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Journal home page: <http://ssjournals.com/index.php/ijap>**Review Article****Drug Dosing in Obese Patients: A Dilemma**Anshika Kaul¹ and Mir S Adil^{*2}¹Pharm.D, Manipal University, India.²Clinical Pharmacologists, Aster Prime Hospital, India***Correspondence Info:**

Dr. Mir S Adil

Clinical Pharmacologist,
Aster Prime Hospital, IndiaEmail: eternalstrings@gmail.com**Keywords:**Body Mass Index,
Drug Dosage Calculations,
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Obesity,
Pharmacokinetics**Abstract**

Prevalence of obesity has increased over the past few years and is still growing. Usually obesity is accompanied by co-morbid conditions which may be caused because of it too. Due to this it is not unusual for a physician to have a lot of obese patients. Now, the dosing of the drug is a major issue. The dose given for normal patients may not be accurate for obese patients and it is highly likely to worsen the condition of the patient on account of the fact that pharmacokinetic parameters of an obese individual differs from a normal person. During clinical trials, the dose is calculated for normal weight patients, but the scenario changes in obese. Due to the lack of sufficient evidence, the dose modification poses to be a threat to patients especially the ones who are on drugs with a narrow therapeutic index. Various scales have been formulated to help but more research needs to be done to get precise doses.

1. Introduction

Obesity has turned into a global epidemic which was earlier present in developed countries but has started to spread in developing countries as well [1,2]. According to WHO, 1.6 billion people are overweight out of which 400 million are obese [3]. Obesity itself can lead to various metabolic, cardiovascular and/or pulmonary disorders [4]. Obesity is defined by the WHO based on the BMI of a person. BMI is calculated using weight in kg and height in meter. The BMI is calculated by the following formula:

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}$$

According to WHO, obesity is classified by the values obtained by the BMI. If a person's BMI is $<18.5 \text{ kg/m}^2$ they are considered underweight, $18.6\text{-}24.99 \text{ kg/m}^2$ is normal and $>25 \text{ kg/m}^2$ is overweight. The overweight is again stratified into 4 classes as shown in Table 1.

Table 1: Classification of overweight based on BMI

Overweight	BMI
Pre-obesity	25 to 29.99 kg/m^2
Obesity class I	30 to 34.99 kg/m^2
Obesity class II	35 to 39.99 kg/m^2
Obesity class III	$>40 \text{ kg/m}^2$

When the BMI is more than 40 kg/m^2 , it's known as morbid obesity [5]. Accurate dosage regimens for obese patients are still vague. The pharmacokinetics of each person varies with a change in weight. As the number of obese patients with comorbidities such as diabetes mellitus and hypertension increases, physicians will encounter more problems regarding doses as the normal dose may not show therapeutic effect. The clearance and distribution of obese patients are different from a normal person [6-10].

2. Pharmacokinetics

The pharmacokinetics of an obese person is different from a normal person. If we understand them the calculation of dose might be more accurate and easier.

2.1 Absorption:

Absorption depends on the lipophilicity of the drug. Adipose tissue does not affect the absorption. Studies show that there is no major alteration in the absorption in obese patients [11-14].

2.2 Distribution:

Lipophilic drugs show increased volume of distribution than lipophobic or hydrophilic drugs as they are distributed in the fat tissue and the lean mass. For example volume of distribution of Benzodiazepines is high [15,16]. Hence TBW should be used. According to various studies, IBW should be used in case of hydrophilic drugs because the distribution is only limited to the lean tissue. Hence the distribution of both kinds of drugs varies greatly making it more difficult to obtain the correct dose [17-19].

2.3 Metabolism:

Increased level of serum proteins changes the metabolism in obese patients that leads to different half-lives of the drug in an obese patient from a normal person [20]. An increase in phase II metabolism is noticed. Phase I metabolism either increases or remains the same [21].

2.4 Excretion:

Liver and kidney are the most important organs for the excretion of the drug. Any change in the physiology may affect the clearance of the drug. In some cases, obesity can cause fatty liver which impairs the blood flow. That creates an impact on the clearance in the liver [22]. According to Han *et al* obese patients exhibit higher clearance than non-obese [23]. The kidney weight, renal blood flow glomerular filtration rate is higher in obese people hence clearance is high [24]. In an attempt to calculate the dosage regimen various formulae or dosing scales have been formulated. Ideally the dosing formula should consider height, weight, pharmacokinetic factors etc but so far that kind of formula doesn't yet exist yet [25]. It is mandatory that whenever medications are administered to an obese patient, especially the ones with narrow therapeutic index, he or she should be monitored closely. Some of the commonly used parameters for dose calculation include:

Body mass index (BMI): As explained before, BMI is officially used to obtain dosage regimens. According to Michael J Henley *et al* BMI is not the most appropriate dosing scalar because it does not consider adipose tissue and lean body mass separately [26].

Body Surface Area (BSA): It is calculated using height, weight and constants as [27]:

$$BSA (m^2) = [(TBW) \times (\text{height in cm}) / 3600]^{1/2}$$

BSA is extensively used in dosing of anti-cancer agents, however its use in calculating drug dose in obese patients is still questionable [28]. Just like BMI, BSA cannot differentiate between adipose tissue and lean body mass [28].

Total Body Weight: This method is usually used for normal patients [29]. Lean body mass and fat depositions do not increase proportionally in morbidly obese patients [30]. Since majority of the blood supply goes to regular muscles instead of adipose tissue, using this method for calculation may cause toxicity in morbidly obese patients [29].

