Which weight for weight-based dosage regimens in obese patients?

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In addition to age and measures of organ dysfunction, body weight is a variable that is often required to determine the most appropriate medication dosage. Dosage that is inappropriate for the patient's weight may increase the risk of adverse events and increase the cost of care. In one tertiary care institution, dosage that was inappropriate for patients' weight and renal function resulted in 42% of all the adverse drug events reported in the investigation. All of these events were considered to be preventable. Each adverse drug event in the study was estimated to result in an excess hospitalization cost of $2262 (p < 0.001 compared to matched controls without events).

To avoid the deleterious consequences for both the patient and the institution if inappropriate dosage regimens are used, a number of medications have weight-based (e.g., milligram per kilogram) dosage recommendations. This raises the question, particularly for obese patients, of which weight should be used. Depending on factors such as the relative lipophilicity of the medication, the clinician may choose to use actual or total body weight (TBW) or an adjusted weight, such as ideal body weight (IBW) or some other adjusted weight. In patients who are not obese or extremely underweight, the decision to use TBW or an adjusted weight for calculating medication dosages is of little clinical importance, since either calculation would yield similar results. However, with increasing degrees of obesity, the dosages derived by TBW, IBW, or adjusted weight will be increasingly disparate.

The pervasiveness of terms, such as IBW, throughout the pharmacy literature belies the uncertainties surrounding such estimations. The calculations themselves are quite straightforward and are typically learned in pharmacy school. As a clerkship preceptor, I find that most students have memorized an equation for IBW, and those who do not can generally find it in their pharmacokinetics books. But it is much less common that these same students understand the limitations of the equation, the most important of which may be that weight-adjusted calculations may never have been demonstrated to improve patient outcomes, either through increased medication efficacy or reduced toxicity.

The purpose of this discussion is to examine the rationale for using a weight other than TBW for weight-based medication calculations in adult obese patients and to elucidate the major limitations of these calculations. Some of the terminology related to weight adjustment that is commonly associated with weight-based dosage regimens will be reviewed, and a discussion of the rationale for common dosing equations will be provided. Obesity-related changes in organ function, which may necessitate alterations in dosage regimens, will be briefly discussed along with the limitations of available pharmacokinetic and pharmacodynamic literature relative to drug dosing in obese patients. Finally, issues related to choosing a weight for the initiation of weight-based dosage regimens will be discussed.

Terminology

Lean body mass. Lean body mass (LBM) is comprised of non-fat-cell mass (except for the small amount of fat in the cell membranes) and intercellular connective tissue; it accounts for more than 99% of the body's metabolic activity. All of the methods used to determine LBM have limitations relative to availability, cost, need for technical expertise or equipment, or accuracy. For example, whole body densitometry measurements by underwater immersion are accurate, but the system is not portable and requires the cooperation of patients. On the other hand, anthropometric measurements can be easily performed in most clinical settings, but interrecorder reproducibility of measurements is a problem, and edema may limit its use. Similarly, bioelectric impedance has received increasing attention because it requires little technical expertise to...
measure, and the equipment is not particularly elaborate. As with anthropometry, this method lacks accuracy in patients with edema.2

In addition to the cumbersome methods of measuring LBM, there are equations that have been used to estimate it.3 LBM estimations may be better for predicting drug concentrations than IBW or TBW for loading doses of hydrophobic drugs as well as maintenance doses of drugs eliminated by the liver in nonelderly adults (since clearance is proportional to lean mass).3 Comparisons between the various LBM and IBW estimations are needed, as are comparisons with body surface area (BSA) calculations in children.

**IBW.** IBW is often described as a surrogate for LBM; but in contrast to the equations used for calculating IBW (which only require patient height and sex), at least one published equation for estimating LBM requires body weight as well as height and sex.4 The vast majority of pharmacokinetic investigations of medications in obese patients have used equations for IBW rather than LBM. While the concept of LBM was developed on the basis of metabolic activity, IBW is often used as a surrogate for LBM when estimating drug distribution into lean (i.e., nonadipose) tissue. One particular equation, by Devine,5 is widely cited, but no attempt at validation was made at the time of publication. In fact, its origin was not stated in the original publication, although it has since been determined that it was created by Devine’s mentor.6 An equation created by Robinson et al.7 is very similar to that created by Devine.5 Table 1 lists the equations commonly used to calculate LBM and IBW in published pharmacokinetic investigations involving obese patients and for medication dosing in the clinical setting.

