

RQHR Pharmacy Services

Medication Dosing Guidelines in Obese Adults

Adapted and modified from the UWHC Center for Drug with permission.

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A. Introduction

In 2005, 16.4% of the population within the RQHR were identified as being obese. Overweight is defined as a body mass index of 25 to 29.9 kg/m² and obesity as a body mass index of 30 kg/m² or more. Appropriate drug dosing in the obese patient is a challenge for health care practitioners. Obesity causes physiologic alterations which can affect drug pharmacokinetics. In the obese patient, body composition is characterized by a relatively higher percent of fat and lower percent of water and lean tissue mass than the non-obese patient. In spite of increased cardiac output and total blood volume, the blood flow per gram of fat is less than in the non-obese patient. Histological hepatic changes and an increased glomerular filtration rate have also been reported in obese individuals. Limited kinetic studies have been conducted in the obese, leaving the clinician with few resources to turn to for dosing information. The following guidelines summarize what is known about drug pharmacokinetics in the obese patient and provide dosing information for selected drugs.

B. Pharmacokinetic Parameters

1.0 Absorption

1.1 No change in absorption with obese patients.

2.0 Distribution

In general, lipid soluble drugs have an increased volume of distribution, but significant exceptions exist. An increased volume of distribution can also result in an increased half-life.

$$t_{1/2} = [(Vd) \times (0.693)] / Cl$$

$$t_{1/2} = \text{half-life} \quad Vd = \text{volume of distribution} \quad Cl = \text{clearance}$$

The majority of obese patients have a larger amount of lean body mass as well as fat. The lean body mass accounts for 20% to 40% of the excess body weight

$$\begin{aligned} \text{IBW(males)} &= 50 \text{ kg} + 2.3 (\text{height} - 60) \text{ kg} & \text{IBW(females)} &= 45.5 \text{ kg} + 2.3 (\text{height} - 60) \text{ kg} \\ \text{IBW} &= \text{ideal body weight in kg} & \text{Height} &= \text{inches: } 1''=0.0254 \text{ m} \end{aligned}$$

3.0 Protein Binding

3.1 Albumin and total protein concentrations are unchanged.

3.2 AAG concentrations may be increased, but changes in acidic drug binding are not clinically significant.

3.3 Lipoproteins, such as cholesterol and triglycerides, are usually increased in obesity, but the clinical significance of these changes on drug binding is unknown.

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4.0 Metabolism

- 4.1 Fatty infiltrates in the liver occur in obese patients. The extent is proportional to the degree of obesity. The correlation between fatty infiltrates and metabolic changes is not well understood.
- 4.2 Phase I metabolism - oxidation, reduction, or hydrolysis is increased or unchanged in obesity.
- 4.3 Phase II metabolism - glucuronidation and sulfonation can be enhanced and cause an increased clearance of drug. Conjugation of drugs can be increased or unchanged.
- 4.4 High-extraction elimination - there is no significant difference in hepatic blood flow or clearance of these drugs.

5.0 Renal Elimination

- 5.1 Drugs eliminated primarily through glomerular filtration have increased renal clearance. Filtered and secreted drugs have increased renal clearance. None of the empirically derived equations correlate well with the actual creatinine clearance in critically ill obese patients. Using IBW underestimates creatinine clearance. Using ABW overestimates creatinine clearance. It is best to obtain a measured creatinine clearance in these patients.

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Table 1. Drug Dosing in Obesity

Drug	Dosing Wt			Comments
	IBW	ABW	DW	
Acyclovir	X ¹			Maximum dose of 500 mg/m ²
Alprazolam	X			It will take longer to reach steady state in long term therapy, but the final concentration will be similar in obese patients
Amikacin			X ^{2,3}	DW = 0.4 (ABW-IBW) + IBW
Amphotericin B		X ¹		Use ABW for conventional and liposomal amphotericin products
Ampicillin		X ¹		Larger volumes of distribution in obese patients
Atracurium		X ⁴		
Carbamazepine	X ⁵			Time to reach steady state may be prolonged. Eighteen healthy obese patients with BMI 38.8 ± 6 kg/m ² and TBW 111.4 ± 19.9 kg were compared to 13 healthy lean patients.
Cefazolin				Use a 2G dose in adult obese patients. ⁶
Ciprofloxacin			X ^{7,8,9}	Increased clearance with partial distribution to adipose tissue; DW=0.45(ABW-IBW) + IBW
Cyclophosphamide		X ¹¹		Dose initially on TBW and adjust subsequent doses based on clinical response
Cyclosporine	X ¹²			
Daptomycin		X ¹⁶		Study of subjects 18-65 years old: 6 moderately obese (BMI 25-39.9 kg/m ²), 6 morbidly obese (>40 kg/m ²) and 12 matched controls (matched for age and renal function, BMI 18-24 kg/m ²). The AUC was 30% higher in obese patients, but was within the range of safety and tolerated well.
Diazepam				Obese patients experience a longer half life. ¹⁷

