Alpha-2 Adrenergic Receptor Agonists: A Review of Current Clinical Applications

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The α-2 adrenergic receptor agonists have been used for decades to treat common medical conditions such as hypertension; attention-deficit/hyperactivity disorder; various pain and panic disorders; symptoms of opioid, benzodiazepine, and alcohol withdrawal; and cigarette craving.[1] However, in more recent years, these drugs have been used as adjuncts for sedation and to reduce anesthetic requirements. This review will provide an historical perspective of this drug class, an understanding of pharmacological mechanisms, and an insight into current applications in clinical anesthesiology.

Key Words: Procedural sedation; General anesthesia; Alpha-2 agonists; Clonidine; Dexmedetomidine.

In early scientific theory of adrenergic mechanisms, it was believed that adrenergic receptors were classified into 2 groups: those whose actions resulted in either excitation or inhibition of effector cells.[2] This theory was the accepted concept until Ahlquist[2] demonstrated that there were 2 subtypes of receptors in the class, which he termed α and β (Table 1). Each had both excitatory and inhibitory effects based upon where that receptor was located.[2] Further study led researchers to discover that one of the α receptors inhibited neurotransmitter release from the presynaptic neuron.[3] The α-receptor antagonists prazosin and yohimbine were used to further subclassify these receptors as α-1 and α-2.[4] Later, many α-2 adrenergic agonists were developed for use in the clinical setting, including their use as anesthesia adjuncts. The use of α-2 agonists as adjuncts gained popularity when early reports by Brodsky and Bravo[5] found that withholding a single dose of clonidine prior to anesthesia caused a patient to experience an acute hypertensive crisis. It was discovered that α-2 agonists produce effects within both the central and peripheral nervous systems. Centrally within the locus ceruleus, for example, α-2 agonists are able to produce sedation, analgesia, and euphoric effects and partially block acute withdrawal symptoms in chronic opioid users.[4] More potent α-2 selective drugs, such as dexmedetomidine, have been formulated for clinical use as sole sedative agents or as adjuncts to drastically reduce the patient's requirement for additional sedatives or general anesthetics. Also, α-2 agonists are gaining popularity in children's hospitals throughout the United States as a preventative measure of and treatment modality for emergence delirium after general anesthesia.[6]

MECHANISM OF ACTION

Most studies to differentiate the various subtypes of α-2 receptors have been performed with molecular cloning using rat and human models. Ruffalo et al[7] demonstrated that administering yohimbine, a selective α-2 antagonist, can differentiate the types of receptors. He suggested that blockade of α receptors in bladder tissue is not competitive, and that more than one type of α-

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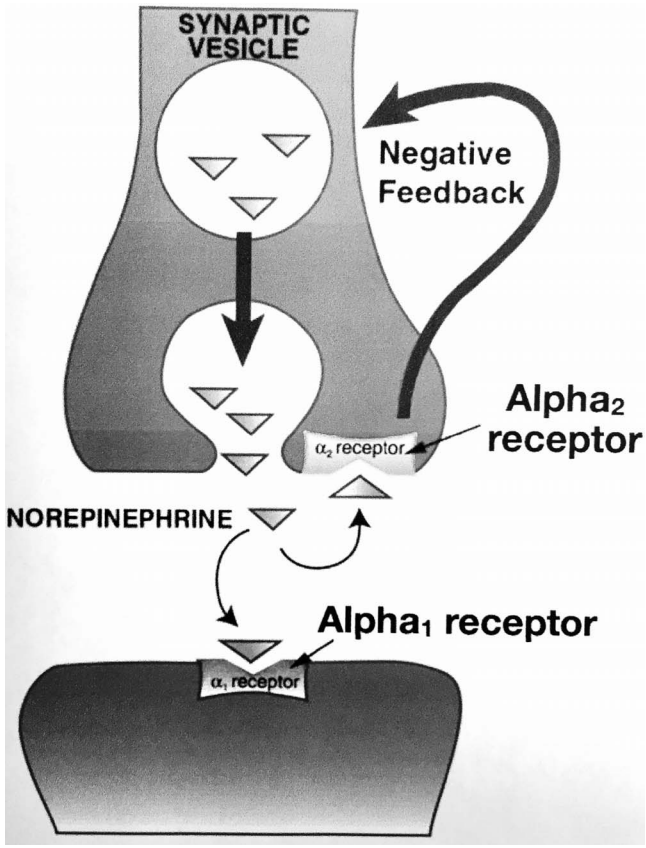
Table 1. Adrenergic Receptor Subtypes and Their Physiologic Functions

