Clinical Pharmacology of Obese Patients

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1. Introduction

The prevalence of obesity is increasing in both human and veterinary populations, presenting unique challenges for clinical pharmacology. Understanding how excess adiposity alters drug behaviour in the body is crucial for safe and effective therapeutic interventions. Pharmacokinetics (PK), which describes what the body does to a drug, is nominally divided into four phases: Absorption, Distribution, Metabolism, and Elimination (ADME). First principles suggest that all four phases could be affected by obesity. These effects are unlikely to be uniform across different drugs, largely depending on their physicochemical properties.

Furthermore, pharmacodynamics (PD), the effect of the drug on the body, is generally assumed to correlate with drug concentration. Changes in PK can alter drug concentrations at any given time after dosing. This could manifest as a reduced concentration of an antibiotic or antiepileptic drug that requires concentrations above a certain threshold to be clinically effective. Conversely, drug concentrations may be increased, extending into the range where more adverse events or toxicity are observed.

2. Key Pharmacokinetic Parameters and Dosing Metrics in Obesity

2.1. Pharmacokinetic Phases (ADME) As mentioned, obesity can influence all ADME phases:

- **Absorption:** Altered gastric emptying or intestinal transit time may affect drug absorption.
- **Distribution (Vd):** Increased adipose tissue can significantly increase the volume of distribution for lipophilic drugs.
- **Metabolism:** Changes in liver blood flow or enzyme activity (e.g., cytochrome P450) can alter drug metabolism.
- **Elimination (Clearance, CL):** Renal or hepatic clearance mechanisms can be affected.

2.2. Dosing Metrics Most human formularies for adults dose drugs in a "per human" fashion, i.e., a fixed dose regardless of size. The first correction for obesity in human literature involves dosing based on **total body weight (TBW)**, which veterinarians would understand as expressing dose on a per kilogram of liveweight basis. Other metrics include:

- **Ideal Body Weight (IBW):** An estimate of weight if the person were of normal adiposity.
- **Lean Body Weight (LBW):** Calculated from TBW. It is important to note that LBW is not the same as IBW; the excess weight in obesity does comprise some lean mass (approximately 20-40% in humans).
- **Body Mass Index (BMI):** A measure of body fat based on height and weight.
- **Body Surface Area (BSA):** Calculated using height and weight.

3. Research Findings

3.1. Human Studies Multiple studies, including reviews [1] and meta-analyses [2], have examined the effect of obesity on pharmacokinetics in humans. Mahmood [3] demonstrated that clearance (CL) is often best estimated from lean body weight using an allometric scalar of 0.75. While the precision of CL estimates in obese patients was good using this approach, there was more variability in the estimation of volume of distribution (Vd). The review by Harskamp-van Ginkel et al. [4] also found that clearance did not significantly differ between obese and lean children. Volume of distribution did vary, but the physicochemical properties of the drugs were not consistently good predictors of these changes.

3.2. Veterinary Studies Two key studies [5, 6] have examined the effect of obesity on pharmacokinetics in veterinary species, both using an induced obesity model. In these models, researchers offered lean animals greater than maintenance energy requirements to induce obesity. This methodology means the animals were recently obese and are unlikely to have developed other co-morbidities often associated with chronic obesity. In effect, this isolates the direct impact of increased adiposity but may reduce the external validity of the studies to clinical populations with long-standing obesity.

The first study [6] examined the impact of three macrocyclic lactones (ivermectin, moxidectin, and eprinomectin) co-administered to dogs. Although the model was initially designed for extrapolation to humans for COVID-19 treatment, these molecules are commonly used in endectocide products for both dogs and cats. The study found that these drugs were highly distributed to adipose tissue, resulting in a higher volume of distribution in obese dogs compared to lean counterparts. However, the absolute clearance of these molecules was unaffected by obesity, aligning with human study findings.

Clark et al. [5] studied pioglitazone, an anti-diabetic drug that is lipid-soluble and highly protein-bound. They administered it orally and intravenously to lean and obese cats. The results showed no statistically significant differences in the pharmacokinetic parameters across the 12 cats. The Mean Residence Time (MRT) and elimination half-life were numerically increased by approximately 20% in the obese animals dosed orally, and the variation of these parameters also increased. However, these changes were within the typical inter-individual variation observed.

