DRUG DOSAGE – HOW MANY INCHES SHOULD YOU GIVE?

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Numerous recommendations have been made about how much drug we should give our patients. In particular, how should we adjust drug dose in otherwise healthy patients for obesity and age. The literature is very confused with numerous models for adjusting drug dose having been described. The confusion mainly results from a lack of clarity in conceptual thinking and a plethora of small studies describing limited populations.

The first truth is – *a model only describes the population that it was created from*. However even though all drug dose models are empirical, the second truth is that *a good model will allow extrapolation beyond the population it was created from*.

There are two basic questions I try and answer about some common anaesthetic drugs, how to scale –

1. Induction (bolus) doses
2. Infusion rates

Obesity

Numerous models have been suggested for scaling to body size –

Total body weight (TBW)		Wt
Body mass index (BMI)	Quetelet[1]	Wt / Ht^2
Lean tissue mass (LTM)	James[2]	$1.1 \times Wt - 128 \times (Wt / Ht)^2$
Body surface area (BSA)	Dubois[3]	$Wt^{0.425} \times Ht^{0.727} \times 0.007184$
Fat free mass (FFMd)	Deurenberg[4]	$40 - (1.2 \times BMI) + 0.23 \times Age - 16.2$
Fat free mass (FFM)	Janmahasatian[5]	$(9270 \times Wt) / (6680 + 216 \times BMI)$
Ideal body weight (IBW)	Devine[6]	$45.4 + 0.89 \times (Ht - 152.4) + 4.5$
Adjusted (IBWa)	la Colla[7]	$IBW + 0.4 \times Wt$
Allometric size model (ASM)	Cortinez[8]	$(Wt / 70)^{0.75}$

(Note – LTM, FFM and IBW are male formula only)

Some of these models are entirely empirical, usually derived from a description of drug dosage in obesity from a single study and some are based on research into body composition. For instance, Deurenberg studied changes in body composition with age, showing the reduction in body fat that occurs. Janmahasatian described changes in body composition with obesity in a group of middle-aged adults. James didn't study obese people and the equation shape is fundamentally flawed.

Graphing these equations for a 70kg, 170cm male who grows fatter makes them much easier to understand (Figure 1). Notice that between the extremes of total body weight, that increases linearly, and ideal body weight, that doesn't change, there is little to choose between the various curves. If all the equations were redrawn in the simple form $ABW = a + b(TBW)^c$ they would be easier to compare. Induction dose is largely distributed into the ECF and there is a correlation with cardiac output.[9] In obesity, CO and blood volume are increased only slightly and cardiac index is unchanged.[10,11] They follow closely to the FFM line on figure 1.

