

CLINICAL PHARMACOLOGY

DOSING IN THE OBESE PATIENT

Many drugs are dosed according to the weight of the patient. The amount of drug per kilogram of body weight required to achieve therapeutic levels is usually derived from pharmacokinetic studies in normal-weight volunteers.

Obesity, defined as a body mass index (BMI) > 30, is associated with numerous physiological changes which influence the manner in which the body interacts with drugs. Despite this, very few studies have been conducted to determine the correct dose requirements of individual drugs in obese individuals. As a result, it is difficult to decide what dose of a drug should be administered to an obese patient.

Case

A 37-year-old, 86 kg lady presents to an emergency department with a 5-day history of signs and symptoms of pyelonephritis. The medical officer decides to treat her with intravenous gentamicin. Given that the patient is obese with a BMI of 35, should he administer gentamicin at the usual dose of 5 mg/kg per day (430 mg), considering that a high percentage of her 86 kg is adipose tissue?

Pharmacokinetic considerations in the obese patient

Pharmacokinetics is defined as the relationship between time and the drug concentration in different regions of the body, during and after dosing. The components of pharmacokinetics consist of absorption, distribution, metabolism and excretion. The obese patient demonstrates differences in these areas and the recognition of these differences is essential as they may affect the way a particular drug is dosed. The most important alteration in obesity affects drug distribution. In addition, alterations in metabolism and elimination may increase the clearance of drugs. Absorption is unaffected by obesity.

Distribution is the movement of drugs from the circulation into body tissues. The extent to which a particular drug distributes into tissue compartments is affected by its lipid solubility and protein binding, and is described by the volume of distribution (Vd). The volume of distribution is the volume into which the drug distributes in the body when there is equilibrium between drug in the tissues and drug in the plasma. It is an index of the extent that a drug is distributed to the tissues compared with plasma. A drug that is completely retained in the plasma would have a Vd of about 3 litre whereas a lipophilic drug which enters all tissue compartments may have a Vd of over 200 litre.

The anaesthetic agent thiopentone and the benzodiazepines are highly lipid-soluble and distribute readily into body tis-

ues. Benzodiazepines have a Vd of about 90 litre while the Vd of heparin and gentamicin is 5 litre and 15 litre respectively.

In the obese patient, the Vd of lipophilic drugs is increased even further because of the higher percentage of body fat. Therefore dosing according to actual body weight would be appropriate for lipophilic drugs. On the other hand, hydrophilic/water-soluble drugs are largely confined to the intravascular compartment and obesity will have less influence on its Vd. Not all the excess weight in obesity is adipose tissue, so dosing according to ideal weight for all hydrophilic drugs might not be adequate, and an adjusted body weight (see below) should be used instead.

The increased Vd is important for the following reasons:

- Vd determines the loading dose, i.e. the dose required to rapidly achieve the desired therapeutic concentration. Thiopentone therefore requires a higher dose in the obese patient to achieve a similar plasma concentration to that of the non-obese patient.
- An increased Vd also affects the half-life, as illustrated by the following equation:

$$t_{1/2} \text{ (plasma half-life of the drug)} = \frac{\text{constant} \times Vd}{\text{clearance}}$$

If the Vd of a drug increases and the clearance remains the same, then the half-life of the drug will increase. The half-life of a drug is the time it takes for the concentration of the drug in the plasma to be reduced by 50%. The half-life is used to predict the time taken to achieve steady-state plasma concentration (concentration where accumulation and elimination are equal). It takes approximately 4 half-lives to reach 90% of the steady-state concentration and similarly 4 half-lives for the drug to decrease to 10% of its original plasma value. This is represented in Fig. 1.

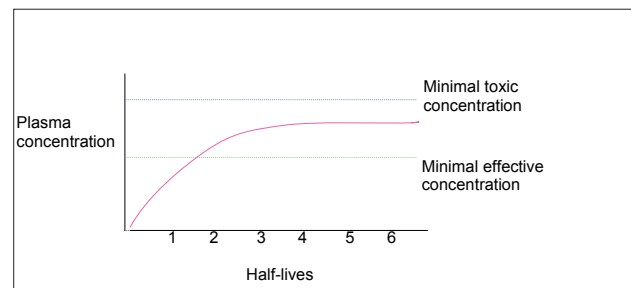


Fig. 1. The relationship between half-lives and time to reach steady state.

From the above, when administering lipophilic drugs to the obese patient:

- the loading dose should be higher
- it will take longer to reach steady-state concentration
- it will take longer for the drug to be cleared from the body once dosing is halted.