Receptor	*Physiologic Action (Agonism)*
α1	Constriction of vascular smooth muscle
	Contraction of radial muscle of the eye
	Contraction of the vas deferens smooth muscle
α2	Inhibition of norepinephrine release from presynaptic neuron
	Centrally induced sedation via locus ceruleus
	Centrally mediated pain modification via dorsal horn
	Inhibition of insulin release from pancreatic β cells
β1	Increased cardiac output (increased chronotropy, dromotropy, inotropy)
	Increased renin release from kidney
β2	Bronchial smooth muscle relaxation
	Vascular smooth muscle relaxation (vasodilation)
	Reduction of mast cell degranulation and histamine release
β3	Increased adipose tissue lipolysis

adrenergic receptor exists.[7] Microbiologists have been able to subdivide the various classes of α-2 receptors based upon affinities for agonists and antagonists. The α-2 receptors constitute a family of G-protein–coupled receptors with 3 pharmacological subtypes, α-2A, α-2B, and α-2C. Endogenous agonists, such as norepinephrine and epinephrine, have similar affinities for all 3 subtypes. However, prazosin, a selective α-antagonist drug used to treat high blood pressure, has a 60-fold affinity for the α-2A receptor on rat lung cells.[8]

The α-2A and -2C subtypes are found mainly in the central nervous system. Stimulation of these receptor subtypes may be responsible for sedation, analgesia, and sympatholytic effects.[9] The α-2B receptors are found more frequently on vascular smooth muscle and have been shown to mediate vasopressor effects. All 3 subtypes have been shown to inhibit adenylyl cyclase, in turn reducing the levels of cyclic adenosine monophosphate and causing hyperpolarization of noradrenergic neurons in the medial dorsal pons, specifically in the locus ceruleus.[10] As cyclic adenosine monophosphate is inhibited, potassium efflux through calcium-activated channels prevents calcium ions from entering the nerve terminal, leading to a suppression of neural firing. This suppression inhibits norepinephrine release and reduces activity of the ascending noradrenergic pathways, resulting in hypnosis and sedation.[11] Activation of this negative feedback loop may also produce reductions in heart rate and blood pressure and attenuation of the sympathetic stress response (Figure). Stimulation of α-2 receptors in the dorsal horn of the spinal column inhibits nociceptive neurons and reduces the release of substance P. Although there is some evidence for supraspinal and peripheral sites of action, it is thought that the spinal mechanism produces most of the α-2 agonist drugs' analgesic action.[12,13]



Synaptic influences of α-1 and α-2 receptors. Postjunctional α-1 receptors mediate effects on target tissues whereas prejunctional α-2 receptors inhibit neurotransmitter release and provide negative feedback.

Guanabenz, guanfacine, clonidine, tizanidine, medetomidine, and dexmedetomidine are all α-2 agonists that vary in their potency and affinities for the various α-2 receptor subtypes. Clonidine, tizanidine, and dexmedetomidine have received the greatest clinical use and will be addressed more thoroughly. Summary data are provided in Table 2.

CLONIDINE

Clonidine is the prototypical α-2 agonist, with an affinity predilection of 200 : 1 for α-2 versus α-1 receptors, respectively. It was first used as a nasal decongestant, but is now most frequently used in the management of hypertension because it was discovered coincidentally to lower systemic blood pressure through central brainstem adrenergic stimulation. Clonidine is rapidly and almost completely absorbed after oral administration, and may exhibit transient increases in blood pressure after initial

Table 2. Summary of α-2 Receptor Agonists and Pharmacological Properties*

Drug Name	*Trade Name*	*Pharmacokinetics*	*Clinical Uses*	*Precautions*
Clonidine	Catapres, Nexiclon XR, Kapvay	Metabolism: liver (~50%) Excretion: 40–60% unchanged in urine, 20% bile/feces Half-life: 12–16 h	Treatment of: Hypertension Anxiety ADD/ADHD Chronic pain Withdrawal symptoms Postoperative shivering	Transient increases in blood pressure after initial dosing (stimulation of postsynaptic α1 receptors) Rebound hypertension after sudden cessation
Tizanidine	Zanaflex	Metabolism: Liver Excretion: 60% urine, 20% feces Half-life: 2.5 h	Treatment of: Muscle spasm and cramps associated with CNS disorders Myofascial pain disorders of head and neck Spasticity of cerebral palsy	Potential for hepatotoxicity Fluoroquinolone antibiotics increase serum concentration
Dexmedetomidine	Precedex	Metabolism: Liver Excretion: 95% urine, 4% feces Half-life: 2 h	ICU sedation Procedural sedation	Hypotension, bradycardia Tachyphylaxis (if infused >24 h)

