Childhood obesity: Pharmacokinetic considerations for drugs used in the intensive care unit

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ABSTRACT

An adequate drug dosage at treatment initiation is particularly relevant for critically ill patients. An inadequate dosage may result in therapeutic failure, potentially severe adverse events, and unnecessary health expenditures.

At present, due to the higher incidence of childhood obesity, primary care physicians are more commonly faced with this population, so they need to make appropriate therapeutic decisions. Knowledge of the resulting pharmacokinetic alterations caused by increased body fat is critical. The optimal drug dosage is not completely defined and the correct body descriptor should be used, although there is no consensus on which is the most adequate one. The objective of this update is to gain insight on pharmacokinetic alterations that affect dosage in the critically ill obese pediatric patient and, specifically, those related to the drugs most commonly used in this population during their stay in the pediatric intensive care unit.

Key words: obesity, critical care, pharmacokinetics, dosage, body weight.

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INTRODUCTION

Childhood obesity is a worldwide epidemic.¹⁻³ At present, there is a high prevalence of hospitalized obese children.^{4,5} These patients present their own pathophysiological characteristics⁶ and a higher risk for chronic disease. Complex medical interventions are sometimes necessary;^{7,8} for this reason, drug treatment may be a challenge for health care providers.⁹

An optimal drug dosage is based on both the pharmacokinetic and pharmacodynamic properties of the drug and the patient's specific characteristics (presence of associated diseases), which may eventually affect drug pharmacokinetics, and this

should be taken into consideration to minimize toxicity and prevent sub-therapeutic levels.¹⁰ However, there is still no consensus in relation to the adequate dosage to be used for different conditions.^{10,11}

The effects of obesity on drug dosage in the adult population are well documented.¹²⁻¹⁴ However, the pharmacokinetic assessment of drugs used in children is more limited, especially in the case of obese patients and, moreover, if they are critically ill.¹⁵

Drug dosage in pediatrics is based on the changes occurred during normal growth and development, such as protein binding, body water, fat mass, cytochrome P450 (CYP450) enzymatic ability, and functional maturity of the kidney.^{10,11}

Obese patients have a larger amount of fat body mass and lean body mass¹⁶ and a higher proportion of extracellular water compared to total body water.¹⁷ In addition, an increased blood volume, cardiac output,¹⁸ and renal blood flow have also been described in obese adults.¹⁹ These alterations may alter pharmacokinetic parameters, such as drug absorption, volume of distribution (Vd), and clearance,¹⁴ thus generating significant consequences on obese children.^{6,20}

The objective of this update is to gain insight on pharmacokinetic alterations that affect dosage in the critically ill obese pediatric patient and, specifically, those related to the drugs most commonly used in this population during their stay in the pediatric intensive care unit (PICU).

Patients younger than 2 years old were excluded from these recommendations due to the pathophysiological characteristics typical of obesity in this age group.

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Pharmacokinetic alterations

Given the prevalence of childhood obesity, as well as its impact on public health, it is concerning that there are few recommendations in relation to drug dosage in this population.^{10,11,21-23} Available data correspond to case reports and retrospective cohort studies; most included a small number of cases. Besides, data sheets usually do not point out specific recommendations.

Few systematic reviews have been done to assess pharmacokinetics and dosage in obese children, and they concluded that more information is required to establish a safe and effective dosage in this population.^{15,24,25}

The extrapolation of results based on studies conducted in the adult population has proven inaccurate to predict pharmacokinetic parameters in children due to the differences in body composition, enzymatic activity and expression maturity, and the various metabolic pathways.^{12,26} In addition, a large number of pharmacokinetic studies are done in patients who are not critically ill, so results should be analyzed with caution.

Obese patients have several physiological characteristics that may cause alterations in drug absorption (studied only in adults), distribution, and metabolism.^{27,28} Likewise, they have shown increased body volume, total water content, fat body mass, lean body mass, and bone mineral density compared to non-obese children of the same age, height, and sex.¹⁶ In addition, lean body mass is more hydrated in obese children, as a result of an increase in extracellular water.^{16,29}

Vd and clearance are the determining primary pharmacokinetic outcome measures to be considered when prescribing a systemic drug.³⁰ Vd (L/kg) is a theoretical parameter correlated to the total amount of drug distributed in the body and the resulting plasma level, which determines the loading dose.

