

Dexmedetomidine: A Useful Adjunct to Consider in Some High-Risk Situations

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Dexmedetomidine is a relatively selective α_2 agonist with sympatholytic, sedative, amnestic, and analgesic properties. It is indicated for the short-term sedation of patients needing mechanical ventilation in the intensive care unit. Recent reports have been published describing dexmedetomidine as a useful adjunct in both regional and general anesthesia. A few case studies have demonstrated successful use of dexmedetomidine as a replacement agent for opioids in patients in whom airway compromise was a concern.

This article will provide the reader with a comprehensive review of the pharmacology, pharmacokinetics, and adverse effects of dexmedetomidine. A thorough understanding of this drug will enable the anesthesia provider to determine situations in which dexmedetomidine may be a useful drug to consider, whether as an adjunct or as a sole agent.

Keywords: Adjunct, analgesia, anxiolysis, dexmedetomidine, sedation.

Dexmedetomidine (DEX) is a selective α_2 agonist approved for use in 1999.¹⁻⁶ It has approximately 7 to 8 times the α_2 selectivity than that of clonidine. An imidazole compound, DEX is the dextroisomer of medetomidine that demonstrates selective α_2 agonist action because of its pharmacological activity. Alpha₂ agonists produce sedation, anxiolysis, sympatholysis, and possess some analgesic properties. These characteristics of DEX have made this drug particularly useful in the perioperative period and for sedation of patients in the intensive care unit (ICU)(Figure 1).

History/Review of the Literature

Alpha₂ receptors have been found in the peripheral and central nervous system, platelets, liver, pancreas, kidney, and eye.^{1,4,7,8} These receptors appear to possess presynaptic, postsynaptic, and extrasynaptic sites of action. The presynaptic sites of action are clinically significant because they modulate the release of norepinephrine and adenosine triphosphate. The physiological responses regulated by α_2 receptors vary depending on their location. The stimulation of α_2 receptors in the brain and spinal cord inhibit neuronal firing, which leads to hypotension, bradycardia, sedation, and analgesia. The responses from other organs containing α_2 receptors include decreased salivation, secretion, and gastric motility; inhibited renin release; increased glomerular filtration rate; increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin secretion from the pancreas. The stimulation of α_2 receptors decreases calcium entry into nerve terminals, which may contribute to its inhibitory effect on neurotransmitter release.

The sedation effects of DEX are postulated to be in the locus coeruleus (a small bilateral nucleus that contains

many adrenergic receptors) in the brainstem.^{1,8,9} The locus coeruleus is the primary site in modulating wakefulness and is considered to contribute to the sedative-hypnotic and analgesic properties of DEX. The locus coeruleus is also the origination site for the descending medullospinal adrenergic pathway, which is known to be a key mechanism in regulating nociceptive neurotransmission. The similar mechanisms of α_2 receptors and opioid receptors in this area of the brain have contributed to the thought that there must also be extraspinal sites of action. When these sites are stimulated, they decrease the firing of nociceptor neurons stimulated by peripheral A and C fibers and also inhibit the release of their neurotransmitters. The analgesic effects are believed to be in the dorsal horn of the spinal cord.

