Richard B. Weiskopf, M.D., Editor

This month's Clinical Concepts and Commentary is composed of an article coauthored by Dr. Mervyn Maze, one of the leading authorities in α_2 agonists. Dr. Maze is also a consultant for Abbott Laboratories Inc., Abbott Park, Illinois, and played a major role in that company's development of dexmedetomidine, an α_2 agonist, which recently has been approved for limited use in the United States. This raises a potential conflict of interest, an issue about which this journal's editorial board has had a long record of concern. The board recognizes that there is a special consideration regarding conflict of interest for articles in which an author's opinions and selection of citations are a prominent feature. This article was prepared with extensive editorial input to ensure balance and objectivity, which we hope will enable our readers to derive the maximum educational benefit.

Richard B. Weiskopf, M.D., Editor

Michael M. Todd, M.D., Editor-in-Chief

Anesthesiology 2000; 93:1345–9

Clinical Uses of α_2-Adrenergic Agonists

Takahiko Kamibayashi, M.D., Ph.D., Mervyn Maze, M.B., Ch.B., F.R.C.P., F.R.C.A.†*

SINCE the early 1970s, α_2-adrenergic receptor agonists have been used successfully to treat patients with hypertension and patients withdrawing from long-term abuse of drugs or alcohol. α_2 Agonists produce diverse responses, including analgesia, anxiolysis, sedation, and sympatholysis, each of which has been reported in the treatment of surgical and chronic pain patients. Recently, the Food and Drug Administration registered two novel α_2-adrenergic agonists. A role has been found for epidural clonidine (Duraclon, Fujisawa USA, Melrose Park, IL) in the management of pain in a variety of clinical settings. Because this has been discussed extensively in a recent review,[1] studies up to that time will not be discussed exhaustively herein. Dexmedetomidine (Precedex, Abbott Laboratories Inc., Abbott Park, IL) has been registered for use as a sedative–analgesic in the intensive care setting. In addition to this approved setting, α_2 agonists also have been studied in several other perioperative settings, which will be discussed. Allusion to these "off-label" uses does not necessarily indicate that these applications are advocated by the authors. The pharmacologic basis and the clinical application of α_2-adrenergic agonists will be discussed.

Pharmacology

In Vitro *Studies*

α_2-Adrenergic agonists produce clinical effects after binding to α_2-adrenergic receptors, of which there are three subtypes (α_{2A}, α_{2B}, and α_{2C}). These receptor subtypes are distributed ubiquitously, and each may be uniquely responsible for some, but not all, of the actions of α_2 agonists; for example, the α_{2B}-adrenoceptor subtype mediates the short-term hypertensive response to α_2 agonists,[2] whereas the α_{2A} adrenoceptor is responsible for the anesthetic and sympatholytic responses.[3]

All the subtypes produce cellular action by signaling through a G-protein; a functional assay of G-protein activation has been implemented to screen for subtype specificity and effectiveness of the various α_2 agonists. From these and other related studies, it is apparent that there are no subtype-selective agonists; therefore, the goal of producing a single discrete desirable α_2 action (*e.g.*, analgesia) without producing another unwanted effect (*e.g.*, hypotension) is elusive. G-proteins couple to effector mechanisms, which appear to differ depending on the receptor subtype (and possibly the location of the receptor). For example, the α_{2A}-adrenoceptor subtype seems to couple in an inhibitory fashion to the L-type calcium channel in the locus ceruleus, whereas, in the vasculature, the α_{2B}-adrenoceptor subtype couples in an excitatory manner to the same effector mechanism.

Because all of the clinically available α_2 agonists have an imidazole ring in their structure, these compounds interact with the imidazoline receptor. It is unlikely that these receptors transduce the cardiovascular responses to α_2 agonists because studies of genetically engineered

* Assistant Professor, Department of Anesthesiology and Acute Critical Medicine, Osaka University Graduate School of Medicine. † Magill Professor of Anaesthetics, Imperial College School of Medicine, Magill Department of Anaesthetics, Chelsea and Westminster Hospital.