Vd is a parameter specific to each individual and may vary in physiological (age, sex) and pathological (shock) conditions. It is the outcome measure that is most affected by obesity¹³ and is mostly determined by the physicochemical properties of the drug (lipid partition coefficient and plasma protein binding). Highly lipophilic drugs distribute extensively into adipose tissue and, therefore, have a high Vd. Because of this, dosage should be estimated based on total body weight and would potentially require increasing drug dosage. Conversely, hydrophilic drugs should be dosed based on ideal body weight (IBW) because they remain in the

intravascular space and bind, to a lesser extent, to adipose tissue, thus generating a lower Vd and a potential risk for overdose.²⁴

Clearance (mL/min or L/h) is necessary to estimate the maintenance dose required to achieve an effective drug plasma level and is regulated by metabolic and organ perfusion capacity, mainly in the liver and kidneys, which excretes the drug continuously, proportionally and in a plasma level-dependent manner (first order or linear kinetics).

This way, in obese children, Vd and clearance are better represented by total body weight (TBW) and lean body weight (LBW), respectively.^{31,32}

Therefore, some drugs may be administered in a supra- or infratherapeutic dose, depending on the body descriptor used, leading to drug toxicity³³ or therapy failure.^{34,35} Recently, in a retrospective cohort study, Burke et al.³⁶ reported that obese children received anesthetic agents at non-recommended doses. Likewise, the use of potentially harmful doses during cardiopulmonary resuscitation,³⁷ which leads to a worse vital prognosis,³⁵ has been described.

Obesity is also associated with a significant increase in subcutaneous adipose tissue, and this may potentially interfere with transdermal, subcutaneous or intramuscular drug absorption. However, most published studies conducted in the adult population reported that absorption in obese and normal weight patients is similar.¹⁴

The effect of obesity on plasma lipid or protein binding of several drugs is uncertain.^{28,38} Obesity does not change serum albumin levels but the increase in triglyceride, lipoprotein, cholesterol, and free fatty acid levels may affect drug affinity with serum proteins and increase their free plasma level.³⁹

Changes in the liver may alter drug metabolism and clearance. Fatty infiltration and non-alcoholic steatohepatitis are very frequent in obese patients,⁴⁰ especially in adults with morbid obesity.^{41,42} These conditions may alter functional morphology and, secondarily, modify liver blood flow,⁴³ which affects clearance. The effect of an altered liver blood flow on drug metabolism in obese children is not clear yet. In addition, the outcomes of studies about the effect of obesity on CYP450 function and expression are not conclusive, except for CYP3A4 (primary responsible for phase I metabolic pathway) and CYP2E1, whose function and expression have been described to increase and reduce, respectively.⁴⁴ However, currently there is no experimental evidence that demonstrates

the impact of obesity-induced liver damage on clearance.

The effects of obesity on renal function,⁴⁵ and therefore, drug excretion, are still under discussion, especially in the pediatric population.⁴⁶ An increase in kidney size, blood flow, and glomerular filtration rate has been described in obese patients.^{19,47} These factors may modify the dosing frequency of drugs excreted by the kidneys in order to achieve a specific therapeutic level.^{11,28} Available evidence indicates a greater use of LBW in the Cockcroft-Gault formula to estimate creatinine clearance in obese patients.^{48,49} However, there are no validated formulas to estimate the glomerular filtration rate in pediatric patients.¹¹

Table 1 shows the physiological and body composition changes in obese patients that affect drug disposition in the body.

Weight and size body descriptors

Approximately 30-50 % of body weight in an obese subject is fat mass that is poorly vascularized. In addition, it is responsible for 75 % of excess weight; the rest corresponds to lean body mass.^{10,16,22} The large amount of adipose tissue changes body size and the amount of total water, which may modify the pharmacokinetics of a specific drug.

In clinical practice with pediatric patients, drugs are dosed based on TBW (kg) or body surface area (BSA, m²); in the latter case, the Mosteller formula ($BSA = \sqrt{\text{height (cm)} \times \text{weight (kg)} / 3600}$)⁵⁰ is used, which also considers the possible presence of organ dysfunction. However, this is not valid for obese children because their body composition proportions are different from those of normal weight children. Therefore, these changes should be taken into consideration,⁵¹ but they are difficult to estimate through indirect measures.