* ADD indicates attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; and ICU, intensive care unit.

dosing because of mild stimulation of peripheral postjunctional α-1 receptors. Sudden withdrawal of clonidine after chronic administration has been associated with rebound hypertension, which may occur up to 20 hours after cessation of the drug. It should not be withheld prior to dental procedures.

More recently, clonidine has been used as a premedicant in patients with significant pretreatment anxiety.[14] It has been shown to improve mask application upon induction of anesthesia in the pediatric population, and to decrease anesthetic requirements by 40–60%.[15] Clonidine has been used orally for pediatric procedural sedation with success. Cao et al[16] evaluated 45 children aged 2–8 years comparing oral midazolam (0.5 mg/kg) and oral clonidine (2 or 4 mcg/kg) in providing level of sedation, quality of parenteral separation, mask acceptance, and postoperative analgesia. Both clonidine groups achieved better sedation, separation, and mask acceptance scores than the midazolam group. There was less postoperative shivering with clonidine, but the onset time was delayed with clonidine, 60 minutes versus 30 minutes for midazolam.

Clonidine and guanfacine may be used to treat attention-deficit/hyperactivity disorder in children and adolescents. The reduced firing of presynaptic neurons releasing norepinephrine into the prefrontal cortex improves the impulsive and hyperactive behavior seen in attention-deficit/hyperactivity disorder.[17] Adjunctive effects on serotonin and γ-aminobutyric acid receptors make α-2 agonists the most widely used medications to treat insomnia in children with attention-deficit/hyperactivity disorder.[18] Clonidine is also useful in the treatment of chronic pain disorders and opiate, benzodiazepine, alcohol, cocaine, food, and tobacco withdrawal.

TIZANIDINE

Tizanidine is another α-2 agonist, similar to clonidine, but with some important differences. Like clonidine, it has sedative, anxiolytic, and analgesic properties, but it has a shorter duration of action and less effect on heart rate and blood pressure. In a study of 70 patients undergoing general anesthesia, Tabori et al[19] evaluated the effect of tizanidine versus placebo on the hemodynamic response to direct laryngoscopy. Subjects received either 4 mg of tizanidine or a placebo 90 minutes prior to the induction of general anesthesia with propofol. The tizanidine group had less fluctuation in blood pressure and heart rate than the control group following direct laryngoscopy and intubation. They also found that tizanidine reduced the propofol requirement by 25% and significantly reduced the incidence of postoperative shivering (11.4 vs 28.6%). They concluded that tizanidine provides cardiovascular stability during induction of general anesthesia, and that it could have utility in attenuating the stress of direct laryngoscopy and intubation.

Tizanidine has also been used in the treatment of myofascial pain disorders of the head and neck. It can reduce spasticity by increasing the presynaptic inhibition of motor neurons in the brain and spinal cord, and by reducing painful muscle spasms in the neck and shoulder. In a study evaluating its effectiveness in the treatment of myofascial pain, tizanidine was shown to

significantly reduce pain and tissue tenderness and to improve the quality of sleep. It was rated as good to excellent in relieving pain by 89% of the subjects studied.[20] The reduction in spasticity has also led other investigators to evaluate the effectiveness of tizanidine in patients with cerebral palsy. In a study of patients with infantile cerebral palsy, tizanidine was shown to significantly decrease spasticity by 78.8% as compared to 7.6% for placebo.[21] It seems apparent that tizanidine may be useful as a sedative premedicant prior to general anesthesia and as a management tool for patients with cerebral palsy or other spastic disorders.

DEXMEDETOMIDINE

Dexmedetomidine is a highly selective α-2 agonist similar to clonidine but with a greater affinity for the α-2 receptor. Clonidine has a specificity of 220 : 1 (α-2 : α-1), whereas dexmedetomidine exhibits a specificity of 1620 : 1.[22] It is the pharmacologically active d-isomer of medetomidine, a full agonist of α-2 adrenergic receptors.

