugs is variable. Although there is a delay in gastric emptying in obese patients, haemodynamic studies did not show any changes in oral absorption.[4] This is not necessarily the case when evaluating the distribution and elimination of drugs. In obesity, there is not only an increase in fat mass, but also in lean mass, in different proportions, and there are changes in the proportion of extracellular water volume and percentage of total water in the body that modify the distribution of the drug and its metabolites.[1] In addition, there is an increase in cardiac output, which also influences the drug distribution, considering that adipose tissue is less irrigated, receiving only 5% blood flow, while the remaining 22% is distributed to lean mass and 73% to organs.[3] The serum levels of plasma proteins, such as albumin and α1-glycoprotein, are higher in obese children compared to normal weight children.[5] There are several drugs that bind to albumin which, despite being high in obese patients, does not seem to influence the drug distribution. This is not necessarily the case of α1-glycoprotein,[6] which results in a percentage decrease of free drug and, consequently, in a decrease in hepatic drug metabolism and its distribution in tissues, considering that only the free fraction can be metabolised and crosses the cell membranes (Table 1). On the other hand, in the presence of high levels of serum triglycerides, fatty acids and cholesterol, there may be an inhibition of drug binding to plasma proteins, by competition, with increased drug metabolism.[5]

These physiological differences between obese and non-obese patients result in differences in drug distribution, depending on its physicochemical properties, affinity for adipose tissue and influence of pH of the environment.[2,7] A lipophilic drug is easily absorbed, has a larger volume of distribution and a high affinity for plasma proteins, but its renal clearance is difficult, which means it needs to be metabolised in the hepatocyte to become more water-soluble.[4] Examples of lipophilic drugs are fluoroquinolones, macrolides, rifampicin, benzodiazepines, tricyclic antidepressants and some beta-blockers such as metoprolol, propranolol and timolol. Hydrophilic drugs, on the other hand, have a lower volume of distribution and lower affinity for plasma proteins, and they are predominantly eliminated non-metabolised via the kidneys,[7] as it is the case of beta-lactams, aminoglycosides, glycopeptides and some beta-blockers such as atenolol.

Table 1. Effect of obesity on pharmacokinetic parameters

		Pharmacokinetic parameters	
	Changes in obesity	**Volume of distribution**	**Clearance**
Adipose tissue	↑↑	↔ or ↑	↔
Non-adipose tissue	↑	↔	↑
Liver function	↔ or ↓	↔	↔ or ↓
Renal function	↔ or ↑	↔	↔ or ↑
Albumin ↑↑	↔	↔	↔
1-glycoprotein	↔ or ↑	↔ or ↑	↔ or ↑
Blood flow	↓	↔ or ↓	↔

Adapted from Mulla H., et al. Arch Dis Child Educ Pract Ed 2010; 95:1127.[8]

Drugs with acidic properties (acetylsalicylic acid, warfarin, pentobarbital) tend to accumulate in the more alkaline compartment, while the inverse occurs with basic drugs (amphetamines, morphine, lidocaine). Weak bases in non-ionised form concentrate in the intracellular space; weak acids in non-ionised form, on the other hand, concentrate in the extracellular space.[6]

In the presence of hepatic steatosis, changes in the metabolic activity may occur, but the underlying mechanisms are not yet completely known.[4] In addition, an increase in the size of glomeruli, filtration rate and glomerular perfusion in obese children influences the renal elimination of a drug, with a higher clearance rate.[1]

Consequently, there are differences in the volume of distribution, metabolism and clearance (CL) which modify the drug effect on the body of obese patients, significantly influencing the therapeutic effectiveness and toxicity threshold (Table 1).[2]

What is the most appropriate anthropometric measurement to calculate the dose in obese children?

The use of anthropometric measurements is the method most commonly used in the literature for drug dose adjustment in obese patients. Amongst the anthropometric measurements most commonly used to correct the effect of obesity for dose adjustment are body mass index (BMI), total body weight (TBW), ideal body weight (IBW), adjusted body weight (ABW), lean body weight (LBW) and body surface area (BSA).[3]

It is important to consider the specific pharmacokinetics of the drug in question to calculate the therapeutic dose in obese children. When using TBW to calculate the dose of some drugs, there is a risk of overdose and, when using IBW, there is a risk of a lack of efficacy caused by the subtherapeutic dosing (Table 2).[1, 8,9]

LBW is represented by the muscles that provide support and allow body movement. This anthropometric measurement is considered the most appropriate to calculate the loading dose of hydrophilic drugs as well as the maintenance dose of drugs with mainly hepatic elimination. IBW is often used as an alternative to LBW, especially in cases of more severe obesity.[4] There are different methods to estimate IBW, such as Devine, Moore and McLaren methods, and linear equations, such as [2x(*age* + 4)].[10] These methods proved to be useful for different paediatric age subgroups, and the result of BMI_{50} multiplied by height squared is used in a wider range of ages and heights.[9] ABW, on the other hand, is a measurement frequently used when IBW is considered underestimated and TBW is considered overestimated in relation to the drug distribution in the body.[4] In addition, whereas BMI and IBW are anthropometric measurements that do not allow the evaluation of the percentage difference between adipose tissue and non-adipose tissue, ABW allows that evaluation.