Metabolism. Drugs that undergo glucuronidation and sulphation in the liver are metabolised faster in the obese patient, e.g. paracetamol. No substantial differences have been demonstrated for drugs undergoing phase I metabolism (e.g. oxidation via the cytochrome P450 enzyme system). The clinical significance of these findings is not established.

Elimination. There are conflicting data from studies of the effect of obesity on the glomerular filtration rate, with some studies showing higher filtration. The standard Cockcroft-Gault equation to estimate creatinine clearance has been shown to overestimate clearance in obesity. The clearance of drugs such as gentamicin, which are cleared by glomerular filtration, may thus be altered by obesity. However, the lack of substantial evidence prevents any recommendation for dosing based on this parameter.

What measure of body weight should be used to calculate dosage in the obese patient?

Ideal body weight, actual body weight, and an adjusted body weight are used when calculating dosage based on body weight. Which measure to employ depends in part on the characteristics of the drug. Because of inadequate data, it can be difficult to decide which is most appropriate for a particular patient.

Actual body weight is used for drugs that are highly lipophilic, e.g. thiopentone, as discussed above. However, subcutaneous low-molecular-weight heparin has a low Vd, yet studies have shown that dose requirements are best predicted by dosing according to actual body weight. This may be due in part to differences in rates and extent of subcutaneous absorption.

Ideal body weight or lean body weight is estimated by the formulae below. This is best employed for drugs known to have a small Vd and a narrow therapeutic index/range. Quinine is associated with serious cardiovascular and central nervous system adverse effects and in severe malaria, the volume of distribution is low by virtue of high acute-phase protein binding. Thus in obese patients, maintenance doses of quinine are best determined by ideal body weight. The intravenous loading dose of the water-soluble aminophylline should also be calculated in this way, due to its narrow therapeutic range and small Vd.

$$\text{Ideal body weight (males)} = 0.9 \times \text{height in cm} - 88$$

$$\text{Ideal body weight (females)} = 0.9 \times \text{height in cm} - 92$$

Adjusted body weight. This weight lies between the ideal and actual body weight. Its use is based on the rationale that obese patients have an increased circulating blood volume and, as mentioned above, not all the excess weight in obesity is adipose tissue. Thus, even those drugs known to have a small volume of distribution (largely confined to

the intravascular space) will need greater doses than predicted by ideal body weight.

The formula for adjusted body weight relies on the addition of a fraction of the difference between ideal and actual body weight to the calculated ideal body weight. This accounts for the increased blood volume in the obese patient.

$$\text{Adjusted body weight} = 40\% \times (\text{actual body weight} - \text{ideal body weight}) + \text{ideal body weight}$$

Gentamicin is an example of a drug that should be dosed by the adjusted body weight. It has a relatively small volume of distribution. The peak concentration of gentamicin correlates best with its activity. Dosing according to ideal body weight is likely to result in suboptimal levels. Utilising the formula for adjusted body weight in the clinical case presented above:

$$\text{Adjusted body weight} = 40\% \times (86 \text{ kg} - 49.3 \text{ kg}) + 49.3 \text{ kg} = 64 \text{ kg,}$$

and thus the appropriate gentamicin dose would be to 320 mg rather than 430 mg.

Role of therapeutic blood monitoring

It is important to acknowledge that the principles described above are aids to decision making and are based on principles and a small number of pharmacokinetic studies. It is difficult to predict what levels will be achieved in an obese patient as the relationship between obesity and dosing is complex. Wherever possible, therapeutic drug monitoring should be done in obese patients, and dose adjustments should be based on the plasma levels obtained. If therapeutic drug monitoring is not available, other markers of efficacy or toxicity should be used. These may be clinical (e.g. heart rate for beta-receptor blockers) or laboratory (e.g. PTT estimations during unfractionated heparin administration).

Conclusion

The choice of the correct dose of a drug in an obese patient is often difficult due to inadequate data. Applying basic principles about the pharmacokinetic changes in obesity and the degree of lipophilicity of the drug can be used to estimate doses. Actual body weight, adjusted body weight and ideal body weight are used depending on the nature of the drug. Therapeutic drug monitoring should be performed where available. Careful clinical assessment of efficacy and toxicity is essential.

Further reading available on request.

Ronald Gounden, MB ChB

Marc Blockman, MB ChB, BPharm, MMed, Dip Int Res Ethics

*Division of Clinical Pharmacology
University of Cape Town*