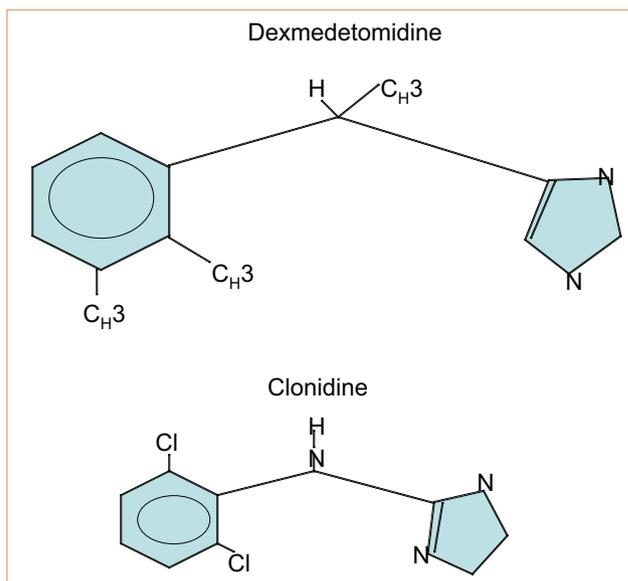


Figure 1. Chemical Structure of Dexmedetomidine and Clonidine

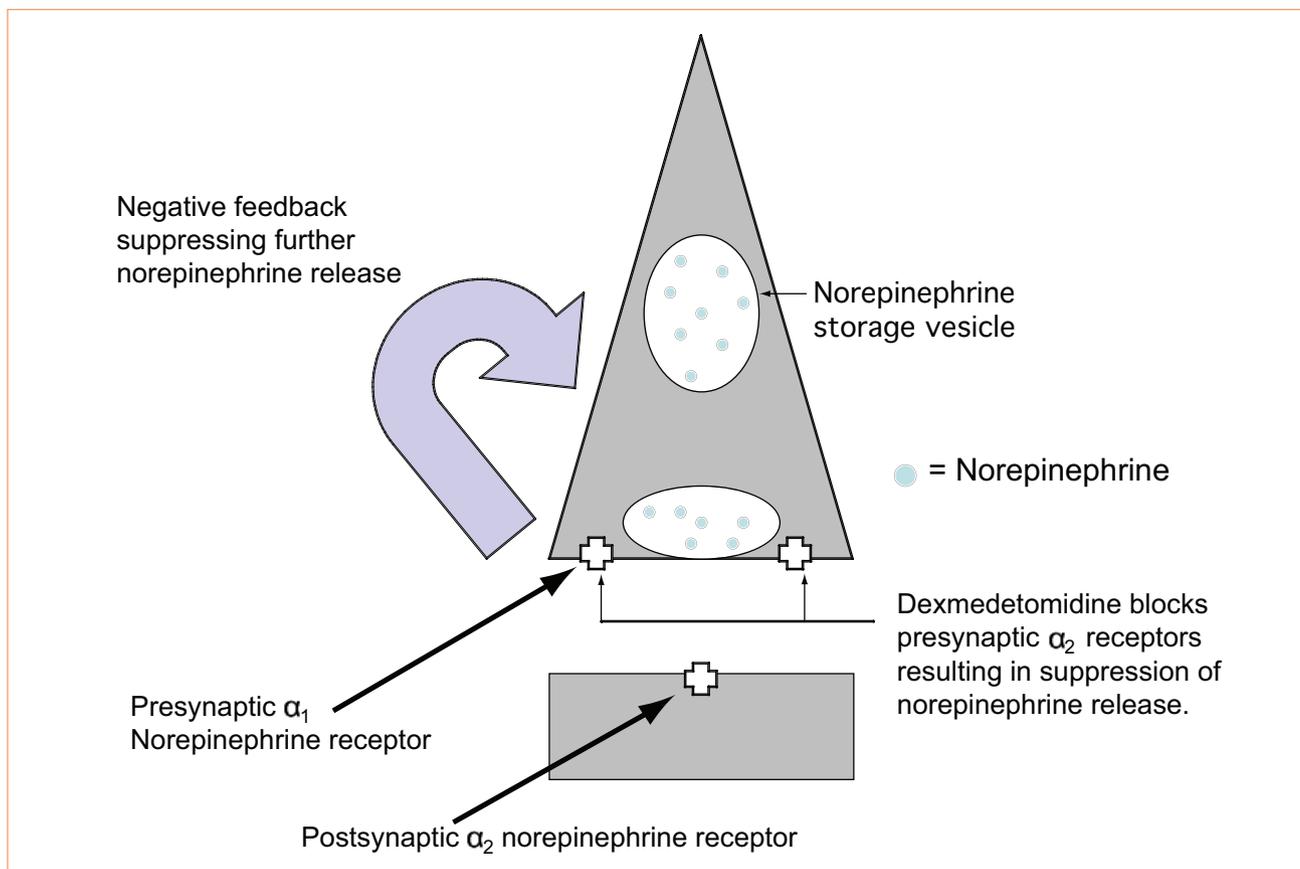


Figure 2. Action of Dexmedetomidine at the Presynaptic α_2 Receptor
Negative feedback loop modulating norepinephrine release.

