

Dexmedetomidine: Clinical Update

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BECAUSE of the unusually disruptive nature of the intensive care unit (ICU) environment, pharmacological management of agitation and anxiety is often essential to the care of the critically ill patient. Sedative and anxiolytic agents, however, are associated with significant side effects. Respiratory depression, hemodynamic instability, tolerance to drug effect, accumulation of drug over time, and prolonged cognitive compromise can all complicate the use of sedation in the ICU and adversely impact patient outcomes. In addition, appropriately titrating sedation can be an elusive goal. One recent review and comment indicated that ICU patients are maintained in their targeted sedation range only about 50% of the time, suggesting not only deficiencies in knowledge regarding optimal sedation strategies, but also inadequacies in traditional sedative agents.^{1,2}

Dexmedetomidine (Precedex[®], Abbott Laboratories, Inc., Abbott Park, IL, USA) is the first marketed sedative to make use of highly selective alpha-2 agonist activity. As a result, sedation with dexmedetomidine (Dex) differs in several important ways from sedation with other agents. First, unlike commonly used sedatives such as propofol or midazolam, Dex produces an "interactive" form of sedation, in which patients may be aroused easily with stimulation, and are cooperative once aroused. Second, Dex has analgesic properties and may significantly reduce concomitant opioid use when given to patients with pain. Third, Dex is accompanied by virtually no respiratory depression at clinically relevant doses. Finally, Dex has predictable sympatholytic effects that are characteristic of its mechanism of action. This review will discuss dexmedetomidine with emphasis on its pharmacology, mechanism of action, clinical use, and known effects on critical organ systems.

HISTORY AND PHARMACOLOGY

Since the advent of clonidine as an antihypertensive four decades ago, alpha-2 agonists have seen extensive use. Although anesthesiologists have attempted to use clonidine perioperatively to reduce anesthetic requirements, control shivering,

and protect against nausea and vomiting, difficulties in drug dosing have prevented widespread acceptance. Dexmedetomidine differs from clonidine in two important respects: significantly greater (8x) affinity for the alpha-2 receptor, and increased titratability. The chemical platform for dexmedetomidine is the racemic drug medetomidine, which has been used as a sedative in veterinary anesthesia in Europe since 1987, and in the US since 1996 (Domitor[®], Pfizer, Inc., New York, NY, USA). Dexmedetomidine is constituted from the dextro-rotatory isomer only of medetomidine, which appears to result in superior sedative and fewer cardiovascular side effects than the levorotatory isomer.³ Because of its sympatholytic properties, dexmedetomidine was initially developed as a surgical premedicant and anesthetic adjunct, with the goal of attenuating the sympathetic response to perioperative stresses such as laryngoscopy and intubation.⁴ However, an emerging need for effective sedative strategies in the ICU, combined with the agent's remarkable ability to produce anxiolysis and analgesia with respiratory stability, ultimately shifted its developmental focus to critical care sedation.

Dex received approval from the US Food and Drug Administration (FDA) in 1999 for the sedation of initially intubated patients in a critical care-like setting for no greater than 24 hours. In addition to the USA, Dex is approved in more than 27 countries worldwide, including Australia, Brazil, and Israel. It has seen an estimated 85,000 patient uses at the time of this publication.

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① Intubation
② Analgesia
③ Sublingual depression
④ Sympatholytic

Available for intravenous use only, Dex is a colorless, water-soluble agent at physiologic pH. The redistribution half-life ($t_{1/2\alpha}$) of Dex is 6 minutes, and its elimination half-life ($t_{1/2\beta}$) is approximately 2 hours (see Table 1). The pharmacokinetic profile is unchanged in elderly patients. Metabolism is primarily hepatic with approximately 15% overall dependence on the cytochrome P450 system (CYP 2A6). Because of the dependence on the liver to clear the drug, subacute dosage reductions (following loading and stabilization with an efficacious dose) should be considered for patients with hepatic impairment. The metabolites of Dex have not been recognized to date as having any pharmacological activity or toxicity.

