

Dexmedetomidine in Trauma Anesthesiology and Critical Care

Joseph D. Tobias, MD

Vice-Chairman, Department of Anesthesiology

Chief, Division of Pediatric Anesthesiology

Russell & Mary Shelden Chair in Pediatric Intensive Care Medicine

Professor of Anesthesiology and Pediatrics

University of Missouri

Department of Anesthesiology, 3W40H

One Hospital Drive

Columbia, MO 65212

Tobiasj@health.missouri.edu

Learning Objectives: The participant will be familiar with the cellular mechanism of action of dexmedetomidine, its physiologic effects, and its potential applications in the field of trauma anesthesiology and critical care medicine.

Abstract

Dexmedetomidine (Precedex) is an α_2 -adrenergic agonist that is currently approved by the Food and Drug Administration for the short-term (<24 hours) sedation of adult patients in the intensive care unit. Its clinical effects include sedation, anxiolysis, analgesia, a decrease of the minimum alveolar concentration of inhalational anesthetic agents, blunting of the sympathetic nervous response to surgery, and lowering of heart rate and blood pressure. These beneficial physiologic effects, combined with its relatively low incidence of adverse hemodynamic and respiratory effects, have led to its use in various intraoperative and postoperative clinical scenarios, including sedation during mechanical ventilation, prevention of emergence agitation following general anesthesia, provision of procedural sedation, and prevention of the withdrawal following the prolonged use of opioids and benzodiazepines. This article reviews the basic pharmacology of dexmedetomidine, its end-organ effects including its adverse effect profile, and reports of its use in various clinical scenarios. Its potential applications in the practice of trauma anesthesiology and critical care are explored.

Dexmedetomidine (Precedex), the pharmacologically active dextroisomer of medetomidine, is an α_2 -adrenergic agonist with physiologic effects similar to those of clonidine. The α_2 -adrenergic agonists are subclassified into three groups: imidazolines, phenylethylamines, and oxalozepines. Both dexmedetomidine and clonidine are members of the imidazole compounds, which exhibit a high ratio of specificity for the α_2 versus the α_1 receptor. Clonidine exhibits an α_2 : α_1 specificity ratio of 200:1, and that of dexmedetomidine is 1600:1.¹ As such, dexmedetomidine is considered a complete agonist at the α_2 -adrenergic receptor. Another difference between the two agents is that dexmedetomidine has a short half-life (2-3 hours vs. 12-24 hours with clonidine) and is commercially available for intravenous administration as opposed to the epidural formulation for clonidine.

The author has financial interest in one of the products named in this article.

The physiologic actions of dexmedetomidine are mediated via stimulation of postsynaptic α_2 -adrenergic receptors that activate a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein),² resulting in inhibitory feedback and decreased activity of adenylyl cyclase.³ This results in a reduction of intracellular cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase activity, resulting in a dephosphorylation of ion channels.⁴ This process subsequently modifies ion translocation and membrane conductance, resulting in decreased neuronal activation and the clinical effects of sedation and anxiolysis.⁵ The centrally acting α_2 -adrenergic agonists including dexmedetomidine also activate receptors in the medullary vasomotor center, reducing norepinephrine turnover and decreasing central sympathetic outflow, resulting in decreased heart rate and blood pressure. Additional effects result from the central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus ceruleus in the brainstem. The latter effect plays a prominent role in the sedation and anxiolysis produced by these agents as decreased noradrenergic output from the locus ceruleus allows for increased firing of inhibitory neurons including the α -amino butyric acid (GABA) system.⁶⁻⁸

The activation of α_2 -adrenergic receptors in the dorsal horn of the spinal cord inhibits the release of substance P, resulting in primary analgesic effects as well as potentiation of opioid-induced analgesia. The latter effect has been shown in clinical trials to result in opioid-sparing and analgesia in acute pain syndromes and during intraoperative anesthetic care (see following discussion). The interactions with α_2 -adrenergic receptors throughout the central nervous system and spinal cord result in physiologic effects in various organs systems including sedation, anxiolysis, analgesia, a decrease of the minimum alveolar concentration of inhalational anesthetic agents, decreased renin and vasopressin levels leading to diuresis, blunting of the sympathetic nervous response to surgery, and lowering of heart rate and blood pressure.^{9,10}

Currently, the only Food and Drug Administration (FDA)-approved indication for dexmedetomidine is the provision of sedation in adult patients in the intensive care unit (ICU) setting for up to 24 hours.¹¹ However, given its favorable physiologic effects as well as its limited adverse effect profile, there is increasing interest in the use of this agent in patients of all ages and various clinical scenarios. This article reviews the basic pharmacology of dexmedetomidine, its end-organ effects and adverse effect profile, and reports from the literature regarding its use in various clinical scenarios.

Pharmacokinetics

Based on data from healthy volunteers, the pharmacokinetic profile of dexmedetomidine includes a rapid distribution phase with a distribution half-life of approximately 6 minutes, an elimination half-life of approximately 2 hours, and a steady-state volume of distribution of approximately 118 liters.¹² Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when delivered via intravenous infusion for up to 24 hours. It is 94% protein-bound to serum albumin and α_1 -glycoprotein. It undergoes extensive hepatic metabolism with very little unchanged drug excreted in the urine and feces.

The pharmacokinetic profile of dexmedetomidine following intravenous administration has been investigated in patient populations with comorbid features including hepatic or renal dysfunction. Cunningham et al¹³ evaluated dexmedetomidine pharmacokinetics following the administration of 0.6 mcg/kg infused during 10 minutes in five individuals with severe hepatic failure and compared the results to five age-matched controls with normal hepatic function. Patients with hepatic dysfunction had a significantly increased volume of distribution at steady state (3.2 vs. 2.2 L/kg, $P <$

0.05), an increased elimination half-life (7.5 vs. 2.6 hours, $P < 0.05$), and a decreased clearance (0.32 vs. 0.64 L/hr/kg; $P < 0.05$) when compared with age-matched controls. De Wolf et al¹⁴ compared the pharmacokinetics of a 0.6 mcg/kg bolus dose of dexmedetomidine in six patients with severe renal disease versus that of six volunteers with normal renal function. The subjects with severe renal disease had a prestudy 24-hour creatinine clearance of 30 mL/min or less, and stable renal disease with no prior dialysis. They noted no statistically significant differences between the renal disease and control groups in the volume of distribution at steady state (1.81 ± 0.55 vs. 1.54 ± 0.08 L/kg) or the elimination clearance (12.5 ± 4.6 vs. 8.9 ± 0.7 mL/min/kg). However, the elimination half-life was decreased in the renal disease group (113.4 ± 11.3 minutes vs. 136.5 ± 13.0 minutes, $P < 0.05$). Despite the shorter elimination half-life, they also noted prolonged sedation in patients with renal failure. Patients with renal failure had a 1-hour postinfusion visual analogue score of sedation (scale of 0 to 100) of 49.2 ± 25.4 versus 26.2 ± 18.3 in patients with normal renal function ($P < 0.05$). The authors postulated that the increased level of sedation was related to decreased protein binding in patients with renal impairment, resulting in an increased free fraction of the drug. Venn et al¹⁵ evaluated the potential impact of critical illness on dexmedetomidine pharmacokinetics in 10 adult patients requiring mechanical ventilation following complex abdominal or pelvic surgical procedures. Dexmedetomidine was administered as a loading dose of 0.4 mcg/kg during 10 minutes followed by an infusion of 0.7 mcg/kg/hr. No difference in half-life, volume of distribution, or clearance was noted when compared with data from healthy volunteers.

End-organ Effects of Dexmedetomidine

Cardiovascular and Hemodynamic Effects

Heart rate, blood pressure, and cardiac output. Hypotension and bradycardia have been reported with dexmedetomidine administration in adults, particularly in patients with preexisting cardiac disease, with the concomitant administration of medications with negative chronotropic effects or with large bolus doses. The hemodynamic effects following the intravenous administration of dexmedetomidine have been studied in healthy adult volunteers.¹⁶ There is a biphasic effect with an immediate increase in systolic blood pressure (BP) and a reflex decrease in heart rate (HR) during initial administration, followed by a stabilization of systolic BP and HR at a value that is below the baseline. The initial increase in BP is mediated by stimulation of peripheral postsynaptic α_{2B} -adrenergic receptors, which results in vasoconstriction, and the subsequent decrease in BP and HR is caused by central presynaptic α_{2A} -adrenergic receptor-stimulated sympatholysis. The central presynaptic α_{2A} -adrenergic receptor is a negative feedback receptor, so its stimulation results in decreased catecholamine release from the nerve terminal.