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Digoxin	X			
Doxorubicin		X ^{11,18}		Dose initially on TBW and adjust subsequent doses based on clinical response.
Drotrecogin		X ¹⁹		Twenty patients > 135 kg (136-227 kg) were compared to 32 patients < 135 kg (50-133 kg). The assay used to measure plasma concentrations of activated protein C did not distinguish between endogenous activated protein C and drotrecogin.
Enoxaparin		X ^{13,14,15}		Use TBW up to 150 kg and monitor anti-Xa concentrations (heparin level).
Erythromycin	X ¹			
Fluconazole		X ²⁰		Based on one patient with BMI 48.3 kg/m ² (227 kg) and steady state plasma concentrations.
Flucytosine	X ¹			
Fluorouracil		X ¹¹		Dose initially on TBW and adjust subsequent doses based on clinical response.
Fluoxetine	X ²¹			
Ganciclovir			X	DW = 0.4 (TBW-IBW) + IBW
Gentamicin			X ^{3,22}	DW = 0.4 (TBW-IBW) + IBW
Glipizide	X ²³			
Heparin		X ^{24,25}		Case reports show increased requirements in obesity with a maximum bolus of 10,000 units and infusion rate of 15,000 units/hour
Ifosfamide				Increased volume of distribution and half-life, clearance is about the same ²⁶
Lepirudin		X ²⁷		Use actual body weight up to 110 kg
Lidocaine	X			
Linezolid			X ^{28,29}	One case report (patient with BMI 89 kg/m ²) ² suggests using a dosing weight of IBW + 0.27(TBW-IBW). ²⁴ Another study with 7 patients, mean weight 146 ± 37 kg, revealed ↓ concentrations relative to normal-weight people, but inhibitory activity occurred in the serum for each isolate except one (MRSA).
Lithium	X ³⁰			
Lorazepam	LD ⁴	MD		
Methotrexate				Increased volume of distribution and clearance, half-life the same. ³¹ Monitor concentration in obese patients.
Methylprednisolone	X ³²			
Midazolam	MD ⁴	LD		Increased volume of distribution and elimination half-life in obese patients. Loading dose based on TBW, maintenance dose based on IBW.

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Moxifloxacin			X ^{33,34}	Weight is a significant determinant in pharmacokinetics and it distributes extensively to adipose tissue. Consider doses of 600 mg daily.
Phenobarbital		X ³⁶		Monitor serum concentrations
Phenytoin		MD ³⁷	LD ³⁸	Use an adjusted weight of IBW + 1.33(TBW-IBW) for the loading dose only
Procainamide	X			
Propofol		X ^{4,39}		Studied in general anesthesia, not ICU sedation
Ranitidine	X ⁴⁰			
Rifampin	X ⁴¹			
Rocuronium		X ^{4,42}		
Sotolol	X ⁴³			
Succinylcholine		X ⁴⁰		
Theophylline	LD ⁴⁴	MD		
Thiopental	LD ⁴	MD		Although thiopental distributes to adipose tissue, obese patients may be more sensitive to thiopental.
Tobramycin			X ^{3,22}	DW = 0.4 (TBW-IBW) + IBW
Trazodone	MD	LD		Loading dose based on TBW, maintenance dose based on IBW
Trimethoprim/ Sulfamethoxazole			X	DW = 0.4(TBW-IBW) + IBW, monitor serum sulfamethoxazole concentrations
Valproic acid	X ³⁶			Changes in body weight will affect clearance. Monitor concentrations
Vancomycin			X	DW = 0.4(TBW-IBW) + IBW. ⁴⁵⁻⁴⁸ Monitor trough serum concentrations.
Vecuronium	X ⁴⁹			
Verapamil	MD	LD		Loading dose based on TBW, maintenance dose based on IBW ³⁹
Voriconazole		X		Per communication with Pfizer Pharmaceuticals 7/27/04
Warfarin		X ⁵⁰		

ABW – actual body weight

IBW – ideal body weight

Males: 50 kg + 2.3 kg [height (inches) – 60]

Females: 45.5 kg +2.3 kg [height (inches) – 60]

TBW – total body weight

DW – dosing weight for drugs (not for creatinine clearance calculation)

LD – loading dose

MD – maintenance dose

BMI – body mass index

AUC – area under the curve

MRSA – methicillin resistant staph aureus

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