

Alpha-2 Adrenergic Agonists

Gregory B. Hammer, MD

Professor, Anesthesia and Pediatrics
Stanford University School of Medicine

The alpha₂-receptors are involved in regulating the autonomic and cardiovascular systems. Alpha₂-receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release. Alpha₂-receptors also are located within the central nervous system, and their activation leads to sedation, a reduction of tonic levels of sympathetic outflow and catecholamines, and an augmentation of cardiac-vagal activity. In addition, alpha₂-receptors within the spinal cord modulate pain pathways, thereby providing some degree of analgesia.

Alpha₂-induced sedation qualitatively resembles normal sleep; specifically, the endogenous, nonrapid eye movement, sleep-promoting pathways may mediate alpha₂-mediated sedation (Venn: Critical Care 2000; 4:302). Endogenous sleep pathways are causally involved in dexmedetomidine-induced sedation. Thus, the participation of nonrapid eye movement sleep pathways seems to explain why patients who appear to be “deeply asleep” from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep.

The respiratory sparing effects of alpha₂-agonists have been closely examined. They are associated with minimal respiratory depression and a preservation of the ventilatory response to CO₂. In healthy volunteers, plasma levels of dexmedetomidine eightfold to 10-fold higher than the clinical range resulted in unarousable volunteers who did not respond to a painful stimulus but maintained their respiratory drive. The PaCO₂ increased from a baseline of 43 mm Hg to only 47 mm Hg (Ebert: Anesthesiology 2000; 93:382).

In high doses, alpha₂-agonists have the potential for causing both systemic and pulmonary hypertension and direct or reflex bradycardia. In the lower, clinical range, alpha₂-agonist infusions decrease blood pressure, presumably as a result of a central sympatholytic effect. At higher plasma levels, peripheral alpha₂-receptor mediated vasoconstriction overrides the sympatholytic effects, resulting in increased pulmonary artery and systemic blood pressures. In healthy patients with intact baroreflexes, this can lead to bradycardia. Reflex bradycardia in conjunction with the vagal mimetic property of alpha₂-agonists could lead to severe bradycardia or asystole.

Dexmedetomidine is the pharmacologically active dextroisomer of medetomidine. It was approved by the US Food and Drug Administration in 1999 as a short-term medication (< 24 h) for sedation of patients in the intensive care unit, and it has also been shown to act as a general anesthetic. Its specificity for the alpha₂-adrenoceptor, and relative selectivity for the alpha_{2A}-adrenoceptor subtype (which is responsible for its sedative properties), provides for a more effective sedative and analgesic agent than clonidine. Dexmedetomidine is approximately 8 times more “alpha₂-specific” than clonidine, with a ratio of alpha₂ and alpha₁ receptor affinity of 1,600:1. Dexmedetomidine has a distribution half-life more than twice as short as clonidine (<5 vs. 11 minutes), a more rapid clearance (0.75 L/hr/kg vs. 0.2 L/hr/kg), and a terminal elimination half-life of 2 hours, compared to 9 hours for clonidine.

A variety of perioperative effects of alpha₂ agents have been studied. These include effects on the stress response to

surgery; myocardial ischemia; sedation, anxiolysis, and analgesia; hemodynamics; prevention of delirium; and mitigation of drug withdrawal.

Stress Response

Intraoperative clonidine (7µg/kg IV) has been shown to increase stroke volume, decrease heart rate, and decrease shivering after abdominal aortic aneurysm repair, while decreasing plasma norepinephrine, epinephrine, and vasopressin levels (Quintin: BJA 1991;66:108). Postoperatively, dexmedetomidine infused for sedation (0.2-0.25µg/kg/hr) decreases IL-6 levels and heart rate compared to propofol (17-50µg/kg/hr) (Venn: BJA 2001;86:650).

Myocardial ischemia

In patients undergoing coronary surgery, clonidine 5µg/kg resulted in decreased plasma catecholamines and fewer episodes of ST segment depression compared to placebo (Dorman: JCVA 1993;7:386). In a quantitative systematic review of 3,646 patients undergoing major non-cardiac surgery, the use of beta blockers and alpha2 agonists (clonidine, mivazerol) were associated with a decrease in ischemic events and death compared with no benefit from calcium-channel blockers and nitroglycerin (Stevens: Anesth Analg 2003;97:623). A meta-analysis of randomized, controlled trials including 3,395 patients having cardiac surgery revealed that alpha2 agonists decreased myocardial ischemia (Wijeysundera: Am J Med 2003;114:742).