The V_D is a parameter related to body structure, defined by the volume of the drug that will theoretically be distributed. However, it does not allow for evaluating whether a drug is distributed evenly in a single compartment or in several compartments. A study found that the relationship between the V_D and anthropometric measurements is very variable.[11] Physiological changes associated with obesity have a significant effect on the distribution of some drugs, especially lipophilic drugs, which are distributed preferentially in adipose tissue. There is evidence that TBW is the best descriptive factor of the V_D.[9] On the other hand, clearance, a parameter related to the intrinsic capacity of the different organs of elimination of several drugs, does not increase proportionally to TBW. As the adipose tissue does not have any drug elimination properties, TBW is not a reliable predictive factor of clearance. There is evidence that LBW is the best predictive factor of clearance.[1,9]

Table 2. Calculation of main anthropometric measurements used for therapeutic dose adjustment in obese patients

Anthropometric measurement	Formula
BMI	$TBW/height^2$
IBW[14]	BMI_{50} x $height^2$
ABW[8,14]	IBW + factor* x (TBW - IBW)
LBW[6,8,11]	males = (1.10 x weight) - 0.0128 x BMI x weight females = (1.07 x weight) - 0.0148 x BMI x weight
BSA[6,8]	$(height \times weight)/3600^{1/2}$

ABW - adjusted body weight; BMI - body mass index; BSA - body surface area; - height in cm; IBW - ideal body weight; LBW - lean body weight; TBW - total body weight; - weight in Kg.
* Variable according to the drug in question.

How to obtain the ideal loading and maintenance dose in obese children?

The loading (initial) dose is the dose that must be administered at the beginning of a treatment, with the purpose of rapidly achieving an effective concentration (target concentration). In turn, the maintenance dose is the dose required to maintain an effective plasma concentration, in a constant equilibrium state (steady state).

To calculate the loading dose, the V_D is the most important parameter to be considered, as it is expected that lipophilic drugs have a more extensive distribution in adipose tissue which as a higher percentage in obese children. Due to the affinity of lipophilic compounds to adipose tissue, making their Vd higher and potentially necessitating incresead dosing, TBW is the most appropriate anthropometric measurement to calculate the loading dose.[2,7] However, the association between the lipophilic properties of the drug and its distribution in adipose tissue is not always completely linear . There are other factors that influence the dose to be administered, including body composition, cardiac output – which is increased in obese patients – and larger plasma protein binding observed in lipophilic drugs (Table 1). In hydrophilic drugs, due to their lower affinity for adipose tissue, the V_D is lower and the most appropriate anthropometric measurement to calculate the loading dose will be IBW in order to avoid the risk of overdose.[7]

The calculation of the maintenance dose is even less consensual.[6] The maintenance dose depends on the clearance and perfusion of organs such as the liver and the kidney, which are part of LBW. Although there is an increase in lean mass, it is not as pronounced as the large increase in adipose tissue, and the percentage of lean mass per kilogram of TBW is, therefore, reduced. Consequently, drug clearance does not increase proportionately to the increase in body weight, and it should be calculated using an anthropometric measurement that illustrates LBW, such as lean body weight or IBW, in the absence of changes in renal function. If the drug clearance is predominantly hepatic, LBW may be the most appropriate measurement.[4,6]

In conclusion, considering that clearance has no proportional relationship to TBW, the maintenance dose must be calculated using an anthropometric measurement that illustrates the percentage of lean mass, such as IBW or LBW, in the absence of renal and/or hepatic pathology[10,11] (Fig. 1).

