Dose scaling for the morbidly obese

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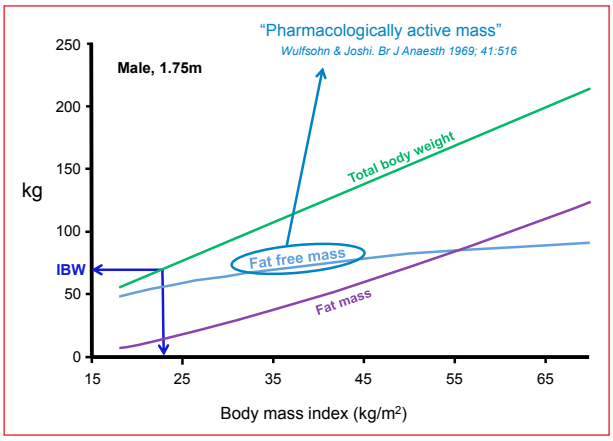
Introduction

It has long been realised that linear dosing according to total body weight (TBW) results in oversdosing the obese and underdosing small children. As far back as 1969, in a study on induction doses of thiopentone, Wulfsohn and Joshi[1] concluded that thiopentone was better administered according to lean body mass (LBM) than TBW. They reasoned that endomorphic somatotypes required less thiopentone than mesomophs and ectomorphs of the same TBW, because they had less LBM. They pointed out that there is a strong association between LBM, cardiac output and basal metabolic rate, and suggested that the LBM contained the "pharmacologically active mass". Recently, several publications have emerged that suggest that dosing of other anaesthetic drugs to obese patients, such as remifentanil[2] and propofol,[3,4] should be based on LBM.

An obese person's weight gain is not solely due to increased fat tissue. Figure 1 illustrates that should a person who is 1.75-m tall and with an ideal body weight [approximately 70 kg and a body mass index (BMI) of 23 kg/m^2] become obese, this would mainly be due to a roughly parallel increase of fat. However, the weight gain is not only the result of an increase in fat tissue, but is also owing to nonlinear increases in the size of other organs, such as muscle, liver, gut, etc (Figure 1). As a result, there is a nonlinear association between TBW and drug disposition. Many nonlinear weight adjustors for dosage to obese patients have been suggested, e.g. body surface area. In 2004, after an extensive literature review, Green and Duffull concluded that LBW was the best dose adjustor for pharmacokinetic (PK) studies in the obese.[5]

The most common method of calculating LBM is by the "James" equations.[6] However, they cannot be applied to morbidly obese patients (BMI > 40 kg/m^2) because of an



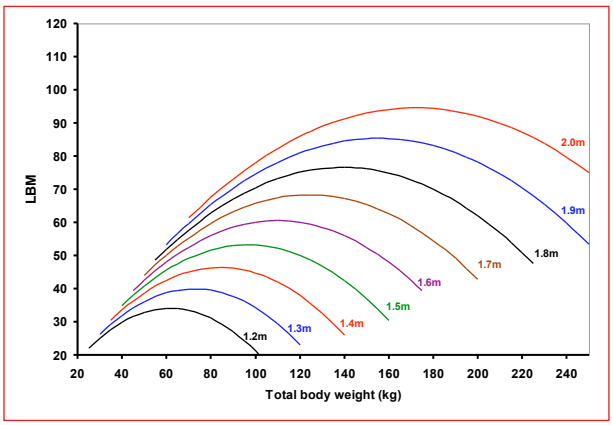
IBW: ideal body weight

Figure 1: Weight gain of a 1.75 m tall male due to obesity. The weight gain results from increased fat mass as well as fat-free mass (e.g. muscle).

anomalous feature of the James' equations whereby after a BMI of roughly 40 kg/m^2, LBM starts to decline with increasing TBW. This can even result in a negative value in the super-obese (Figure 2).