Received from the Department of Anesthesia and Acute Critical Medicine, Osaka University Graduate School of Medicine, Osaka, Japan; and Imperial College School of Medicine, Magill Department of Anaesthetics, Chelsea and Westminster Hospital, London, United Kingdom. Submitted for publication August 6, 1999. Accepted for publication May 5, 2000. Support was provided solely from institutional and/or departmental sources. Dr. Maze consults for Abbott Laboratories, Abbott Park, Illinois, which markets the α_2 agonist dexmedetomidine.

Address reprint requests to Dr. Maze: Imperial College School of Medicine, Magill Department of Anaesthetics, Chelsea and Westminster Hospital, 369 Fulham Road, London SW 10 9NH, United Kingdom. Address electronic mail to: m.maze@ic.ac.uk.

Key words: α_2-Adrenergic receptor; anesthesia; anxiolysis; clonidine; dexmedetomidine; pain; sedation; sympatholysis.

The illustration for this section is prepared by Dmitri Karetnikov, 7 Tennyson Drive, Plainsboro, New Jersey 08536.

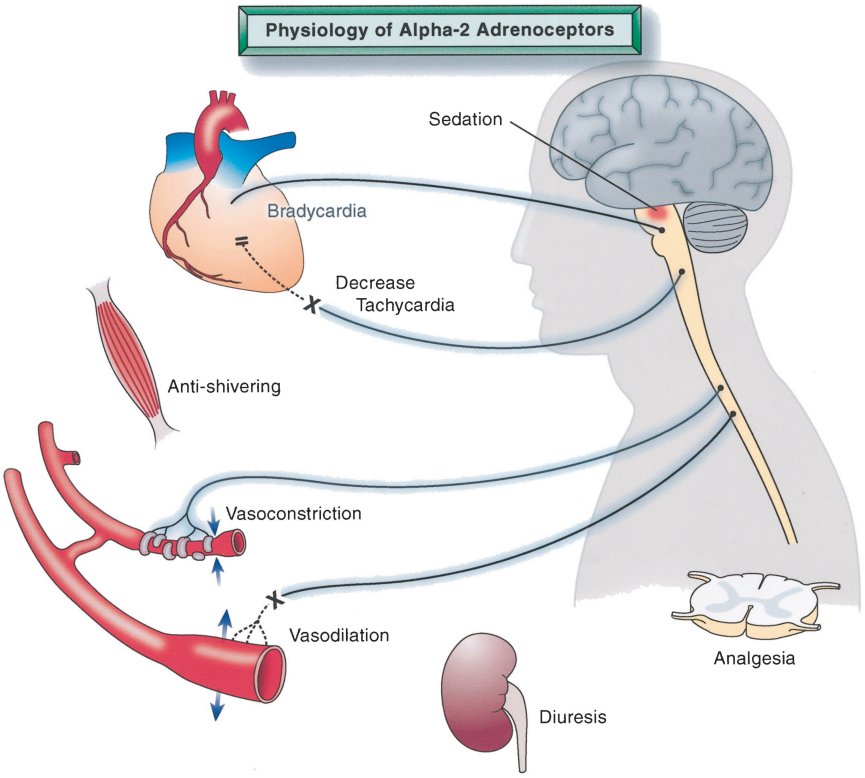

Fig. 1. Responses that can be mediated by α_2-adrenergic receptors. The site for the sedative action is in the locus ceruleus of the brain stem, whereas the principal site for the analgesic action is probably in the spinal cord; however, there is clear evidence for both a peripheral and a supraspinal site of action. In the heart, the dominant action of α_2 agonists is a decrease in tachycardia (through block of the cardioaccelerator nerve) and bradycardia (through a vagomimetic action). In the peripheral vasculature, there are both a vasodilatory action *via* sympatholysis and vasoconstriction mediated through the receptors in the smooth muscle cells. The mechanism for the antishivering and diuretic actions have yet to be established firmly.

mice have indicated that each of the cardiovascular properties of the α_2 agonists seem to be mediated by α_2 adrenoceptors (with the possible exception of enhanced vagal tone).