Sedation, anxiolysis, analgesia

One of the highest densities of alpha2-adrenoceptor has been detected in the pontine locus ceruleus (LC), a key source of noradrenergic innervation of the forebrain and an important modulator of vigilance. The sedative effects of alpha2-adrenoceptor activation have been attributed to the inhibition of this nucleus. After dexmedetomidine binds to [alpha]2-adrenoceptors in the LC, transmembrane signaling results in activation of an inwardly rectifying potassium channel facilitating a K⁺ efflux and inhibition of voltage-gated Ca²⁺ channels. The resulting hyperpolarization decreases the firing rate of LC neurons and allows presynaptic inhibition of their terminals. Hyperpolarization of noradrenergic LC neurons appears to be a key factor in initiating the anesthetic mechanism of action of dexmedetomidine (Nelson: Anesthesiology 2003;98:428).

Dexmedetomidine infusion (loading dose of 1.0µg/kg over 10 minutes, then 0.2-0.7µg/kg/hr) after major surgery causes a reduction in the amount of propofol, midazolam, and morphine required for sedation and analgesia (Venn: Anaesthesia 1999;54:1136, Triltsch: Crit Care Med 2002;30:1007).

Hemodynamics

Dexmedetomidine typically causes a decrease in heart rate and blood pressure during continuous infusion, commensurate with the reduction in plasma catecholamine levels (Talke: Anesth Analg 1997;85:1136). Hemodynamic parameters return to baseline within one hour of stopping the infusion. A transient increase in blood pressure may be seen with bolus dosing, due to stimulation of the alpha2 adrenergic receptors in the peripheral vasculature (Bloor: Anesthesiology 1992;77:1134). This effect is overridden by the central hypotensive effects once the drug crosses the blood-brain barrier within several minutes. Reflex bradycardia may be observed in association with the acute increase in blood pressure during bolus dosing.

In summary, bolus dose infusions of dexmedetomidine (and high-dose infusions) cause a reduction in plasma catecholamines, an increase in systemic and pulmonary vascular resistances, and a decrease in stroke volume, heart rate, and blood pressure.

Lower dose continuous infusions of dexmedetomidine produce a decrease in plasma catecholamines, minimal change in vascular resistances, and mild reductions in heart rate and blood pressure.

Delirium

Postoperative delirium is common in adult patients after cardiac surgery. The surgical procedure and cardiopulmonary bypass effects have been implicated. Recently, however, off-pump cardiac surgery has become more common, but the incidence of postoperative delirium has not decreased significantly in these patients. The role of sedative and analgesic agents in postoperative delirium has been a subject of greater scrutiny. A recent study at Stanford compared postoperative sedation with dexmedetomidine to standard regimens of propofol and midazolam. Fentanyl was used for analgesia in all three groups. Delirium, as defined by DSM-IV criteria, occurred in 50% of patients in the propofol and midazolam groups, but in only 2% of the patients sedated with dexmedetomidine. Delirium is much more difficult to define in infants and children but may be prevalent. The role of dexmedetomidine for postoperative sedation in the pediatric population remains to be defined.

Drug withdrawal and rebound

Clonidine has been used to mitigate or prevent as well as to treat signs of withdrawal from alcohol, opioids, and other drugs (Jasinski: Arch Gen Psychiatry 1985;42:1063). Alpha₂ adrenergic agonists probably play a primary role by binding to opioid and other receptors in the CNS. They also decrease the signs and symptoms of drug withdrawal by decreasing sympathetic outflow in the CNS, thereby diminishing tachycardia, sweating, and tremor. There are several reports in the literature describing the use of dexmedetomidine for the prevention and treatment of signs of withdrawal from midazolam, lorazepam, and opioids (Macciolo: Anesthesiology 2003;98:575, Multz: Anesth Analg 2003;96:1054). Unlike morphine, dexmedetomidine does not cause hyperalgesia after cessation of long-term administration (Davies: Anesth Analg 2003;96:195).

Dexmedetomidine: Pediatric experience

Few studies of dexmedetomidine have been done in children. The pharmacokinetics and pharmacodynamics of dexmedetomidine have been described in one recent study of 18 children between the ages of 2 and 18 years. After beginning a 10-minute infusion, the onset of sedation was rapid and the effects were dissipated within one hour (Lerman, submitted for publication). There was a mild, dose-dependent reduction in heart rate and no respiratory depression was observed during infusions of 2, 4, and 6 µg/kg/hr. The volume of distribution was slightly larger and the plasma clearance was slightly prolonged compared with adults, resulting in a comparable terminal half-life. Several case reports describing the use of dexmedetomidine in infants and children have shown similar sedative, opioid-sparing, and hemodynamic effects as in adults.