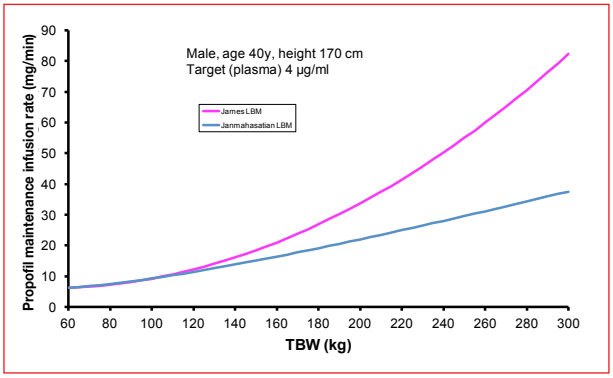
This anomaly presents a problem with the administration of two commonly used drugs in anaesthesia by target-controlled infusion (TCI). In the case of propofol, the weight, gender and age-adjusted "Schnider" PK parameter set[7] has been implemented in the commercially available TCI infusion pumps that are available today in most countries outside the USA. The equation for calculating total body clearance for morbidly obese patients results in exponentially increasing calculations for clearance, and therefore in gross overdosing when propofol is administered by infusion (Figure 3).

The opposite occurs with remifentanil using the "Minto" PK parameter set,[8] namely calculations that result in decreasing clearance for the morbidly obese (Figure 4).



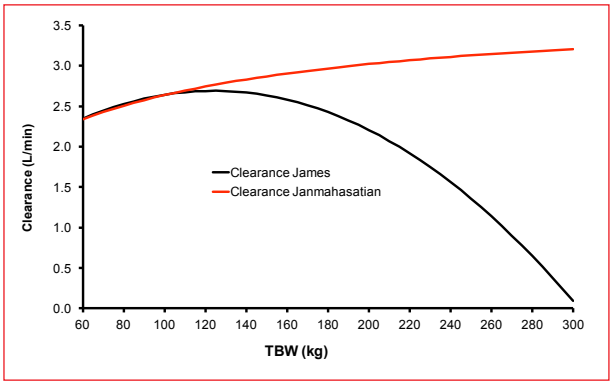
LBM: Lean body mass

Figure 2: Anomalies resulting from calculations of lean body mass (LBM) for males of various heights using the "James" equation. At body mass indices of about 40 kg/m^2, LBM values begin to decrease.



LBM: lean body mass, TBW: total body weight

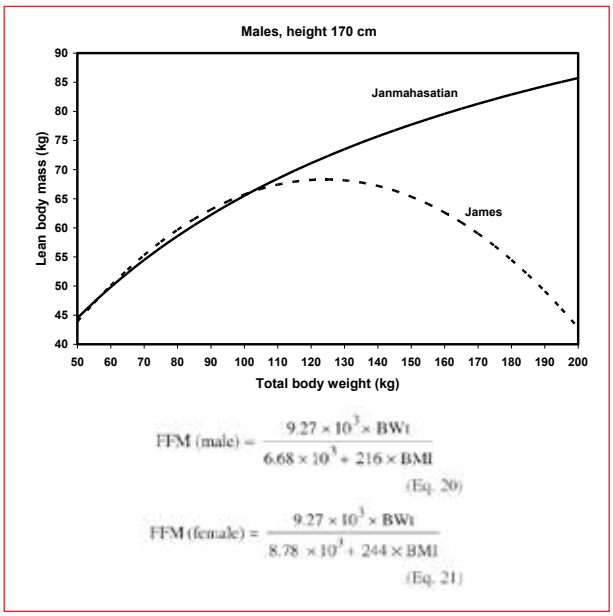
Figure 3: Maintenance propofol infusion rates to 40 year old, 1.7 m tall males, using the "Schnider" pharmacokinetic parameter set in which the "James" and "Janmahasatian" equations are used to calculate LBM.



TBW: total body weight

Figure 4: Calculated remifentanil total body clearances of 40 year old, 1.7 m tall males, using the "Minto" pharmacokinetic parameter set in which the "James" and "Janmahasatian" equations are used to calculate LBM.

As a result, TCI pump manufacturers will not permit users to enter TBW that results in BMIs that are greater than 42 kg/m^2 in men, and 35 kg/m^2 in women. This is unfortunate for anaesthesiologists who manage morbidly obese and super-obese patients.