MECHANISM OF ACTION: PHYSIOLOGY AND CLINICAL RAMIFICATIONS

Alpha-2 receptors are a subgroup of noradrenergic receptors (receptors utilizing norepinephrine as their agonist) that mediate the function of the sympathetic nervous system. Widely distributed both within and outside the central nervous system (CNS), these receptors modulate the function of a variety of organ systems, including cardiovascular, endocrine, and hematologic. Some alpha-2 effects may actually be antagonistic to each other; an example would be central sympatholysis occurring concurrently with peripheral vasoconstriction. Several subsets of alpha-2 receptors exist in the human, including alpha-2a, alpha-2b, and alpha-2c. Dexmedetomidine is equally active at all three subtypes, but sedative effects of dexmedetomidine occur primarily by actions on alpha 2a receptors, which participate in control of arousal in the brain and analgesia in the spinal cord. Alpha-2b receptors appear post-ganglionically on blood vessels outside the CNS and produce vasoconstriction. Al-

pha-2c receptors are diffusely distributed throughout the brain, particularly in the basal ganglia, but their function is unclear.⁵ As with receptors for opioids, adenosine, histamine, and dopamine, all alpha-2 receptors are G-protein coupled receptors.⁶ Activation of the alpha-2 receptor produces a conformational change in the transmembrane G-protein, which in turn leads to a series of cellular responses that include inhibition of adenylyl cyclase activity and reduction in intracellular concentrations of cAMP.

The apparent purpose of the alpha-2 system is to attenuate inappropriate increases in sympathetic nervous system (SNS) activity. Centrally-induced upsurges in sympathetic tone, such as those produced in the "fight or flight" response, are accomplished through initiation of a neural signal in the hypothalamus, transmission of that signal through the brainstem and the spinal cord to the sympathetic chain, and finally activation of effector organs such as the adrenal medulla. Within the brainstem, norepinephrine (NE) appears to act as the primary neurotransmitter communicating SNS activation. Release of NE into the synaptic cleft and its subsequent binding to post-synaptic alpha-1 receptors leads to propagation of the SNS-activating signal to the periphery.

Binding of alpha-2 agonists to their receptors impedes transmission of these SNS-triggering signals. Alpha-2 receptors in the brain are concentrated primarily in the pons and medulla, areas involved in communicating SNS activation from higher brain centers to the periphery. Activation of alpha-2 receptors reduces conduction down noradrenergic neurons via presynaptic and postsynaptic mechanisms. Presynaptically, alpha-2 receptor activation reduces NE release, and activation of postsynaptic alpha-2 receptors hyperpolarizes neural membranes. Activation of these receptors by NE thus acts as an inhibitory feedback loop, reducing further release of NE. The alpha-2 system thus allows the body to increase sympathetic activity dramatically to manage major threats while at the same time preventing excessive responses that may be physiologically detrimental.

Because Dex is an imidazole derivative, it interacts with imidazoline receptors as well as alpha-2 receptors. Although not as well understood as the alpha-2 system, imidazoline receptors mediate many critical functions including regulation of blood pressure and insulin secretion.⁷ The imida-

*are sympath
↓ NE release
hyperpolarize
neural membrane
(posts)*

Table 1. Dexmedetomidine: Basic Pharmacokinetic Profile

Loading dose	Up to 1 µg/kg over at least 10 min
Maintenance dose	0.2-0.7 µg/kg/hr
1/2 α	6 min
1/2 β	2 h
Volume of distribution	118 liters
Clearance	39 l/h
Protein bound	94%
Excreted unchanged in urine	0% (Virtually all drug is metabolized; 95% of metabolites excreted in urine.)

zoline system probably has little impact on Dex's ability to sedate or augment general anesthesia, but effects of Dex on imidazoline receptors may play a role in its sympatholytic effect.⁸