Size and body mass indirect measures use the patient's weight and height and include body mass index (BMI), BSA, IBW, LBW, TBW, and adjusted body weight (ABW). All of these measures have clinical application; however, they have limitations because they do not correlate accurately to body fat percentage in children.

As pointed out before, obese children have more lean body mass and absolute fat mass, but their percentage of lean tissue per TBW kilogram is lower, whereas the percentage of fat tissue is higher.

1. General body size equations

BMI: it is determined by TBW divided by the square of the height in meters (kg/m²). It correlates adequately to the relative proportions of adipose tissue in children and adolescents.⁵²

TABLE 1. Physiological changes in the obese population and their effects on pharmacokinetics

	Expected physiological change	Pharmacokinetic parameter
Body composition		
Fat per kg	Increases	Vd
Fat-free mass, fat tissue, and mineral content	Increases	Vd
Lean tissue	Increases	Vd
Proportion of extracellular water	Increases	Vd
Cardiovascular		
Blood volume	Increases	Vd
Cardiac output	Increases	Vd
Plasma proteins	No change	Vd
Plasma lipids	Increases	Vd
Hepatic		
Liver blood flow	No change	Hepatic clearance
CYP activity	Not conclusive	Hepatic clearance
Gastrointestinal		
Gastric emptying	Increases	Bioavailability
Intestinal blood flow	Increases	Bioavailability
Renal		
Kidney size	Increases	Renal clearance
Glomerular filtration rate	Not conclusive	Renal clearance
Renal blood flow	Increases	Renal clearance

CYP: cytochrome; Vd: volume of distribution.

BSA: there is a non-linear relation between weight and glomerular filtration rate, cardiac output, and drug metabolism.⁵³ However, it makes no distinction between adipose tissue and lean tissue. It is usually used to dose fluid therapy and chemotherapeutic agents. The Mosteller formula is the most common in hospital practice.⁵⁰

2. Body mass equations

IBW: it is defined as the desirable body weight for a specific age and height. It cannot be measured directly. There are different methods to estimate it in children: the McLaren method,⁵⁴ the Moore method,⁵⁵ and the BMI method.⁵³ The latter correlates to body fat measures and can be used to estimate IBW in patients aged 2-20 years; at present, it is the recommended method to estimate IBW.⁵⁶ Recently, Callaghan and Walker developed an alignment chart to estimate it.⁵⁷ If the patient's IBW is more than 40 kg, the dose established for the adult population should be used.

LBW: it is similar to the concept of fat-free mass (sum of vital organs, extracellular fluid, muscles and bones), but it also includes the fat accumulated in cell membranes, the bone marrow, and the nervous system. Obese children have excess lean body mass, particularly in the lower limbs. It has been pointed out that, in average, 30 % of excess weight in obese children corresponds to lean tissue.^{58,59} This may be estimated in children older than 5 years in an easy and quick manner; however, its use is not validated.⁵⁷

ABW: it reflects lean body mass plus excess fat mass determined by a cofactor [$ABW = IBW + \text{cofactor} (TBW - IBW)$]. This descriptor is used to dose drugs with partial distribution in adipose tissue.²¹ In the pediatric population, it is used infrequently.⁶⁰

To sum up, the body descriptor selection should consider drug lipophilicity and dose type (loading or maintenance) (Table 2).

The body descriptors used in pharmacokinetic studies and clinical practice are summarized in Table 3.

PHARMACOKINETICS

Below we describe the most relevant pharmacokinetic considerations for some of the drugs most commonly used in the intensive care unit (ICU).⁶¹ Others are exclusively mentioned in Table 4.

Benzodiazepines

Benzodiazepines are highly lipophilic drugs. Several studies have demonstrated that both their Vd and elimination half-life are increased.^{27,62,63} Thus, when using a single intravenous benzodiazepine dose, it should be adjusted based on TBW.^{63,64} However, given its distribution profile, it may reach high levels rapidly, so the recommendation is to use mini loading doses due to the risk for dose-dependent respiratory depression. On the contrary, if administered in a continuous infusion, the dose should be adjusted based on IBW because its total clearance is not affected by body weight.

In relation to the pharmacokinetic profile of midazolam in obese adolescents, Van Rongen et al.⁶⁵ suggested that the maintenance dose should be established at a fixed rate (mg/h) instead of at mg/kg/h.