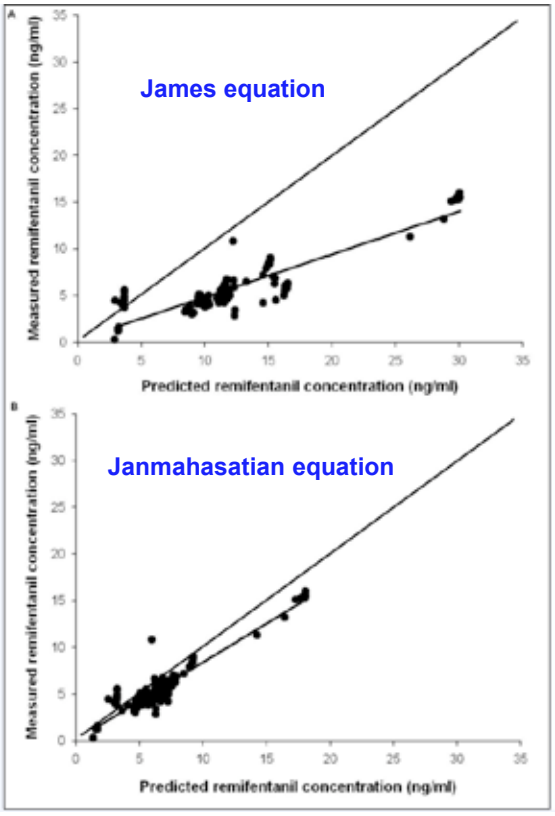


BMI: body mass index, BW: body weight, Eq: equation, FFM: fat-free mass, LBM: lean body mass

Figure 5: Estimation of LBM of the obese (Janmahasatian et al. Clin Pharmacokinet 2005; 44:1051-1065)

A new method of calculating LBM has recently been introduced. Janmahasatian et al[9] measured fat-free mass (FFM) using dual-energy X-ray absorptiometry in a study on 373 patients whose BMIs ranged from 17.1-69.9 kg/m^2. (For clinical purposes, LBM and FFM can be regarded as being equivalent).[9] The resulting "Janmahasatian" equations do not suffer from the "James" anomaly (Figure 5). Subsequent studies using the "Janmahasatian" equations suggest improved TCI of remifentanil[2] (Figure 6) and propofol[4] to morbidly obese patients, as well as improved induction of anaesthesia using propofol.[3] Whether or not implementing the "Janmahasatian" equations in the "Schnider" model for propofol will result in satisfactory TCI to morbidly obese patients remains to be demonstrated.

Allometric scaling has recently come to the fore as an alternate method of dose scaling in anaesthetic pharmacology. Allometry is the study of the relationship between size and shape. If an object increases in size while retaining its shape, i.e. grows isometrically, its surface area and volume (and therefore its weight) increase exponentially in proportion to its increased length, but at different rates. Examples of isometric change include a cube or a sphere. If the length of the side of a cube (or the radius of a sphere) is doubled, the surface area increases fourfold, but the volume (and therefore the weight) increases eightfold. Simply put, as length increases, weight increases more rapidly than surface area. This simple relationship, also known as geometric similarity, has important biological consequences. For example, as the size of an animal increases, it cannot remain isometric, otherwise its skeleton would not be able to tolerate its weight. The result is that its shape changes. Simply put, if a whippet were to increase to the size of an elephant, structural considerations would require that it take on the proportions of an elephant.



TCI: target-controlled infusion

Figure 6: Improved predictive performance of the "Minto" pharmacokinetic parameter set for remifentanil using the "Janmahasatian" equations for calculating LBM

The general allometric relationship is given by the exponential equation:

$$y=b.x^{a}$$

Where "y" is the biological descriptor to be predicted, "x" the body weight, "b" a constant, and the exponent "a" the allometric coefficient. An allometric coefficient of 0.75 has been found to apply empirically to many descriptors in physiology, pharmacology and morphology. Examples include oxygen consumption rate, glucose metabolism, cardiac output, drug clearance and respiratory minute volume.[10] The clearance of drugs with high extraction ratios (a metabolic process) in human pharmacology can be scaled to a standard body weight, using an allometric coefficient of 0.75, according to the relationship:

$$CL_i=CL_{std}.\frac{(BW_i)^{0.75}}{BW_{std}}$$

Where "CL_{std}" is the clearance of a standard individual of body weight (BW_{std}) (often 70 kg), and "CL_i" is the clearance of the individual of body weight ("BW_i"). Many estimates of the allometric exponent for drug clearance only approximate the value of 0.75. However, it appears that there is insufficient evidence to indicate that these are significantly different from 0.75.[10] Physiological volumes, e.g. blood volume, cardiac stroke volume, tidal volume, vital capacity and skeletal muscle mass, are generally directly proportional to body weight, i.e. the allometric coefficient is approximately unity.