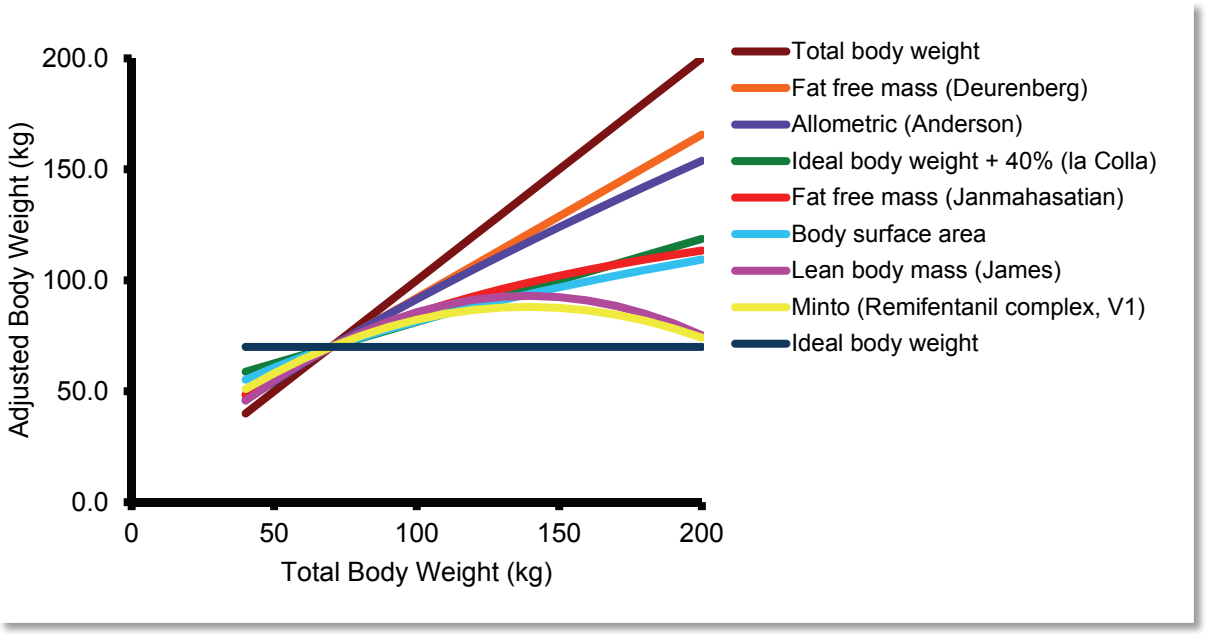


Figure 1. How each model describes a 70kg, 170cm adult male who grows fatter

Propofol

Propofol has been extensively studied. The drug is highly lipid soluble and so bolus dosage and infusion dosage behave differently. Analysis of a composite data set of thin, typical and obese patients [Short unpublished[12,13,14]] shows a dual picture. For bolus dosage, FFM and IBW performed similarly. For infusion adjustment ASM or TBW performed best, presumably because fat takes up propofol almost infinitely, although it is rather slow to get there and therefore does not influence induction dose. Measuring cardiac output confirmed FFM as an appropriate scalar for induction, although IBM was not assessed in this study.[15] The subject requires further analysis to come up with one model that predicts all patients. The Marsh model performed very poorly in obese subjects, presumably because none were included in the original study. None of the studies provided evidence that there were pharmacodynamic differences in obesity.

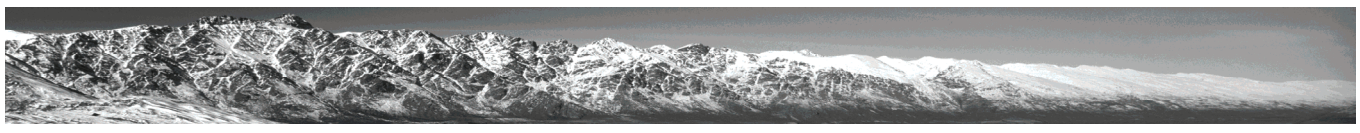
Opioids

Fentanyl should be dosed by either FFM, or linearly until TBW is 100 – 110 kg and then no further adjustment. It is noted that there may be greater respiratory depression for a given plasma concentration in the obese.[16]

Remifentanil has been studied in obesity [Egan 1998]. LTM was found to be an accurate predictor of blood concentration. The Minto model is based on an age stratified group of patients, and did not specifically look at the influence of obesity.[17] It scales the pharmacokinetics to LBM. This equation is flawed as explained in Figure 1. If FFM is substituted for LBM, then the model works better in obesity.[18] When the data are reanalysed using Egan's data taken in obese patients as well it performs better using FFM. The question is what to do with PK model controlled dosing in obese patients, such as is available in the Alaris pumps. Simulation analysis indicates that adjusting weight up to 100 – 110 kg with no further adjustment performs adequately.

