

## EDITORIAL VIEWS

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### Does Size Matter?

INTRAVENOUS drugs used in anesthesia range from compounds with low margins of safety, such as opioids and hypnotics, to deadly poisons, such as muscle relaxants. During general anesthesia, patients often are paralyzed, their tracheas are intubated, their lungs are mechanically ventilated, and their vital signs are continuously scrutinized. In this environment, we rarely see injury from anesthetic drugs, because anesthesiologists have become highly skilled at titrating toxic drugs within their narrow therapeutic window and at managing the occasional toxic effects that develop. The therapeutic window for intravenous anesthetic drugs is diminished greatly in the awake, spontaneously breathing patient. Yet even during conscious sedation, the incidence of adverse events is very low when sedation is administered by an anesthesiologist. In this issue of the journal, Egan *et al.*<sup>1</sup> use complex models to help us get the dose of remifentanyl just right. Why should we care about getting the dose just right? We are clearly skilled at getting close to the right dose. Isn't "close" close enough?

During general anesthesia, this is probably close enough. During conscious sedation, close may cross the line between hypoventilation and apnea. But why not do the best job we can? We want our patients to be unconscious, immobile, and hemodynamically stable during anesthesia. We want them to awaken promptly, yet comfortably, after anesthesia. Even if close is close enough, why not adjust the dose for weight, age, gender, organ function, and type of surgery? Much research has been done to understand how patient factors such as age, gender, and weight relate to the pharmacokinetics and pharmacodynamics of thiopental,<sup>2,3</sup> fentanyl and

alfentanil,<sup>4</sup> sufentanil,<sup>5</sup> propofol,<sup>6</sup> and remifentanyl,<sup>7</sup> to give just a few examples.

At a minimum, we should at least adjust adult doses to weight. Many package inserts, including those of propofol and remifentanyl, explicitly provide per-kilogram adult-dosing guidelines. Doesn't this tell us that the drugs should be given per kilogram of body weight? That is the message, but it may be wrong.

Egan *et al.*<sup>1</sup> administered remifentanyl to obese patients and nonobese control patients. To estimate pharmacokinetic parameters for an extended period, the authors chose a remifentanyl dose that was large, 10  $\mu\text{g}/\text{kg}$  during 1 min, but that had been well tolerated in his previous studies with nonobese persons. This dose proved to be a big mistake in large persons. Two of the first three patients had profound bradycardia associated with hypotension, necessitating a change in protocol to reduce the dose for subsequent patients. Yet this was a setting in which we think opioid overdoses are well tolerated: the paralyzed, intubated, and ventilated patient.

Spontaneously breathing patients have little tolerance for opioid overdoses. Remifentanyl is approved for use in conscious sedation. Dosing remifentanyl according to the package insert recommendations of a 1  $\mu\text{g}/\text{kg}$  bolus followed by a 0.05  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  infusion may result in a profound overdose and injury in spontaneously breathing obese patients. So what options do we have?

We can scale anesthetic drugs to lean body mass instead of weight. Lean body mass can be calculated from weight, in kilograms, and height, in centimeters, as follows:<sup>8</sup>

$$\text{LBM} = 1.1 \cdot \text{weight} - 128(\text{weight}/\text{height})^2 \text{ for men,}$$
 and

$$\text{LBM} = 1.07 \cdot \text{weight} - 148(\text{weight}/\text{height})^2 \text{ for women.}$$

Scaling drugs to lean body mass instead of weight has been recommended for thiopental,<sup>9</sup> methohexital,<sup>10</sup> muscle relaxants,<sup>11,12</sup> and propofol.<sup>13,14</sup> However, the formula for lean body mass is complex, with implications for dosing that are not immediately obvious. Figure 1 shows lean body mass as a function of weight (x axis) and height (different lines) for men (upper graph) and women (lower graph). The equation has an odd property: For every height there is weight associated with a peak lean body mass, beyond which, increases in weight

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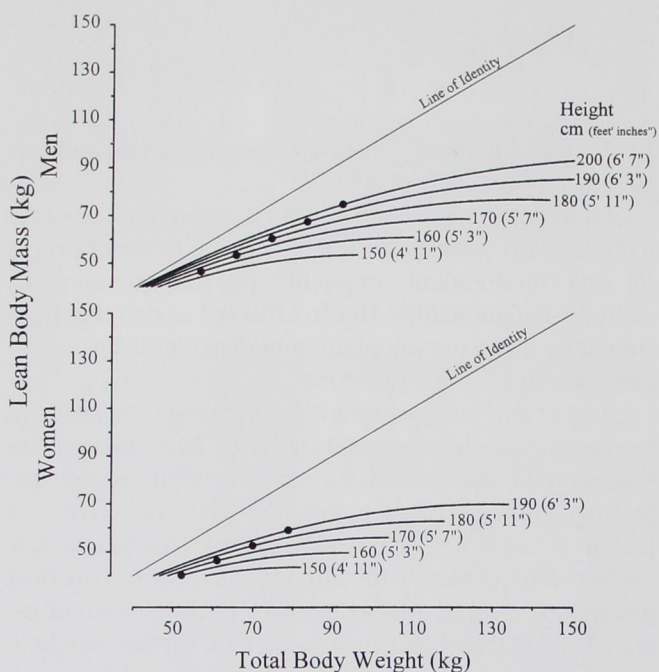