The primary cardiovascular action of DEX is sympatholysis by decreasing sympathetic outflow of the autonomic nervous system.¹⁻⁴ Presynaptic α_2 receptors serve as a negative feedback system modulating norepinephrine release from sympathetic nerve terminals (Figure 2).

Despite its sympatholytic properties, a transient elevated blood pressure reading occasionally manifests on initial administration of DEX^{9,10} because the α_{2b} receptors on the resistance vessels of smooth muscle cells cause vasoconstriction (Figure 3). This response can be minimized by avoiding bolus administration of the drug.

Pharmacokinetics

Intravascular administration of DEX exhibits a rapid distribution phase with a distribution half-life of approximately 6 minutes and an elimination half-life of approximately 2 hours.^{1,3,4,6} Dexmedetomidine follows linear or zero-order kinetics, meaning that a constant amount of the drug is eliminated per hour rather than a constant fraction of the drug eliminated per hour, which is characteristic of first order kinetics (Figure 4).

Distribution

The steady state volume of distribution of DEX is approximately 118 L.^{3,6,11} Protein binding is reported to be

approximately 94% and remains constant despite varied concentrations of the drug. No significant displacement of DEX was noted when given concomitantly with phenytoin, warfarin, ibuprofen, propranolol, theophylline, and digoxin.

Metabolism

The biotransformation of DEX is nearly complete by direct glucuronidation and cytochrome P450-mediated metabolism.^{1,3,6,8} No differences have been seen between healthy patients and those with renal impairment. Considering that the majority of the DEX metabolites are excreted in the urine, there is a theoretical risk that accumulation may result with prolonged administration. Clearance has been shown to be decreased in those with hepatic impairment. Therefore, it may be necessary to decrease the drug dose in the patient with hepatic insufficiency (Figure 5).

Pharmacodynamics

A brief biphasic cardiovascular response has been reported after the initial administration of DEX. The bolus dose of 1 $\mu\text{g}/\text{kg}$ results in an initial increase in blood pressure and a reflex drop in heart rate. This response is seen more often with young and healthy patients. The stimulation of