Opioids

The opioids most commonly used in the ICU are morphine (hydrophilic molecule) and phenthanile (lipophilic opioid derived from phenylpiperidine). In the case of morphine, the initial dosage should be adjusted by the IBW and with titration of the desirable effect.^{21,59,66,67}

Phenthanile, due to its short half-life, allows for an easier titration and its use as continuous infusion. The use of ABW may help to prevent the potential accumulation due to its high lipophilicity.^{21,68} In a publication by Shibutani

TABLE 2. Body descriptor to be used based on pharmacokinetics and dose type

Degree of lipophilicity	Body descriptor used for the loading dose	Body descriptor used for the maintenance dose
Lipophilic drug	Total body weight*	Lean body weight
Partially lipophilic drug	Adjusted body weight	Lean body weight
Hydrophilic drug	Ideal body weight	Lean body weight

* To prevent the risk for toxicity, ideal body weight should be used.

TABLE 3. *Body size descriptors and body mass*

Body mass and body size descriptors	Population	Formula	Application
Term	Definition		
TBW		Patient's current weight in kilograms	Used to establish dosage in the pediatric population.
BMI	Older than 2 years old	TBW (kg) divided by height ² (m)	Used to categorize the degree of obesity. Rarely used to establish drug dosage.
IBW in adults		Man: 49.9 kg + 0.89 × (height in cm – 152.4) Woman: 45.4 kg + 0.89 × (height in cm – 152.4)	Considers sex difference.
IBW in children*	Older than 2 years old	Desirable weight for a specific height and age. It corresponds to the P50 of BMI for age × height ² (cm).	Suggested for hydrophilic drugs and to establish the maintenance dose.
BSA (m ²)**	Children and adults	√ height (cm) × weight (kg)/3600	Frequently used for chemotherapy and fluid therapy.
ABW	Mainly adults	IBW + drug factor × (TBW - IBW) Usual factor 0.3-0.4	Suggested for aminoglycoside dosage.
LBW		TBW - fat weight Child: IBW + 0.29 (TBW - IBW) Man: 1.10 × TBW – 0.0128 × BMI × TBW Woman: 1.07 × TBW – 0.0148 × BMI × TBW	Considers sex difference.

*t** As per the BMI method. ** As per the Mosteller formula (*N Engl J Med.* 1987;317:1098).

TBW: total body weight; IBW: ideal body weight; ABW: adjusted body weight; BSA: body surface area; BMI: body mass index.

TABLE 4. *Recommended drug dose as per the body descriptor used for obese children*^{11,12,22,34,36}

Drug	Body descriptor	Remarks
Antiviral agents		
Acyclovir	IBW	Maximum dose in adults 10 mg/kg/dose every 8 hours
Antifungal agents		
Voriconazole		Maximum dose in adults 300 mg/dose
Antibiotics		
Amikacin	ABW (factor 0.4)	Plasma levels should be determined. Maximum dose in adults 1.5 g/day
Gentamicin	ABW (factor 0.4)	Plasma levels should be determined. Maximum dose in adults 5-7 mg/kg/day, max. 480 mg/day
Clindamycin	TBW	Maximum dose in adults 2.7 g/day
Cephalosporins	TBW	Maximum dose in adults Ceftriaxone: 4 g/day Cefotaxime: 12 g/day Ceftazidime: 9 g/day Cefazoline: 8-12* g/day * Life-threatening infections
Linezolid		Standard dose 600 mg/12 hours Maximum dose in adults 1.2 g/day
Meropenem	TBW	Increased distribution in obese patients. Maximum dose in adults 6 g/day (9 g/day in the case of meningitis)
Metronidazole	TBW	Maximum dose in adults 2.0 g/day
Piperacillin/tazobactam	TBW	Maximum dose in adults 16 g/day
Quinolones (ciprofloxacin)	TBW ABW (factor 0.4)	Some authors recommend using TBW in case a sufficient dose is not achieved. Maximum dose in adults 1.2 g/day
Vancomycin	TBW (loading and maintenance doses)	The recommendation assumes a normal kidney function. Plasma levels should be determined. Maximum dose in adults 4 g/day

