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
α₂-agonists to humans is not feasible—the sedative and sympathetic 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 α₂-agonists is peripheral α₂-receptor-mediated vasoconstriction. Fortunately, the sedative and vasoconstrictive effects of α₂-agonists appear to be mediated by different receptor subtypes, suggesting that it may be possible, in the future, to develop a subtype-specific α₂-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 α₂-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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