In Vivo *Studies*

Cardiovascular System. α_2 Agonists can produce either hypotension or hypertension. At lower doses, the dominant action of α_2 agonists is sympatholysis, *i.e.*, the ability to block the sympathetic arm of the autonomic nervous system, which is mediated by the α_{2A}-adrenergic receptor subtype.[3] There are several well-documented mechanisms for this activity, including inhibition of firing of the locus ceruleus (the pivotal noradrenergic relay nucleus in the brain stem) and inhibition of norepinephrine release at the neuroeffector junction. Bosnjak *et al.*[4] have suggested that the central and peripheral sympatholytic effects of α_2-adrenoceptor stimulation may be augmented further by inhibition of ganglionic transmission (fig. 1).

At higher doses of α_2 agonists, the hypertensive action dominates *via* the activation of α_{2B} adrenoceptors, located on smooth muscle cells in the resistance vessels. There is even some suggestion that this receptor subtype may be involved in the pathogenesis of essential hypertension.[5] Pretreatment with a peripherally restricted antagonist before intravenous administration of α_2 agonists may become a useful pharmacologic strategy to facilitate the advantageous sedative–hypnotic and central sympatholytic actions while avoiding the possible detrimental hemodynamic effects of vasoconstriction, which are mediated in the periphery. Thus far, no peripherally restricted antagonist is clinically available.

Central Nervous System.

In addition to the well-documented hypnotic–sedative, analgesic, and anxiolytic actions of α_2 agonists, spatial working memory also may be modulated *via* the α_{2A} adrenoceptor subtype.[6] If confirmed in humans, this would represent the first sedative–hypnotic class of agent that enhances, rather than diminishes, cognitive performance. Using experimental strategies that either "knocked out" or overexpressed the gene that encodes α_{2C} adrenoceptors, Scheinin *et al.*[7] have shed light on the mechanism for the anxiolytic action of α_2 agonists. Mice with targeted inactivation of the gene that encodes α_{2C} adrenoceptors had enhanced startle responses and shortened attack latency in the isolation–aggression test; conversely, if the mice were engineered to overexpress α_{2C} adrenoceptors, the opposite behavioral effects were noted. Therefore, drugs acting *via* α_{2C} adrenoceptors may have therapeutic value in disorders associated with enhanced startle responses and sensorimotor gating deficits, such as schizophrenia, attention deficit hyperactivity disorder, posttraumatic stress disorder, and drug-withdrawal states. α_2 Agonists have been shown to limit the morphologic and functional effects after ischemic (focal and global) and traumatic injury to the nervous system. The efficacy of α_2 agonists as neuroprotectant agents in humans has not been investigated.

Intractable pain after neuropathic injury is a particularly difficult problem to treat. The combination of sub-

effective doses of MK 801 (the *N*-methyl-D-aspartate [NMDA] antagonist) and clonidine resulted in significant antihyperalgesic action in an animal model of neuropathic pain; interestingly, the neurotoxic effects of NMDA antagonists also could be blocked by relatively small doses of clonidine.[8] In another paradigm of neuropathic pain, the antihyperalgesic action of dexmedetomidine was blocked by a peripherally restricted α_2-antagonist, indicating that an α_2 agonist that does not cross the blood–brain barrier (and, therefore, does not produce sedation) may be useful in the management of neuropathic pain.

Clinical Studies

In well-conducted randomized clinical trials, α_2 agonists have been shown to be effective for their analgesic, sedative–hypnotic, and sympatholytic properties. As such, this class of agent has been shown to decrease intraoperative and postoperative stress response effectively. After emergence from general anesthesia with use of a potent volatile anesthetic agent, patients may show a hyperdynamic hemodynamic profile, which can be attenuated with α_2 agonists. Thus, α_2 agonists may prove to be of value in agitated hypertensive patients in the postanesthesia care unit. Despite their relatively long history of clinical use (clonidine was introduced in the 1970s), no idiosyncratic adverse effects have been discovered, other than an extension of its pharmacologic profile (*i.e.*, hypotension, bradycardia, xerostomia, and hypertension). This class of drug seems to have a remarkably wide safety margin. Without the need for cardiovascular or ventilatory support, all but 2 of a cohort of 10 volunteers could tolerate a plasma concentration of dexmedetomidine that was fourfold greater than the projected therapeutic concentration of dexmedetomidine; adverse effects, which are an extension of the pharmacologic actions of this class of drugs (increases in systemic and pulmonary vascular resistance; hypertension, bradycardia, and a decreased cardiac output), are evident at concentrations twofold greater than the therapeutic level.[9]