Anticonvulsant agents

Valproic acid	TBW	Wide therapeutic range and drug level monitoring. Maximum dose in adults. Loading dose: 800 mg Maintenance dose: 30 mg/kg/day
Carbamazepine	IBW (loading and maintenance doses)	Drug levels should be monitored.
Phenytoin	ABW (loading dose) IBW (maintenance dose) or fixed dose at 300 mg/day	Plasma levels should be determined. Maximum dose in adults 2 g
Phenobarbital	TBW	Drug levels should be monitored.
Levetiracetam	ABW	Volume of distribution similar to total body water. Maximum dose in adults. Loading dose: 2.5 g
Benzodiazepines (diazepam, lorazepam, midazolam)	TBW (loading dose) IBW (maintenance dose)	Clinical monitoring is necessary.

Inotropes and vasoactive agents

Adrenaline	TBW	Small volume of distribution Maximum dose in adults 1 mg/dose
Catecholamines (dopamine, dobutamine)	IBW	Titrate to achieve the effect. Rapid initiation and short half-life. Hydrophilic drug with a small therapeutic window. Wide titration range.
Milrinone	TBW	Pharmacokinetics suggest using lean body mass to estimate the dose; however, there is a risk for insufficient dose.
Sodium nitroprusside	TBW	Obesity may be inversely related to drug response. May require higher doses.

Anesthetic agents

Dexmedetomidine	IBW	High risk for bradycardia and other adverse events in critically ill patients.
Phenthanile	IBW	Adjusted to 0.25 ²¹ ; clinical monitoring is necessary.
Ketamine	IBW	The use of IBW may reduce adverse events. Maximum dose in adults (intravenous): 5 mg/kg
Methadone	IBW	Maintenance dose: 80-120 mg/day
Morphine	IBW	Intermittent doses may be preferred over continuous infusion. Clinical monitoring is necessary.
Propofol	IBW (loading dose) TBW (maintenance dose)	The dose should start at 2 mg/kg and then titration is required.
Rocuronium	ABW	Clinical response should be assessed and dose titration is required.
Vecuronium	IBW	Kinetic values are similar in obese and normal weight patients.

Anticoagulants

Enoxaparin	TBW	If total body weight is used, doses above 30 % of the standard dose may be required. A single dose should be avoided if BMI > 27 kg/m ² .
Heparin	Prophylaxis with standard dose 5000-7500 U 3 times/day Treatment of deep vein thrombosis and TBW	For treatment, the bolus could be reduced or dosing may be started as per schedule. Adjust as per activated partial thromboplastin time.

Antidotes

Flumazenil	IBW	Maximum dose in adults 0.2 mg/dose (accumulated max.: 1 mg)
Naloxone	TBW	Maximum dose in adults: 10 mg
Neostigmine	ABW (cofactor 0.4)	Less adverse events and faster action.
Protamine sulfate	ABW (cofactor 0.4)	The dose should be based on the heparin dose using ABW.
Fluids and electrolyte solutions		
Fluids for baseline requirement	IBW or BSA	
Sodium bicarbonate	IBW	Small therapeutic window when used chronically.
10% sodium chloride	IBW	Dose based on the patient's individual requirements, either age, weight or sodium plasma levels.
Vial: 1 mL = 1.7 mEq		
10% potassium chloride	IBW	Small therapeutic window.
Vial: 1 mL = 1.3 mEq		
Calcium gluconate	IBW	Orally: 20 mEq/dose. Intravenously: 200-400 mEq/day (if K < 2) Electrolytes are charged ions, hydrophilic with low volumes of distribution.
Magnesium sulphate	IBW	Small therapeutic window.

