New anesthesia dosing models may increase safety of remifentanil for obese patients and children

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Researchers have developed new dosing models that may provide the scientific basis for more accurate administration of remifentanil, a synthetic opioid commonly used during surgery, in children and obese patients. The dosing models, described in two studies in *Anesthesiology*, the peer-reviewed medical journal of the American Society of Anesthesiologists (ASA), could help prevent children from receiving too little remifentanil, and morbidly obese patients from receiving too much.

Current models for remifentanil dosing are based on more average-sized adult patients, which can result in inaccurate dosing for some patients. If a child receives too little remifentanil, the result could be needless pain, while an obese patient receiving too much could be at risk of an overdose, resulting in life-threatening depression of breathing and circulation.

"Providing accurate anesthesia dosing guidelines for obese patients is becoming increasingly important as the obesity epidemic grows and more of these patients require surgery," said Talmage D. Egan, M.D., chair in the Department of Anesthesiology at the University of Utah Health Sciences Center, Salt Lake City. "The percentage of American adults who are seriously overweight has dramatically increased. The question we wanted to answer in our study was how to personalize therapy for obese patients so that we give them just the right dose."

Traditionally, physician anesthesiologists have based dosing on a patient's actual total body weight. "The difficulty comes when you have a patient with a lot of excess body weight, because as a person becomes more and more obese, the relationship between the drug/anesthetic dose and total body weight is not as reliable," said Dr. Egan. "This is because most of the processes important in terms of how the body metabolizes anesthesia happen in lean tissue, as opposed to fatty tissue."

Previous studies on remifentanil have been conducted on average-weight patients. However, in their new study, Dr. Egan and colleagues developed a model based on data from nine previously published data sets containing nearly 4,500 blood concentration measurements from a combination of 229 obese and non-obese patients. Researchers were able to develop a model for remifentanil dosing - which included the distribution and elimination of the drug from the body - that provided the calculations required for accurate drug administration in both obese and non-obese patients. Although the authors caution that more study is required before widespread use of their dosing model.

"We found that in very obese patients (e.g., a BMI greater than 35), we cannot simply calculate the amount of remifentanil needed based solely on a patient's measured weight. We must take into account factors such as fat-free mass (internal organs, bone, muscle, water, etc.) and age," said Dr. Egan. "If you base the dose solely on total body weight for an obese patient, the dose will be much too high. A person who weighs five times as much as a lean person doesn't need five times the anesthetic dosage."

In a second study, Douglas Eleveld, Ph.D., MEng., an assistant professor at the University of Groningen, Netherlands, and colleagues developed the first model for administration of remifentanil that is suitable for both children and adults.

"If separate anesthetic dosing models for children and adults are used, there's always the possibility of a mistake because the wrong model could be chosen," said Dr. Eleveld. "Having a single model

for both children and adults is safer. Our model appears to work better than adult-only or children-only models."

Using data from previous studies on remifentanil in adults and children, researchers developed a model that takes into account patients' fat-free mass, weight, age and sex. They found infusion rates are different for children under age 5, compared to those between the ages of 5 and 20. Between 5 and 20 years, the remifentanil infusion rate for non-obese children should be about 1.5 times the dose in adult patients. Under 5 years of age, the infusion rate should be closer to 1.75 times the dose in adult patients.

The predictive performance of the model was better than that of more widely used models, particularly in young children, Dr. Eleveld noted. "Our study can help physician anesthesiologists better understand when children and adults need more or less remifentanil to provide optimal care," he said. He added that the safety and applicability of the model needs to be further evaluated.

An accompanying editorial commented favorably on the studies:

"The greater contribution of these articles is that their precise mathematics can facilitate the development of novel drug delivery systems that will increase the safety of opioid delivery and improve patient outcomes," said editorial authors Steven L. Shafer, M.D., Department of Anesthesiology, Perioperative and Pain Medicine at Stanford University in California and Dennis M. Fisher, M.D., "P Less Than" Company, San Francisco.

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