Ideal Body Weight (IBW): Its equation is based on size which relates it to mortality of a subject. An empirical equation to estimate IBW was derived by Devine [31]:

$$IBW (kg) = 45.4 \text{ kg (49.9 kg if male)} + 0.89 \times (\text{height in cm} - 152.4)$$

IBW is different from BMI and BSA because it considers gender while calculating. The use of ideal body weight is limited because it implies that patients with same height should receive the same dose and the changes occurring in the body due to obesity [29].

Lean Body Weight (LBW): It is the weight of a person devoid of all the fat mass. It does not take the weight of the adipose tissue into consideration [26]. $LBW (kg) = (9270 \times TBW) / (A + B \times BMI)$, where values of A and B are 6680 and 216 for males, and 8780 and 244 for females [30].

Predicted Normal Weight: It is used to predict the normal weight of an obese individual [32]. It is usually not accurate when height and weight are extreme [33].

$$\text{For males, PNWT (kg)} = 1.57 \times TBW - 0.0183 \times BMI \times TBW - 10.5.$$

$$\text{For females, PNWT (kg)} = 1.75 \times TBW - 0.0242 \times BMI \times TBW - 12.6$$

A compilation of drug list along with the formulae that can be used to calculate dosage regimens is depicted in

Table 2.

Table 2: Drugs with formulae to calculate dosage regimens

Drug	Formula
Anaesthetic	
Propofol [34-37]	Induction: IBW Induction: LBW assessed by BIA Maintenance: TBW or IBW + 0.4 excess weight
Thiopental [38,39]	7.5 mg/kg IBW TBW
Lidocaine [40]	IBW
Ketamine [41]	IBW
Anti- depressant	
Midazolam [42,43]	TBW for initial dose IBW for continuous dose
Lorazepam [44]	Loading doses should be adjusted on actual weight and maintenance doses should be adjusted on ideal body weight.
Benzodiazepine [45]	IBW
Skeletal muscle relaxants	
Vecuronium [46]	IBW
Cisatracurium[47]	TBW IBW
Rocuronium[48]	IBW
Succinylcholine [49]	TBW
Atracurium [50]	IBW or ABW
Muscle stimulants	
Neostigmine [51]	TBW
Suggamadex [52]	IBW + 40% excess weight
Analgesics	
Alfentanil [12,53,54]	IBW or corrected weight TBW
Fentanyl [55-57]	TBW Corrected weight = $IBW + (0.4 \times \text{excess weight})$ pharmacokinetic mass = $52/[1 + (196.49 e^{-0.025kg} - 53.66)/100]$
Sufentanil [58,59]	TBW
Remifentanil [12,60]	LBM (James equation) LBM (Janmahasatian equation)
Morphine [61]	IBW
Paracetamol [62]	IBW
Opiates [45]	IBW
Anti-viral	
Acyclovir [40]	IBW
Ganciclovir [40]	ABW
Anti-fungal	
Amphotericin B [63]	TBW
Fluconazole [64]	TBW
Flucytosine[65]	IBW
Anidulafungin[40]	Loading dose: 200 mg Maintenance dose: 100 mg
Antibiotics	
Erythromycin [66]	IBW
Daptomycin[64]	TBW
Penicillins[67]	TBW
Carbapenem[45]	TBW
Cephalosporin [45]	TBW
Ciprofloxacin [68,69]	$(0.45 [TBW-IBW]) + IBW$
Gentamicin [68]	$(0.4 [TBW-IBW]) + IBW$
Amikacin [45]	$(0.4 [TBW-IBW]) + IBW$
Vancomycin [68]	TBW
Tobramycin [68]	$(0.4 [TBW-IBW]) + IBW$

Clindamycin [70]	Maximum of 4.8g/day in divided doses
Metronidazole [71]	500mg TDS
Anti-tubercular	
Ethambutol[40]	IBW
Isoniazid [40]	IBW
Pyrazinamide[40]	IBW
Rifampin [72]	IBW
Anticoagulants	
Heparin [73,74]	ABW
Lepirudin [40]	TBW (Use actual body weight up to 110 kg)
Warfarin [75]	ABW
Enoxaparin [76]	TBW
Argatroban[77]	TBW
Anti-epileptics	
Phenytoin [78]	Dosing weight= $IBW + [1.33(ABW - IBW)]$
Valproic Acid [79]	IBW
Carbamazepine [45]	IBW
Cardiovascular drugs	
Procainamide [40]	IBW
Digoxin [45]	IBW
Anti- neoplastic agents	
Busulphan [80]	BSA
Cyclophosphamide [81]	Adj Body Weight= $IBW + 40\%(TBW - IBW)$
Melphalan [40]	BSA
Thiotepa[81]	Adj Body Weight= $IBW + 40\%(TBW - IBW)$
Carboplatin [81]	Adj Body Weight= $IBW + 40\%(TBW - IBW)$
Doxorubicin [11]	BSA
Topotecan [11]	BSA
Irinotecan[11]	BSA
Cisplatin [11]	BSA
Paclitaxel [11]	BSA
Docetaxel[11]	BSA
Methotrexate [82]	BSA
Miscellaneous	
Cyclosporine [83]	IBW
Theophylline [40]	IBW
Immunoglobulin [7]	Dose Determining Weight= $IBW + 0.4[\text{actual body weight(kg)} - IBW]$
G-CSF (Filgrastim) [40]	Actual Body Weight

3. Conclusion

Various scales have been formulated to calculate drug dosing in obese population but more research needs to be done to get precise doses.

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