

Drug Dosing in Obesity

The global epidemic of obesity has led to an increase in co-morbidities along with associated drug treatments. Obesity is a major health concern, with 1 in 3 New Zealanders being termed 'overweight' (BMI 25-30) and an additional 1 in 5 'obese' (BMI>30). Drug dosing in these patients is particularly difficult and there are very limited data on which to base dosing guidelines. The aim of this bulletin is to highlight the issues around drug dosing in obese patients.

Physiological changes in obesity

Obesity causes physiological changes that can alter both the pharmacokinetics and pharmacodynamic properties of drugs. These include;

- dramatically increased adipose tissue
- slightly increased lean tissue mass
- increased cardiac output
- increased glomerular filtration rate
- fatty infiltration of liver

Dosing weight?

Obese patients have a dramatic increase in fat mass as well as a smaller increase in lean tissues. This can make it difficult to determine a dosing weight for an obese patient. A number of different 'weights' are used for different purposes – see table below.

Weight	How to Measure	Use
Total Body Weight (TBW)	Weigh patient.	Loading dose for some lipophilic drugs.
Ideal Body Weight (IBW)	Male = 50kg + 0.9kg for each cm >150cm height. Female = 45kg + 0.9kg for each cm >150cm height	Maintenance dose of drugs where clearance is not changed in obesity.
Lean Body Weight (LBW)	= IBW + 1/3 X (TBW-IBW). Estimate of fat free mass.	Maintenance doses of most drugs with increased clearance in obese

For example a 160 kg man whose height is 170cm

TBW = **160kg**

IBW = 50 + 0.9 X 20 = **68kg**

LBW = 68 + 1/3(160-68) = **96kg**

Pharmacokinetics in obesity

Oral availability (F)

Oral availability in obese patients does not appear to be different from in non-obese patients.

Volume of Distribution (Vd) – (determines loading dose)

Hydrophilic drugs: generally no change in Vd. These drugs have limited distribution in body fat and no increase in loading dose is required e.g. lithium.

Lipophilic drugs: studies have shown discrepancies between different drugs. Some exhibit a large increase in Vd e.g. phenytoin, which is distributed into excess fat, while others show no significant change e.g. fluoxetine.

Clearance – (determines maintenance dosing)

The clearance of many drugs is increased in obesity although not to the full extent of the increased weight.

Renal clearance

- Glomerular filtration increases in obesity resulting in increased clearance of many renally cleared drugs.
- Tubular function i.e. tubular secretion and reabsorption of some drugs may also be increased in obesity.

Hepatic clearance

- CYP - There is some evidence of increased CYP activity in obesity. CYP2E1 activity is increased and some studies show increased clearance via CYP3A4.
- Glucuronidation – some studies have shown increased glucuronidation in obesity. This may necessitate increased doses of benzodiazepines and paracetamol although no clear dosing guidelines exist.
- **BUT** patients with severe fatty infiltration of liver have poor hepatic function and reduced drug clearance.

Some examples

Phenytoin is a lipophilic drug that has an increased Vd and clearance in obese patients. This means;

- loading doses need to be increased: one recommendation is 14mg/kg up to ideal body weight + 19mg/kg for the weight in excess of ideal body weight.
- maintenance doses may need to be increased, however due to saturable kinetics increases may be modest.
- monitoring of plasma concentrations and dose adjustment is required.

Lithium is a hydrophilic drug with no change in Vd with obesity. Clearance is increased due to reduced renal tubular reuptake.

This means;

- starting dose should be based on ideal body weight.
- maintenance doses likely to be higher than normal.
- monitoring of plasma concentrations and dose adjustment is required.

Low molecular weight heparins (LMWH)

- Total body weight should be used to calculate the treatment dose of LMWH.
- Safety data in patients over 150kg is lacking, and therefore, factor Xa monitoring is recommended.

Recommendations

- Be aware that obese patients may require dose adjustment especially for low therapeutic index drugs.
- Maximum recommended doses should not normally be exceeded.
- Monitor the effects of medication both clinically and with therapeutic drug monitoring if appropriate, and be prepared to make dose adjustments.
- Larger loading doses may be required..
- Maintenance dose – for most drugs should be based on Lean Body Weight, a weight of approximately Ideal weight + 1/3 X (Total weight – Ideal Weight)