Remifentanil Dosing at Extremes of Body Weight

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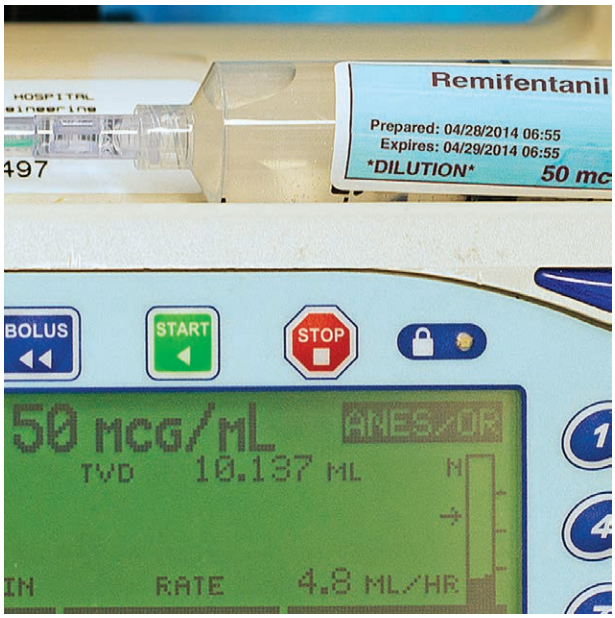
ANESTHESIOLOGISTS are expected to be equally competent treating a 5-kg child and a 250-kg adult. For infused drugs, such as remifentanil, this means selecting an initial infusion rate appropriate for the patient. A practice we have observed is to set a dose that is "close enough," *e.g.*, 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and then forget about it. Unfortunately, pharmacokinetics typically do not scale linearly to weight,[1] particularly at extremes of weight. The child may be underdosed, resulting in needless suffering, and the morbidly obese adult may be overdosed, resulting in life-threatening apnea. Rapid adjustment of the infusion rate to compensate for underdosed and overdosed patients may result in rapid oscillations in remifentanil concentration and opioid drug effect, producing further complications. "Close enough" is not acceptable when we have access to greater precision in drug delivery. We need to tailor anesthetic drug delivery to the individual patient as precisely as possible based on the best available science and technology.



"How should remifentanil dose be scaled to body size?"

Two consequential articles[2,3] in this issue of ANESTHESIOLOGY present complex pharmacokinetic models of remifentanil, addressing the question of how remifentanil dose should be scaled to body size. These models provide the scientific basis for more accurate administration of remifentanil in patients at the extremes of body size.

Kim *et al.*[2] focus on the influence of obesity on remifentanil pharmacokinetics. Using data from nine published pharmacokinetic data sets, they developed a pharmacokinetic model that predicts remifentanil blood levels with a typical accuracy of approximately 20% in both normal and obese individuals. This is impressive! However, implementing the model reported by Kim *et al.* is not for the faint of heart. One first calculates the patient's lean body mass. This is not trivial. Minto *et al.*[4] approached this 20 yr ago using the James equations.[5] These equations work for people who are modestly overweight. However, the equations yield upside-down parabolas, *i.e.*, at the extremes of weight, they suggest that lean body mass *decreases* with weight (and can even become negative!). Neither Minto, nor probably James, anticipated that today's massively obese patients would appear on the descending side of the parabola. Fortunately, investigators have published models for lean body mass that have been validated for massively obese patients. Kim *et al.* calculate lean body mass (called "fat-free mass" in their article) using the equations published by Janmahasatian *et al.*[6] Once the fat-free body mass is determined, the starting and maintenance infusion rates that will achieve and maintain any desired remifentanil concentration can be calculated quickly by computer. Without a computer the calculations are intractable.

