Drug dosing in Extremes of Weight

The Plump & Heavy versus The Skinny & Light

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• Clinical response to medication can differ between patients.

• Among the known sources of variability is an individual's nutrition status.

• This lecture defines some pharmacokinetic terms, provides relevant body size metrics and describes the physiologic influences of obesity and protein-energy malnutrition on drug disposition.
Objective: To do good without harm

Dose Optimization
• Weight-based drug dosing, which presumes a healthy BMI, can be problematic in the obese patient or protein-energy malnourished.

• The use of total body weight, lean body weight, or an adjusted body weight depends on the drug and how it is differently handled in obesity or malnutrition.

The Challenge
“The Right Dose of the Right Drug at the Right Time for the Right Patient”
Distribution

• Distribution or movement of an active drug from the bloodstream to the site(s) of effect are determined by
  
  • **drug factors** (e.g. lipophilicity, plasma protein binding, degree of ionization and tissue affinity) and

  • **body factors** (e.g. body composition, blood flow, tissue size and permeability)

Pharmacokinetics
Distribution

- The Vd is an expression that uniquely reflects the distribution of each drug and is described in litres per kilogram of body weight (litres/kg).

- Vd relates the serum drug concentration to the amount of drug in the body.

- Higher values indicate extensive distribution and tissue binding.
Distribution

• Drugs bind to three major serum proteins:
  • albumin, α1-acid glycoprotein, and lipoproteins

• Since bound drugs are generally unavailable for hepatic extraction, for metabolism, and for renal excretion, increased protein binding may result in decreased metabolism or clearance.

Pharmacokinetics
Metabolism

• Phase I metabolism - addition/subtraction of a functional group.
• Phase II - conjugation with an endogenous substance.

• Metabolic reactions take place not only in the liver, but also in plasma and other tissue sites (e.g. intestinal mucosa) to some degree.
Metabolism

- Phase I hepatic metabolic reactions (oxidation, reduction, hydrolysis) are substrate-dependent and are usually increased or unchanged in obesity.

- In contrast, metabolism of drugs by some phase II reactions (conjugation by sulfation or glucuronidation) is consistently increased in obesity.

Pharmacokinetics
Excretion

• Excretion reflects the volume of blood that is cleared of a drug per unit of time as observed from sequential serum drug concentrations following an administered dose.

• This occurs predominantly through renal and biliary routes of excretion.

Pharmacokinetics
Excretion

• Clearance is used to define the elimination of a drug from the body and is described in litres per hour (litres/h).

• The term clearance refers to the sum of multiple routes of elimination when more than one route exists for a drug.
• Many drugs rely on weight-based (mg/kg) dosing.

• The size of the initial or loading dose of a drug depends on its Vd, while maintenance doses are based on drug clearance.
• The use of ‘ideal’ body weight in practice or in drug studies is problematic.

• The equations are empirically derived and only take height and sex into account rather than being based on actual body composition data.

• The ‘ideal’ body weight is NOT a true reference weight and NOT a surrogate for a patient’s lean body weight (LBW).

Ideal Body Weight
### Equations Commonly Used To Estimate Lean Body Mass (LBM) and Ideal Body Weight (IBW)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Equations</th>
</tr>
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<tbody>
<tr>
<td>James⁴</td>
<td>LBM in males = 1.10 TBW⁻¹ - 120 (TBW/height in cm)²</td>
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<tr>
<td></td>
<td>LBM in females = 1.07 TBW - 148 (TBW/height in cm)²</td>
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<tr>
<td>Devine⁵</td>
<td>IBW in males = 50 kg + 2.3 kg/in for height over 5 ft</td>
</tr>
<tr>
<td></td>
<td>IBW in females = 45.5 kg + 2.3 kg/in for height over 5 ft</td>
</tr>
<tr>
<td>Robinson et al.⁷</td>
<td>IBW in males = 50 kg + 1.9 kg/in for height over 5 ft</td>
</tr>
<tr>
<td></td>
<td>IBW in females = 49 kg + 1.7 kg/in for height over 5 ft</td>
</tr>
</tbody>
</table>

⁴TBW = total body weight.
As a part of usual clinical practice, the height and weight are obtained to calculate the BMI.

<table>
<thead>
<tr>
<th>Condition</th>
<th>BMI Range</th>
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<tbody>
<tr>
<td>Underweight</td>
<td>BMI of &lt; 18.5 kg/m²</td>
</tr>
<tr>
<td>Normal</td>
<td>BMI = 18.5 - 24.9 kg/m²</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI = 25 - 29.9 kg/m²</td>
</tr>
<tr>
<td>Obese</td>
<td>BMI = 30 - 39.9 kg/m²</td>
</tr>
<tr>
<td>Morbidly Obese</td>
<td>BMI &gt; 40 kg/m²</td>
</tr>
</tbody>
</table>
• BMI is not easily applied in determining drug dosing because at a given value it does not distinguish between excess adipose tissue and muscle mass.
• Body composition can be conceptually divided into fat mass (FM) and fat-free mass, which resemble the anatomic adipose tissue and lean body mass, respectively, allowing recognized distinctions.
Normal body composition. Lean body mass contains all the body protein and is essential for survival while fat mass is mainly a reservoir for energy.
• The clinical term LBW is used to reflect fat-free mass.