Perez et al. [7] examined the dose of alfaxalone required to induce anaesthesia in overweight and lean dogs. They demonstrated that ideal body weight (IBW) was the most significant determining factor for the required dose.

4. Drug Dosing Design in Obese Patients

4.1. Initial/Loading Dose The initial or loading dose is calculated to achieve a target concentration (Ctarget) based on the volume of distribution (Vd):

$$\text{Dose} = C_{target} \times Vd$$

As the volume of distribution can change with obesity, particularly for drugs that distribute into adipose tissue, this needs to be considered for the loading dose.

4.2. Maintenance Dose The maintenance dose is calculated to maintain the target concentration, based on clearance (CL) and bioavailability (F) for non-intravenous administration:

$$\text{Dose rate} = (C_{target} \times CL)/F$$

Where Dose rate is in mg/hour. For intermittent dosing, this rate is multiplied by the dosing interval (e.g., 12 hours).

In veterinary literature, both Vd and CL may be expressed per kilogram (L/kg and L/h/kg respectively). Thus, the doses calculated can be in mg/kg or mg/h/kg.

5. Influence of Co-morbidities

Obesity is associated with several co-morbidities in both humans and veterinary species. Some of these co-morbidities, such as cardiovascular disease, diabetes, and hypertension, may influence the pharmacokinetics of drugs, in some cases to a greater extent than obesity itself. In addition, hepatic cytochrome P450 enzyme activity can be increased in obesity, leading to increased clearance for drugs that are substrates for these enzymes.

6. Practical Dosing Recommendations

- **Drugs with Large Therapeutic Windows:** Those drugs with large therapeutic windows, low rates of adverse events, and mild adverse events can often be dosed at the "normal" per kilogram (TBW) rate.
- **Single-Dose Drugs Given to Effect:** Induction agents (e.g., for anaesthesia) are unlikely to need significant alterations if dosed to effect. Lean body weight (LBW) is often the best predictor of the required dose for these drugs, despite their lipophilicity and large volumes of distribution, because the induction effect typically occurs before significant distribution to peripheral adipose tissues has occurred, especially with intravenous administration.
- **Repeated Dosing of Drugs with Adverse Event Potential:** For repeated dosing, including constant rate infusions (CRIs), of drugs where there is significant potential for adverse events, doses should be adjusted for obesity. In most cases, extrapolation from human-derived data will be required. A general rule of thumb is:
    - **Loading Dose:** Use TBW to account for increases in Vd for lipophilic drugs. For hydrophilic drugs or those with limited distribution, LBW may be more appropriate.
    - **Maintenance Dose:** Use LBW for ongoing dosing, as this is driven by clearance, which is typically less affected by increased adiposity than Vd.
- **Specific Drug Examples:**
    - **Fentanyl and Propofol CRIs:** May require higher loading doses (based on TBW) and relatively lower maintenance doses (based on LBW).
    - **Remifentanil:** Dosed on LBW as its metabolism is rapid and occurs before extensive distribution.
    - **Beta-lactams:** Generally do not require substantial dose adjustment [1]. Dosing at the higher end of the recommended range is often advised to ensure efficacy. Note that clavulanic acid is responsible for most adverse events associated with amoxicillin-clavulanic acid preparations; consider increasing only the amoxicillin portion if higher doses are contemplated.

- **Aminoglycosides:** Have a specific dose correction term, “adjusted body weight” (ABW), but LBW can often be used as an alternative [1]. Therapeutic drug monitoring is advisable for these drugs.

7. Conclusion

Obesity can significantly alter drug pharmacokinetics, necessitating careful consideration when dosing patients. While TBW may be appropriate for initial loading doses of some lipophilic drugs, LBW is often a better predictor for maintenance doses, as clearance is less affected by obesity than the volume of distribution. The presence of co-morbidities can further complicate dosing regimens. For drugs with narrow therapeutic indices or significant potential for adverse events, individualised dosing strategies, potentially guided by therapeutic drug monitoring where available, are crucial for optimising outcomes in obese veterinary patients.

8. References

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