Fig. 1. A nomogram relating total body weight, height, and gender to lean body mass. Adapted from equations in the text. The dots show the ideal body weight at each height, computed from standard formulas.<sup>15</sup> The formulas for lean body mass are calculated for a representative sample of the population, and they do not apply to highly trained athletes who may have 10% body fat or less.

are matched by a decrease in lean body mass. This is probably an artifact of the equation, so the relation beyond the peak lean body mass has been truncated from the lines shown in figure 1. This illustration also shows the ideal body weights for each height as a round dot on each curve, calculated from standard formulas (for men:  $49.9 + 0.89(\text{height} - 152.4)$  kg; for women:  $45.4 + 0.89(\text{height} - 152.4)$  kg).<sup>15</sup>

Let us assume that scaling to lean body mass, as suggested by Egan *et al.*<sup>1</sup> and others,<sup>10-13</sup> is a reasonable choice for intravenous anesthetic drugs. If this is true, figure 1 shows that the problem with scaling to total body weight is asymmetrical. At weights less than ideal body weight (to the left of the dot on each line), total body weight is a good approximation of lean body mass, because small people do not have a lot of fat. Because total body weight and lean body mass are similar, either can be used to scale drug doses. When the total body

weight exceeds ideal body weight (to the right of the dot on each line), total body weight increasingly overestimates lean body mass.

The nomogram in figure 1 can be used to estimate lean body mass from weight, height, and gender. Unfortunately, we cannot calculate the correct dose by multiplying the lean body mass by the recommended dose because recommended doses in package inserts and published guidelines are scaled to total body weight, not lean body mass. However, let us assume that scaling to lean body mass is appropriate for most intravenous drugs used in anesthesia and that the recommended doses, scaled to total body weight, are correct for persons of ideal body weight. Based on these assumptions, we can scale figure 1 to produce a nomogram showing the weight we should enter into our calculations to accurately reflect the extent to which a patient's lean body mass is larger or smaller than the lean body mass in a person of ideal body weight. In this process, the curves in figure 1 scale upward so that dots, showing ideal body weight, lie on the line of identity, as seen in figure 2.\*

Figure 2 shows the weight to use clinically with pub-

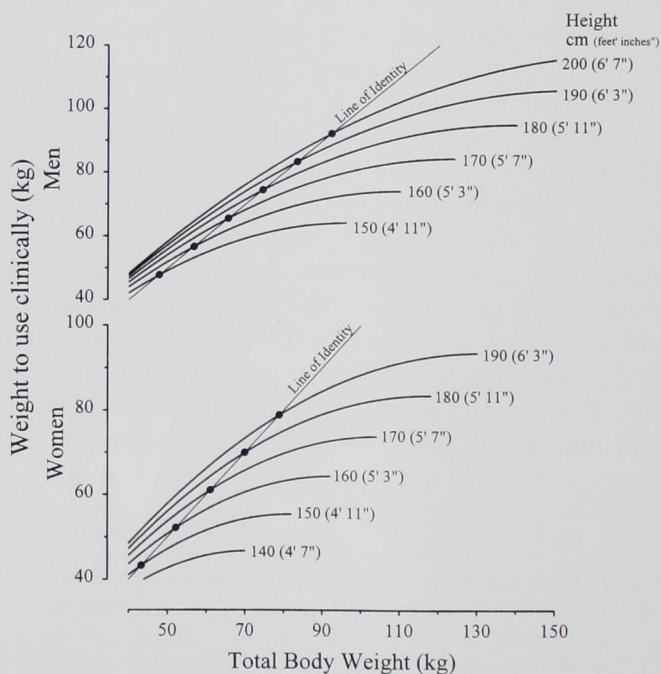


Fig. 2. A nomogram relating total body weight, height, and gender to the body weight that should be used to calculate dose from recommendations that are scaled to total body weight. The dots show ideal body weight, as in figure 1. The scaling between figures 1 and 2 assumes that published dosing recommendations scaled to total body weight are exactly correct for persons of ideal body weight, which accounts for the finding that the dots line up on the line of identity.

\* The actual calculation used to produce figure 2 multiplied all points in figure 1 by the ideal body weight for each height (x value of the dot) divided by the lean body mass calculated for a person of ideal body weight (y value of the dot).



lished doses scaled total body weight, as a function of patient sex, height, and total body weight. For example, if the patient is a 170-cm woman who weighs 90 kg, doses should be calculated as though the woman weighs 72 kg. When the remifentanyl package insert calls an infusion of  $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , this patient should get 72  $\mu\text{g}/\text{min}$ , not 90  $\mu\text{g}/\text{min}$ . Figure 2 also illustrates that weight scaling is a problem for persons who are much heavier than ideal body weight. Below ideal body weight, the total body weight and the weight that should be used to scale by lean body mass are not very different.