• As expected, and documented by MRI, BMI is strongly correlated with FM, while LBW includes body water and is correlated with body cell mass.

What is the right dose?
• So if ‘ideal’ body weight is not appropriate, and BWt fails to differentiate between FM and LBW, then what dosing weight should be used for the patient with obesity or PCM?

What is the right dose?
• The answer to this question depends on the drug being dosed and how it is handled differently, if at all, in the patient with obesity or protein calorie malnutrition (PCM).

• In other words, the ‘dosing weight’ should be based on the characteristic behaviour of the drug rather than in relation to a standard weight-for-height metric.

What is the right dose?
• For practical purposes, the BWt is used as the dosing weight most often except for the volume overloaded patient and for the patient with obesity.

• LBW may be used as the dosing weight for some drugs in PCM and obesity.

• In other cases, an adjusted body weight (Adj-BW) that lies between BWt and LBW is often used clinically to empirically adjust the altered body composition expected in obesity.
• Since ~30% of adipose is water, an empirical approach is use of the Devine formula to calculate lean body weight (LBW), to which is added a dosing weight correction factor (cf) of 0.3 times the difference between actual total body weight (BWt) and LBW

\[
\text{Adj-BW} = \text{LBW} + (\text{cf})(\text{BWt} - \text{LBW})
\]
Obesity
• In the obese patient, the focus on drug dosing should go beyond excess FM, to appreciate that the totality of change in body composition and function influence the tissue distribution of a drug, its clearance and ultimately its clinical effects.

• Arbitrary dose reductions or dose capping in obesity may be counterproductive by adversely influencing the clinical outcome.
The incorporation of accurate height and weight data into validated equations for LBW derived from individuals across the BMI spectrum is recommended.

• **Men** \((1.1013)(\text{kg}) - (0.01281)(\text{BMI})(\text{kg})\)

• **Women** \((1.07)(\text{kg}) - (0.0148)(\text{BMI})(\text{kg})\)

• **Men** \((9270)(\text{kg})/(6680 + 216(\text{BMI}))\)

• **Women** \((9270)(\text{kg})/(8780 + 244(\text{BMI}))\)

**Drug Dosing in Obesity**


• The distribution of a drug in the body can involve both compartments, while drug clearance is correlated with LBW.

• This correlation between systemic drug clearance and LBW is recognized.

• Although BWt may correlate with liver volume, LBW was the only variable to correlate with hepatic drug clearance.

• The renal function is also closely related to LBW.

Drug Dosing in Obesity

**Obesity-associated physiological changes**

- Increased body mass, including both lean body mass and adipose tissue
- Increased cardiac output and blood volume
- Increased renal clearance
- Hepatic metabolic changes
- Changes in serum protein levels

**Physiologic Changes in Obesity**
• Approximately 20–40% of the excess body weight in obesity is made up of lean mass across BMI of 29–47 kg/m².

• All tissue compartments (e.g. visceral organs, muscle mass, adipose tissue and body water), with the possible exception of bone, have a higher mass at higher BMI values.
Absorption

- It is not known if absorption, whether from oral or intramuscular sites, is changed by obesity.
Absorption

- Although hemodynamic studies performed by Alexander et al. found that obese subjects had a greater splanchnic blood flow as compared with lean controls.
- There is no evidence that the oral absorption of drugs is increased in obesity.
Absorption

• A report by Cockshott et al. showed that most “intramuscular” injections are actually “intralipomatous”

• The kinetics of drug absorption from adipose are not known.

Pharmacokinetics in Obesity
Distribution

- In assessing the distribution of drugs in obese individuals, the lipid partition coefficient, a measure of the tendency of a drug to localize in lipid tissue, is used.

- However, lipophilic compounds do not always have larger volumes of distribution in obese patients.

Pharmacokinetics in Obesity
Distribution

- Albumin levels are not altered in obesity.
- The levels of α1-acid glycoprotein may increase in morbid obesity.
Metabolism

- Histopathologic changes in the liver (fibrosis, cirrhosis, fatty infiltration) and alterations in cytochrome activity may result from obesity and could affect hepatic drug metabolism.
Excretion

• Compared with lean controls, obese patients have a higher creatinine clearance (CrCl).

• The exact cause of the increased clearance in obese humans is unknown, although possible reasons include
  • an increase in the number or size of nephrons and
  • an increase in blood flow (due to increased blood volume and cardiac output) to the kidney.
• Although the clearance of the β-lactam antimicrobials (e.g. penicillins and cephalosporins) is increased in obesity requiring more frequent dosing to maintain adequate drug concentrations, the available data on Vd appear to differ by drug.

• For example, the Vd for ampicillin and piperacillin is increased, while Vd for ertapenem is reduced in obesity.

Pharmacokinetics in Obesity
Pharmacokinetics in Obesity

• The Vd for vancomycin is not appreciably different in obesity, but the clearance of the drug is increased.