Intraoperative Applications

Since the mid 1980s, many publications have reported the significant volatile anesthetic minimum alveolar concentration reduction produced by α_2 agonists; in animal studies, no apparent ceiling effect was noted for halothane minimum alveolar concentration reduction when the highly selective α_2 agonist dexmedetomidine was used. This has led to the suggestion that this drug may be a "complete" anesthetic agent. In a tolerability study performed by Ebert *et al.*,[9] profound sedation ("no arousal with very vigorous shaking") was noted in two healthy volunteers who tolerated the highest dose of dexmedetomidine that achieved a plasma concentration of approximately 13 ng/ml (for comparison, the sedative concentration for intensive care unit patients is approximately 0.7 ng/ml).

Analgesia

Epidural clonidine for cancer pain is the only approved analgesic application of this class of compound, and a warning against its use in nonapproved clinical settings because of side effects (hypotension and bradycardia) is provided in its package insert. However, α_2 agonists have been administered *via* a variety of routes for long-term and short-term perioperative pain control. In keeping with the animal studies that indicate a potential peripheral target for α_2 agonists in neuropathic pain, Reuben *et al.*[10] reported that a Bier block with clonidine (1 μg/kg) resolved sympathetically maintained pain. Because the plasma concentration of clonidine 30 min after deflation of the tourniquet (0.12 ng/ml) was significantly less than that necessary for a central sympatholytic effect (1.5–2.0 ng/ml), the authors concluded that clonidine exerted a peripheral analgesic action in patients with sympathetically maintained pain. Interestingly, in a volunteer study of inflammatory pain, a central, rather than a peripheral, α_2-receptor target has been proposed.[11]

A plethora of studies have shown that α_2 agonists, either alone or in combination with local anesthetics or opiate narcotics, are highly effective in the treatment of short-term pain. Intraoperative (including during cesarean section) analgesic requirements were reduced significantly when clonidine was included in a neuraxially administered combination. In parturients, extremely small doses of intrathecal clonidine (30 μg) provided analgesia comparable to that of 2.5 μg intrathecal sufentanil for approximately 60 min.[12] α_2 Agonists have been used successfully for postoperative pain management in surgical populations as diverse as obstetric and pediatric, and they have been administered *via* many different routes, including intercostal block.[13] It is possible that the parturient is uniquely sensitive to the analgesic properties of α_2 agonists because clonidine alone has been shown to be effective for pain control after cesarean section. Using α_2 agonists in lieu of opioids avoids the problems of respiratory depression, pruritus, urinary retention, and abuse liability. However, of potential concern are the overlapping dose–response profiles for α_2-induced sedation and analgesia when the compound is administered neuraxially. Because subjects sedated with α_2 agonists can be aroused easily and demonstrate attentiveness,[14] this property may not be deleterious and may facilitate care in settings in which the ratio of patients to nursing staff is high. If and when subtype-selective α_2 agonists become available, it may be possible to mitigate the sedative action while ameliorating some types of pain states that can be modulated by a different receptor

subtype than that which transduces the sedative response.[15]

Pain management after thermal injury may be troublesome because of the rapidly escalating opioid dose requirements and the high addiction potential. The attendant tachycardia and hypertension may pose problems in patients susceptible to cardiac disease. Recently, clonidine was shown to decrease fentanyl requirements by more than 50% and also attenuated the hyperdynamic hemodynamic state.[16]

