Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170–82

7. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. ANESTHESIOLOGY 1997; 86:10–23

8. James WPT: Research on Obesity. London, Her Majesty's Stationary Office, 1976

9. Wulfsohn NL, Joshi CW: Thiopentone dosage on lean body mass. Br J Anaesth 1969; 41:516–21

10. Wulfsohn NL, Joshi CW: Methohexital induction dosage based on lean body mass. J Oral Surg 1974; 32:426–8

11. Nickorick E, Reynolds FB: Clinical comparison of D-tubocurarine and pancuronium: Dosage schedule based on lean body mass. Can Anaesth Soc J 1973; 20:217–26

12. Beemer GH, Bjorksten AR, Crankshaw DP: Pharmacokinetics of atracurium during continuous infusion. Br J Anaesth 1990; 65:668–74

13. Leslie K, Crankshaw DP: Lean tissue mass is a useful predictor of induction dose requirements for propofol. Anaesth Intensive Care 1991; 19:57–60

14. Chassard D, Berrada K, Bryssine B, Guiraud M, Bouletreau P: Influence of body compartments on propofol induction dose in female patients. Acta Anaesthesiol Scand 1996; 40:889–91

15. Abernathy DR, Greenblatt DJ, Divoll M, Harmotz JS, Shader RI: Alterations in drug distribution and clearance due to obesity. J Pharmacol Exp Ther 1981; 217:681–5

Anesthesiology
1998; 89:560–1


# *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: Scheinen H, Aantaa R, Antilla M, Hakola P, Helminen A, Karhuvaara S: Reversal of the sedative and sympatholytic effects of desmedetomidine with a specific $\alpha_2$-adrenoceptor antagonist atipamexole—A pharmacodynamic and kinetic study in healthy volunteers. ANESTHESIOLOGY 1998; 89:574–84.

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$\alpha_2$-agonists to humans is not feasible—the sedative and sympatholytic effects of these drugs may last for several hours because of a relatively long half-life. However, Scheinin *et al.* have shown that these effects are fully reversible. A remaining obstacle to the clinical use of high concentrations of $\alpha_2$-agonists is peripheral $\alpha_2$-receptor–mediated vasoconstriction. Fortunately, the sedative and vasoconstrictive effects of $\alpha_2$-agonists appear to be mediated by different receptor subtypes, suggesting that it may be possible, in the future, to develop a subtype-specific $\alpha_2$-agonist with sedative but not vasoconstrictive effects.

Have Scheinin *et al.* opened a door to a new, exciting era of receptor-specific anesthesia? The discovery of a new subtype-specific $\alpha_2$-agonist with sedative but not vasoconstrictive effects could provide the basis for a reversible intravenous anesthetic technique that could permit rapid recovery from anesthesia, independent of duration of surgery. Whether this ideal is achievable, Scheinin *et al.* are to be applauded for a significant advance in exploring reversible methods of sedation.

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