In healthy volunteers, dexmedetomidine in doses of 0.25, 0.5, 1.0, and 2.0 mcg/kg administered during 2 minutes resulted in a decrease of the mean arterial pressure (MAP) of 14%, 16%, 23%, and 27% from baseline at 60 minutes. With a dose of 1 mcg/kg, cardiac output (measured by thoracic bioimpedance) was $81\% \pm 13\%$ of baseline at 1 minute, $88\% \pm 14\%$ of baseline at 10 minutes, and $91\% \pm 11\%$ of baseline at 60 minutes. With a dose of 2 mcg/kg, cardiac output was $58\% \pm 32\%$ of baseline at 1 minute, $76\% \pm 33\%$ of baseline at 10 minutes, and $85\% \pm 28\%$ of baseline at 60 minutes.

The potential clinical impact of the cardiovascular effects of dexmedetomidine are illustrated by the study of Venn et al¹¹ in an adult ICU population of 98 cardiac and general surgery patients who received dexmedetomidine for sedation during mechanical ventilation. Dexmedetomidine was administered as a bolus dose of 1

mcg/kg during 10 minutes, followed by an infusion of 0.2-0.7 mcg/kg/hr. Hypotension (MAP ≤ 60 mm Hg or a $\geq 30\%$ decrease from baseline) occurred in 18 of 66 patients receiving dexmedetomidine. Eleven of the episodes occurred during the bolus infusion. Six of 66 patients manifested hypertension during the loading dose related to the effects of dexmedetomidine on peripheral α_{2A} -adrenergic receptors on the vasculature. Although no morbidity or mortality was reported related to the hemodynamic effects of dexmedetomidine, these episodes necessitated temporary ($n = 3$) or permanent ($n = 3$) cessation of the infusion and treatment with atropine ($n = 2$) or temporary cardiac pacing ($n = 4$).

In addition to hypotension, bradycardia or sinus arrest has been reported with dexmedetomidine.^{17,18} In a study evaluating the effects of dexmedetomidine on dose requirements of propofol to induce anesthesia, Peden et al¹⁷ reported that two of the first four patients had brief and self-limited sinus arrest after laryngoscopy. These patients received propofol in addition to dexmedetomidine, which was administered as a bolus dose of 1 mcg/kg during 15 minutes followed by an infusion of 0.4 mcg/kg/hr for a total mean dose of 1.47 mcg/kg. The adverse effects resulted in the authors amending their protocol with a decrease of the dexmedetomidine dose to bolus doses of 0.7 mcg/kg during 15 minutes followed by an infusion of 0.27 mcg/kg/hr. No other problems were noted after changing the infusion protocol.

We have previously reported bradycardia in a 5-week-old infant with trisomy²¹ who was receiving dexmedetomidine for sedation during mechanical ventilation.¹⁹ Concomitant medications included digoxin for the treatment of chronic congestive heart failure caused by an unrepaired atrioventricular canal defect. Twelve hours after the initiation of the dexmedetomidine infusion, the infant's HR decreased to 40-50 beats/minute with a stable BP. No therapy other than discontinuation of the dexmedetomidine infusion was required and the HR returned to baseline within 1 hour.

Scheinin et al²⁰ studied 192 patients with American Society of Anesthesiologists (ASA) scores of I and II who were premedicated with either intramuscular dexmedetomidine and intravenous saline, intramuscular dexmedetomidine and intravenous fentanyl, or intramuscular midazolam and intravenous fentanyl. Anesthesia was then maintained with 70% nitrous/30% oxygen, fentanyl, and either enflurane or isoflurane. There was a significant increase in the incidence of transient intraoperative bradycardia and hypotension in the dexmedetomidine groups when compared with the midazolam group. There was one patient who developed severe bradycardia (HR 35 beats/minute), which required therapy. Khan et al,²¹ in their study of nine male volunteers assessing the effects of low (0.3 ng/mL) and high (0.6 ng/mL) dexmedetomidine plasma concentrations on isoflurane requirements, reported five hypotensive events in the low dexmedetomidine group and seven in the high dexmedetomidine group. Five subjects required interventions with crystalloid alone, crystalloid end-tidal isoflurane $\geq 1\%$.

Despite reports of hemodynamic compromise related to the bradycardia induced by dexmedetomidine, a lowering of HR and thereby myocardial oxygen consumption may be viewed as desirable in patients with coronary artery disease. Talke et al²² randomized 24 adult patients undergoing vascular surgery to receive either placebo or dexmedetomidine administered by a computer-controlled program to achieve a target plasma concentration of 0.15 ng/mL (low dose), 0.3 ng/mL (medium dose), or 0.45 ng/mL (high dose). The infusion was started 1 hour prior to anesthetic induction and continued for 48 hours. Intraoperatively, there was an increased need for vasoactive medications (atropine and phenylephrine) in patients receiving dexmedetomidine. Postoperatively, no such differences were noted and there was more tachycardia (minutes/monitored hour) in the placebo group (23 min/hr) than in the low-dose (9 min/hr, $P = 0.006$), medium-dose (0.5 min/hr, $P = 0.004$), and high-dose (2.3

min/hr, $P = 0.004$) dexmedetomidine groups. Anecdotally, the negative chronotropic effect of dexmedetomidine has also been used as a therapeutic maneuver when a patient is tachycardic during off-pump coronary artery bypass grafting and is unresponsive to α_2 -adrenergic blockade.²³

In the majority of patients, the decrease in BP and HR that occur with dexmedetomidine are modest and require no therapy. The current clinical experience and the literature suggest that the potential for negative chronotropic effects may be greater when dexmedetomidine is administered with other medications that have negative chronotropic effects (propofol, succinylcholine, digoxin, pyridostigmine) or during vagotonic procedures such as laryngoscopy.¹⁷⁻¹⁹

In summary, the effects of dexmedetomidine on cardiac output are related to: (1) bradycardia, (2) an increase in systemic vascular resistance from peripheral α_{2B} -induced vasoconstriction, (3) alteration in endogenous catecholamine levels, and (4) decreased peripheral oxygen requirements. Animal studies have not demonstrated direct effects on myocardial performance or intracellular calcium regulation.²⁴ When studied in isolated right ventricular papillary muscles of ferrets, dexmedetomidine has been shown to have no effect on amplitude and time variables of isometric, isotonic, and zero-loaded clamped twitches. Additionally, no effects were noted in the intracellular calcium transients, thereby suggesting that dexmedetomidine has no intrinsic or direct effects on myocardial contractility.

Sympathetic nervous system. The effects of dexmedetomidine on the sympathetic nervous system are illustrated by the study of Talke et al,²⁵ who evaluated the sympatholytic effects of dexmedetomidine in eight female patients following transphenoidal pituitary hypophysectomy for a pituitary microadenoma. Dexmedetomidine was infused postoperatively by a computer-controlled infusion protocol for 60 minutes to achieve a plasma concentration of 600 pg/mL. The plasma norepinephrine concentration decreased from 2.1 ± 0.8 to 0.7 ± 0.3 nmol/L, the plasma epinephrine concentration decreased from 0.7 ± 0.5 to 0.2 ± 0.2 nmol/L, HR decreased from 76 ± 15 to 64 ± 11 beats/minute, and systolic BP decreased from 158 ± 23 to 140 ± 23 mm Hg. The same group of investigators evaluated changes in plasma and urinary catecholamines in 41 adult patients undergoing vascular surgery.²⁶ Dexmedetomidine was started intraoperatively and continued for the initial 48 postoperative hours. Plasma norepinephrine concentrations were 2-3 times greater in the placebo group at the time of tracheal extubation and 60 minutes after arrival in the postanesthesia care unit (PACU) when compared with patients receiving dexmedetomidine. Urinary norepinephrine levels increased significantly from baseline preoperative values in the placebo group, and no change was noted in patients receiving dexmedetomidine.