Another strategy is simply not to adjust weights in adults. For example, Gepts *et al.*<sup>5</sup> concluded that weight did not affect the pharmacokinetics of sufentanil, implying that sufentanil doses should not be weight adjusted. In comparing individual volumes and clearances between obese patients and nonobese controls, Egan *et al.*<sup>1</sup> did not identify any statistically significant differences provided the parameters were not normalized to weight. A NONMEM analysis identified an effect of lean body mass that was statistically significant, but the improvement was very small. Egan *et al.*<sup>1</sup> recommend scaling to lean body mass, but they observe that not scaling at all did nearly as well. Either choice was acceptable, and either was preferable to scaling the remifentanyl dose to total body weight.

What can we conclude from Egan *et al.*'s article and other recent publications<sup>6,7</sup> on pharmacokinetics? First, the tradition of scaling adult pharmacokinetic parameters to total body weight is not *a priori* correct. Whether pharmacokinetic parameters scale to weight is a hypothesis that can be tested before a decision is made on how to report pharmacokinetics. Second, scaling adult pharmacokinetics to lean body mass is also a hypothesis that can be tested. Egan *et al.* show how to do so: Study patients at the extremes of weight, and use formal statistical tests to prove (or disprove) the hypothesis. Third, the Food and Drug Administration and the pharmaceutical industry need to critically examine the assumptions underlying published dosing guidelines. Any choice (scaling to weight, lean body mass, ideal body weight, body surface area, or not scaling at all) represents an assumption about the relation between size and pharmacokinetics. The choice should be based on data, not tradition.

Fourth, we must still administer our anesthetic drugs. Often we do not have information on how to best scale the dose to patient size. Egan *et al.*<sup>1</sup> show that we cannot depend on published dosing information in obese persons. Figure 2 suggests a strategy for drug dosing when we are unsure about the true rela-

tion between size and pharmacokinetics. For persons smaller than ideal body weight, simply scale the dose to total body weight. For persons larger than ideal body weight, either scale the dose to ideal body weight or to ideal body weight plus some fraction of the difference between total weight and ideal body weight, as suggested by figure 2. Figure 2 also suggests that it is rarely appropriate to scale dose to a weight  $>80$  kg in a woman or to 100 kg in a man.

Size does matter. The Food and Drug Administration has been remiss in approving adult dosing recommendations scaled to weight without adequate scientific evidence that the pharmacokinetics are weight proportional. Fortunately, anesthesiologists reduce doses in obese persons based on experience and intuition alone. Still, the pharmaceutical industry, the Food and Drug Administration, and clinical investigators have an obligation to provide clinicians with the best possible dosing recommendations. We need to provide the scientific foundation to get the dose just right so we can help prevent the complications that arise when close isn't close enough.

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## Receptor-specific Reversible Sedation

### Beginning of New Era of Anesthesia?

IMAGINE a reversible intravenous anesthetic that could be administered without having to be titrated to effect; anesthesia machines without vaporizers, fewer concerns for environmental pollution, no need to adjust anesthesia based on duration of surgery or concern for delayed recovery from prolonged exposure to anesthetics. Although this technique does not exist, a study reported in this issue of *ANESTHESIOLOGY* by Scheinin *et al.* establishes the groundwork for such a technique, potentially revolutionizing the way anesthesia will be administered in the future.

These investigators have shown that  $\alpha_2$ -agonist (dexmedetomidine)-mediated sedative and sympatholytic effects can be reversed rapidly and completely by a highly selective  $\alpha_2$ -antagonist (atipamezole). This finding is significant for several reasons. First, it defines the

$\alpha_2$ -agonist/antagonist combination as a novel method for achieving sedation. Providing reversible sedation with a drug that also produces analgesia without respiratory depression is very exciting, and could increase patient safety in certain situations. Second, by reversing the sedative effect of dexmedetomidine with a highly specific  $\alpha_2$ -antagonist, the investigators provided further proof that the sedative effect of dexmedetomidine is mediated by the  $\alpha_2$ -receptor. This makes the  $\alpha_2$ -agonist one of the few anesthetic compounds for which we understand the mechanism of action. Third, the combination of  $\alpha_2$ -agonist/antagonist offers anesthesiologists another class of receptor-specific reversible anesthetic drugs for use in surgical practice. We are comfortable already with the use of receptor-specific drugs such as muscle relaxants and opioids, therefore, the learning curve for use of this new combination should be manageable. Fourth, these concepts and this new class of drugs have significant potential to influence the way general anesthesia is provided in the future.

$\alpha_2$ -Adrenergic agonists have sedative, analgesic, and sympatholytic effects. At high dosages,  $\alpha_2$ -agonists cause unresponsiveness. Medetomidine, which is a racemic mixture of dexmedetomidine and levomedetomidine, is marketed as a reversible intravenous anesthetic for animals. However, administration of high concentrations of

This Editorial View accompanies the following article: Scheinin H, Aantaa R, Anttila M, Hakola P, Helminen A, Karhuvaara S: Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific  $\alpha_2$ -adrenoceptor antagonist atipamezole—A pharmacodynamic and kinetic study in healthy volunteers. *ANESTHESIOLOGY* 1998; 89:574-84.

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