Steroids		
Dexamethasone	TBW	Pharmacokinetic profile similar to prednisone.
Hydrocortisone	TBW	Maximum dose in adults 200-300 mg. 6 g for shock
Methylprednisolone	IBW	Maximum dose in adults, pulse therapy 1 g.
Antiarrhythmics		
Adenosine	IBW	Hydrophilic drug with a small volume of distribution Maximum dose in adults, first 6 mg/second 12 mg
Atropine	TBW	Large volume of distribution into the extravascular space.
Amiodarone	TBW	Recommended with caution due to the potential reduced clearance in the long term. Maximum dose in adults. Loading dose: 150 mg 1.2 g/day
Lidocaine	TBW (loading dose), IBW (maintenance dose)	High volume of distribution in obese patients; however, clearance is the same in obese and normal weight patients.
Diuretics		
Furosemide	IBW	Risk for ototoxicity. Maximum dose in adults 40 mg
Immunosuppressors		
Ciclosporin	IBW	Monitoring is required because it has a small therapeutic window. Obese children require lower maintenance doses.
Insulin therapy		
Crystalline insulin	TBW IBW (infusion)	Conservative initial dose to prevent hypoglycemia.
Bronchodilators		
Ipratropium	TBW	
Salbutamol	TBW	Supported by current practice. Maximum dose in adults: Nebulization: 10 mg/day Spray: 1.6 mg/day
Theophylline	TBW (loading dose), IBW (maintenance dose)	Plasma levels should be determined. Minimum distribution into adipose tissue. Volume of distribution decreases as adiposity increases.
Blood components		
<i>Blood products</i>		
Red blood cells	IBW	Maximum dose 1 U (200-300 mL)
Platelets	IBW	Maximum dose in adults 5-7 platelet concentrates
Plasma	IBW	Maximum dose in adults 10-20 mL/kg
Non-specific immunoglobulin	IBW	IBW should be used when TBW is > 20 % of the IBW.
Analgesics		
Acetaminophen	IBW	Maximum dose in adults 1 g/dose - 4 g/day

TBW: body weight total; IBW: ideal body weight; ABW: adjusted body weight;
BSA: body surface area; K: potassium.

et al.,⁶⁹ they reported that the infusion based on TBW may lead to overdose, whereas clearance correlated to the pharmacokinetic mass (similar to LBW) and not to TBW.

However, currently, there is no precise knowledge on which is the best body descriptor to establish the dosage of opioid agonists in obese children and, since these drugs have a narrow therapeutic range, they should be used with caution.

Antibiotics

Obesity is considered a risk factor for antibiotic therapy failure; therefore, an optimal dosage

should be confirmed to prevent poor infection management in critically ill obese patients.⁷⁰

Beta-lactam antibiotics

Beta-lactam antibiotics are probably the most frequently prescribed antibiotics in pediatrics. Cefazoline is a water-soluble antibiotic with wide distribution; 90 % of the dose is excreted unchanged in urine. Changes in the Vd and clearance have not been demonstrated, so the suggestion is to establish the dosage based on TBW (maximum dose as per the recommendations for adults).⁶⁰

Vancomycin

Vancomycin is one of the most studied antibiotics in obese children.⁷¹⁻⁷⁵ It is widely distributed in fluids and body tissues and is mostly excreted by glomerular filtration. Pharmacokinetic studies in adults show a strong correlation between TBW and the Vd and clearance. On the contrary, in the pediatric population, no differences between obese and normal weight children have been demonstrated.⁷⁴

Three retrospective cohort studies conducted in the pediatric population^{71,72,75} concluded that obese children had higher vancomycin levels (trough level) than normal weight children at a similar dose of mg/kg of TBW.

In children, the use of a 20 mg/kg loading dose based on TBW achieves the area under the curve (AUC)/minimum inhibitory concentration (MIC) therapeutic goal of > 400 in the first 12 hours of treatment.⁷⁶ At present, the recommendation is to use a 60 mg/kg/day maintenance dose (divided in doses every 8 hours) adjusted by TBW accompanied by monitoring of therapeutic levels.⁷⁴

For patients with severe infections, a 25-30 mg/kg initial loading dose adjusted by TBW is recommended so that trough levels are achieved rapidly (15-20 mcg/mL).^{77,78}

CONCLUSIONS

Currently, it is difficult to establish the pharmacokinetic differences between normal weight and obese children because there are scarce clinical trials available, so the knowledge of pharmacokinetics in obese children is still limited.

In addition, it should be considered that most drugs administered to the pediatric population are prescribed based on body size measures, such as TBW and height, assuming that they are normal for age. However, there is no consensus on which is the most appropriate body descriptor to establish drug dosage in critically ill obese children. Such adequate knowledge is a critical safety event for patients.

In addition to the selected body descriptor, obesity-associated pathophysiological disorders that may predict changes in drug pharmacokinetics and pharmacodynamics should always be taken into consideration, as well as the possible presence of organ dysfunction, drug interactions, and associated diseases. ■

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