Volatiles

Obesity can reduce functional residual capacity, expiratory reserve volume and total lung capacity. It has little effect on uptake and elimination of volatiles. Desflurane uptake in intubated, ventilated patients was virtually unaltered.[19] Isoflurane had a slightly larger ratio of F_i/F_{ET} consistent with its higher lipid solubility.[20] The results are consistent with the low perfusion of fat and small change in CI at rest in the obese. Sevoflurane has yielded similar results and demonstrated no change in either $T_{½}k_{eo}$ or pharmacodynamic effect as measured by BIS.[21]



Relaxants

All muscle relaxants are highly ionized molecules with low lipid solubility, they distribute in a volume equivalent to ECF. Clinical studies demonstrate duration of action is significantly longer if TBW dosing is used and IBW has been found to be the best descriptor of dose for atracurium, cisatracurium, vecuronium and rocuronium.[22-26] The dose of suxamethonium has been studied clinically. Intubating conditions were better when TBW dosing was used, however, examination of the graphs reveals that NMB was almost as profound with LTM or IBW dosing, but lasted 7 and 8 minutes, rather than 11.5 minutes with TBW dosing for recovery of 90% of twitch height.[27]

Other Drugs

There are no studies of ketamine or dexmedetomidine in obesity. Looking at their ionization and distribution volumes, a guess is that ketamine would adjust by IBW and dexmedetomidine by FFM.

Drug	Recommended Model in Obesity
Propofol	TBW or ASM
Remifentanil	FFM
Fentanyl	FFM
Relaxants	IBW
Volatiles	No adjustment
Ketamine	IBW my guess
Dexmedetomidine	FFM my guess

Table 1. Recommended models in obesity for common drugs. For intravenous drugs, recommendations are for infusions. For bolus dosing, FFM or IBW appears best for most drugs

Age

There are only a few high definition studies for many commonly used drugs.

Propofol

Schnider studied eight young, eight middle aged and eight elderly patients in a detailed PKPD study.[12,28] The analysis shows a similar decrease with age to remifentanil, using the EEG as a measure of effect. T_{peak} was increased from 1.5 minutes at age 20 to about 1.8 minutes, but was highly variable.

Opioids

Remifentanil has been studied in detail by Minto, who studied 20 young, 20 middle aged and 20 elderly patients.[17,29] There was a significant reduction in dose requirement with age for the same observed effect. T_{peak} was also doubled from 1.5 at age 20 years to 3 minutes by age 80 years.

Volatiles

These have been summarised by Nickalls and Mapleson.[30] There is a less severe reduction in MAC than for intravenous agents (figure 2). One small study measuring isoflurane concentrations in arterial blood found no change in end-tidal to arterial gradient for with age.