Sedation

For more than a decade, α_2 agonists have been used to provide preoperative sedation and axiolysis and to decrease intraoperative anesthetic requirements. Recently, its use for sedation[17] has been explored in a multicenter randomized clinical trial that included several hundred postoperative patients who required mechanical ventilation. Patients who were administered dexmedetomidine required significantly less propofol than did placebo-treated patients for the same level of clinical sedation; qualitatively, a unique type of sedation was produced in which patients could be aroused readily and then returned to a sleep-like state when left alone.[14] Maintenance of attentiveness has been documented by use of the Critical Flicker Fusion test, in which no difference is observed in the frequency at which a flickering light source is first seen as a fused line between dexmedetomidine-sedated and saline-treated volunteers. Therefore, one may anticipate that patients sedated with α_2 agonists may be more cooperative and communicative than patients sedated with current strategies in the intensive care setting. The effectiveness of clonidine as a supplemental analgesic in thermal-injured patients bodes well for future sedative studies that include wound-dressing changes.[16] However, the usefulness of α_2 agonists in diagnostic or therapeutic settings in which a state of "conscious sedation" is desirable has yet to be studied rigorously. The only approved sedative indication is dexmedetomidine for the intensive care treatment of postoperative surgical patients for up to 24 h. Because of its sympatholytic and vagomimetic actions, dexmedetomidine is approved with a warning about hypotension, bradycardia, and sinus arrest and can be used only in a monitored situation (which invariably occurs in the intensive care setting).

Because the target for the sedative action of α_2 agonists is known precisely, it raised the possibility that strategies to discontinue this action could be used readily. In a landmark article, Scheinin *et al.*[18] reported about the ability of atipamezole, a novel (unregistered) selective α_2-adrenoceptor antagonist, to reverse the sedative properties of dexmedetomidine in volunteers. Both the sedative and the sympatholytic effects of intramuscular dexmedetomidine were dose-dependently antagonized by intravenous atipamezole; however, the sensitivity for reversal of these two responses may be different. Because the agonist and the antagonist have similar elimination half-lives, the likelihood of recurrence of the clinical effects of dexmedetomidine after reversal by atipamezole is small. Therefore, the α_2 agonists provide a titratable form of hypnotic sedation that can be reversed readily. This holds the promise that we may be able to achieve the same type of control at the anesthetic site of action that we use for the production and reversal of muscle relaxation.

Shivering

In patients undergoing elective ear, nose, or pharyngeal surgery with general anesthesia (induction with propofol, vecuronium, and fentanyl and maintenance with isoflurane in 70% nitrous oxide), the incidence of postoperative shivering (40%) could be eliminated by administering 1.5 μg/kg clonidine before emergence.[19] Similarly, intravenous clonidine (1 μg/kg) reduced the incidence of shivering in patients undergoing knee arthroscopy with epidural anesthesia.

Perioperative Myocardial Ischemia

The main approaches for reducing perioperative myocardial ischemia and thus improving long-term survival include preoperative assessment, modification of anesthetic techniques, and prophylactic therapy. In a placebo-controlled dose-ranging study of 300 patients who experienced perioperative sympatholysis with mivazerol, intraoperative myocardial ischemia and postoperative tachycardia were significantly reduced.[20] Previously, clonidine was shown to ameliorate angina in patients with coronary artery disease. Whether these transient actions change outcome is not known. Such outcome data are needed because there are theoretical reasons why α_2 agonists may be proischemic through hypotensive and vasoconstrictive properties.

Comparison of Clinically Available α_2 Agonists

Dexmedetomidine has an α_2:α_1-adrenoceptor ratio of 1,600:1, more than 7 times greater than that of clonidine. Its elimination half-life is approximately 2 h, whereas that of clonidine is more than 8 h. The distribution half-life of dexmedetomidine is approximately 5 min whereas that of clonidine is more than 10 min.

Conclusion

Because of their registration for analgesic and sedative indications, α_2-adrenergic agonists have become part of the anesthesiologists' therapeutic armamentarium. The use of α_2 agonists as adjuncts in pain management is attractive because of the multiplicativity that occurs through their action at the central (spinal and supraspinal) and peripheral sites. Clinicians should be mindful

that many of the perioperative applications of α_2 agonists remain "off-label."