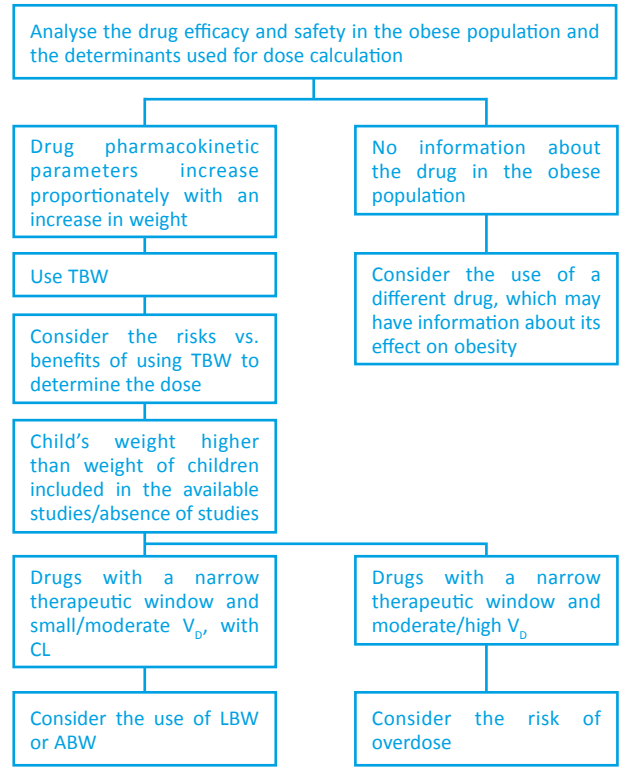
What are the effects of obesity on the pharmacokinetics of specific drug classes?

Penicillins

Typically hydrophilic drugs. It was demonstrated that TBW is the most appropriate parameter to calculate the dose of amoxicillin, ampicillin or piperacillin-tazobactam.[7,13-15] The risk of toxicity is lower than the risk of administering a subtherapeutic dose, considering the range of the therapeutic window of penicillin. Therefore, TBW is the most appropriate anthropometric measurement (Table 3).

Cephalosporins

Predominantly hydrophilic drugs. A study with few children showed that the administration of cefazolin to obese children has no significant differences in the pharmacokinetic parameters, and the dose to be administered should be based on TBW.[15] This was also shown in another study,[14] suggesting that the dose to be administered of cefazolin, cefepime, cefotaxime, ceftazidime and ceftriaxone should be based on TBW, and the risk-benefit balance should always be considered.



ABW: adjusted body weight; TBW: Total body weight; CL - clearance; LBW - lean body weight; V_D - volume of distribution.

Figure 1. Diagram for determining the therapeutic dose in obese children[12] (adapted).

Table 3. Quick reference table. Therapeutic dosing recommendations in obese children and adolescents

Drug	Anthropometric measurement (loading/maintenance dose)	Remarks
Antibiotics		
Carbapenems	TBW	
Aminoglycosides	TBW or ABW = [0.4 (TBW - IBW)] + IBW	Monitoring
Cephalosporins	TBW	
Penicillins	TBW	Monitoring
Gentamicin	LBW	
Vancomycin	TBW	Decreased dose intervals + monitoring
Tobramycin	ABW = [0.4 (TBW - IBW)] + IBW	Monitoring
Anticonvulsants		
Phenytoin	TBW or ABW = [1.33 (TBW - IBW)] + IBW / IBW	Monitoring
Carbamazepine	TBW or IBW / IBW	
Miscellaneous		
Acyclovir	IBW	
Benzodiazepines	IBW	Consider TBW in the loading dose
Digoxin	IBW	Monitoring
Lidocaine	TBW / IBW	
Opioids	TBW or IBW / IBW	For bolus dosing
Acetaminophen	IBW or ABW = [0.4 (TBW - IBW)] + IBW / IBW	
Ibuprofen	IBW / IBW	
Insulin	No information	IBW-based infusion
Enoxaparin	TBW / ABW = [0.4 (TBW - IBW)] + IBW	Anti-Xa monitoring
Heparin	Do not exceed 5,000 U/TBW	Monitoring

ABW - adjusted body weight; IBW - ideal body weight; LBW - lean body weight; TBW - total body weight.
Recommendations based on the data derived from studies in adults, with inherent limitations and requiring a case-by-case assessment.
Adapted from Hanley MJ, Abernethy DR, Greenblatt DJ. Clin Pharmacokinet 2010;49:71-87; Rowe S, Siegel D, Benjamin D. Clin Ther 2015;37:1924-32; Mulla H, Johnson TN. Dosing dilemmas in obese children. Arch Dis Child Educ Pract Ed 2010;95:1127.[6-8]

Aminoglycosides

Predominantly hydrophilic drugs. In obese children, a relationship between the V_D and TBW was shown to be significantly reduced compared with normal weight children.[15] It was also shown that the V_D is lower in obese children when compared with normal weight children, but this does not change the half-life.[16] Therefore, the dose should be based on TMW or ABW.