Both Devine’s5 and Robinson et al.’s7 equations appear to be based on life insurance tables that listed “desirable” weights for men and women ages 25 years and over.8 The demographic of the U.S. population at the time of the tables’ publication are illustrated by the relatively restricted range of heights (5 ft 2 in–6 ft 4 in for men and 4 ft 10 in–6 ft 6 in for women) and weights (112–204 lb. for men and 92–173 lb. for women) listed. Also, desirable weights may change with time. However, insurance companies’ definitions of IBW continue to be used today.

**Other weight adjustments.** An adjusted weight is often used in clinical settings when IBW is thought to underestimate and TBW to overestimate drug distribution in the body. Typically, some percentage of the excess weight is added to the estimated IBW of the patient. This practice is based on studies suggesting that medications, such as the aminoglycosides, distribute into the excess lean mass of obese patients. For example, one equation commonly used for calculating aminoglycoside dosages in obese patients is based on pharmacokinetic studies that found an increased volume of distribution (V) in morbidly obese compared with normal weight patients when examining IBW:9–11:

\[
\text{Adjusted weight} = 0.4(\text{TBW} - \text{IBW}) + \text{IBW}
\]

**Body mass index (BMI).** Although less commonly used in pharmacokinetic12–14 and clinical settings to calculate medication dosages, a World Health Organization (WHO) obesity classification system, which was subsequently revised by the National Institutes of Health (NIH), is the standard for epidemiologic investigations.15,16 With this system, a BMI of <18.5 kg/m2 is defined as underweight, 18.5–24.9 kg/m2 as normal, 25–29.9 kg/m2 as overweight, 30–39.9 kg/m2 as obesity (NIH has further subdivisions of obesity that account for waist circumference, since this has been shown to be a marker for increased disease risk, even in normal weight patients), and ≥40 kg/m2 as extreme obesity.

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<th><strong>Equations Commonly Used To Estimate Lean Body Mass (LBM) and Ideal Body Weight (IBW)</strong></th>
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| James | LBM in males = 1.10 TBWa – 120 (TBW/height in cm)2  
LBM in females = 1.07 TBW – 148 (TBW/height in cm)2 |
| Devine | LBM in males = 50 kg + 2.3 kg/in for height over 5 ft  
LBM in females = 45.5 kg + 2.3 kg/in for height over 5 ft |
| Robinson et al. | IBW in males = 50 kg + 1.9 kg/in for height over 5 ft  
IBW in females = 49 kg + 1.7 kg/in for height over 5 ft |

*aTBW = total body weight.
tional implications for dosing medications, since lean tissue receives 22% of cardiac blood flow compared with 5% for fat and 73% for viscera.\textsuperscript{19}

There is much to be learned about the effects of obesity on heart and liver function, particularly with respect to how changes in function may affect the disposition or effects of medications. There is some evidence to suggest that obesity may result in impaired cardiac function.\textsuperscript{20} Similarly, obesity may influence the hepatic cytochrome P-450 isoenzyme system; in vivo probes, such as chloroxazone, have been studied as indicators of specific enzyme activity.\textsuperscript{21} In hepatic phase II reactions, glucuronidation may be enhanced to a greater degree than sulfation in obesity.\textsuperscript{19}

Whereas the effects of varying degrees of obesity on renal function (and associated medication elimination) need further elucidation, it is clear that estimates of function based on creatinine clearance equations can be misleading, particularly in morbidly obese patients. In a study involving 12 men and 31 women who weighed at least 195% of their IBW (as calculated by Devine\textsuperscript{5}), creatinine clearance estimated by five methods differed significantly from measured creatinine clearance.\textsuperscript{22} The various methods overestimated creatinine clearance by 51–61 mL/min/1.73 m\textsuperscript{2} when using TBW and underestimated creatinine clearance by 36–40 mL/min/1.73 m\textsuperscript{2} when using IBW. The authors concluded that none of the formulas were accurate for morbidly obese patients.