CLINICAL USE: SEDATION AND ANALGESIA

Dex has been demonstrated to be an effective sedative in critical care settings. Early studies comparing premedication between Dex and midazolam noted no difference in the quality of anxiolysis.^{4,9,10,11} There is a dose-response relationship that correlates increasing Dex plasma levels with the greater degrees of sedation. Dex has been documented as being used clinically in doses up to 2.5 $\mu\text{g}/\text{kg}/\text{hr}$; since the package insert indicates an upper limit of infusion of 7 $\mu\text{g}/\text{kg}/\text{hr}$, the aforementioned data suggest that Dex can be readily titrated in its clinically relevant range.¹²

Although the mechanism by which dexmedetomidine attenuates arousal to produce sedation is not precisely known, one recognized site of action is the locus coeruleus (LC), a dorsolateral pontine nucleus of approximately 30,000 neurons. So named (translated from Latin, the locus coeruleus is the "blue spot") because of a high concentration of the blue-staining neuromelanin, the LC is the origin of practically all noradrenergic neurons within the CNS.^{13,14} As a result, the LC plays a critical role in communicating sympathetic nervous system activity from the CNS to the periphery. Additional roles for this tiny nucleus include modulation of anxiety and attentiveness levels, control of arousal and sleep, and mediation of sedative drug withdrawal and rebound syndromes.¹⁵ More recent research has also suggested an association between LC dysfunction and altered emotional states such as depression.¹⁶

Although several neurotransmitters are involved in LC-mediated activity, transduction of SNS activity from higher brain centers to the brainstem via the LC occurs primarily by activity of NE at post-ganglionic noradrenergic receptors.¹⁷ Through its action on pre and post-synaptic alpha-2 receptors, Dex reduces transmission across the synapse. Since noradrenergic output from the LC plays a vital role in arousal, reduced NE output resulting from Dex infusion results in anxiolysis and sedation.

This ability of Dex to modulate LC activity is more than a neuroanatomic curiosity: it may explain how it can produce sedation without obscur-

ing cognitive function. Although the precise brain location where propofol and midazolam act is unknown, both are presumed to sedate by interacting with GABA receptors in the brainstem and cortex. Clinically, propofol and midazolam incrementally attenuate cerebral cortical function with increasing dose, producing not only a sedative effect but also an inability to interact meaningfully. By acting specifically on brain centers controlling attentiveness and anxiety, Dex may separate sedation from cognitive compromise.

Cognitive aspects of sedation with Dex have been evaluated experimentally using the Critical Flicker Fusion (CFF) Test. Designed to assess the functional capacity of British pilots in World War II, this test measures the subject's ability to differentiate flashing lights from a continuous beam, and has been found to assess cognitive function accurately and reproducibly.¹⁸ In one study, healthy volunteers sedated with low concentrations of Dex performed as well as subjects receiving no infusion at all.¹⁹ In a separate study comparing Dex to equi-sedative doses of midazolam, performance was markedly better among the Dex subjects.²⁰

In clinical use, patients sedated with Dex usually become alert without a "startle" reflex, and are frequently capable of cooperating with diagnostic or therapeutic procedures while sedated.²¹ This ability to preserve cognitive function while sedated has clear utility where optimal patient management includes serial examinations of patient cognition, such as in CNS trauma. In addition, the increased responsiveness of patients sedated with Dex may enhance communication between patient and family, leading to improved orientation and affect. Finally, because patients on Dex are generally arousable and often conversant, pain management may frequently be guided by the patient rather than by vital signs or other, less reliable measures of pain intensity.