Cardiovascular function during hypovolemia. Although the sympatholytic effects of dexmedetomidine are generally viewed as beneficial by attenuating the potential deleterious effects of the surgical stress response, the sympathetic response may be protective in certain clinical scenarios including hemorrhage, hypovolemia, and heart failure. In these settings, the normal hemodynamic response mediated by baroreceptors and the sympathetic nervous system includes vasoconstriction to maintain BP at near-normal levels. At a critical level of intravascular blood volume, vasoconstriction fails with a fall in BP and cardiac output. Blake et al²⁷ evaluated the effects of dexmedetomidine on the BP response to incremental decreases in intravascular blood volume in instrumented dogs. Gradual inflation of an inferior vena cava cuff reduced cardiac index by 8% per minute with a progressive increase in HR and peripheral vasoconstriction to maintain MAP. When cardiac index was approximately 40% of baseline, there was a sudden decompensation with failure of vasoconstriction and a fall in MAP. Dexmedetomidine

administration via an intravenous route or directly into the fourth ventricle of the central nervous system resulted in a decrease of both HR and MAP from baseline as well as an earlier decompensation with the simulation of intravascular hypovolemia by inflation of the inferior vena cava cuff. Similar findings were reported in animals (rabbits) that had been treated with doxorubicin to induce a chronic congestive heart failure-like state prior to the induction of intravascular hypovolemia by inflation of an inferior vena cava cuff.²⁸ Of note was the fact that the investigators did not notice a difference in the HR and BP response with the administration of dexmedetomidine to rabbits with doxorubicin-induced congestive heart failure and the control group prior to the inflation of the inferior vena cava cuff.

Additional cardiovascular effects. Despite the potential for adverse hemodynamic effects including bradycardia and hypotension, additional potentially beneficial effects of dexmedetomidine on myocardial performance and function have been reported. Preliminary clinical data suggest that the perioperative administration of dexmedetomidine may decrease the risk of adverse cardiac events including myocardial ischemia.²⁹ Clinical trials with mivazerol, another α_2 -adrenergic agonist, have demonstrated improved outcome with a decreased incidence of emergence-related ST depression and fewer postoperative deaths in a high-risk surgical cohort.³⁰ These clinical trials are supported by animal studies providing some insight into the mechanisms of the protective effect of the α_2 -adrenergic agonists. In an animal model of coronary artery stenosis, Roekaerts et al³¹ investigated the effects of dexmedetomidine on blood flow to ischemic and nonischemic areas of the myocardium. Dexmedetomidine reduced blood flow in the nonischemic myocardium and in the ischemic epicardial layer, but had no effect on blood flow in the ischemic midmyocardial and subendocardial layers, thereby increasing the ischemic-nonischemic blood flow ratio. Additionally, myocardial oxygen demand decreased with dexmedetomidine, thereby further reducing the oxygen deficiency of the ischemic myocardium.

Similar findings were reported by Willigers et al³² in their animal study of the effects of dexmedetomidine during coronary stenosis. Graded coronary occlusion was applied until lactate production was noted from the poststenotic myocardium. In the dexmedetomidine group, the cumulative lactate release during emergence was 46% less and the endocardial/epicardial blood flow ratio increased by 35% compared with the control group. The anti-ischemic effects of dexmedetomidine were also noted prior to emergence as lactate release in none of the eight dogs receiving dexmedetomidine versus four of seven in the control group ($P = 0.03$). The authors postulated that the anti-ischemic effects were related to decreased levels of plasma epinephrine (158 vs. 1909 pg/mL), norepinephrine (126 vs. 577 pg/mL), and decreased HR (123 ± 6 vs. 160 ± 10 beats/minute).

Additional protective effects of dexmedetomidine on myocardial performance include preservation of myocardial function following ischemia and prevention of catecholamine-induced arrhythmogenesis.^{33,34} Hypoxia and subsequent reoxygenation can expose the myocardium to oxidative stress, which can result in a cascade of events leading to tissue injury, tissue death, and myocardial dysfunction. In a rat model of hypoxic injury to the myocardium (exposure to 60 minutes of hypoxia), dexmedetomidine administered prior to, but not after, hypoxia significantly improved the development of left ventricular pressure after reoxygenation.³³ This effect was blocked by the administration of yohimbine, an α_2 -adrenergic antagonist. In a separate study, dexmedetomidine increased the dysrhythmogenic dose of epinephrine in halothane-anesthetized dogs (mean dose of 3 mcg/kg/min in control animals vs. 6 mcg/kg/min in animals receiving dexmedetomidine).³⁴

One area of significant controversy, and one that may have significant clinical impact, is the effect on pulmonary vascular resistance (PVR). Despite the relative wealth of information regarding the systemic hemodynamic effects of dexmedetomidine, there is a relative paucity of information regarding its pulmonary vascular effects. In six healthy, instrumented sheep, dexmedetomidine (2 mcg/kg during 1 minute) has been shown to transiently increase mean pulmonary artery pressure (MPAP) and PVR.³⁵ PVR increased from a baseline value of 81 ± 16 to a maximum of 141 ± 27 dynes/s/cm⁵ and MPAP increased from 15 ± 1 to 18 ± 0 mm Hg. A corresponding increase in MAP (86 ± 2 to 93 ± 6 mm Hg) and systemic vascular resistance (1416 ± 83 to 1889 ± 64 dynes/s/cm⁵) occurred. No significant change in pulmonary capillary wedge pressure was noted. Similar transient pulmonary hemodynamic changes have been reported in healthy human volunteers with graded dexmedetomidine infusions to achieve a plasma concentration of 1.9 ng/mL.³⁶ Given the obvious potential clinical impact of these effects, especially in patients with baseline elevations in MPAP or PVR, future studies are needed to delineate these effects and define their clinical significance.

Respiratory Effects

Ventilation. A significant concern with any sedative agent is the potential for direct respiratory depression or potentiation of respiratory depression caused by other agents such as opioids. Belleville et al¹⁰ evaluated the ventilatory effects of increasing doses of dexmedetomidine (0.25, 0.5, 1, and 2 mcg/kg during 2 minutes) in 37 healthy adult volunteers. The ventilatory effects were evaluated by measurement of oxygen saturation (SaO₂) using pulse oximetry, PaCO₂, CO₂ response curves during CO₂ rebreathing, and respiratory inductance plethysmography. PaCO₂ increased significantly, with the two highest doses of dexmedetomidine with the maximum effect noted at 10 minutes following the dose. The average PaCO₂ increase from baseline was 5.0 and 4.2 mm Hg with the 1.0 and 2.0 mcg/kg dose, respectively. The effect persisted for 60 minutes following 1 mcg/kg and for 105 minutes following 2 mcg/kg. Resting ventilation was decreased following 1.0 and 2.0 mcg/kg, with the maximal effect noted at 60 minutes following the dose. In patients receiving 2.0 mcg/kg, minute ventilation decreased from 8.7 ± 0.7 to 6.3 ± 1.5 L/min ($P < 0.05$). The decrease was predominantly caused by decreased tidal volume with less of an effect on respiratory rate.

Significant changes were also noted when evaluated using CO₂ response curves as the minute ventilation at an ETco₂ of 55 mm Hg was depressed following the 1.0 and 2.0 mcg/kg doses. Additionally, the authors commented that they noted short episodes of apnea and irregular breathing in some of the subjects. These occurred more commonly with the two highest doses (7 of 10 who received 2 mcg/kg and 5 of 6 who received 1 mcg/kg vs. 1 of 6 with both the 0.5 and 0.25 mcg/kg dose). Respiratory inductance plethysmography tracings of abdominal and thoracic movements indicated that these respiratory problems were obstructive and not central in nature. Although there were decreases in SaO₂ with the obstructive episodes, the mean room air SaO₂ remained above 95% following all of the doses of dexmedetomidine. The SO₂ decrease was greatest at 10 minutes following 1 mcg/kg with a decrease from $98.5\% \pm 0.7\%$ to $96.2\% \pm 1.3\%$, and at 60 minutes following 2.0 mcg/kg with a decrease from $98.3\% \pm 0.8\%$ to $95.4\% \pm 1.2\%$. Similar respiratory effects have been demonstrated in experimental animals, although a paradoxical effect has been noted with less of an effect on ventilation when evaluating 1 versus 10 mcg/kg in one study and 10 or 30 mcg/kg versus 50 mcg/kg in another.³⁷⁻³⁹

Somewhat conflicting results are reported in a study comparing the respiratory effects of dexmedetomidine with remifentanyl in a cohort of six healthy adult volunteers.⁴⁰ Compared with baseline,

remifentanyl infusions to achieve a step-wise plasma concentration of 1, 2, 3, and 4 ng/mL resulted in significant respiratory depression with a decrease in respiratory rate and minute ventilation, increased PaCO₂, blunting of the CO₂ response curve, and apnea resulting in oxygen desaturation. In contrast, during step-wise dexmedetomidine infusions to achieve plasma concentrations of 0.6, 1.2, 1.8, and 2.4 ng/mL, there was an increase in respiratory rate, a decrease in the hypopnea/apnea index when compared with baseline, and no change in the ETco₂. With dexmedetomidine, the authors also noted in some patients a periodic increase in minute ventilation during CO₂ response curves (hypercapnic arousal), which correlated with changes in the Bispectral Index. The authors relate that similar changes occur during natural sleep and that these findings may relate to the mechanism of action of dexmedetomidine in the locus ceruleus and its convergence on the natural sleep pathway. The authors conclude that dexmedetomidine stands apart from other sedatives in that it seemed clinically safe from a respiratory point of view, even in doses high enough to cause unresponsiveness.