Both lean-mass and adipose-tissue binding of medications may be affected by obesity. Whereas binding to lean tissue depends on the chemical structure of a medication, binding to adipose tissue is more a function of lipophilicity, and estimating its extent is complicated by difficulties in measuring adipose storage.\textsuperscript{23} The issue is further complicated by inconsistent findings among studies involving medication effects on protein binding, part of which may be related to the difficulties in controlling the effects of other binding substances in blood (cholesterol, free fatty acids, lipoproteins, and triglycerides).\textsuperscript{19}

**Pharmacokinetic and pharmacodynamic investigations in obese patients**

While there is a substantial body of research and discussion about obesity as a health problem,\textsuperscript{16} there are few studies of how excess weight influences the pharmacokinetics or pharmacodynamics of the numerous medications given to obese patients.\textsuperscript{18,19} There are even fewer combined pharmacokinetic–pharmacodynamic investigations, so the clinician usually has to assume that the findings of pharmacokinetic investigations have pharmacodynamic correlates. Of the pharmacokinetic investigations available, the majority involved single i.v. doses given to small numbers of healthy volunteers or patients with a relatively uncomplicated health status.\textsuperscript{18,19}

The dearth of pharmacokinetic and pharmacodynamic information concerning dosing in obese patients is not surprising for newly marketed medications, since this information is not required for FDA to grant marketing approval. While preregulatory studies may involve patients with a wide range of weights, patients are rarely stratified by weight before study initiation, and there is often a limited number of patients weighing much more or less than their IBW. Once a medication has received marketing approval, there is little incentive for the manufacturer to conduct dosing studies in patients of varying weights. The remainder of this discussion relates to choosing a weight for weight-based dosage regimens in the absence of well-established dosing guidelines for medication administration in obese patients.

**Choice of weight**

Given all the uncertainties regarding weight-based dosing equations and medication disposition in obesity, what practical information can be gleaned from the existing literature? At best, the available information may provide guidance for initiating a medication regimen (i.e., the loading dose) in obese patients with subsequent modifications made on the basis of clinical responses and therapeutic drug monitoring (when available and useful). Such qualifications aside, some general statements can be made relative to medication dosing in obesity assuming there is no concomitant organ dysfunction or change in body composition unrelated to the effects of obesity itself.

As mentioned earlier, the majority of pharmacokinetic studies have used IBW for defining obesity. In these studies, 120–130% of IBW was commonly used as the minimum weight for defining obesity. It seems reasonable to conclude that patients whose TBW is within 120% of their IBW are likely to have few clinically important consequences relative to the use of an actual versus an ideal weight for designing the initial medication dosage regimen. This presumes, of course, that the patient being treated has a relatively normal body composition. For example, the generalization may not apply to an underweight and malnourished patient who has lost 10 kg of lean weight before surgery but then gains 15 kg of water weight in the postoperative period.

For patients who are more than 120–130% of IBW, the choice of weight becomes more important since the dose of a medication could be substantially different depending on whether the TBW or an adjusted body weight is used for calculating a loading dose. As in normal weight patients, a medication’s V is the most useful pharmacokinetic property for determining loading doses in obese patients. In general, V tends to increase with more lipophilic medications,\textsuperscript{17,19} and, in contrast to infor-
mation such as a medication’s lipophilicity, estimates of $V$ are usually obtainable from published pharmacokinetic studies involving obese patients or from pharmacokinetics handbooks. For the remainder of this article, examples will be provided to illustrate the benefits and risks of using $V$ estimates for helping the clinician to choose an initial dosing weight for obese patients. A more comprehensive compilation of dosing recommendations for specific medications in obesity is beyond the scope of this overview, but more detailed references are available.