Cardiovascular Effects

Dexmedetomidine exhibits a biphasic blood pressure response in a dose-dependent fashion.[23] Intravenous infusion of low doses results in a reduction of mean arterial pressure because of selectivity for central and peripheral α-2 receptors. The resultant decreases in heart rate and systemic vascular resistance indirectly decrease cardiac output and systolic blood pressure. These effects aid in modulating the stress response, promote stability, and may protect against radical fluctuations in cardiovascular parameters intraoperatively. This may be particularly useful in patients at risk for cardiac morbidities who could respond adversely to surgical stressors. Intravenous infusion of high doses or rapid intravenous bolus administration may result in systemic hypertension due to activation of peripheral postjunctional α-1 adrenergic receptors. Dexmedetomidine loses its α-2 receptor selectivity as the dose is increased by intravenous bolus injection or rapid infusion. This loss in selectivity results in an initial increase in blood pressure and concomitant decrease in heart rate, which normalizes within 15 minutes.[24] Hypertension can also be observed because of the transient activation of peripheral α-2B receptors upon rapid bolus injection of the drug. This brief increase in blood pressure is likely due to an overwhelming effect of the competition with vasodilatory effects of the central α-2A receptors.[11] Extreme care should be taken when using dexmedetomidine on patients who are volume depleted or vasoconstricted or who have a severe heart block.

Respiratory Effects

A major advantage of dexmedetomidine compared with other anesthetic drugs is its minimal effect on the respiratory system. In patients with poor airway patency, obesity, and/or limited range of motion, dexmedetomidine produces excellent sedation without compromising the airway or depressing respiration.

Pharmacokinetic Considerations

Dexmedetomidine conforms to a 2-compartment model of distribution and elimination. It has an elimination half-life ($T_{1/2\beta}$) of 2 hours, but it is a highly lipophilic drug that is rapidly distributed and redistributed, with a distribution half-life ($T_{1/2\alpha}$) of only 6 minutes. This provides a very rapid onset but a short duration of clinical effect. Its rapid redistribution and elimination make it an acceptable agent for infusion techniques. Dexmedetomidine undergoes direct glucuronidation and CYP2A6-mediated metabolism. Approximately 80–90% is excreted in the urine, and 5–13% is found in the feces.[25] Typically, pharmacokinetic-based interactions are unusual. However, dosage modifications of simultaneously administered sedatives may need to be made because of drug potentiation. Adding an α-2 agonist to a sedation regimen reduces opioid requirement by 50–75% and benzodiazepine requirement by upwards of 80%.[26] The context-sensitive half-time of dexmedetomidine ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion.[27]

Clinical Considerations

Dexmedetomidine has 3 main clinical applications: (a) prolonged sedation in hospitalized patients, (b) procedural sedation and general anesthesia, and (c) obtunding emergence delirium. It is used as a sedative agent for critically ill patients requiring prolonged sedation and mechanical ventilatory support in a critical care setting. Dexmedetomidine possesses all of the characteristics of an ideal sedative for intensive care. It lacks respiratory depression, is analgesic and anxiolytic, has a rapid onset, is titratable, and produces sedation with hemodynamic stability.

Secondly, dexmedetomidine is used as an adjunctive sedative agent for procedural sedation. It can be used

Table 3. Guidelines for Use of Dexmedetomidine (Precedex) in Procedural Sedation

Method of Use	*Dose*		
	Circumstances	*Loading Dose*	*Maintenance*
Infusion*†	Adult patients	1 mcg/kg over 10 min	0.6 mcg/kg/h Titrate to effect with doses from 0.2 to 1 mcg/kg/h
	Less invasive procedures	0.5 mcg/kg over 10 min	0.6 mcg/kg/h Titrate to effect with doses from 0.2 to 1 mcg/kg/h
	Patients >65 y	0.5 mcg/kg over 10 min	Reduction in maintenance dosage should be considered
	Patients with impaired hepatic or renal function	A dose reduction should be considered	Reduction in maintenance dosage should be considered
Bolus	0.25–0.5 mcg/kg in slow divided doses		

* Infusion dosing is per manufacturer recommendations.