Dex lacks two key characteristics of traditional ICU sedatives. First, although Dex has significant anesthetic-sparing properties and can reduce the need for potent inhaled agents by 17-90%, it cannot act alone as a general anesthetic.²²⁻²⁴ Second, Dex is not a powerful amnestic. Healthy subjects receiving Dex experienced only a modest, dose-dependent impairment of short-term memory.²⁵ Moreover, patients receiving Dex may be amnestic when left undisturbed, but not when stimulated. In one clinical study, mechanically ventilated patients

Preserved
Cognitive
Function

enhance
communication

Pain
management

L'MAC
NOT Amnestic

sedated with Dex were able to accurately identify the duration of their ICU admission when questioned after ICU discharge, unlike a similar cohort of subjects receiving propofol.²¹ Although clearly a disadvantage in the operating room, observations that the incidence of ICU-induced post-traumatic stress syndrome decreases with improved recall suggest that the ability of Dex to preserve memory during sedation may reduce the incidence of post-ICU psychological disorders.²⁵⁻²⁸

In addition to sedative effects, Dex has significant analgesic qualities and has been labeled as "analgesia-sparing" by the FDA. Analgesia with Dex is mediated primarily through interaction at alpha-2a within the spinal cord, where drug activity attenuates nociceptive signal transduction. The actual mechanism of action appears to involve an interaction with opioid receptors, and although Dex alone has been documented to reduce pain, the effect when given jointly with opioids may be additive or synergistic.^{29,30} Evidence is also present for an analgesic site of action for Dex in the LC, which in some animals is heavily invested with mu opioid receptors.^{31,32} Dex may also mimic midazolam's ability to prevent ketamine-induced delirium.³³

In healthy volunteer studies, Dex reduced pain by approximately 30% during the cold pressor test, which induces pain through immersion of the volunteer's hand in ice water for one minute.²⁵ When used clinically for ICU sedation in the acute post-operative period, patients receiving dexmedetomidine required 50-66% less narcotic when compared to those receiving midazolam.^{27,34} Furthermore, although designated by the FDA as analgesic-sparing and not a primary analgesic, Dex reduces the total number of post-surgical subjects requiring any opioid at all.³⁵ Little is known regarding the effectiveness of Dex with different origins or types of pain. However, evidence in rats indicates that the analgesic potency of Dex increases following experimentally-induced nerve injury, suggesting potential efficacy in controlling neuropathic pain.^{36,37}

Clinically, Dex's analgesic properties may result in several potential benefits for patients. Use of Dex may permit a reduction in the total amount of narcotic a patient requires, with a commensurate reduction in opioid-associated side effects such as constipation or nausea. Because Dex has virtually no depressant effects on ventilation at clinically relevant doses (discussed below), the analgesic

effects of Dex may offer a significant advantage for patients at risk for respiratory decompensation. Furthermore, Dex is not a controlled substance and has not been reported to have abuse potential. These characteristics may make Dex an important component of the clinical approach to patients at increased risk for opioid dependence. Dexmedetomidine has not been described to cause the hyper-sympathetic withdrawal syndrome characteristic of clonidine, although published data on prolonged use (>24 hours) is minimal.³⁸⁻⁴⁰

Dex's intense specificity for alpha-2 receptors, including those in the spinal cord, suggest that Dex may produce superior analgesia to clonidine when used neuraxially. Pharmacokinetic studies in sheep have demonstrated prompt CSF uptake and onset of spinal effects as well as significant (10-20%) reductions in blood pressure; all are likely due to the high lipophilicity and rapid systemic absorption of Dex.^{41,42} Aside from a few preliminary and non-peer review studies from Japan, human data supporting the safety and efficacy of neuraxially administered Dex is currently lacking.

AUTONOMIC NERVOUS SYSTEM AND HEMODYNAMIC EFFECTS

The sympathetic nervous system (SNS) prepares the body for physiologic stress through a coordinated, multi-system response described by Cannon in 1915 as the "fight or flight" reaction. Components of this response include enhancement of cardiac output, preservation of intravascular volume, preferential perfusion of key organs, and augmented availability of high-energy substrates. Such a state prioritizes survival behavior over long-term well-being, but if prolonged can significantly compromise intermediate- and long-term outcomes by disrupting normal physiology, demanding excessive resources, and inducing end-organ dysfunction.⁴³