Furst and Weinger⁴¹ found similar effects when evaluating the respiratory effects of dexmedetomidine (10 and 30 mcg/kg) and alfentanil in rats. When compared with saline control, dexmedetomidine in either dose had no effect on PaO₂, PaCO₂, and pH, whereas the administration of alfentanil resulted in a decrease in pH and PaO₂ and an increase in PaCO₂. The administration of dexmedetomidine had no additional effect in rats that had received alfentanil and, in fact, the higher dose of dexmedetomidine (30 mcg/kg) decreased the acidosis and hypercapnia, which occurred following alfentanil, and did not appear to potentiate opioid-induced respiratory depression. Despite these findings, ongoing monitoring of respiratory function appears warranted, especially in high-risk patients or those receiving other agents that may depress respiratory function, especially given the report, albeit anecdotal, of central apnea after a general anesthetic that included dexmedetomidine.⁴²

Airway reactivity. Dexmedetomidine may provide some protection in patients at risk for airway reactivity and bronchoconstriction. In a study in mongrel dogs, the intravenous, but not the inhaled, administration of dexmedetomidine prevented histamine-induced bronchoconstriction.⁴³ The effect of aerosolized histamine on airway bronchoconstriction was evaluated using high-resolution computed tomography. Aerosolized histamine constricted the airways to $66\% \pm 27\%$ of baseline compared with $87\% \pm 30.4\%$ of baseline, when the animals were pretreated with intravenous dexmedetomidine.

Central Nervous System Effects

Sedation. Clinical studies in humans and experimental trials in both humans and animals have demonstrated the sedative effects of dexmedetomidine.^{9,10,36,44,45} In 10 healthy male volunteers, sequential 40-minute infusions of dexmedetomidine were administered to achieve plasma concentrations of 0.5, 0.8, 1.2, 2.0, 3.2, 5.0, and 8.0 ng/mL.³⁶ The visual analogue sedation score (0 = very alert and 100 = very sedated) increased by 36 ± 27 and 62 ± 18 from a baseline of 0 with the first two targeted infusions. The two volunteers who received the highest incremental dose could not be aroused, even with vigorous shaking. Picture recall and recognition were preserved during the first incremental infusion, but were 0% (0 of 10) and 20% (2 of 10), respectively, with the third incremental infusion level.

Qualitatively, dexmedetomidine induces a sedative response that exhibits properties similar to natural sleep.^{44,45} Studies using functional magnetic resonance imaging indicate that the blood oxygen level-dependent signal, which correlates with local brain activity, changes with dexmedetomidine-induced sedation in a similar fashion to that seen during natural sleep compared with the markedly different pattern that occurs with midazolam.⁴⁵ Nelson et

al⁴⁵ assessed c-fos expression in sleep-promoting brain nuclei in rats using immunohistochemistry and in situ hybridization.

Dexmedetomidine induced a qualitatively similar pattern of c-fos expression in rats as that seen during nonrapid eye movement sleep (a decrease in the locus ceruleus and tuberomammillary nucleus and an increase in the ventrolateral nucleus). These effects were attenuated by atipamezole and did not occur in rats that lack α_2 -adrenergic receptors.

Intracranial pressure and cerebral perfusion pressure. Major concerns of any sedative agent in the trauma patient are potential effects on intracranial pressure (ICP) and cerebral perfusion pressure (CPP). Several studies have attempted to evaluate the effects of dexmedetomidine on ICP, CPP, as well as cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen (CMRO₂). Talke et al⁴⁶ evaluated the effects of dexmedetomidine on ICP and CPP in 16 adults (7 dexmedetomidine and 9 placebo patients) following transphenoidal resection of a pituitary tumor. Postoperatively, dexmedetomidine was administered by a computer-controlled infusion to achieve a plasma concentration of 600 pg/mL. ICP was measured from a lumbar intrathecal catheter. No change in ICP was noted in patients receiving dexmedetomidine. The highest ICP values in the dexmedetomidine patients were 19 and 20 mm Hg. Although no change in CPP occurred over time in the placebo patients, there was a decrease in CPP in patients receiving dexmedetomidine (95 ± 8 to 78 ± 6 mm Hg, $P < 0.05$).

Similar effects on ICP were noted in an animal study with escalating doses of dexmedetomidine (20, 80, and 320 mcg/kg).⁴⁷ There were no effects on ICP in animals in the baseline state and also in animals with intracranial hypertension (mean baseline ICP, 16.8 mm Hg) induced by a cryogenic lesion. Dexmedetomidine has also been shown to lower intraocular pressure in animals with both normal and elevated intraocular pressure.⁴⁸

Both animal and human studies have demonstrated a reduction in cerebral blood flow (CBF) following the administration of dexmedetomidine.^{49,50} Karlsson et al⁴⁹ demonstrated a reduction of CBF following the administration to dogs anesthetized with 0.9% halothane; however, the authors noted that because of their study design, they could not determine if dexmedetomidine has a direct cerebral-vasoconstricting effect or if it merely cancelled the cerebral vasodilatation induced by halothane. Prielipp et al⁵⁰ used positron emission tomography scans to evaluate changes in CBF with dexmedetomidine in nine healthy adult volunteers.

Dexmedetomidine was administered as a bolus dose of 1 mcg/kg followed by an infusion of either 0.2 (low dose) or 0.6 mcg/kg/hr. Global CBF (mL/100 g/min) decreased from a mean baseline value of 91 to 64 (low dose) and 61 (high dose).

Seizure threshold. Another issue of importance in the patient with traumatic brain injury may be the relative anticonvulsant or proconvulsant effect of agents used for sedation or analgesia. To date, the literature regarding these effects of dexmedetomidine are mixed, with four different reports examining the relative proconvulsant and anticonvulsant effects of dexmedetomidine when coadministered with other medications.⁵¹⁻⁵⁴ Mirski et al⁵¹ demonstrated a proconvulsant effect of dexmedetomidine (doses of 100 and 500 mcg/kg, but not 20 mcg/kg) in rats treated with pentylenetetrazol and showed that the effect was blocked by the α_2 -adrenergic antagonist, atipamezole. They suggested that their data were consistent with previous data demonstrating that inhibition of central noradrenergic transmission facilitates seizure expression. Similar results were reported by Miyazaki et al,⁵² who demonstrated that dexmedetomidine (doses of 10 and 100 mcg/kg, but not 1 mcg/kg) reduced the seizure threshold during enflurane anesthesia in cats. Anticonvulsant properties of dexmedetomidine were demonstrated by two other groups of investigators. Whittington et al⁵³ demonstrated that dexmedetomidine (20 mcg/kg followed by an

infusion of 1 mcg/kg/min) significantly increased the dose of cocaine required to cause seizures in Sprague-Dawley rats. Cocaine was infused at 1.25 mg/kg/min and the investigators noted that rats treated with dexmedetomidine manifested seizures at 49.3 ± 14.8 minutes versus 25.0 ± 7.7 minutes in the control animals. Likewise, an anticonvulsant effect of dexmedetomidine was demonstrated by Tanaka et al⁵⁴ in Sprague-Dawley rats in their model of local anesthetic toxicity. The dose of either levobupivacaine or bupivacaine required to cause seizures was greater in rats treated with dexmedetomidine than in control animals. Although this may initially seem to be a beneficial effect, one must wonder as to whether this would eliminate an early warning sign of local anesthetic toxicity, with the first manifestation being the difficult-to-treat cardiotoxicity rather than the generally more treatable central nervous system (CNS) toxicity.

Neuroprotection. One of the more intriguing aspects of dexmedetomidine is its potential to ameliorate CNS sequelae during ischemic injury. Its efficacy in this regard was originally thought to relate to the deleterious CNS effects of endogenous catecholamines, which are released during ischemic injury to the CNS, and the ability of dexmedetomidine to blunt this catecholamine surge. Various animal models with complete and incomplete as well as transient and permanent ischemic injury have attempted to define the protective effects of dexmedetomidine during such injury. Hoffman et al⁵⁵ evaluated the effect of dexmedetomidine on neurologic and histopathologic outcome from incomplete cerebral ischemia in rats anesthetized with 70% nitrous oxide and fentanyl. Dexmedetomidine was administered in a dose of either 10 or 100 mcg/kg intraperitoneally 30 minutes prior to ischemia, which was produced by 30 minutes of unilateral carotid occlusion combined with hypotension induced by phlebotomy. After 30 minutes, the carotid occlusion was removed and the withdrawn blood was reinfused. Dexmedetomidine blunted the endogenous release of epinephrine and norepinephrine as well as improved both histopathologic and the neurologic outcome scores when compared with control animals and those animals that received dexmedetomidine plus atipamezole. Also of note, serum glucose concentrations were significantly higher in animals receiving dexmedetomidine. The authors relate this to α_2 -adrenergic inhibition of insulin release.