† ''Precedex Dosing for Procedural Sedation.'' http://www.precedex.com/wp-content/uploads/2010/02/Procedural-Sedation-dosing-Card.pdf.[28]

with agents such as opioids, benzodiazepines, and propofol to enhance sedation and promote and maintain hemodynamic stability. Because it does not produce respiratory depression, it is very useful in patients for whom this would be a concern. Its rapid distribution half-life (6 minutes) and favorable context-sensitive half-time enhance recovery and allow for faster patient discharge. However, recovery could be prolonged in cases where infusion of dexmedetomidine continues over several hours. In these cases, the infusion should be discontinued well in advance of the anticipated discharge time. Dexmedetomidine may be given via bolus injection or continuous infusion. A bolus injection of 0.25–0.5 mcg/kg, given slowly in divided doses to avoid a transient increase in blood pressure, produces a noticeable quieting or mellowing effect without respiratory depression. As an alternative, sedation may be induced by a continuous infusion of dexmedetomidine, 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2–0.7 mcg/kg/h (Table 3).

Finally, dexmedetomidine is very useful in obtunding the emergence delirium sometimes seen after general anesthesia, especially in the pediatric population. It produces profound calming without respiratory depression. This is a major advantage over other drugs that have commonly been used in this situation and deserves further consideration.

EMERGENCE DELIRIUM

Emergence delirium can be a significant problem following outpatient anesthesia because of the potential for serious disruption of the office, damage to instruments and equipment, and injury to the patient or office personnel. Delirium is described as a disturbance of consciousness, characterized by the acute onset of impaired cognitive functioning, significantly impairing a patient's ability to process and store information. Pediatric patients, patients with special needs, and the elderly are particularly prone to emergence delirium following anesthesia, especially when benzodiazepines and potent inhalational agents are used. Patients who develop delirium are more likely to have poor outcomes when hospitalized, including increased length of stay, the need for subsequent institutionalization, and higher mortality. Cognitive impairment has been reported to negatively affect key outcome indicators such as removal from the ventilator, pneumonia, and total length of hospital stay.[29]

Dexmedetomidine has been studied to assess its efficacy in reducing the occurrence of emergence delirium. Riker and others[30] compared the efficacy of dexmedetomidine with midazolam for the maintenance of mechanically ventilated patients, and also examined the incidence of delirium in those patients. Although the 2 drugs produced comparable levels of sedation, dexmedetomidine significantly reduced the incidence of delirium to 54 versus 75% for midazolam. In addition, the duration of delirium was reduced by 48% in the dexmedetomidine group. Patients treated with dexmedetomidine had a statistically significant greater ability to communicate and to cooperate than those treated with midazolam. Pandharipande and colleagues[31] compared the efficacy and incidence of delirium of dexmedetomidine and lorazepam in mechanically ventilated intensive care patients. Lorazepam has been recommended by the Society of Critical Care Medicine for the sustained sedation of mechanically ventilated patients in the intensive care unit. However, it has been proposed that the gamma-aminobutyric acid effects of lorazepam and other benzodiazepines may alter levels of potentially deliriogenic neurotransmitters, with negative conse-

quences. Compared with the lorazepam group, the dexmedetomidine group had a lower prevalence of coma (63 vs 92%) and fewer days with delirium (3 vs 7 days), and the 12-month time to death was 363 versus 188 days.

Emergence delirium is also common in children recovering from deep sedation and general anesthesia. Shukry et al[32] studied 2 groups of children between the ages of 1 and 10 years receiving general anesthesia with sevoflurane. One study group received an infusion of dexmedetomidine and the other received saline. The dexmedetomidine group had an emergence delirium incidence of 26 versus 60% for the saline group. Another study investigated the incidence of emergence delirium in children receiving general anesthesia for a nonsurgical procedure.[33] One group received an infusion of dexmedetomidine after induction of anesthesia and the other group received a placebo infusion. The children who received dexmedetomidine had a 4.8% incidence of delirium compared with 47.6% for the placebo group.

Dexmedetomidine may be used either prophylactically or emergently for the prevention or control of emergence delirium. In patients who are deemed at risk for emergence delirium, 0.25 mcg/kg of dexmedetomidine may be slowly injected intravenously during the maintenance phase of anesthesia. Should emergence delirium occur, another 0.25 mcg/kg could be administered. In cases in which no prophylactic dose is given, emergence delirium may be controlled with the intravenous administration of 0.5 mcg/kg of dexmedetomidine.