A critical function of the alpha-2 receptor system is to act as a "check and balance" system to control exaggerated SNS responses, by moderating transduction of SNS-activating signals from the brain to the periphery. Anatomically, Dex acts to modulate sympathetic responses both centrally at the LC and by direct action on the sympathetic ganglia themselves.⁴⁴ The result of both central and peripheral effects is a profound reduction in circulating catecholamines. In clinical studies of patients undergoing cardiopulmonary bypass or

↓ catecholols

vascular surgery, Dex infusions were found to reduce plasma NE concentrations by as much as 90%, with less consistent reductions in epinephrine concentration.^{39,45,46}

Dex's sympatholytic actions result in reductions in blood pressure and heart rate. Reductions in heart rate are thought to be both sympatholytic as well as vagomimetic in origin.⁴⁷ In healthy volunteers, dexmedetomidine also reduced cardiac output by approximately 15-20% at clinically significant dosages.^{11,48} As Dex does not directly depress myocardial contractility, reduced cardiac output is likely the result of overall sympatholysis.⁴⁹ At doses exceeding the recommended range, peripheral vasoconstrictive effects of Dex may exacerbate reductions in cardiac output (discussed below).

These hemodynamic effects should be factored into the risk-benefit ratio during the selection of appropriate patients for Dex administration. Along with decreases in blood pressure and heart rate, Dex reduces catecholamine levels, total body oxygen consumption, myocardial oxygen consumption, pain and shivering, thus potentially improving the balance between myocardial oxygen supply and demand.^{45,50,51} In a dog model of myocardial insufficiency, Dex reduced myocardial oxygen demand by approximately 25%.⁵² Data such as this adds strength to the hypothesis that alpha-2 agonists specifically protect against myocardial ischemia.^{53,54} Additionally, Dex has been demonstrated in an animal model to act as an antiarrhythmic when excessive catecholamines are a contributory factor.⁵⁵

Because of dose-dependent vasoconstrictive effects of alpha-2b receptors on peripheral blood vessels, Dex has competing vasodilatory (central sympatholytic alpha-2a) and vasoconstrictive (peripheral vascular alpha-2b) effects.⁵⁶ As a result, initiating a Dex infusion may result in transient hypertension as a result of initial high peak plasma levels of drug. Following the rapid redistribution of the loading dose (redistribution half-life is 6 minutes), however, the centrally mediated sympatholytic effects of Dex become dominant, and a predictable attenuation of sympathetic tone follows.

In general, vasoconstrictive effects of Dex have not been associated in animals or humans with adverse consequences. While excessive doses of Dex (10-30 mg/kg) in a porcine model produced coronary vasoconstriction, coronary blood flow

was actually increased and there was no evidence of myocardial ischemia.⁵⁷ It may therefore be that extremely high plasma levels of Dex are necessary for significant vasoconstriction to override the vasodilatory effects of central sympatholysis.

RESPIRATORY EFFECTS

Dex's respiratory stability is perhaps the quality that most profoundly differentiates the drug from other sedatives. This quality was best demonstrated in an early study of Dex in healthy volunteers where plasma levels nearly 14 times that currently recommended were achieved; respiratory rates actually increased with increasing Dex plasma concentrations.¹¹ In another study comparing Dex to placebo (with midazolam and morphine rescue) in 33 patients extubated after major surgery, no difference in respiratory rates and arterial oxygen saturations were noted.⁵⁸ In addition, preliminary data demonstrating that the slope of the CO₂ response curve remains unchanged suggests that Dex minimally affects the central regulation of breathing.⁵⁹

Dex's respiratory safety is underscored by the agent's high therapeutic index. In a 1992 study of healthy volunteers, subjects received a bolus of 2 mcg/kg over 2 minutes.⁶⁰ Even though this dosing regimen represented double the presently recommended loading dose administered over one-fifth the usual time, minute ventilation was reduced by only approximately 30%, and although a small number of subjects became obstructed, this was readily relieved by mild airway manipulation.