Kuhomen et al⁵⁶ evaluated the potential neuroprotective effects of dexmedetomidine in gerbils exposed to 5 minutes of bilateral carotid occlusion. Dexmedetomidine (3 or 30 mcg/kg) was administered prior to and then for 48 hours after the injury or only following the injury. Histopathologic outcome of neuronal cells in the CA1 and CA3 regions of the hippocampus and the dentate gyrus was examined at 1 week postinjury. None of the treatments had any effect on the histopathologic outcome in the CA1 region, while there was a significant decrease in the number of ischemic cells in the CA3 region in rats that received 3 mcg/kg of dexmedetomidine prior to the injury, but not in rats receiving 30 mcg/kg of dexmedetomidine prior to the injury, or in either dose if administered after the injury. In the dentate hilus, decreased numbers of ischemic cells were noted in rats that received 3 mcg/kg of dexmedetomidine prior to the injury and those that received 30 mcg/kg of dexmedetomidine after the injury. The authors concluded that low-dose dexmedetomidine had neuroprotective effects if administration was started prior to the ischemic insult and continued for 48 hours following it.

Additional information is provided by the same group of investigators in a model comparing transient (90 minutes) and permanent ischemia using occlusion of the middle cerebral artery (MCA) in rats.⁵⁷ Dexmedetomidine was administered after MCA occlusion as a bolus of 3 mcg/kg followed for 120 minutes by an infusion of either 3 or 6 mcg/kg/hr. The authors noted a statistically significant increase in the infarct size when comparing transient versus permanent ischemia. No effect of dexmedetomidine was

noted in the animals subjected to a permanent ischemic injury and the authors suggested that, although it was not statistically significant, there was a trend toward decreased infarct size following transient ischemia in animals treated with the higher dose of dexmedetomidine. The infarct volumes in both the cortex and the brainstem were 20%-30% less in dexmedetomidine-treated animals compared with the control animals.

The neuroprotective effects of dexmedetomidine may also have clinical applications in the neonatal arena. Dexmedetomidine decreased infarct size and histopathologic evidence of neuronal death in term, 5-day old mice that received an intracerebral injection of the *N*-methyl-D-aspartate (NMDA) agonist, ibotenate.⁵⁸ An NMDA agonist was chosen because of the evidence implicating the excessive release of glutamate as a causative factor in the development of hypoxic-ischemic encephalopathy and periventricular white matter lesions in premature infants.

The mechanism of action for the neuroprotective effect of dexmedetomidine was presumed to relate to its control of endogenous catecholamine release during ischemia. However, recent evidence has questioned this theory. Although dexmedetomidine has been shown to suppress circulating catecholamine concentrations during cerebral ischemia in rats, it does not suppress brain norepinephrine and glutamate levels, thereby suggesting another mechanism for its neuroprotective effects.⁵⁹ Currently, it has been postulated that the effect is mediated by increased expression of active (autophosphorylated) focal adhesion kinase (FAK), a nonreceptor tyrosine kinase that plays a role in cellular plasticity and survival as well as a reduction in caspase-3 expression (a proapoptotic factor).⁶⁰

Miscellaneous. Additional effects related to the central and peripheral nervous system include antishivering and prevention of opioid-induced muscle rigidity, the latter being demonstrated in an animal model using hindlimb electromyographic activity in which dexmedetomidine abolished increased electromyographic activity associated with alfentanil administration.⁴¹ Another unique property of the α_2 -adrenergic agonists is their ability to prevent or treat shivering in various clinical scenarios.^{61,62} Jalonen et al⁶¹ randomized 80 patients scheduled for coronary artery bypass grafting to receive either saline placebo or dexmedetomidine starting after the induction of anesthesia. Dexmedetomidine decreased the incidence of fentanyl-induced muscle rigidity (15/40 vs. 33/40 patients) and postoperative shivering (13/40 vs. 23/40 patients).

When compared with meperidine in healthy adult volunteers, the shivering threshold was $36.0^\circ\text{C} \pm 0.5^\circ\text{C}$ with dexmedetomidine ($P < 0.001$ compared with control), $35.5^\circ\text{C} \pm 0.6^\circ\text{C}$ with meperidine ($P < 0.001$ compared with control), $34.7^\circ\text{C} \pm 0.6^\circ\text{C}$ with dexmedetomidine and meperidine ($P < 0.001$ compared with control), and $36.7^\circ\text{C} \pm 0.3^\circ\text{C}$ in control patients.⁶² These effects may make dexmedetomidine a useful agent for sedation as well as the prevention of shivering in patients with closed-head injury or those who are postasphyxial arrest in whom hypothermia is used as a therapeutic agent.

Miscellaneous Effects

Gastrointestinal motility. Alterations in gastrointestinal (GI) motility and delays in gastric emptying are of particular concern in the perioperative period and in critically ill ICU patients, in whom it may interfere with enteral feeding, lead to bacterial overgrowth, and promote bacterial translocation. Given these concerns, the effects of sedative and analgesic agents on GI motility must be entertained when decisions are made regarding the optimal sedation regimen. In a whole-animal model (rat), Asai et al⁶³ compared the effects of clonidine, dexmedetomidine, and morphine on GI transit time and

gastric emptying using radio-labelled sodium chromate. All three agents strongly inhibited GI transit time in a dose-dependent manner. Clonidine and dexmedetomidine weakly inhibited gastric emptying time and morphine's effect was greater. Gastric emptying, defined as the percentage of radioactivity that had entered the small intestine at 30 minutes, was 88.2% in the control group, 70.9% with clonidine, 78% with dexmedetomidine, and 23% with morphine. Herbert et al⁶⁴ compared the effects of clonidine and dexmedetomidine in an in vitro segment of guinea pig ileum. In isolated segments of the ileum, the pressure required to induce peristalsis was measured. Inhibition of GI motility as manifested by the requirement for an increased pressure to stimulate peristalsis was noted for both clonidine and dexmedetomidine, but was markedly greater with dexmedetomidine.

Adrenocortical function. Imidazole compounds such as etomidate have been shown to inhibit adrenocortical function and are no longer recommended for prolonged infusions in the ICU setting. Like etomidate, dexmedetomidine is an imidazole compound and therefore, appropriately so, there may be concerns regarding its effect on steroidogenesis. This issue has been addressed in a combined in vitro and animal study as well as a clinical trial. In a series of in vitro and animal studies, Maze et al⁶⁵ investigated the effects of dexmedetomidine on steroidogenesis, on binding to glucocorticoid receptors, and on adrenocorticotrophic hormone (ACTH)-stimulated release of corticosterone. The authors concluded that in concentrations that are used clinically to provide sedation or anesthesia, dexmedetomidine does not cause the clinically significant depression of adrenocortical function that occurs with etomidate, and an important biologic effect on steroidogenesis probably will not occur. However, the studies did demonstrate that high doses of dexmedetomidine are capable of inhibiting steroidogenesis.

In a clinical trial, Venn et al⁶⁶ randomized 20 adult patients who required sedation during mechanical ventilation to receive either propofol or dexmedetomidine. There was no difference in cortisol, ACTH, prolactin, and glucose concentrations between the two groups. However, some of the dexmedetomidine patients had abnormal ACTH stimulation tests, although these were attributed to their acute surgical illness and not the dexmedetomidine. None of the patients were believed to be at risk for adrenocortical failure, or manifested symptoms related to adrenal dysfunction according to the authors. The failure to meet the criteria for an acceptable ACTH stimulation test varied according to the criteria used. If an acceptable response was a peak cortisol level following ACTH administration of ≥ 400 nmol/L, 9 of 10 patients had a normal response. If the peak cortisol level following ACTH administration was ≥ 550 nmol/L, 8 of 10 had a normal response. However, if there was a requirement to increase the serum cortisol by 200 nmol/L, only 5 of 10 met the criteria. Despite these findings, the authors concluded that dexmedetomidine does not inhibit adrenal steroidogenesis when used for short-term sedation after surgery, and that the pattern of serum cortisol and ACTH levels was not similar to what was reported with etomidate administration.