References

1. Eisenach JC, DeKock M, Klimscha W: Alpha$_2$ adrenergic agonists for regional anesthesia: A clinical review of clonidine (1984–1995). ANESTHESIOLOGY 1996; 85:655–74
2. Link RE, Desai K, Hein L, Stevens ME, Chruscinski A, Bernstein D, Barsh GS, Kobilka BK: Cardiovascular regulation in mice lacking α_2-adrenergic receptor subtypes b and c. Science 1996; 273:803–5
3. Lakhlani PP, MacMillan LB, Guo TZ, McCool BA, Lovinger DM, Maze M, Limbird LE: Substitution of a mutant α_{2A}-adrenergic receptor via 'hit and run' gene targeting reveals the role of this subtype in sedative, analgesic, and anesthetic-sparing responses in vivo. Proc Natl Acad Sci U S A 1997; 94:9950–5
4. McCallum JB, Boban N, Hogan Q, Schmeling WT, Kampine JP, Bosnjak ZJ: The mechanism of α_2-adrenergic inhibition of sympathetic ganglionic transmission. Anesth Analg 1998; 87:503–10
5. Makaritsis KP, Johns C, Gavras I, Gavras H: Role of alpha(2)-adrenergic receptor subtypes in the acute hypertensive response to hypertonic saline infusion in anephric mice. Hypertension 2000; 35:609–13
6. Franowicz JS, Arnsten AF: The alpha-2a noradrenergic agonist, guanfacine, improves delayed response performance in young adult rhesus monkeys. Psychopharmacology 1998; 136:8–14
7. Sallinen J, Haapalinna A, Viitamaa T, Kobilka BK, Scheinin M: Adrenergic α_{2C}-receptors modulate the acoustic startle reflex, prepulse inhibition, and aggression in mice. J Neurosci 1998; 18:3035–42
8. Jevtovic-Todorovic V, Wozniak DF, Powell S, Nardi A, Olney JW: Clonidine potentiates the neuropathic pain-relieving action of MK-801 while preventing its neurotoxic and hyperactivity side effects. Brain Res 1998; 781:202–11
9. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD: The effects of increasing plasma concentrations of dexmedetomidine in humans. ANESTHESIOLOGY 2000; 93:382–94
10. Reuben SS, Steinberg RB, Madabhushi L, Rosenthal E: Intravenous regional clonidine in the management of sympathetically maintained pain. ANESTHESIOLOGY 1998; 89:527–30
11. Eisenach JC, Hood DD, Curry R: Intrathecal, but not intravenous, clonidine reduces experimental thermal or capsaicin-induced pain and hyperalgesia in normal volunteers. Anesth Analg 1998; 87:591–6
12. Gautier PE, De Kock M, Fanard L, Van Steenberge A, Hody JL: Intrathecal clonidine combined with sufentanil for labor analgesia. ANESTHESIOLOGY 1998; 88:651–6
13. Tschernko EM, Klepetko H, Gruber E, Kritzinger M, Klimscha W, Jandrasits O, Haider W: Clonidine added to the anesthetic solution enhances analgesia and improves oxygenation after intercostal nerve block for thoracotomy. Anesth Analg 1998; 87:107–11
14. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ: Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg 2000; 90:699–705
15. Maze M, Fujinaga M: α_2 Adrenoceptors in pain modulation: Which subtype should be targeted to produce analgesia? ANESTHESIOLOGY 2000; 92:934–6
16. Viggiano M, Badetti C, Roux F, Mendizabal H, Bernini V, Manelli JC: Controlled analgesia in a burn patient: Fentanyl sparing effect of clonidine. Ann Fr Anesth Reanim 1998; 17:19–26
17. Bachand RT, List W, Etropolski M, Martin E: A phase III study evaluating dexmedetomidine for sedation in postoperative patients. ANESTHESIOLOGY 1999; 91:A296
18. Scheinin H, Aantaa R, Anttila M, Hakola P, Helminen A, Karhuvaara S: Reversal of the sedative and sympatholytic effects of dexmedetomidine with a specific α_2-adrenoceptor antagonist atipamezole: A pharmacodynamic and kinetic study in healthy volunteers. ANESTHESIOLOGY 1998; 89:574–84
19. Horn EP, Standl T, Sessler DI, von Knobelsdorff G, Buchs C, Schulte am Esch J: Physostigmine prevents postanesthetic shivering as does meperidine or clonidine. ANESTHESIOLOGY 1998; 88:108–13
20. McSPI-Europe Research Group: Perioperative sympatholysis: Beneficial effects of the alpha-2 adrenoceptor agonist mivazerol on hemodynamic stability and myocardial ischemia. ANESTHESIOLOGY 1997; 86:346–63