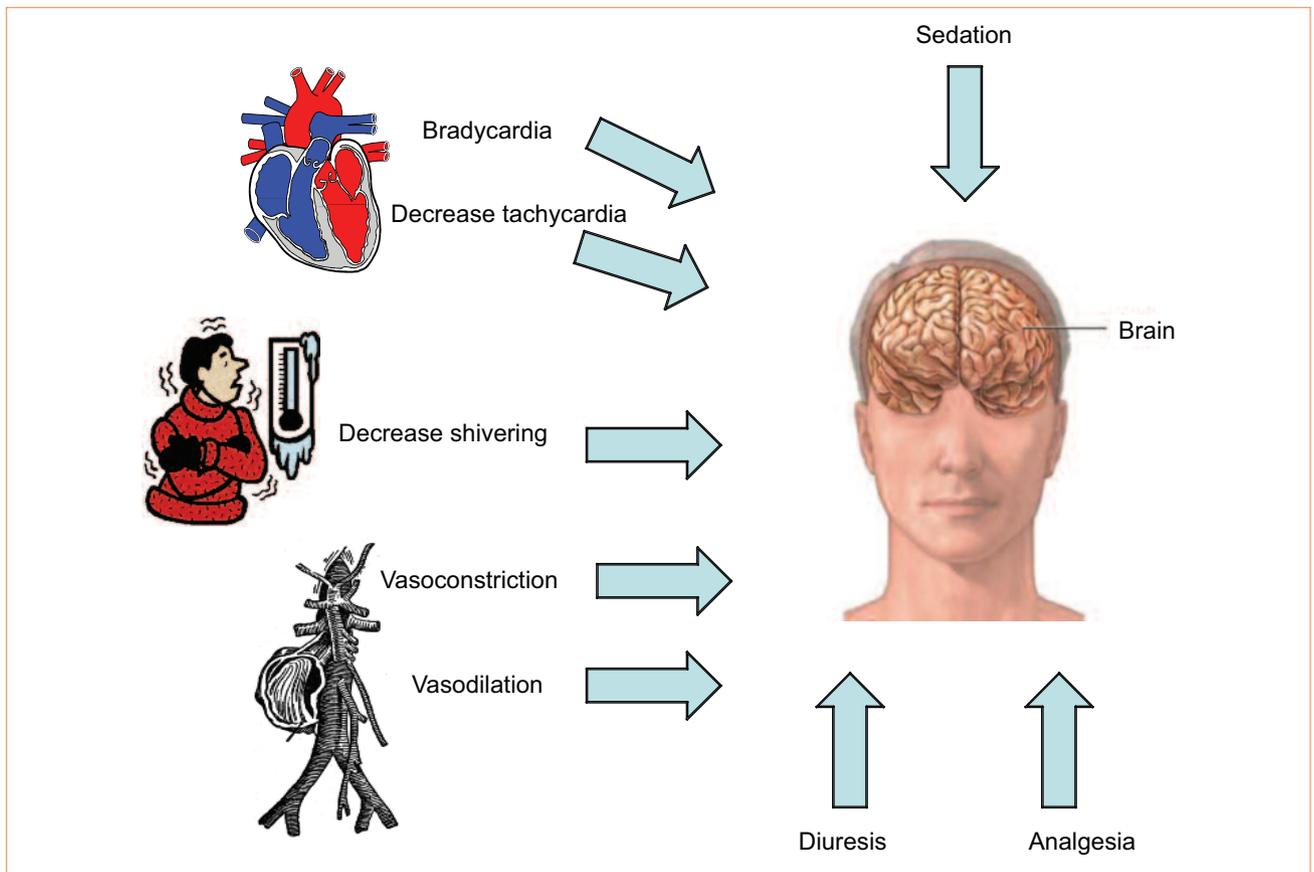


Figure 3. Multiple Sites of Action of Dexmedetomidine (peripherally and centrally)

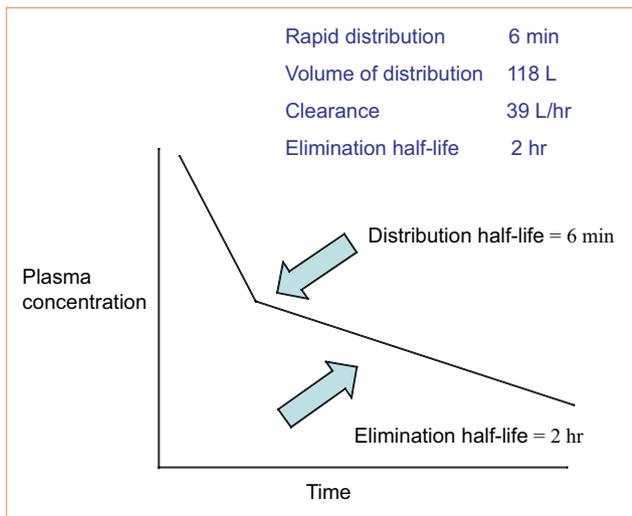


Figure 4. The Pharmacokinetics of Dexmedetomidine

the α_{2b} receptors in vascular smooth muscle is postulated to be the cause of the increase in blood pressure. The rise in blood pressure can be attenuated by a slow infusion. This initial response lasts for 5 to 10 minutes and is followed by a slight decrease in blood pressure due to the inhibition of central sympathetic outflow. The presynaptic α_2 receptors are also stimulated, thereby decreasing norepinephrine release, causing a resultant fall in blood pres-