White blood cell function and inflammatory response.

Previous studies have suggested that several anesthetic agents may inhibit various aspects of white blood cell (WBC) function, including chemotaxis, phagocytosis, and intracellular killing.⁶⁷ In an in vitro study, dexmedetomidine was found to have no effect on WBC chemotaxis, phagocytosis, or superoxide anion production, leading the authors to conclude that there is no concern regarding the use of this agent in patients with acute infectious processes.⁶⁸ However, the authors also cautioned that their data also suggest that there are no beneficial effects of dexmedetomidine in disease processes that involve auto-tissue injury caused by neutrophils. Despite these findings, there are preliminary data to suggest that dexmedetomidine may act to modify the mediators of the

inflammatory response. In the previously mentioned study of Venn et al,⁶⁶ which randomized patients to receive either propofol or dexmedetomidine for sedation during mechanical ventilation, there was a decrease in interleukin-6 levels from baseline in patients receiving dexmedetomidine with no change in patients receiving propofol. A similar effect has been demonstrated in laboratory animals.⁶⁵ Additional work has demonstrated that the ability of dexmedetomidine to control the systemic inflammatory response may be beneficial during endotoxemia.⁶⁹ Taniguchi et al⁶⁸ randomized rats to (1) endotoxin administration, (2) saline control, (3) dexmedetomidine, or (4) endotoxin + dexmedetomidine. Mortality rates at 8 hours after the administration of endotoxin were 94%, 10%, 0%, and 44%, respectively, in the four groups. Hypotension, increases in tumor necrosis factor and interleukin-6 concentrations, and the infiltration of neutrophils in the airspaces and vessel walls were less in the rats that received dexmedetomidine after endotoxin than in rats that received endotoxin alone.

Neuromuscular blockade. An animal study and a human study have evaluated the effects of dexmedetomidine on neuromuscular blockade.^{69,70} In a rat a model, vecuronium was administered by continuous infusion to produce a depression of T1 of the train-of-four (TOF) to $53\% \pm 2\%$ of baseline.⁶⁹ Dexmedetomidine was administered as a bolus dose (10, 30, or 100 mcg/kg) and the T1 was measured for the ensuing 60 minutes. No change occurred in the T1 height during the 30 minutes following any of the three doses of dexmedetomidine. Although at later times there were minor differences between the groups, the authors concluded that these effects were unlikely to be of clinical significance. Similar findings were reported by Talke et al⁷⁰ in a study involving 10 healthy adult volunteers anesthetized with alfentanil and propofol. Rocuronium was administered by continuous infusion to produce a 50% decrease from baseline of the T1 value. Dexmedetomidine was administered by a computer-controlled infusion to produce a plasma concentration of 0.6 ng/mL for 45 minutes. T1 values decreased from $51\% \pm 2\%$ to $44\% \pm 9\%$ ($P < 0.0001$). There was also a statistically significant increase in plasma rocuronium concentrations during the dexmedetomidine infusion. The authors concluded that dexmedetomidine does not have direct effects at the neuromuscular junction, but rather that it alters rocuronium pharmacokinetics. The authors also emphasized, as in the previous study, that this effect is unlikely to be of clinical significance.

Clinical Applications

Perioperative Applications

Clinical trials have demonstrated several of the potential perioperative effects of dexmedetomidine including a reduction of the requirements for both intravenous and inhalational anesthetic agents, improved hemodynamic stability, decreased requirements for β_2 -adrenergic antagonists in patients with cardiovascular disease, and a decreased emergence delirium following general anesthesia in pediatric patients.^{11,15,17,20,21,22,26,60} Dexmedetomidine has been used as a premedication, as an intraoperative infusion, by intraoperative bolus dosing, and for postoperative sedation in both intubated and nonintubated patients.

Preoperative administration (premedication). Jaakola et al⁷¹ randomized 20 adults undergoing hysterectomy to receive either dexmedetomidine, 2.5 mcg/kg intramuscularly 60 minutes prior to surgery and intravenous saline, or intramuscular midazolam and intravenous fentanyl. Both premedication regimens resulted in sedation and anxiolysis. Intraoperatively, systolic and diastolic BP were 15% and 13% lower in patients who received dexmedetomidine and HR was an average of 9 beats/minute less. Supplemental

fentanyl was required more often in patients premedicated with midazolam-fentanyl versus dexmedetomidine (3.5 vs. 2.5 supplemental doses), with the total amount of fentanyl being 57% less in patients premedicated with dexmedetomidine.

Dexmedetomidine premedication decreases the induction dose requirements for barbiturates and the response to endotracheal intubation.⁷² Twenty-four adults of ASA I or II class were randomized to receive dexmedetomidine 0.6 mcg/kg or placebo 10 minutes prior to anesthetic induction. Dexmedetomidine decreased thiopentone requirements (4.4 ± 0.9 vs. 6.9 ± 1.6 mg/kg, $P < 0.001$), attenuated the cardiovascular responses (HR and BP) to endotracheal intubation, blunted the intraoperative increase in plasma norepinephrine concentrations, decreased intraoperative fentanyl requirements, and decreased postoperative oxycodone needs.

Jaakola et al⁷³ randomized 30 adult patients to placebo or dexmedetomidine (1 mcg/kg) prior to intravenous regional anesthesia for hand surgery. Following dexmedetomidine, there was a 16%-20% decrease from baseline of HR and BP. Dexmedetomidine decreased the need for intraoperative supplemental intravenous fentanyl (12 of 15 in the placebo group vs. 4 of 15 who received dexmedetomidine, $P = 0.009$). Dexmedetomidine also blunted the increase in plasma concentration of norepinephrine and epinephrine that occurred with tourniquet inflation. These data suggest the potential role of dexmedetomidine as a component of sedation during regional anesthesia.

Similar results were demonstrated in a study of 96 women undergoing abdominal hysterectomy.⁷⁴ The patients were randomized to receive saline, dexmedetomidine (0.3 or 0.6 mcg/kg), or fentanyl (2 mcg/kg) as a single bolus dose 10 minutes prior to anesthetic induction. Although HR and BP increased in all groups following endotracheal intubation, the HR and BP response was significantly less with high-dose dexmedetomidine compared with placebo, and the HR response was significantly less with high-dose dexmedetomidine versus fentanyl (HR increase of 18 ± 3 vs. 26 ± 3 beats/minute). Intraoperatively, the isoflurane requirement was decreased with high-dose dexmedetomidine (0.35%) compared with saline (0.47%) and fentanyl (0.48%).

Intraoperative administration (balanced anesthetic technique). Jalonon et al⁶¹ randomized 80 adults scheduled for coronary artery to placebo or dexmedetomidine. Dexmedetomidine was administered at 50 ng/kg/min for 30 minutes prior to anesthetic induction, followed by an intraoperative infusion. In addition to decreasing the incidence of fentanyl-induced muscle rigidity (15/40 vs. 33/40 patients) and postoperative shivering (13/40 vs. 23/40 patients), dexmedetomidine decreased the intraoperative requirements for fentanyl and enflurane.

Several other studies have demonstrated the ability of dexmedetomidine to decrease anesthetic requirements as well as improve intraoperative stability.⁷⁵⁻⁷⁷ In a volunteer study, dexmedetomidine was administered to achieve a plasma concentration of either 0.3 or 0.6 ng/mL.⁷⁵ The end-tidal isoflurane concentration at which 50% of the participants responded to a titanic stimulus was 1.05% during the control state, 0.72% with low-dose dexmedetomidine, and 0.52% with high-dose dexmedetomidine. Additionally, the authors noted that isoflurane did not alter the pharmacokinetics of dexmedetomidine. Additional information regarding the ability of dexmedetomidine to decrease inhalational anesthetic requirements is provided by Aho et al⁷⁶ in their study of 20 women undergoing gynecologic surgery. Maintenance anesthesia consisted of 70% nitrous oxide, fentanyl 2 mcg/kg, and isoflurane titrated according to hemodynamic response. Dexmedetomidine, administered as a bolus (170 ng/kg) prior to anesthetic induction and then continued intraoperatively as an infusion of 10 ng/kg/min, reduced isoflurane requirements by more than 90%. Five of 10 patients in the dexmedetomidine group did not require isoflurane

compared with 2 of 10 in the control group. A postoperative interview conducted on day 1 revealed no evidence of recall.