The benefits of a sedative that minimally affects the control of breathing are clear. The lack of respiratory depression with Dex use provides practitioners with a sedative and anxiolytic tool that can be used before, during, and after completion of the extubation process. In the ICU, such a tool may allow control of sympathetic stimulation associated with awake intubation, airway manipulation, and extubation, as well as the anxiety associated with weaning. Dex may also allow control of agitation immediately after extubation, or with the use of mask ventilation where a calm, cooperative patient is essential to successful management. In recognition of this property, Dex is the only ICU sedative approved by the FDA for continuous infusion in patients following their extubation.

↳ BPO
↳ HRP
↳ cholinergic
↳ A. curare
↳ Total block
↳ Myocardial

NERVOUS SYSTEM EFFECTS

Cerebral Blood Flow

Little data are currently available regarding effects of Dex on cerebral blood flow in humans. In healthy volunteers, Dex reduces cerebral blood flow, probably via direct cerebral vasoconstriction.^{61,62} In addition, a comparison of Dex and placebo in dogs anesthetized with either sevoflurane or isoflurane noted less cerebral vasodilatation in the Dex group.⁶³ In dogs, Dex may uncouple cerebral blood flow from cerebral oxygen consumption, but there is no human data suggesting that this effect is clinically significant.^{64,65} Additionally, animal evidence suggests that Dex does not prevent hypoxic cerebral vasodilatation.⁶⁶

Data on the impact of Dex on cerebral autoregulation are inconclusive.⁶⁷ Animal studies demonstrate retention of the cerebrovascular response to CO₂, but that sufficient doses of Dex may override that response. Preliminary human data, however, suggest preservation of CO₂ reactivity in human volunteers subjected to hypercapnia.⁶⁸

Intracranial Pressure

An important concern is the effect of Dex on subjects with increased intracranial pressure (ICP), such as those suffering from CNS trauma. In the only study examining this issue, low doses of Dex reduced ICP in normal rabbits.⁶⁹ When the same study was performed in rabbits with cryogenically-induced space occupying lesions, Dex infusions led to no alterations in ICP. In humans, one investigation in patients receiving Dex after transphenoidal hypophysectomy showed no change in CSF pressure.⁷⁰

Epileptogenicity

Results from animal evaluations of convulsant potential are limited, but the lack of reports of seizures both from experimental data and post-marketing information suggest that reduction of the seizure threshold is not a problem for this agent.⁷¹⁻⁷⁴

Neuroprotection

Animal data are contradictory regarding a potential cerebroprotective effect of Dex. In one rat model of focal ischemia, Dex infusions both pre- and post-insult reduced cerebral infarct size by 40-50%.⁷⁵⁻⁷⁷ In another, similar study, however,

Dex had no effect.⁷⁸ Although the mechanism accounting for these findings is unclear, reduced CNS levels of NE with Dex may play a role, since high NE levels have been implicated in some types of neuronal injury.^{79,80} In addition, reduction in cerebral glutamate levels, a property attributed to Dex, may also play a role.⁸¹⁻⁸³

Overall, Dex's cerebrovascular profile makes it potentially useful as an anesthetic adjunct during neurosurgery, especially if control of the SNS is crucial. In particular, the ability of Dex to control the hemodynamic response to stress while maintaining or lowering ICP may be useful in cases where elevated ICP is a primary concern. The interactive nature of sedation with Dex, along with its analgesia-sparing qualities and lack of respiratory depression, may further allow for credible, serial neurological examinations in the recovery period. In any circumstance, however, attention to hypotensive effects of Dex should be considered.

COAGULATION EFFECTS

The impact of Dex on coagulation is not completely understood, but the effect is probably not significant. Alpha-2c receptors are found on platelet surfaces, and reduced adenylyl cyclase levels resulting from activation of these receptors with Dex may promote platelet aggregation.⁸⁴ Dex may thus theoretically induce a hypercoagulable state. One in vitro study, however, revealed that at clinically relevant concentrations Dex did not alter platelet aggregation.⁸⁵ In Phase III studies (reported in the package insert), in which approximately half of all subjects underwent cardiac surgery, the incidence of bleeding was similar between Dex and placebo groups (3% vs. 4%, respectively).

