

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  $\alpha_2$  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  $\alpha_2$  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.

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## Clinical Uses of $\alpha_2$ -Adrenergic Agonists

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SINCE the early 1970s,  $\alpha_2$ -adrenergic receptor agonists have been used successfully to treat patients with hypertension and patients withdrawing from long-term abuse of drugs or alcohol.  $\alpha_2$  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  $\alpha_2$ -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,<sup>1</sup> 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,  $\alpha_2$  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  $\alpha_2$ -adrenergic agonists will be discussed.

### Pharmacology

#### In Vitro Studies

$\alpha_2$ -Adrenergic agonists produce clinical effects after binding to  $\alpha_2$ -adrenergic receptors, of which there are three subtypes ( $\alpha_{2A}$ ,  $\alpha_{2B}$ , and  $\alpha_{2C}$ ). These receptor subtypes are distributed ubiquitously, and each may be uniquely responsible for some, but not all, of the actions of  $\alpha_2$  agonists; for example, the  $\alpha_{2B}$ -adrenoceptor subtype mediates the short-term hypertensive response to  $\alpha_2$  agonists,<sup>2</sup> whereas the  $\alpha_{2A}$  adrenoceptor is responsible for the anesthetic and sympatholytic responses.<sup>3</sup>

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  $\alpha_2$  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  $\alpha_2$  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  $\alpha_{2A}$ -adrenoceptor subtype seems to couple in an inhibitory fashion to the L-type calcium channel in the locus ceruleus, whereas, in the vasculature, the  $\alpha_{2B}$ -adrenoceptor subtype couples in an excitatory manner to the same effector mechanism.

Because all of the clinically available  $\alpha_2$  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  $\alpha_2$  agonists because studies of genetically engineered

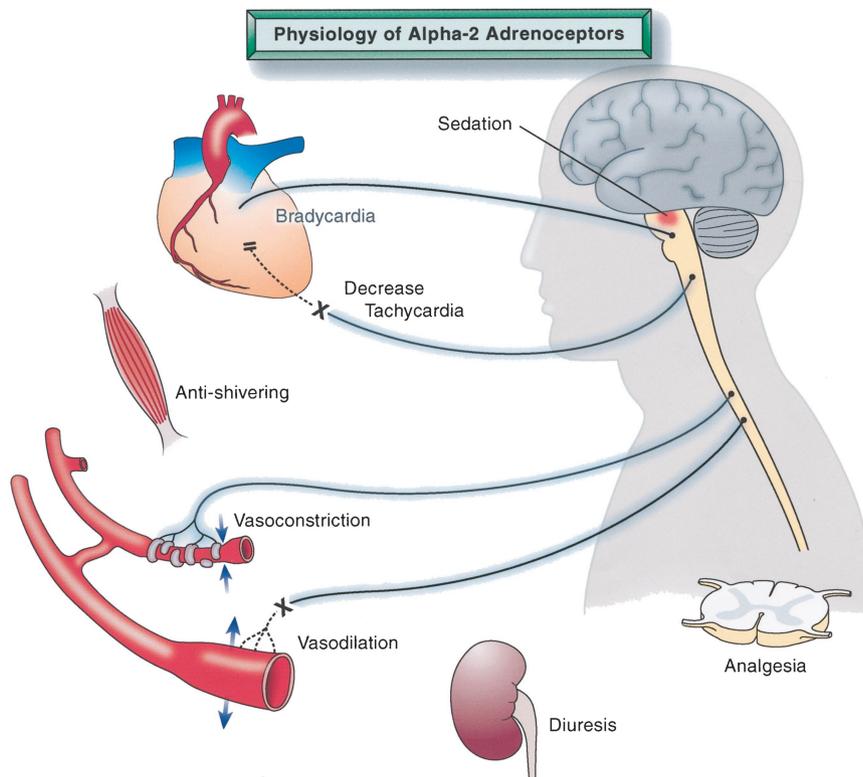
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The illustration for this section is prepared by Dmitri Karetnikov, 7 Tennyson Drive, Plainsboro, New Jersey 08536.



**Fig. 1.** Responses that can be mediated by  $\alpha_2$ -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  $\alpha_2$  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* sympathetic lysis 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  $\alpha_2$  agonists seem to be mediated by  $\alpha_2$  adrenoceptors (with the possible exception of enhanced vagal tone).