Thus:

$$V_i=V_{std}.\frac{(BW_i)^{1.0}}{BW_{std}}$$

"V_i" and "V_{std}" are the volumes of the individuals of body weights "BW_i" and "BW_{std}", respectively. This proportional relationship has also been shown to apply to PK volumes of distribution, including the volume of distribution of the central compartment, the volume of distribution at steady state and the volume of distribution by area.[11] The power law for interspecies scaling became widely accepted after he publications by Kleiber in 1947[12] and Brody in 1945,[13] suggesting that the basal metabolic rate could be scaled between species by using a simple allometric equation with a universal exponent of approximately 0.75. Theoretical and mathematical justification was published independently by West et al,[14,15] Banavar et al[16] and McMahon.[17] However, there has been criticism and debate[18] concerning the existence of a universal exponent for basal metabolic rate and extrapolation from the basal metabolic rate to PK. Many critics argue that the use of fixed exponents is not supported by empirical data.[19]

With regard to allometric scaling of propofol dosing, two recent studies are intriguing. Knibbe et al[20] determined and compared the PK parameters of rats, children and adults, and demonstrated that the clearances (total body clearance, as well as intercompartmental clearances) and the volumes of distribution could be scaled allometrically, with exponents approximating 0.75 for the clearances and unity for the volumes of distribution. On scaling rat PK parameters to humans, they could also predict propofol concentrations in patients receiving propofol for sedation in the intensive care unit with satisfactory accuracy (r^2 = 0.83).

Cortinez et al published a landmark study with regard to obesity and propofol.[21] They studied 19 morbidly obese patients, and in addition, included data from a previous PK study on eight morbidly obese patients,[22] as well as the original "Schnider" model study.[7] They derived a three-compartment mammillary model in which total body clearance, as well as the intercompartmental clearances, were scaled allometrically according to a standard body weight of 70 kg with an exponent of 0.75. Similarly, the apparent volumes of distribution were also scaled to a standard body weight of 70 kg, but with an exponent of unity. It is interesting to note that a graph of clearance calculated according to the PK parameters of Knibbe et al and Cortinez et al form a continuum (Figure 7).

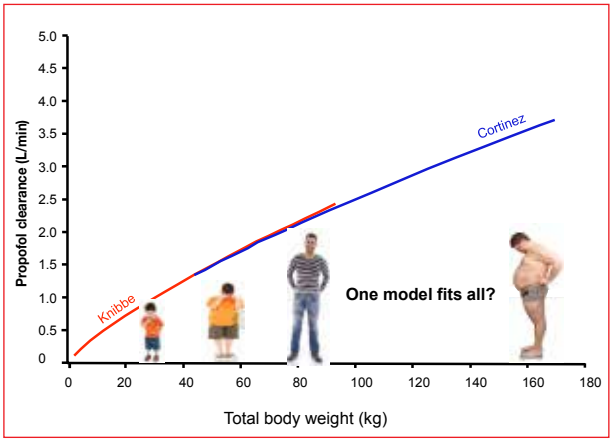
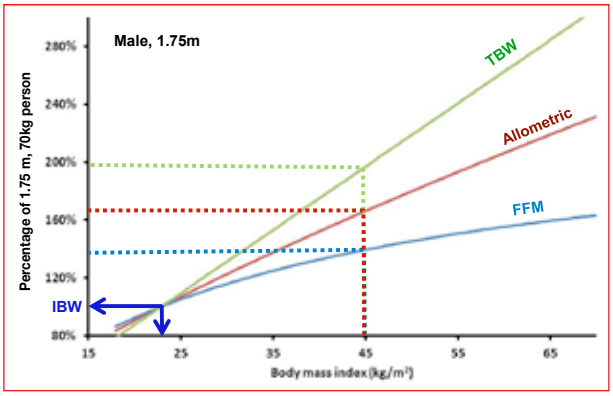


Figure 7: Propofol: allometrically scaled clearance



IBW: ideal body weight, FFM: fat-free mass, TBW: total body weight.