• Dosing of this antibiotic should be based on BWt with a dosing interval frequent enough so that the serum trough concentration remains at a therapeutic level.
## Table 1. Empirical guide to weight-based dosing in obesity

<table>
<thead>
<tr>
<th>Dose</th>
<th>Data in obese compared with non-obese</th>
<th>Weight to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading dose</td>
<td>Markedly reduced Vd (litres/kg)</td>
<td>LBW</td>
</tr>
<tr>
<td></td>
<td>Slightly reduced Vd (litres/kg)</td>
<td>Adj-BW</td>
</tr>
<tr>
<td></td>
<td>Similar or increased Vd (litres/kg)</td>
<td>BWt</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>Similar or reduced total Cl (litres/h)</td>
<td>LBW</td>
</tr>
<tr>
<td></td>
<td>Increased total Cl (litres/h)</td>
<td>BWt</td>
</tr>
</tbody>
</table>

Vd, volume of distribution in litres per kilogram of total body weight; LBW, lean body weight; Adj-BW, adjusted body weight; BWt, total body weight; Cl, clearance in litres per hour.
**Table 2. Suggested dosing weight for antimicrobial examples in obesity**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Loading dose*</th>
<th>Maintenance dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Adj-BW(^{a})</td>
<td>Adj-BW (base on therapeutic response)</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>BWt</td>
<td>BWt</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Adj-BW(^{b})</td>
<td>Adj-BW</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>BWt</td>
<td>BWt or Adj-BW</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>LBW</td>
<td>LBW</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>BWt</td>
<td>BWt</td>
</tr>
<tr>
<td>Fluycytosine</td>
<td>LBW</td>
<td>LBW</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Adj-BW(^{c})</td>
<td>Adj-BW (base on therapeutic response)</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>BWt</td>
<td>BWt</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>BWt</td>
<td>BWt</td>
</tr>
<tr>
<td>Rifampin</td>
<td>LBW</td>
<td>LBW</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>BWt</td>
<td>BWt</td>
</tr>
</tbody>
</table>

LBW, lean body weight; Adj-BW, adjusted body weight; BWt, total body weight.

* Suggested correction factor: \(^{a}0\cdot4; \(^{b}0\cdot5; \(^{c}0\cdot3.\)
• A 43-year-old man hospitalized with bacterial cellulitis received a course of linezolid at the usual dose of 600 mg twice daily after 7 days of cefazolin.

• This patient weighed 286 kg (BMI 86 kg/m²) and had a measured creatinine clearance of 75 ml/min.

• The measured linezolid Vd in this patient was 135.7 litres (0.47 litre/kg) as compared with the normal Vd of approximately 40–50 litres (about 0.64 litre/kg).
Given the information from this case, that the weight-corrected Vd is lower in obesity compared with normal (0.47 litre/kg divided by 0.64 litre/kg = 0.73), an Adj-BW should be used for dosing this drug.

This further indicates that a correction factor of 0.27 (1 - 0.73) can be used in estimating the Adj-BW to account for the difference in Vd.
Final dosage adjustments for antimicrobials with a narrow toxic-therapeutic window should be based on serum concentrations.
• Individuals with PCM have reductions in both adipose tissue and lean tissue (skeletal muscle and organ mass).
• The degree of loss depends on the severity of PCM but may include a FM of only 5% of body weight compared with normal of 20–25%.
• Additionally, extracellular fluid volume may expand relatively from 20 to 40% of body mass.

Pharmacokinetics in PCM
**PCM-associated physiological changes**

- Decreased body mass, including both lean body mass and adipose tissue
- Decreased cardiac output and hepatic blood flow
- Decreased glomerular filtration rate
- Hepatic metabolic changes and protein synthesis
- Changes in serum protein levels

**Physiologic Changes in PCM**
Pharmacokinetics in PCM

• The altered body composition along with reduced transport proteins and regulatory hormones can influence drug distribution.

• The reduced cardiac output, glomerular filtration rate, organ mass and function influence drug elimination.
Pharmacokinetics in PCM

- A drug’s Vd may be increased or decreased in PCM.
- Severe PCM can decrease oxidative metabolism and possibly conjugation reactions.
- Mild PCM may increase or have no effect on oxidative drug clearance by the cytochrome-P450 (CYP) isoenzymes.
- Renal drug clearance may be reduced or unchanged in severe PCM.
In PCM, the V\textsubscript{d} of aminoglycosides (e.g. tobramycin) is increased, while the clearance is reduced.

- Dose adjustment?
- Interval adjustment?
It has been suggested that loading doses of aminoglycosides be increased by a factor of 1.1 in underweight patients. This lends itself to a higher (mg/kg) dose with longer intervals between doses. Recall that maintenance doses are based on drug clearance, while the initial or loading doses are based on Vd.
• A rational approach to evaluate the potential influences of malnutrition and obesity can be used clinically based on available information.

• Until more data are available, routine monitoring by the clinician of the obese or protein-energy malnourished patient receiving weight-based drug regimens is necessary.

Summary