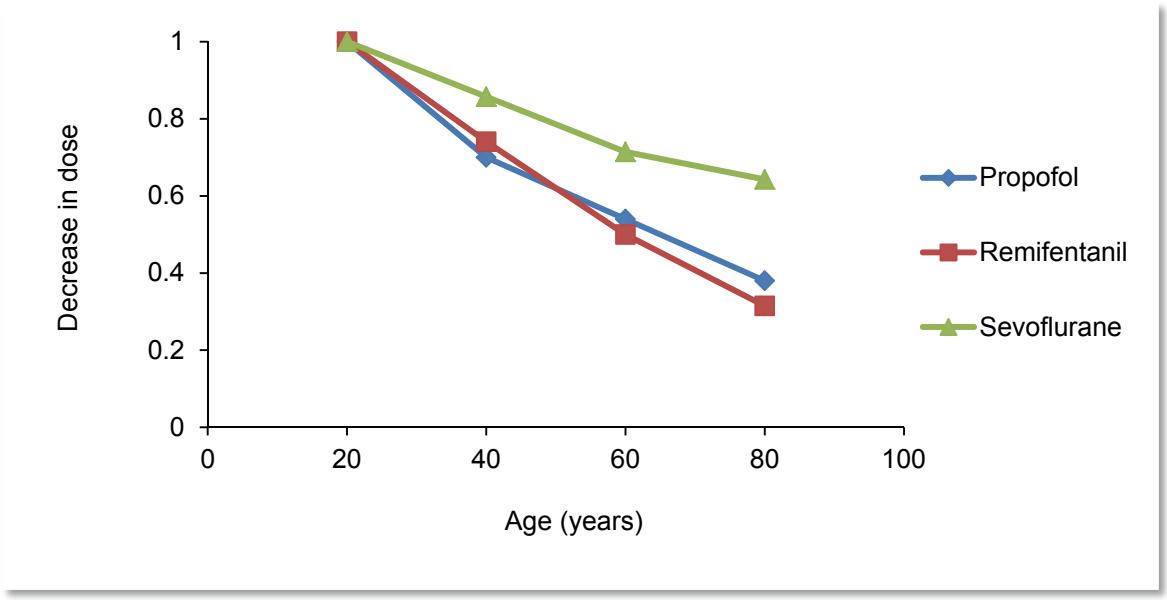


Figure 2. Reduction in dose requirements with age for three common anaesthetic drugs

Relaxants

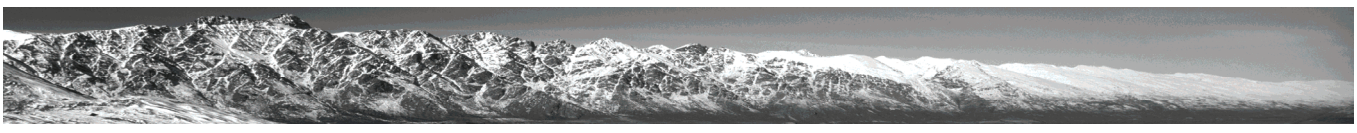
A comparison of patients aged 20 – 40 years with patients aged 60 – 75 years found onset time for rocuronium to be increased from 82 to 127 seconds and duration nearly doubled.[23] Another study found no change in onset time for unadjusted doses of atracurium, rocuronium and vecuronium but a significant increase in duration of effect.[31] Given the increase in duration of effect, it is likely there is a reduction in onset time that is compensated by the relative increase in dose with age. Only a high-resolution study can unravel this, but it is likely these drugs follow a similar path on figure 2 to the drugs graphed.

Conclusion

Obesity reduces drug requirements for intravenous drugs with the exception of propofol when infused, but the degree it is reduced by varies between drugs according to their disposition. Age has a large effect in reducing drug dose requirements, but there have been few high-resolution studies. There are no studies of anaesthetic drug interactions and age. The case for dose titration and direct measurement of effect in the elderly is very strong!

References

1. Quetelet LAJ, eds. Physique Sociale vol 2. Brussels, C. Muquardt,1869: 92
2. James W. Research on obesity. London: Her Majesty's Stationery Office; 1976
3. Du Bois D, Du Bois EF. Clinical calorimetry. Tenth paper. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17: 863
4. Deurenberg P, Deurenberg-Yap M, Foo LF, Schmidt G, Wang J. Differences in body composition between Singapore Chinese, Beijing Chinese and Dutch children. Eur J Clin Nutr. 2003; 57: 405-9
5. Janmahasatian S, Duffull SB, Ash S, et al. Quantification of lean bodyweight. Clin Pharmacokinet 2005; 44: 1051-1065
6. Devine D. Case study number 25 gentamicin therapy. Drug Intell Clin Pharm 1974; 8: 650-5
7. La Colla L, Albertin A, La Colla G, et al. No adjustment vs. adjustment formula as input weight for propofol target-controlled infusion in morbidly obese patients. Eur J Anaesthesiol 2009; 26: 362-369
8. Cortınez LI, Anderson BJ, Penna A, Olivares L, Munoz HR, Holford NHG, Struys MMRF, Sepulveda M. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth 2010; 105: 448-56



