

Does Obesity Affect the Dosage Requirements For Oral Benzodiazepines or Opioids?

Introduction

Drug pharmacokinetics may be altered in an obese individual but there are few cases where these changes will be clinically significant. In this review, the mechanisms by which obesity can affect pharmacokinetic parameters will be discussed, followed by specific data for opioids and benzodiazepines. Opioids and benzodiazepines are chosen for review as there is a misperception that obese individuals will require higher oral doses of these drugs.

General principles

Drug **absorption** is not impacted by obesity (1). It has been hypothesized that since obesity increases splanchnic blood flow, the subsequent increase in perfusion of the small intestine where most drugs are absorbed could result in higher drug bioavailability. However, the effect of this, if it does occur, is not clinically significant (2-5).

Distribution of drugs may be altered in obesity. A higher proportion of a drug could distribute into adipose tissue in an obese individual, significantly increasing the **volume of distribution (V_D)**. This would only affect lipophilic drugs. The consequences of an increased V_D are (6,7):

- delayed onset of action for a drug
- drug accumulation in adipose tissue, which will slowly release into plasma
- prolonged half-life, leading to a longer time to steady-state

Clinically, this is only important when a rapid response from a lipophilic drug is needed (e.g. an intravenous loading dose of lorazepam for status epilepticus). Dosing in this situation should be based on the patient's total body weight (TBW). Otherwise, with chronic oral dosing, plasma concentrations for a given dose will be the same in obese vs. non-obese individuals once steady-state has been reached — it may just take longer to reach steady-state in the obese individual.

Metabolism, specifically liver metabolism, is variably affected by obesity. CYP 2E1, 1A2, 2C9, and possibly 2C19 and 2D6 are induced; CYP 3A4 is inhibited (8). Phase II enzymes (e.g. UGTs) also may be induced. However, these changes are usually insignificant, with a few exceptions. Triazolam (3A4 substrate), showed significantly higher plasma levels in obese individuals due to reduced clearance (9). Lorazepam (UGT substrate) showed increased clearance, but this effect was offset by accumulation of the drug in fatty tissue (9).

Elimination may be increased in obesity because of increased glomerular filtration rate (GFR), increased renal tubular secretion, and decreased tubular reabsorption (1). However, other comorbidities in obesity will often offset the increased excretion and the overall effect is unlikely to be relevant except for drugs with a narrow therapeutic window that are primarily eliminated renally (10). For purposes of drug dosing in an obese patient, it is recommended to use lean body weight (LBW) to estimate GFR (11).

Oral Opioid Dosing in Obesity

Analgesic response to oral (and parenteral) opioids does not appear to be affected by weight according to recent studies (7,12-14). It has also been demonstrated that morphine plasma concentrations do not correlate with analgesic effect (15). Thus, oral opioids should be dosed without regard to weight, following the general recommendation of starting low, then titrating to effect. Also, consider that obesity may increase the risk of sleep apnea and respiratory depression associated with opioids (16). Table 1 summarizes theoretical and actual clinical data for select opioids.

Table 1: Opioid Pharmacokinetic Changes Associated with Obesity

Opioid	Hydrophilic (●) or Lipophilic (V)	Theoretical changes in obesity	Studied Clinical changes in obesity
Morphine	● ●	- Increased clearance if eGFR high, leading to lower duration of analgesia; increased liver metabolism via. UGT2B7 (17)	- Clinical changes not well studied - Increases in clearance likely only significant in morbidly obese (18)
Oxycodone	● ●	- Increased clearance if eGFR high, leading to lower duration of analgesia	- Weight did not impact dosing needs in cancer patients (19)
Hydromorphone	● / V (intermediate)	- Increased V_D ; increased liver metabolism via glucuronidation	- Kinetic changes not studied - No correlation between weight and analgesia (20,21)
Methadone	V V	- Increased accumulation and half-life potential due to lipophilicity; magnitude unstudied	- Weight did not influence clearance, but did increase V_D and accumulation potential (22,23) - Methadone displays high interpatient variability, unrelated to weight (24,25)
Fentanyl (transdermal)	V V V	- High lipophilicity indicates increased accumulation and half-life, and possible increased steady-state concentrations. - Initial analgesic response may be delayed	- Changes in transdermal kinetics in obesity have not been studied - IV dosing based on TBW may lead to over-dosage (26)

Oral Benzodiazepine Dosing in Obesity

Most benzodiazepines are lipophilic, which theoretically means increased half-lives, accumulation potential, and possible delayed onset of action in obesity. In general though, these changes are small and no dosing changes are required for obese individuals. As with opioids, benzodiazepine doses should be started low and titrated to effect, regardless of weight. Table 2 summarizes clinical data on obesity-related kinetic changes in benzodiazepine therapy.

Table 2: Benzodiazepine Pharmacokinetic Changes Associated with Obesity

Benzodiazepine	Theoretical and Observed Data
Alprazolam (25)	<ul style="list-style-type: none"> - Half-life increased from 11h to 22h in obesity - Final plasma concentrations the same in obese and non-obese at steady-state - Metabolism and clearance unchanged
Clonazepam	<ul style="list-style-type: none"> - No kinetic studies available - Likely similar to other benzodiazepines; increased half-life, similar area under the curve (AUC) at steady-state
Diazepam (26)	<ul style="list-style-type: none"> - Half-life markedly prolonged from 56h to 130h in obesity - AUC at steady-state is same in obese and non-obese individuals - Clearance unchanged
Lorazepam (27)	<ul style="list-style-type: none"> - Increased V_D leading to longer half-life - Clearance is increased, but offset by increased V_D and accumulation - Net effect is only a slightly prolonged half-life in obesity
Triazolam	<ul style="list-style-type: none"> - Half-life increased from 2.6h to 4.1h (25) - AUC was slightly greater in obesity due to decreased clearance (3A4 inhibition) (28)

Summary

For oral benzodiazepines and opioids, obesity does not affect dosage requirements. In some cases, obesity will increase half-lives, potential for accumulation and delay onset of action, but steady-state concentrations and overall clinical effect are unchanged.

If you have any questions about this information or would like to discuss a specific situation involving opioid or benzodiazepine dosing, please feel free to contact the medication information consultants at medSask: telephone 306-966-6340 (Saskatoon) or 1-800-667-3425 (anywhere in Saskatchewan) or email druginfo@usask.ca.

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