Editorial

Obesity, Lean Body Mass, and Sugammadex Dosing

Recently, Merck issued a recommendation for sugammadex dosing for reversal of neuromuscular junction (NMJ) blockade.[1] Appropriately, the guideline assumes assessment of residual block using some form of nerve stimulator to assess any residual block. Less appropriate is the recommendation that dosing is based simply on the weight of the patient. With obesity an increasing global health issue, the question of drug dosing by weight is an increasing conundrum. Drug dosing is always an approximation. For the typically fast acting drugs that anesthesiologists employ, the key is to rapidly load the plasma and interstitial fluid volumes, so that drug binds in equilibrium with the plasma/interstitial volume concentration. The paper by Bougouma and Demeere[2] attempts to achieve a rational approach to drug doing in the obese patients, specifically for sugammadex reversal of rocuronium.

Drug dosing based on body weight presumes that the volume of distribution is the plasma/interstitial volume and is some relatively fixed proportion of body weight (~20%). The typically recommended drug doses based on ideal body mass (IDM) are expected to provide a relatively certain concentration, also realizing that protein binding will influence the free drug concentration that interacts with the receptor.

But the increasingly world-wide epidemic of obesity changes drug dosing. Some argue that you should dose the real body weight. However, adipose tissue occupies a large volume but is poorly perfused, and obligates little cardiac output or blood volume. However, an excess of adipose tissue does obligate extra skin to cover it and extra muscle to carry it around, and these tissues increase blood and plasma volume and cardiac output. Thus obesity increases the volume of drug distribution, but not in proportion to weight.[3,4] Using real body weight will result in giving an excess of drug since the volume of distribution is not increased in proportion to weight. But while some might argue to use ideal body weight, obese patients will have some increase in cardiac output, blood volume and interstitial fluid, so that dosing by ideal body weight will result in under-dosing obese patients.

The suggestion has been made to calibrate drug dosing based on lean body mass (LBM) which increases with real body mass, but not in proportion to total body mass. LBM, for someone with normal body mass, is typically about 75-85% of what a person 'should' actually weigh, that is, ideal body mass (IBM); measured LBM typically identifies 15-25% body fat to be normal (higher in women than men). The benefit of using LBM, which includes muscle and skin, is that it will increase with obesity (increased skin to cover the fat and increased muscle to carry it around), but not in proportion to the total mass. The LBM is what obligates cardiac output and blood volume. Unfortunately, most recommended drug dosing uses real body mass (ignoring the obesity issue), therefore doses based on LBM will underdose patients. In the study in question, the drugs administered in mg/kg were appropriately increased.

But how is LBM calculated? A variety of measurements including total body potassium have been used. An often-used formula to calculate the value as in the present paper is that of James[5] that appears to have been based on people of near normal body mass. If one extrapolates to weights approaching twice IBM, the calculated LBM (CLBM) declines; near 3.5x IBM the CLBM eventually goes to zero! Alternative formulae that avoid this problem are those of Hume[6] and Boer[4]. Those formulae achieve a more accurate value, but are both are well below the IBM. Figure 1 below compares the various CLBM for a woman with an IBM of 60 kg, height of 1.65 m (65 inches), as the real body mass (RBM) varies up to 130 kg and body mass index (BMI) increases from 22 to 46.3. The James calculation can be seen to actually decline above a BMI of 41.

An alternative value proposed by Lemmens et al.[7,8] determines a lean scaling factor (LSF) to arrive at a *lean scaled weight* (LSW, using their terminology weight for mass). Lemmens formula uses body mass index (BMI) to appropriately modify the real body mass (RBM):

(LSW), female = RBM x LSF = RBM x 14,148/(8,780 + 244 x BMI).

(LSW), male = RBM x LSF = RBM x 11,432/(6,680 x 216 x BMI).

LSW provides a more accurate estimate of blood volume and interstitial volume (which is what we are loading with our drugs). The LSW is also plotted in Figure 1 and would appear to provide a reasonable estimate for drug dosing in the obese patient, a value between IBM and RBM, between ideal and real. But even with iPhones and calculators, attempting to use such formulas in a busy OR might be distracting and impractical, and the value is an approximation in any case. So perhaps a simpler approximation of weight (or mass) for mg/kg dosing might be to use the simple average of IBM and RBM, i.e. (RBM+IBM)/2. For the 110 kg patient who should weigh 60 kg, use 85 kg. This is not an LBM or LSW calculation, but does give an easily calculated body weight for dosing that approximates the LSW quite nicely (see Figure 1). It would give a dose somewhat lower than that promulgated by the Merck recommendation, but would also depend on the weight base used to calculate the rocuronium dose. In addition, there is variability in obesity as well: some patients with clearly morbid central corpulence and limited function, versus the healthy and vigorous fat patient. Both have