Dexmedetomidine has also been shown to reduce the requirements of IV anesthetic agents including thiopental and propofol.⁷⁸⁻⁸⁰ Women scheduled for dilation and curettage were randomized to receive a single bolus dose of dexmedetomidine (0.5 mcg/kg) or saline placebo 15 minutes prior to transport to the operating room.⁷⁸ There was a 30% reduction of the thiopental dose required to complete the procedure in patients who received dexmedetomidine (316 ± 79 mg vs. 456 ± 151 mg). A subsequent study evaluated the thiopental dose required to achieve burst suppression on the electroencephalogram in healthy adult volunteers.⁷⁹ As with the previous study, dexmedetomidine-treated patients required 30% less thiopental; however, the authors also evaluated pharmacokinetic parameters and found that dexmedetomidine decreased distribution volumes and distribution clearances of thiopental, thereby demonstrating that the mechanism of dexmedetomidine in reducing thiopental requirements may be at least in part the result of a pharmacokinetic effect.

Dutta et al⁸⁰ studied the interaction of propofol and dexmedetomidine. They noted that dexmedetomidine reduced the propofol plasma concentrations required to prevent a motor response to an electrical stimulus, the ability to hold a syringe, and maintain the eyelid reflex. The plasma concentration of propofol at which 50% of patients did not move to an electrical stimulus was 6.63 mcg/mL in the control patients and 3.89 mcg/mL during the administration of dexmedetomidine.

Intraoperative administration (monitored anesthesia care and primary anesthetic technique). Given its favorable physiologic effects, dexmedetomidine may find a role as part of monitored anesthesia care (MAC) combined with a regional anesthetic technique.^{71,81} Arain and Ebert⁸¹ randomized 40 adults receiving regional anesthetic techniques to MAC with dexmedetomidine (1 mcg/kg followed by an infusion of 0.4-0.7 mcg/kg/hr) or propofol (12.5-75 mcg/kg/hr). The sedative infusion was titrated to achieve a Bispectral Index of 70-80. Although sedation was achieved more rapidly with propofol (10 minutes vs. 25 minutes), after 25 minutes, no differences were noted between the two groups. The average MAP was higher with dexmedetomidine than with propofol (86 ± 3 vs. 75 ± 3 mm Hg). Dexmedetomidine patients had a lower visual analog sedation scale, lower pain scores, and required less morphine in the postanesthesia care unit. No difference was seen in regard to recovery and discharge times. Additional intraoperative applications of dexmedetomidine have included sedation during awake craniotomy in both adults and pediatric patients.^{82,83} One case series describes the use of dexmedetomidine in doses up to 10 mcg/kg/hr as the sole anesthetic in three adult patients with the maintenance of spontaneous ventilation, although one patient did require a chin lift for upper airway obstruction.⁸⁴

Postoperative analgesic effects. The analgesic effects of dexmedetomidine have been demonstrated in both clinical and experimental trials.⁸⁵⁻⁸⁸ Dexmedetomidine (1 mcg/kg) administered 10 minutes prior to anesthetic induction reduced morphine PCA requirements following abdominal surgery in adults by 28% during the first 24 hours postoperatively.⁸⁶ Similar findings were reported by Arain et al,⁸⁷ who randomized 34 adult patients who would require at least a 24-hour postoperative hospital admission to receive either placebo or an intraoperative infusion of dexmedetomidine (1 mcg/kg followed by 0.4 mcg/kg/hr for 4 hours). Patients who received dexmedetomidine required less morphine in the PACU (4.5 ± 6.8 vs. 9.2 ± 5.2 mg). After 60 minutes in the PACU, 6 of 17 patients who received dexmedetomidine required morphine versus 15 of 17 in the control group.

Dexmedetomidine may also be a useful adjunct to epidural analgesia. Following thoracotomy, Wahlander et al⁸⁹ randomized patients to receive either dexmedetomidine (0.5 mcg/kg followed by an infusion of 0.4 mcg/kg/hr) or placebo in addition to thoracic epidural analgesia. Although there was no difference in the pain scores between the two groups, patients receiving dexmedetomidine required less supplemental analgesia with epidural fentanyl and had lower PaCO₂ values (40.3 ± 4.1 vs. 43.9 ± 4.3 mm Hg). Adverse hemodynamic effects that required therapy were noted with dexmedetomidine, including bradycardia in one patient who was treated with atropine, and hypotension in four patients who responded to fluid. No sequelae of these hemodynamic changes were noted.

Prevention of emergence delirium. Three reports outline the successful use of dexmedetomidine to prevent emergence delirium following general anesthesia with sevoflurane or desflurane.⁹⁰⁻⁹² Ibacache et al⁹⁰ randomized 90 children to placebo or one of two doses of dexmedetomidine (0.15 or 0.3 mcg/kg) during general anesthesia with sevoflurane. There was no difference in the time to awakening and tracheal extubation. The incidence of emergence delirium was 37% with placebo, 17% with 0.15 mcg/kg dexmedetomidine, and 10% with 0.3 mcg/kg dexmedetomidine. Similar efficacy with the use of dexmedetomidine to prevent emergence agitation was demonstrated in the studies of both Hanafy et al⁹¹ and Guler et al.⁹² Hanafy et al randomized 46 children (4 to 12 years of age) undergoing adenotonsillectomy to dexmedetomidine (0.5 mcg/kg) or placebo administered during general anesthesia with desflurane. Patients who received dexmedetomidine had less agitation in the PACU (2/23 vs. 18/23, $P < 0.05$), were less likely to require treatment for agitation (0/23 vs. 8/23, $P < 0.05$), and had lower pain scores. No difference in time to emergence, time to tracheal extubation, PACU discharge time, or hemodynamic and respiratory variables were noted.

The third trial of the use of dexmedetomidine to prevent emergence agitation included 60 children (3 to 7 years of age) who were randomized to receive dexmedetomidine (0.5 mcg/kg) or placebo with maintenance anesthesia provided by sevoflurane.⁹² As opposed to the two previous studies, Guler et al⁹² administered dexmedetomidine 5 minutes prior to the completion of the surgery instead of after anesthetic induction. Dexmedetomidine decreased the incidence of emergence agitation (5/17 vs. 17/30, $P < 0.05$). The incidence of severe pain was 7 of 30 (23%) with dexmedetomidine versus 16 of 30 (53%) with placebo ($P < 0.05$). They also noted that the incidence of severe coughing on emergence and in the PACU was decreased with dexmedetomidine (0/30 vs. 6/30, $P < 0.05$). However, there was a modest delay in the time to emergence (5.03 ± 2.3 vs. 3.30 ± 1.3 minutes, $P < 0.05$) and extubation (9.30 ± 2.9 vs. 7.20 ± 2.7 minutes, $P < 0.05$) with dexmedetomidine versus placebo, respectively.

Procedural Sedation

Given its limited effects on hemodynamic and respiratory function, dexmedetomidine may be an effective agent for sedation during nonpainful procedures such as computed tomography and magnetic resonance imaging and radiation therapy. Preliminary data were provided by Nichols et al,⁹³ who used dexmedetomidine for "rescue sedation" during radiologic imaging in five pediatric patients, ranging in age from 11 months to 16 years, when chloral hydrate and midazolam were ineffective. Effective sedation was achieved using dexmedetomidine (loading dose of 0.3-1.2 mcg/kg followed by an infusion of 0.5-0.7 mcg/kg/hr) and allowed for the completion of the examination without adverse effects.

Two prospective trials have evaluated the efficacy of dexmedetomidine for sedation during radiologic imaging in pediatric patients. Koroglu et al⁹⁴ randomized 80 children (1 to 7 years of age)

to either dexmedetomidine or midazolam for sedation during magnetic resonance imaging. Dexmedetomidine was administered as a loading dose of 1 mcg/kg during 10 minutes followed by an infusion of 0.5 mcg/kg/hr, and midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 mcg/kg/hr. Inadequate sedation, defined as inability to complete the scan, was treated by a bolus dose of either midazolam or propofol. The quality of sedation was better and the need for rescue sedation was less (8 of 40 vs. 32 of 40) with dexmedetomidine compared with midazolam. No significant adverse effects on hemodynamic or respiratory function were noted in either group.