RENAL AND ADRENOCORTICAL EFFECTS

Dex has diuretic, natriuretic, and kaliuretic properties, probably via a variety of mechanisms including inhibition of renin release, inhibition of antidiuretic hormone secretion and action, and an increase in atrial natriuretic peptide secretion.⁸⁶⁻⁸⁹ Dex's effect on the kidney may also be partially exerted through its actions on sympathetic fibers in renal nerves.⁹⁰ The extent of the diuretic effect has not been quantified in humans, and no data on its clinical impact exist. As hypovolemia is an important risk factor in the development of hypotension in patients receiving Dex, however, practitioners should be careful to monitor patients' urine output

↓ renin
↓ ADH secret
↑ ANP
= Diuresis
↑ Nat out
↑ K⁺ out

and maintain a euvoletic state when Dex is used. When used for 24-hour periods, no effect of Dex is seen on adrenocortical function.^{12,91}

SAFETY AND ADVERSE EVENTS

The most commonly reported adverse events for this agent are extensions of its sympatholytic mechanism of action: hypotension and bradycardia. In Phase III trials, these events occurred at approximately twice the incidence in the Dex group (28% and 7%, respectively) as in a group receiving midazolam or propofol (13% and 3%, respectively). Dex may thus be a poor choice for patients suffering from volume depletion or circulatory shock. Dex has also been reported to enhance conduction blocks at doses much higher than the clinically relevant range. However, the actual incidence of the conduction block potentiation when using the recommended Dex dose is unknown. It is also unknown whether patients with autonomic neuropathies (i.e., patients with diabetes) may be at greater risk of Dex-induced conduction block. In volunteers, bradycardic effects of Dex were not enhanced by concomitant administration of beta-blocking agents such as esmolol.⁹²

Hypertension may occur during the loading infusion, since high plasma levels of drug will cause vasoconstriction through peripheral alpha-2b receptors, overcoming the central sympatholytic effect. This effect is generally mild and transient.

Other reported adverse events include dry mouth, nausea, vomiting, fever, hypoxia, and tachycardia, as described in the Precedex[®] (Dex HCl) package insert. However, the incidence of these events was generally similar or greater in control groups receiving placebo.

SUMMARY

Dex is a sedative agent that acts via a unique alpha-2 agonist mechanism. It produces sedation while frequently preserving the ability of the patient to interact with other individuals such as caregivers or family. Other properties of Dex including respiratory stability, sympatholysis, and analgesia make it an important new drug for patients requiring sedation in the critical care setting. Although only minimally explored at this time, additional areas of potential use may include amelioration of opioid, alcohol, and sedative withdrawal syndromes, use for sedation in settings out-

side the critical care unit, and use in pediatric intensive care.⁹³⁻⁹⁶

The primary known risks of Dex are extensions of its alpha-2 agonist mechanism: hypotension and bradycardia. Both are readily manageable with fluid administration and atropine. At higher plasma concentrations that may occur during loading of the drug, hypertension may be briefly seen. Sympatholytic effects of Dex may be particularly useful for hypertensive or tachycardic patients who require sedation. In hemodynamically marginal or unstable patients, however, the potential for significant hypotension should be considered. A careful consideration of volume status and potential conduction abnormalities is necessary before starting the drug in any patient.

Sedation in the ICU is often administered for days to weeks. Presently, the safety of Dex has only been documented for infusions up to 24 hours due to a lack of controlled studies extending beyond this time frame. As a result, the agent is approved only for <24 hour use. No adverse effects from long-term infusions, however, have been observed in small studies.^{38,39} Unanswered questions include the potential for tolerance and withdrawal, accumulation of parent drug and/or metabolites, and potential changes in the pharmacokinetic profile of long term infusions of Dex. Although Dex already represents a significant addition to the arsenal of ICU sedatives, further work is necessary to identify patient groups most likely to benefit.

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