For those writing computer programs to deliver remifentanil to patients *via* target controlled infusion, the Kim article[2] offers exactly the mathematics required for accurate drug administration and precise titration in obese patients. However, to anesthesiologists looking for the right dose for the next patient on the operating room schedule, the equations *per se* are useless. Realizing this, the authors solved the equations for a variety of clinical scenarios and demonstrate the results graphically. The authors' figure 7A shows that the infusion rate to maintain a target concentration in a 250-kg patient is about twice that in a 50-kg patient. There are two insights here. First, if you gave a 250-kg patient 5 times the dose, you would give to a 50-kg patient (expecting to get the same effect), the resulting concentration would be 2.5-fold higher in the obese patient. From the perspective of remifentanil pharmacokinetics, the 250-kg patient behaves like a 100-kg patient entombed in 150 kg of pharmacokinetically

Image: J. P. Rathmell.

Corresponding articles on pages 1005 and 1019.

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inert fat. Second, to account for remifentanil distribution into tissue, during the first half hour you will need to gradually reduce the infusion rate by 20% to maintain a steady concentration. For example, if one considers 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to be a nominal remifentanil infusion rate, one should probably start at 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and notch it down to 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the first half hour. The "set and forget" approach results in an underdose during the first 30 min as remifentanil accumulates in tissue.

The simulations provided by the authors, anchored in state-of-the-art pharmacokinetic analysis, provide scientific and practical guidance for remifentanil dosing in obese patients. They should be "close enough" to guide remifentanil dosing in the next adult obese patient on your list.

Eleveld *et al.*[3] considered the other side of size adjustment: how to scale remifentanil pharmacokinetics from adults to children. Their goal was to develop an "uber" model of remifentanil for patients of all ages and weights. Like Kim *et al.*, Eleveld *et al.* analyzed previously published remifentanil pharmacokinetic data.[7] Since the remifentanil data sets for adult patients of normal size are the same in both models, the models produce nearly identical predictions of dose for adults of average size. As with both the original Minto model[4] and the Kim model,[2] the first step in applying the pharmacokinetic model reported by Eleveld *et al.* is to calculate lean body mass. Eleveld *et al.*[3] chose the model of Al-Sallami *et al.*,[8] which extends to children the Janmahasatian model[6] used by Kim *et al.*

Pharmacometricians (*e.g.*, scientists who study drug kinetics) will welcome the detailed digital supplement Eleveld *et al.*[3] provided to explain the choice of models for calculating fat-free mass and why they settled on the Al-Sallami model. Often the choices made in pharmacokinetic analysis are opaque to readers. We compliment the investigators' explaining to interested readers how they settled on their final model. There is also an important clinical pearl in their supplement: the Al-Sallami model was not chosen because of any fundamental scientific insight but simply because it gave the most accurate predictions.

The mathematics reported by Eleveld *et al.*[3] are even more complex than that reported by Kim *et al.*[2] All of the pharmacokinetic parameters are scaled to a "reference individual," a 70-kg, 170-cm, 35-yr-old man. To apply the Eleveld approach, you need to calculate the fat-free mass for this reference individual (54.5 kg, based on the Al-Sallami equations). You then calculate the volumes and clearances with specific adjustments to incorporate patient age as well as weight since the model is intended for use in children as well as adults.

The Eleveld article teaches us about remifentanil dosing in children relative to equivalent doses in adults. Between 5 and 20 yr, the remifentanil infusion rate for nonobese children, in $\mu g \cdot kg^{-1} \cdot min^{-1}$, should be ~1.5 times the dose in the adult patient. Below 5 yr of age, the infusion rate is closer to 1.75 times the dose in the adult patient. Although the mathematics permit calculations in obese children, the data included few, if any, obese children. Thus, the pharmacokinetic adjustment for obesity in children is based on observations in obese adults.

Clinicians can apply the simulations provided in the Kim *et al.*[2] and Eleveld *et al.*[3] articles to improve remifentanil dosing in the very small and very large patients we see every day. The pharmacokinetic implications of the extremes of weight are likely consequential in clinical practice. The greater contribution of these articles is that the precise mathematics can facilitate the development of novel drug delivery systems that will increase the safety of opioid delivery and improve patient outcomes.

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Competing Interests

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