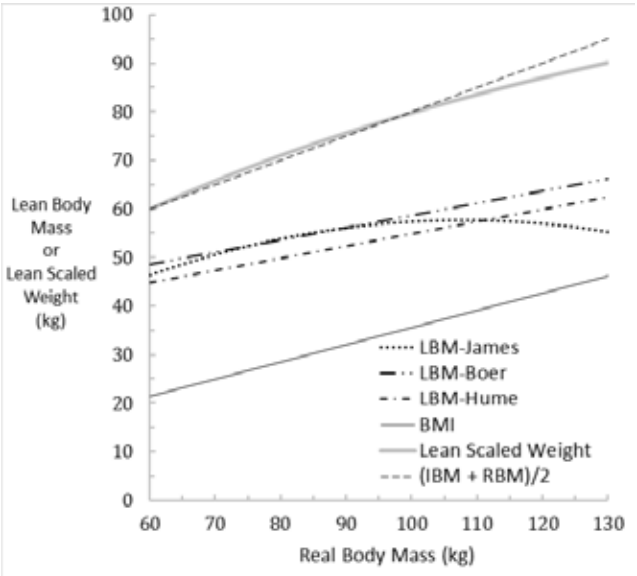

Figure 1. Comparison of Various Calculations of Lean Body Mass or Lean Scaled Weight for 1.65 m tall women with an Ideal Body Mass of 60 kg and BMI 22.

the same height and weight but certainly different lean body masses to carry the extra weight.

But there are other considerations. Sugammadex dosing represents a unique situation. For most pharmaceuticals administered, a drug is given to compete with another agent at a specific binding site (e.g. beta-adrenergic blockers), or a drug is given to induce an opposite action to counteract some effect. But sugammadex reversal of rocuronium blockade of the NMJ is unlike any other drug used by anesthesiologists since it involves the specific and very high affinity binding of one drug to another. In theory, because there is binding of a single rocuronium molecule by one sugammadex molecule, all one has to do is give the same number of molecules of sugammadex. Based on the molecular weights (rocuronium: 530 Da; sugammadex: 2178 Da), 4 mg of sugammadex is required to bind 1 mg of rocuronium (approximately $1.1x10^{18}$ or about one quintillion molecules of each!). Sugammadex does bind other steroid molecules, but with far lower affinity. In the present study, dosing the rocuronium based on CLBM is perfectly appropriate, and it worked well to use the same CLBM dosing of sugammadex.

However, to calculate the dose of sugammadex required, one might instead use the given dose of rocuronium minus the amount estimated to have been metabolized. For example, if 50 mg of rocuronium is given, and half of the amount is presumed metabolized after 30 minutes, one might give 100 mg sugammadex to bind the 25 mg rocuronium presumed remaining. Based on the original dose of rocuronium (50 mg) it would represent a 2:1 ratio (mg). In the present study the authors actually ended up giving the 20 patients an average mg ratio of 1.42±0.24. Since reversal was complete, presumably even more than 50% of the rocuronium was metabolized.

A problem may arise when an excess of sugammadex is given. A high dose ratio, say 16:1 instead of 4:1, should mean a more rapid reversal since it markedly increases the likelihood of a sugammadex molecule 'bumping into' (to use non-statistical term) a rocuronium molecule. But in addition to being far more expensive, an excess of sugammadex molecules might bind other steroids in the blood (e.g. steroid birth control agents, corticosteroids given for nausea or to prevent allergic responses).

Thankfully, the presence of sugammadex represents a superior alternative to neostigmine (or even edrophonium). Whereas if an excess of neostigmine is used, it has the potential to cause weakness, an excess of sugammadex is unlikely to have consequences in reversal of NMJ blockade. The paper by Bougouma and Demeere provides a useful reminder to be thoughtful and calculating in drug administration.

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References

1. BRIDION dosing based on actual body weight and depth of block. Copyright 2018 Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc**.** All rights reserved
2. Bougouma CTHW-P, Demeere J-LRJ. Dosage of sugammadex according to the calculated lean body mass in obese patients and time to reverse moderate neuromuscular blockade induced by rocuronium. South African J Anesth Analg 2019; XX:XX
3. Messerli FH, Christie B, DeCarvalho JG, Aristimuno GG, Suarez DH, Dreslinski GR, Frohlich ED. Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion, and plasma renin activity. Arch Intern Med 1981;141:81-5.
4. Boer P. Estimated lean body mass as an index for normalization of bodv fluid volumes in humans. Am J Physiol 1984; 247 (Renal Fluid Electrolyte Physiol. 16): F632-F636.
5. James W. Research into Obesity, HMSO; 1976, p 9. ISBN 11 450034 7
6. Hume R, Weyers EJ. Relationship between total body water and surface area in normal and obese subjects. Clin Pathol. 1971;24:234-8.
7. Lemmens HJ, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. Obes Surg. 2006;16:773-6
8. Friesen JHP. Lean-scaled weight can be used to estimate blood volume for obese patients. Can J Anesth. 2014;61:1059-60.