#### In Vivo Studies

**Cardiovascular System.**  $\alpha_2$  Agonists can produce either hypotension or hypertension. At lower doses, the dominant action of  $\alpha_2$  agonists is sympatholysis, *i.e.*, the ability to block the sympathetic arm of the autonomic nervous system, which is mediated by the  $\alpha_{2A}$ -adrenergic receptor subtype.<sup>3</sup> 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.*<sup>4</sup> have suggested that the central and peripheral sympatholytic effects of  $\alpha_2$ -adrenoceptor stimulation may be augmented further by inhibition of ganglionic transmission (fig. 1).

At higher doses of  $\alpha_2$  agonists, the hypertensive action dominates *via* the activation of  $\alpha_{2B}$  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.<sup>5</sup> Pretreatment with a peripherally restricted antagonist before intravenous administration of  $\alpha_2$  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 me-

diated 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  $\alpha_2$  agonists, spatial working memory also may be modulated *via* the  $\alpha_{2A}$  adrenoceptor subtype.<sup>6</sup> 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  $\alpha_{2C}$  adrenoceptors, Scheinin *et al.*<sup>7</sup> have shed light on the mechanism for the anxiolytic action of  $\alpha_2$  agonists. Mice with targeted inactivation of the gene that encodes  $\alpha_{2C}$  adrenoceptors had enhanced startle responses and shortened attack latency in the isolation-aggression test; conversely, if the mice were engineered to overexpress  $\alpha_{2C}$  adrenoceptors, the opposite behavioral effects were noted. Therefore, drugs acting *via*  $\alpha_{2C}$  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.  $\alpha_2$  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  $\alpha_2$  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.<sup>8</sup> In another paradigm of neuropathic pain, the antihyperalgesic action of dexmedetomidine was blocked by a peripherally restricted  $\alpha_2$ -antagonist, indicating that an  $\alpha_2$  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,  $\alpha_2$  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  $\alpha_2$  agonists. Thus,  $\alpha_2$  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.<sup>9</sup>

### *Intraoperative Applications*

Since the mid 1980s, many publications have reported the significant volatile anesthetic minimum alveolar concentration reduction produced by  $\alpha_2$  agonists; in animal studies, no apparent ceiling effect was noted for halothane minimum alveolar concentration reduction when the highly selective  $\alpha_2$  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.*,<sup>9</sup> 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,  $\alpha_2$  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  $\alpha_2$  agonists in neuropathic pain, Reuben *et al.*<sup>10</sup> reported that a Bier block with clonidine (1  $\mu$ g/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,  $\alpha_2$ -receptor target has been proposed.<sup>11</sup>

A plethora of studies have shown that  $\alpha_2$  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  $\mu$ g) provided analgesia comparable to that of 2.5  $\mu$ g intrathecal sufentanil for approximately 60 min.<sup>12</sup>  $\alpha_2$  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.<sup>13</sup> It is possible that the parturient is uniquely sensitive to the analgesic properties of  $\alpha_2$  agonists because clonidine alone has been shown to be effective for pain control after cesarean section. Using  $\alpha_2$  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  $\alpha_2$ -induced sedation and analgesia when the compound is administered neuraxially. Because subjects sedated with  $\alpha_2$  agonists can be aroused easily and demonstrate attentiveness,<sup>14</sup> 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  $\alpha_2$  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.<sup>15</sup>

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.<sup>16</sup>

### Sedation

For more than a decade,  $\alpha_2$  agonists have been used to provide preoperative sedation and axiolysis and to decrease intraoperative anesthetic requirements. Recently, its use for sedation<sup>17</sup> 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.<sup>14</sup> 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  $\alpha_2$  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.<sup>16</sup> However, the usefulness of  $\alpha_2$  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  $\alpha_2$  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.*<sup>18</sup> reported about the ability of atipamezole, a novel (unregistered) selective  $\alpha_2$ -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 sensitiv-

ity 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  $\alpha_2$  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  $\mu\text{g}/\text{kg}$  clonidine before emergence.<sup>15</sup> Similarly, intravenous clonidine (1  $\mu\text{g}/\text{kg}$ ) 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 mivazero, intraoperative myocardial ischemia and postoperative tachycardia were significantly reduced.<sup>20</sup> 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  $\alpha_2$  agonists may be proischemic through hypotensive and vasoconstrictive properties.

### Comparison of Clinically Available $\alpha_2$ Agonists

Dexmedetomidine has an  $\alpha_2:\alpha_1$ -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,  $\alpha_2$ -adrenergic agonists have become part of the anesthesiologists' therapeutic armamentarium. The use of  $\alpha_2$  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  $\alpha_2$  agonists remain "off-label."

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