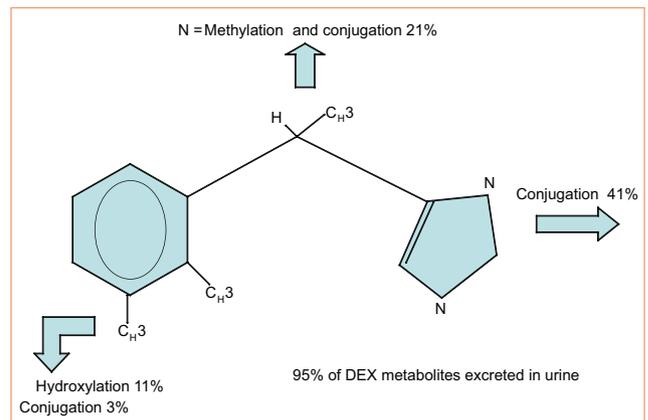


Figure 5. The Pathways in the Metabolism of Dexmedetomidine (DEX)

sure and heart rate. The incidence of postoperative bradycardia has been reported to be as high as 40% in healthy patients. These temporary effects have been managed with atropine, ephedrine, and volume infusion. Caution should be taken in those clinical situations where the sympatholytic actions of α_2 receptor agonists prove detrimental, such as in patients with left ventricular dysfunction.

Discussion of State of the Art

The analgesic effects of α_2 agonists were first described in

1974, when clonidine was administered to rats and nociceptive thresholds were increased.^{1,12} Several multicenter trials subsequently showed decreased opiate use after the administration of DEX for patients after laparoscopic tubal ligation and cardiac surgical procedures. These findings were significant to care of the ICU patient because opioid-sparing effects may result in a shorter time to extubation.⁹ Multiple studies have demonstrated that DEX possesses important postsurgical analgesia, yet it appears to have little significant respiratory depression.

Reports suggest that there is much less respiratory depression caused by DEX than by other sedatives due to its nonopioid analgesic mechanism of action,^{1,12} but coadministration of DEX with anesthetic agents, sedative-hypnotics, or opioids may have an additive effect. The preservation of respiratory function is what led to the use of DEX in the ICU setting. The sedation from α_2 agonists is unique in that patients can be easily aroused and then can return to a sleep-like state when not stimulated. Patients sedated with α_2 agonists may be more cooperative and communicative than patients sedated with other drugs in the ICU.

The characteristics of DEX may make it a useful anxiolytic, especially in those patients in whom preoperative stress is undesirable.^{1,8} Shown to be an effective anxiolytic for intravenous regional anesthesia, DEX reduces patient anxiety and opioid requirements.

Intraoperatively, DEX is being used off label in the dose range of 0.2 $\mu\text{g}/\text{kg}$ per hour to 0.7 $\mu\text{g}/\text{kg}$ per hour. Dexmedetomidine attenuates the sympathetic response to laryngoscopy, intubation, and surgery and provides more hemodynamic stability. It potentiates all intraoperative anesthetics (intravenous, inhalational, regional). Administration of DEX during anesthesia has been shown to reduce opioid and anesthetic requirements. These properties have resulted in a more rapid recovery from anesthesia and a reduced need for opioids in the recovery room, thereby reducing length of stay in the hospital during the recovery phase.

Summary

Dexmedetomidine is indicated for use as a sedating agent for patients requiring short-term mechanical ventilation.^{1,12,14-18} Because of its anxiolytic, sedative, analgesic, and sympatholytic properties, DEX has been shown to be a useful adjunct as a premedication, especially for those patients at risk for preoperative and perioperative stress. Dexmedetomidine demonstrates anesthetic-sparing effects and reduced hemodynamic stress responses to tracheal intubation.

Further research may lead to greater than 24-hour ICU use and use as postoperative pain management. Recent literature reported off-label uses as an adjunct to regional or general anesthesia, in craniotomy procedures when the patient must remain awake, and as a sole sedating or

anesthetic agent in certain patients in whom airway compromise is a concern, as noted in a few case reports.¹⁷

A recently published case report described the use of DEX in lieu of opioids for a gastric bypass procedure of a morbidly obese patient.¹³

A recent published study evaluated the hemodynamic and respiratory changes following the administration of DEX with sevoflurane or desflurane during general anesthesia in pediatric patients. The study demonstrated a slight decrease in heart rate in both the sevoflurane group and the desflurane group but no differences between the groups.¹⁹

The unique characteristic of providing sedation and analgesia while producing less respiratory depression than more commonly used sedative-hypnotic agents and opioids makes DEX a potentially attractive drug for use in select, high-risk populations such as the morbidly obese. Further research, especially randomized controlled trials of the use of DEX vs established regimens of ICU and perioperative care, are indicated.

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