When considering the examples that follow, it must be stressed that $V$ estimates for any given medication belie the complexities involving medication distribution into lean and adipose compartments and the difficulties in measuring the distribution patterns in both the preclinical and clinical phases of medication development. $V$ is a function of the properties of a medication (e.g., lipophilicity, polarity, and degree of ionization at physiological pH) and the human body (e.g., blood flow, plasma protein and tissue binding). Of these properties, the degree of ionization and lipophilicity of a medication, in conjunction with lean- and adipose-tissue binding, are most likely to influence distribution in obesity. Even assuming the physicochemical properties of a medication are not altered by the increased adipose tissue in obese patients, it is difficult to reliably anticipate the result of the binding processes between lean and adipose tissues in the clinical setting.

Neuromuscular blocking agents. The nondepolarizing neuromuscular blocking agent rocuronium is representative of medications that have a small $V$ (<15 L). Rocuronium’s $V$ is ≤0.2 L/kg in normal weight and obese patients. This small $V$ reflects the restriction of the agent to the extracellular compartment, which is not surprising since the agent is weakly lipophilic and would be expected to have limited distribution in adipose tissue. Plasma concentrations achieved with loading doses in obese patients are most easily predicted in this situation, since $V$ is based on IBW. A relatively limited portion of a medication with a small $V$ would be expected to distribute into the aqueous portion of the adipose tissue. In contrast to a conservative dosing approach based on IBW, the clinician could take the aqueous portion of adipose-tissue binding into consideration by increasing the loading dose by the expected portion of the increased distribution. For example, if it is assumed that 20% of the adipose tissue is water, total $V$ (in volumeteters) could be calculated by multiplying the weight-based $V$ value (in volume per weight) by 0.2 (TBW - IBW) + IBW.

$V$ for another nondepolarizing neuromuscular blocking agent, vecuronium (approximately 0.8 L/kg based on IBW for both normal weight and obese patients), is larger than that of rocuronium and may reflect distribution beyond the plasma and extracellular fluid compartments. The larger $V$ for vecuronium compared to rocuronium would suggest that an adjusted weight might be needed when administering vecuronium to obese patients. But as with rocuronium, vecuronium is a polar (hydrophilic) medication, so its $V$ (based on liter per kilogram) is decreased in obese patients because of its limited binding to adipose tissue. Therefore, as with rocuronium, a conservative approach is to dose vecuronium on the basis of a patient’s IBW.

Phenytoin and antimicrobials. Phenytoin and the aminoglycosides are examples of medications with moderate volumes of distribution (approximately 0.2-1 L/kg) in normal weight patients. It is typically recommended that a larger portion of the excess weight be used for adjusting drug dosages when dealing with medications that have moderate volumes of distribution. Based on studies conducted in obese subjects, it is usually recommended that vancomycin loading doses be based on TBW to avoid underdosing, particularly in patients with more serious infections.

Lipophilic drugs. The disposition of medications in obese patients is most unpredictable for highly lipophilic medications with expected large volumes of distribution. It is difficult to generalize dosing suggestions for these drugs, even when the recommendations are limited to the estimation of loading doses. A good example of this is digoxin, which is generally dosed on IBW despite its expected distribution into adipose tissue that would suggest TBW should be used. With other lipophilic medications, such as remifentanil, serious adverse effects associated with higher doses argue for more conservative initiation regimens with subsequent dosage adjustment to clinical response.

Although supporting clinical studies have not been conducted, a similar approach has been recommended for calculating loading doses with other antimicrobials with expected distribution patterns similar to the aminoglycosides (e.g., β-lactam antimicrobials, ciprofloxacin). For antimicrobials that have a good safety profile in commonly recommended dosing ranges, such as the penicillins and cephalosporins, another approach would be to use the upper end of dosing ranges in obese patients. Subsequent dose adjustment should be based on clinical response and possibly on results of therapeutic drug monitoring.

