Drug Dosage – How Many Inches Should You Give?

Dr Tim Short
Auckland City Hospital,
Auckland

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 –

<table>
<thead>
<tr>
<th>Model</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body weight (TBW)</td>
<td>Wt</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>Wt / Ht^z</td>
</tr>
<tr>
<td>Lean tissue mass (LTM)</td>
<td>1.1 × Wt – 128 × (Wt / Ht)^2</td>
</tr>
<tr>
<td>Body surface area (BSA)</td>
<td>Wt^{0.425} × Ht^{0.727} × 0.007184</td>
</tr>
<tr>
<td>Fat free mass (FFMd)</td>
<td>40 – (1.2 × BMI) + 0.23 × Age – 16.2</td>
</tr>
<tr>
<td>Fat free mass (FFM)</td>
<td>(9270 × Wt) / (6680 + 216 × BMI)</td>
</tr>
<tr>
<td>Ideal body weight (IBW)</td>
<td>45.4 + 0.89 × (Ht – 152.4) + 4.5</td>
</tr>
<tr>
<td>Adjusted (IBWa)</td>
<td>IBW + 0.4 × Wt</td>
</tr>
<tr>
<td>Allometric size model (ASM)</td>
<td>(Wt / 70)^{0.75}</td>
</tr>
</tbody>
</table>

(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. In obesity, CO and blood volume are increased only slightly and cardiac index is unchanged. 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 unpublished12,13,14] 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.

Volatile

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/FET 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 T1/2 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.\textsuperscript{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.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Model in Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>TBW or ASM</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>FFM</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>FFM</td>
</tr>
<tr>
<td>Relaxants</td>
<td>IBW</td>
</tr>
<tr>
<td>Volatiles</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Ketamine</td>
<td>IBW my guess</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>FFM my guess</td>
</tr>
</tbody>
</table>

*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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
Drug Dosage – How Many Inches Should You Give?

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. Another study found no change in onset time for unadjusted doses of atracurium, rocuronium and vecuronium but a significant increase in duration of effect. 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

Annual Queenstown Update in Anaesthesia, 2012

Drug Dosage – How Many Inches Should You Give?

29. Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. Anesthesiology 1997; 86: 24-33