PEDIATRIC CONSIDERATIONS

Although an off-label use, dexmedetomidine is very useful in providing pediatric sedation for a variety of procedures in the critical care setting and for facilitating computed tomography and magnetic resonance imaging evaluations.[34] Dexmedetomidine has been shown to provide superior sedation to midazolam in children undergoing computerized imaging.[35] Unlike with benzodiazepines and opioids, dexmedetomidine provides for an unchanged respiratory rate and end-tidal CO_2 during spontaneous ventilation anesthesia. Dexmedetomidine is also useful in the perioperative management of pediatric cardiac patients.[36] Its sympatholytic effects could be potentially beneficial for children undergoing cardiac procedures.

ALTERNATE ROUTES OF ADMINISTRATION

Although intravenous administration is the most popular form of administering dexmedetomidine, it has also been given intramuscularly, submucosally, buccally, and intranasally. In adult volunteers, intramuscular administration demonstrated a 73% bioavailability as compared with intravenous administration. A biphasic hemodynamic response was not observed. Bioavailability following intranasal administration was 80% and produced sedation similar to oral midazolam in pediatric patients.[11] Mason and others[37] demonstrated the safety and efficacy of intramuscular dexmedetomidine in pediatric patients aged 0.2–17 years undergoing electroencephalographic evaluation. Subjects received 1–4.5 mcg/kg intramuscularly based upon the discretion of the anesthetist and the perceived need. The mean onset to clinical effectiveness occurred within 15 minutes, and the clinical duration was almost 1 hour. Dexmedetomidine as an oral rinse was studied by Karaaslan and colleagues.[38] As a premedicant prior to arthroscopic knee surgery, subjects received either placebo or intramuscular or buccal dexmedetomidine 2.5 mcg/kg. The buccal dexmedetomidine was administered as an oral rinse in which the subjects swished the solution for 15 minutes before expectorating. Both routes of administration provided similarly effective levels of anxiolysis and sedation, but the buccal administration provided better analgesia. Alternative routes of administration of dexmedetomidine offer a rich area for future clinical investigation, especially in the pediatric dental patient.

REVERSAL AGENTS

Atipamezole is effective in reversing the clinical effects of α-2–agonist drugs. This highly selective α-2 antagonist is widely used in veterinary medicine for the reversal of dexmedetomidine sedation in dogs.[39] Two similar studies have demonstrated the effectiveness of atipamezole in reversing the effects of dexmedetomidine in humans.[40,41] Atipamezole provided rapid reversal of both the sedative and sympatholytic effects of dexmedetomidine. With the increasing use of dexmedetomidine as a sedative agent in critical care and outpatient anesthesia, further research into the safety and efficacy of this reversal agent is warranted.

SUMMARY

The α-2 adrenergic receptor agonist drugs have established a place in the modern anesthetic armamentarium because of their ability to produce a calming effect without causing respiratory depression, and by promoting cardiovascular stability while reducing anesthetic requirements. The oral administration of clonidine or

tizanidine provides a useful alternative for the premedication of difficult patients or to provide prophylactic cardiovascular protection during laryngoscopy and intubation. In addition, tizanidine may be useful in managing the spasticity associated with conditions such as cerebral palsy. At present, the high cost of dexmedetomidine may limit its use, especially in the doses required for effective intramuscular premedication or continuous maintenance infusion. However, in the authors' opinion the advantages of the drug as a sedation adjunct and for the prevention or control of emergence delirium far outweigh the expense. Furthermore, the subsequent reduction in anesthetic requirements of concomitantly administered drugs results in additional cost containment.

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CONTINUING EDUCATION QUESTIONS

1. Stimulation of α-2 receptors in the central and autonomic nervous systems may produce which of the following effects?

   (1) sedation (2) analgesia (3) transient hypertension

   A. 1 and 2
   B. 1 and 3
   C. 2 and 3
   D. 1, 2, and 3

2. Which of the following α-2 agonists has specific indications for the management of myofascial pain disorders and spasticity?

   A. dexmedetomidine
   B. clonidine
   C. guanabenz
   D. tizanidine

3. Which of the following is a specific reversal agent for α-2 agonist drugs?

   A. atipamezole
   B. caffeine
   C. flumazenil
   D. naloxone

4. Which of the following has the greatest affinity for the α-2 adrenergic receptor?

   A. clonidine
   B. dexmedetomidine
   C. medetomidine
   D. tizanidine