Figure 8: Three, dose scaling models

Remifentanil and propofol are examples of lipid-soluble drugs that are excreted rapidly. Consequently, these considerations may apply to drugs with similar physicochemical and pharmacological properties. It appears that dose-scaling methods for morbidly obese patients, either according to LBM or allometrically, have merit. It cannot be said which should be preferred at this stage. Whereas LBM is usually limited to adults, allometric scaling has the potential advantage of including children, obese children, normal adults and obese adults. Figure 8 depicts a graph of drug dosage for 1.75 m-tall males with BMI on the abscissa, and the dosage on the ordinate expressed as a percentage of the dose of a person of ideal body weight. Figure 8 illustrates that a morbidly obese person (BMI 45 kg/m^2) would receive 200% of the dose for a person of ideal body weight if the dosage was scaled according to TBW. On the other hand, allometric scaling would result in a 170% increase and scaling according to LBM/FFM, in a 140% increase. Whether either method will prove to be of greater clinical significance remains to be seen because other factors must be considered in the morbidly obese, and most importantly the co-morbidities that are associated with the condition.

References

1. Wulfsohn NL, Joshi CW. Thiopentone dosage based on lean body ms. Br J Anaesth. 1969;41(6):516-521.
2. La Colla L, Albertin A, La Colla G, et al. Predictive performance of the "Minto" remifentanil pharmacokinetic parameter set in morbidly obese patients ensuing from a new method for calculating lean body mass. Clin Pharmacokinet. 2010;49(2):131-139.
3. Ingrande J, Brodsky JB, Lemmens HJ. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg. 2011;113(1):57-62.
4. McLeay SC, Morrish GA, Kirkpatrick CM, Green B. Encouraging the move towards predictive population models for the obese using propofol as a motivating example. Pharm Res. 2009;26(7):1626-1634.
5. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004;58(2):119-133.
6. James WPT. Research on obesity: a report of the DHSS/MRC Group. DHSS/MRC Group, London;1976.
7. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology. 1998;88(5):1170-1182.
8. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology. 1997;86(1):10-23.
9. Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. Clin Pharmacokinet. 2005;44(10):1051-1065.
10. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-332.
11. Mahmood I. Interspecies scaling: predicting volumes, mean residence time and elimination half-life. Some suggestions. J Pharm Pharmacol. 1998;50(5):493-499.
12. Kleiber M. Body size and metabolic rate. Physiol Rev. 1947;27(4):511-541.
13. Brody S. Bioenergetics and growth. New York: Reinhold Publishing Corporation; 1945.
14. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science, 1997;276(5309):122-126.
15. West GB, Brown JH, Enquist BJ. The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science. 1999; 84(5420):1677-1679.
16. Banavar JR, Maritan A, Rinaldo A. Size and form in efficient transportation networks. Nature. 1999;399(6732):130-132.
17. McMahon T. Size and shape in biology. Science. 1973;179(4079):1201-1204.
18. Mahmood I. Theoretical versus empirical allometry. Facts behind theories and application to pharmacokinetics. J Pharm Sci. 2010;99(7):2927-2933.
19. White CR, Seymour RS. Allometric scaling of mammalian metabolism. J Exp Biol. 2005;208(Pt 9):1611-1619.
20. Knibbe CA, Zuideveld KP, Aarts LP, et al. Allometric relationships between the pharmacokinetics of propofol in rats, children and adults. Br J Clin Pharmacol. 2005;59(6):705-711.
21. Cortinez LI, Andersen BJ, Penna A, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth. 2010;105(4):448-456.
22. Servin FF, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide: a clinical and pharmacokinetic study. Anesthesiology. 1993;78(4):657-665.