Vancomycin

The pharmacokinetic parameter of vancomycin which is the most influenced by obesity is an increase in clearance, related to the increase in TBW. As there is an increase in drug clearance, the half-life is shorter and, therefore, the intervals between doses should be reduced and serum concentration monitored.[1,11,15]

Anticonvulsants

Phenytoin, carbamazepine and benzodiazepines are lipophilic drugs, which have a longer half-life in obese children due to the larger V_D. In this case, IBW is the most appropriate anthropometric measurement to calculate the maintenance dose due to the higher probability of accumulation in tissues when administered as maintenance therapy.[15] The optimal method for the calculation of the loading dose is, however, controversial as both TBW and IBW are reported in the literature. Some studies[9] suggest the use of TBW for the calculation of the loading dose of phenytoin[1,15] which is the most appropriate anthropometric measurement and, in the calculation of the maintenance dose, the use of IBW. Still regarding phenytoin, according to some authors,[7] the loading dose in certain cases must be calculated using ABW, with a cofactor of 1.33.

Oral contraceptives

Although hormone serum levels are more reduced in obese female adolescents, several studies showed that this difference has no effect on the efficacy of oral contraception.[17-19]

Analgesics

The doses of acetaminophen and ibuprofen, used daily, must be calculated using IBW.[7] ABW is also an anthro-

pometric measurement appropriate for calculating the maintenance dose of acetaminophen.[15] Acetaminophen is partially distributed in adipose tissue, with a 40% distribution in lean mass. Regarding the half-life of the drug, it seems that there is no difference between obese and non-obese children.[15]

Opioids

Predominantly lipophilic drugs. The V_D correlates directly with the degree of obesity. In contrast, the relationship between the V_D and TBW is similar to that relationship in normal weight children. These indicate that the drug is distributed equally in adipose and non-adipose tissue and, therefore, the loading dose should be calculated based on TBW. The slight clearance difference in obese children compared with normal weight children causes an increase of the half-life in obese children, suggesting that the maintenance dose should be lower, based on IBW.[4] However, there are exceptions. Clearance and the V_D of remifentanil were significantly lower in obese patients. Consequently, the loading doses used in obese patients should be calculated using IBW.[5]

Heparin

It binds with high affinity to plasma proteins, and its volume of distribution is close to blood volume. Using TBW, no significant difference was shown in the bolus dose of heparin between obese children and normal weight children.[20]

Enoxaparin

When using TBW for calculating the dose in obese children, studies show that there is a more marked increase in the initial concentration of anti-Xa compared with normal weight children.[21-22] The maintenance dose of enoxaparin should be calculated using ABW (with a cofactor of 0.4) with the simultaneous monitoring of the concentration of anti-Xa.[15]

Conclusion

Currently, there is no consensus on the measurements for therapeutic adjustment or on the ideal anthropometric measurement to adopt in order to calculate a drug dose in obese children. The presented dosing strategies have limitations, as they are predominantly derived from studies in adults. Furthermore, it is worth mentioning that obesity is often an exclusion criterion in several pharmacokinetic studies. There is an urgent need for specific pharmacokinetic studies in obese children.

Changes in pharmacokinetic parameters arising from obesity are reflected in different ways in the various therapeutic classes and, therefore, it is not possible to establish the general rules of its effect. The relationship between the pharmacokinetic parameters (e.g. V_D and clearance) and anthropometric measurements is variable. Consequently, it is not possible to identify a single measurement that allows you to account for the effect of obesity on the various pharmacokinetic parameters, considering the specificities of each drug distribution and their different tissue affinities.

This review shows that obesity must be considered when determining a drug dose. There are significant differences, explained by different degrees of enzyme maturation, expression and activity, leading to different routes of metabolism and elimination of the drug.[7]

Information about the relationship between body composition and pharmacokinetic behaviour of the various drugs is limited, which is particularly problematic in drugs with a narrow therapeutic window.

The challenge is to draw predictive models to identify the specificities of pharmacokinetics and pharmacodynamics of drugs at the time of their prescription in obese children. It is also imperative to establish quick reference guidelines, aiming to reduce errors and improve safety in prescribing drugs in obese children.

WHAT THIS STUDY ADDS

- It is not possible to identify a single anthropometric measurement that allows clinicians to account for the effect of obesity on the various pharmacokinetic parameters.
- It is imperative to establish guidelines with the goal of optimizing drug prescription in obese children and adolescents as well as decreasing the inadequate response to drugs and the possible adverse side effects.
- A quick reference database on the most appropriate anthropometric measurement for different types of drugs is proposed.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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