9. Ingrande J, Brodsky JB, Lemmens HJM. Lean Body Weight Scalar for the Anesthetic Induction. Dose of Propofol in Morbidly Obese Subjects. Anesth Analg 2011; 113: 57-62
10. Stelfox, HT, Ahmed SB, Ribeiro RA, Gettings EM,Pomerantsev E, Schmidt U. Hemodynamic monitoring in obese patients: The impact of body mass index on cardiac output and stroke volume. Crit Care Med 2006; 1243-6
11. Wennesland R, Brown E, Hopper J, Hodges JL, Guttentag E, Scott KG, Tucker IN, Bradley B. Red cell, plasma and blood volumein healthy men measured by radiochromium(Cr1) cell tagging and haematocrit. Influence of age, somatotype and habits of physical activity on the variance after regression of volumes to height and weight combined. J Clin Invest 1959; 1065-77
12. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998 May; 88: 1170-82
13. Servin F, 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: 657-65
14. Egan TD, Huizinga B, Gupta SK, et al. Remifentanil pharmacokinetics in obese versus lean patients. Anesthesiology 1998; 89: 562-73
15. Ingrande J, Brodsky JB, Hendrikus JM, Lemmens JM. Lean body weight scalar for the anesthetic induction dose of propofol in morbidly obese subjects. Anesth Analg 2011; 113: 57-62
16. Shibutani K, Inchiosa MA, Sawada K, Bairamain M. Accuracy of phamracokinetic models for predicting plasma fentanyl concentrations in lean and obese surgical patients. Derivation of dosing weight ('pharmacokinetic mass'). Anesthesiology 2004; 101: 603-13
17. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997 Jan; 86(1): 10-23
18. 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: 131-9
19. La Colla G, La Colla L, Turi S, Poli D, Albertin A, Pasculli N, Bergonzi PC, Gonfalini M, Ruggieri F. Effect of morbid obesity on kinetic of desflurane: wash-in wash-out curves and recovery times. Minerva Anestesiol. 2007; 73: 275-9
20. Lemmens HJ, Saidman LJ, Eger EI 2nd, Laster MJ. Obesity modestly affects inhaled anesthetic kinetics in humans. Anesth Analg 2008; 107: 1864-70
21. Cortínez LI, Gambús P, Trocóniz IF, Echevarría G, Muñoz HR. Obesity does not influence the onset and offset of sevoflurane effect as measured by the hysteresis between sevoflurane concentration and bispectral index. Anesth Analg 2011; 113: 70-6
22. Leykin Y, Pellis T, Lucca M, Lomangino G, Marzano B, Gullo A. The effects of cisatracurium on morbidly obese women. Anesth Analg 2004; 99: 1090-4
23. Adamus M, Hrabalek L, Wanek T, Gabrhelik T, Zapletalova J. Influence of age and gender on the pharmacodynamic parameters of rocuronium during total intravenous anesthesia. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2011; 155: 347-53
24. Schwartz AE, Matteo RS, Ornstein E, Halevy JD, Diaz J. Pharmacokinetics and pharmacodynamics of vecuronium in the obese surgical patient. Anesth Analg 1992; 74: 515-8
25. Meyhoff CS, Lund J, Jenstrup MT, et al. Should dosing of rocuronium in obese patients be based on ideal or corrected body weight? Anesth Analg 2009; 109: 787-92
26. van Kralingen S, van de Garde EM, Knibbe CA, Diepstraten J, Wiezer MJ, van Ramshorst B, van Dongen EP.Comparative evaluation of atracurium dosed on ideal body weight vs. total body weight in morbidly obese patients. Br J Clin Pharmacol 2011 Jan; 71(1): 34-40
27. Lemmens HJ, Brodsky JB. The dose of succinylcholine in morbid obesity. Anesth Analg 2006; 102: 438-42
28. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. Anesthesiology 1999; 90: 1502-16
29. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997; 86: 24-33
30. Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. Br J Anaesth. 2003; 91: 170-4
31. de Almeida MC, Latorre F, Gervais HW, Kleeman PP. The effects of age on onset and recovery from atracurium, rocuronium and vecuronium blockade. Anaesthesist 1996; 45: 903-6