Vancomycin, which has a $V$ (0.6 L/kg) not much larger than that for the aminoglycosides (0.3 L/kg), serves as a good example of an exception to using adjusted weight for loading doses when dealing with medications that have moderate volumes of distribution. Based on studies conducted in obese subjects, it is usually recommended that vancomycin loading doses be based on TBW to avoid underdosing, particularly in patients with more serious infections.
published information for dosage guidance, the choice of initial dosing weight should be based on considerations such as the need for rapid attainment of therapeutic concentrations and the safety profile of the medication. When possible, if dosing medications with a large $V$, a series of miniloading doses followed by an assessment of effect after each dose is preferable to the administration of a single, large dose aimed at achieving the desired therapeutic effect. Additionally, therapeutic drug concentration monitoring (if available) may be helpful when published studies suggest a positive relationship between concentrations and toxicity or efficacy.

**Summary of loading dose recommendations.** Despite the limitations of the IBW equations as estimators of lean mass, their results are preferable to TBW and other larger adjusted weight estimates for use in obese patients receiving medications determined in studies conducted in normal weight patients to have a small $V$. This is particularly true when the clinician wants to err on the conservative side of dosing recommendations. For medications with a somewhat larger $V$ in normal weight patients, an adjusted weight may be more appropriate for calculating loading doses in the obese patient, particularly when a less conservative approach is desirable (e.g., $\beta$-lactam antimicrobial therapy for a severe infection). For medications with a large $V$, any generalizations pertaining to loading doses in obese patients based on studies in normal weight patients are unreliable. Knowledge of the distribution of the medication into adipose tissue (i.e., partition coefficient) might help improve predictability of these loading dose regimens, but such information is usually not readily available to the clinician, and predictive equations using such values have not been validated.

**Weight for maintenance dosage.** The above comments addressed choosing among body weights to determine appropriate loading doses, but they may apply beyond the first dose of medication. For example, patients with normal renal function who are receiving once-daily aminoglycoside therapy typically have undetectable serum concentrations at the end of the dosing interval. In this situation, there is no drug accumulation that needs to be accounted for with maintenance dosing. In other words, each dose can be thought of as a loading dose and would be based on the chosen weight. The dose may eventually be modified based on therapeutic drug monitoring and clinical progress of the patient.

The situation becomes more complicated when attempting to make generalizations regarding the choice of weight for maintenance dosing in obese patients when accumulation of medication is expected to occur between doses. A study involving carbamazepine illustrates this point. A single 200-mg dose of carbamazepine was given to six healthy volunteers before and after a weight loss program. The mean weight loss was about 30 kg (from 106 to 78 kg, $p < 0.01$) over approximately 11 months. Given the substantial lipophilicity of carbamazepine, it was not unexpected that the mean $V$ decreased substantially after the weight loss. However, mean carbamazepine clearance was higher after the weight loss (20 mL/min before and 32 mL/min after, $p < 0.05$). These results suggest that, while an adjusted weight or possibly IBW (using a series of miniloading doses) should be used for loading dose purposes, IBW should be used for maintenance dosing of carbamazepine.

One remaining consideration relates to changes in patient weight during a course of drug therapy. This is of particular concern in the critical care setting where fluid gains and losses result in rapidly fluctuating weights as well as distributional changes. As a general rule, unless there was a clear mistake in the choice of initial weight for dosage calculations, it is best to use the same weight (i.e., the initial dosing weight) for calculations in the critical care setting. While there are no studies supporting this recommendation, it seems logical that multiple changes in dosing calculations relative to changes in weight could increase the propensity for medication errors.

**Conclusion**

Despite the questionable validity of equations used to estimate IBW and adjusted body weight, the equations have usefulness in the clinical setting for the initial dosing of medications in obese patients. The use of IBW for weight-based dosing is most applicable in obese patients when dosing hydrophilic medications with $V$ values that are small and based on pharmacokinetic studies with normal weight patients. Other intermediate adjustments of weight pertaining to obese patients are usually better for dosing medications that have a moderate $V$ determined in studies in normal weight patients, particularly when the medications under consideration have good safety profiles. Finally, medications that have a large $V$ are the most difficult to dose in obese patients due to unpredictable distribution patterns. For these medications, generalizations relative to choice of weight cannot be made.

**References**


COMMENTARIES  Weight-based dosage regimens