In an open label trial, Berkenbosch et al⁹⁵ evaluated the use of dexmedetomidine for sedation during magnetic resonance imaging in a cohort of 48 pediatric patients ranging in age from 5 months to 16 years. Dexmedetomidine was administered as a loading dose of 0.5 mcg/kg during 5 minutes and repeated as needed to achieve an acceptable level of sedation. Once adequate sedation was achieved, a continuous infusion was started that was equivalent in micrograms per kilogram per hour to the initial loading dose. Fifteen of the patients received dexmedetomidine after other agents had failed, and the other 33 received dexmedetomidine as the primary agent. Sedation was induced with a loading dose of 0.92 ± 0.36 mcg/kg followed by an infusion of 0.69 ± 0.32 mcg/kg/hr. Effective sedation was achieved in all patients. Although there was a statistically significant decrease in HR and BP, no values were outside of the normal range for age. $ETCO_2$ measured from the nasal cannula exceeded 50 mm Hg in 7 of the 404 (1.7%) measurements. Recovery time was longer in patients who had received other agents prior to dexmedetomidine than in those who received dexmedetomidine as a primary agent (117 ± 41 vs. 69 ± 34 minutes). Additional anecdotal reports have demonstrated the efficacy of dexmedetomidine for sedation in various clinical scenarios in pediatric patients, including cardiac magnetic resonance imaging and radiation therapy.⁹⁶⁻⁹⁸

Despite the successes outlined here, dexmedetomidine has not been effective as the sole agent for painful, invasive procedures. Tobias et al⁹⁹ noted that, although successful in other scenarios (sedation during mechanical ventilation and as an adjunct to controlled hypotension), dexmedetomidine did not provide effective sedation during gastroduodenoscopy in an 11-year-old patient. Likewise, Jalowiecki et al¹⁰⁰ found dexmedetomidine to be ineffective during colonoscopy in adults. Sixty-four patients were randomized to receive dexmedetomidine (1 mcg/kg during 15 minutes followed by 0.2 mcg/kg/hr), meperidine (1 mg/kg) plus midazolam (0.05 mg/kg) or fentanyl (100-200 mcg on demand). Supplemental analgesia with fentanyl was available as needed. The authors had planned to study 90 patients, but terminated the study early because of the inefficacy and high adverse effect profile that they noted in the dexmedetomidine group. With dexmedetomidine, 2 of 19 patients developed bradycardia with a HR less than 40 beats/minute, and 4 of 19 had hypotension (BP less than 50% of baseline). Supplemental fentanyl was required in 47% of patients receiving dexmedetomidine versus 42.8% of those receiving meperidine/midazolam. Time-to-home readiness was also longer with dexmedetomidine than with meperidine/midazolam or fentanyl.

Given its limited analgesic effects when used as the sole agent, dexmedetomidine is not an ideal agent for painful procedures if used alone. Anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be an effective combination in these scenarios.^{101,102} Scher and Gitlin¹⁰¹ reported the successful use of dexmedetomidine as a bolus of 1 mcg/kg followed by an infusion of 0.7 mcg/kg/hr combined with ketamine (15 mg followed by an infusion of 20 mg/hr) for procedural sedation (awake fiberoptic intubation in an adult patient). We have previously reported our experience with a combination of ketamine and dexmedetomidine for sedation during magnetic resonance imaging in three children

with trisomy 21 and obstructive sleep apnea.¹⁰² Additionally, we have found that this combination provides effective sedation during cardiac catheterization in children (unpublished data). The combination of dexmedetomidine with ketamine makes pharmacologic sense as these two medications may prevent each other's adverse effects, in addition to having limited effects on respiratory function and providing adequate sedation. Dexmedetomidine may prevent the tachycardia, hypertension, salivation, and emergence phenomena from ketamine, and ketamine prevents the bradycardia and hypotension that has been reported with dexmedetomidine.¹⁰³

Sedation During Mechanical Ventilation

Sedation for up to 24 hours in initially intubated and mechanically ventilated adults is the only FDA-approved indication for dexmedetomidine. In one of the earlier studies, Venn et al¹¹ randomized adult patients who required mechanical ventilation following cardiac and general surgical procedures to receive dexmedetomidine in a dose of 1 mcg/kg during 10 minutes followed by an infusion of 0.2-0.7 mcg/kg/hr or placebo. Patients receiving dexmedetomidine required 80% less midazolam and 50% less morphine than placebo patients. Similar results were reported in a comparison of adults following cardiac and general surgical procedures who were randomized to dexmedetomidine or placebo with supplemental analgesia provided by morphine and propofol.¹⁰⁴ Patients receiving dexmedetomidine required approximately 50% less morphine and propofol.

A subsequent study by Venn and Grounds¹⁰⁵ randomized 20 adult patients who required mechanical ventilation for at least 8 hours following surgery to receive either dexmedetomidine or propofol. Depth of sedation, measured using the Bispectral Index monitor, was equivalent between the two groups; however, patients receiving dexmedetomidine required less supplemental sedation/analgesia with alfentanil (2.2-2.9 mg/hr vs. 0.65-1.2 mg/hr, $P = 0.004$). No adverse effects were noted in either group. There was no difference in MAP between the groups, and the HR was lower with dexmedetomidine. Time to extubation was likewise similar between the two groups.

Similar efficacy when comparing a continuous infusion of propofol to dexmedetomidine was noted in a randomized trial of Herr et al¹⁰⁶ in 295 adults who received sedation following coronary artery bypass grafting surgery. Twenty-eight percent of the patients receiving dexmedetomidine required supplemental morphine analgesia during mechanical ventilation compared with 69% of the patients receiving propofol ($P < 0.001$). Propofol patients required 4 times as much morphine as the patients receiving dexmedetomidine. A 5% incidence of ventricular tachycardia was noted with propofol versus 0% with dexmedetomidine ($P = 0.007$). No clinically significant differences were noted in respiratory parameters or hemodynamic function. Fewer dexmedetomidine patients received β_2 -adrenergic antagonists, nonsteroidal anti-inflammatory agents, antiemetics, and high-dose diuretics.

However, all of the literature does not favor dexmedetomidine. Corbett et al¹⁰⁷ randomized 89 adult patients to receive either dexmedetomidine or propofol for sedation following coronary artery bypass grafting surgery. They noted no difference in length of ICU stay or time until to extubation. Using postoperative satisfaction surveys, they noted a higher incidence of discomfort, pain, and sleeping difficulties in patients receiving dexmedetomidine compared with propofol. They concluded that dexmedetomidine does not offer any significant advantages over propofol.

To date, there is only one prospective trial regarding the use of dexmedetomidine during mechanical ventilation in infants and children. Tobias and Berkenbosch¹⁰⁸ randomized 30 infants and

children who required sedation during mechanical ventilation to receive either a continuous infusion of midazolam starting at 0.1 mg/kg/hr or a continuous infusion of dexmedetomidine starting at either 0.25 or 0.5 mcg/kg/hr. The efficacy of sedation was assessed using the Ramsay sedation score and the Bispectral Index with supplemental analgesia/sedation provided by intermittent doses of morphine as needed, with an increase of the midazolam or dexmedetomidine infusion in 20% increments if repeated doses of morphine were required. Dexmedetomidine at 0.25 mcg/kg/hr was as effective as midazolam at 0.22 mg/kg/hr, and a higher dose of dexmedetomidine (0.5 mcg/kg/hr) was more effective. The improved efficacy of the higher dose of dexmedetomidine was demonstrated by equivalent sedation scores and Bispectral Index with a decreased need for supplemental morphine (0.28 ± 0.12 mg/kg/24 hours with dexmedetomidine vs. 0.74 ± 0.5 mg/kg/24 hours with midazolam) as well as fewer patients (2/10 vs. 6/10) who manifested a Ramsay score of 1 at any time during the study protocol. Additionally, there were a decreased total number of Ramsay scores of 1 (5 with dexmedetomidine at 0.5 mcg/kg/hr vs. 14 with midazolam at a mean dose of 0.22 mg/kg/hr). The authors speculated that dexmedetomidine may be less effective in younger patients as five of the six patients who manifested a Ramsay score of 1 in either of the two dexmedetomidine groups (0.25 or 0.5 mcg/kg/hr) were less than 12 months of age.

A second report in infants and children regarding the use of dexmedetomidine during mechanical ventilation used dexmedetomidine as part of a rotating sedation regimen in an effort to prevent the development of tolerance and eliminate issues of withdrawal following prolonged sedation with a single agent.¹⁰⁹ The cohort for the study included patients who required 5-6 days of sedation and mechanical ventilation following laryngotracheoplasty, and included two patients, a 10- and a 14-month-old infant. Both patients were admitted to the pediatric ICU and received a continuous infusion of cis-atracurium titrated to maintain one twitch of the train-of-four. The sedation regimen included midazolam 0.1-0.2 mg/kg/hr with as needed doses of morphine on day 1, fentanyl 2-3 mcg/kg/hr with as needed doses of lorazepam on day 2, and dexmedetomidine 0.25-0.5 mcg/kg/hr with as needed doses of morphine on day 3. Midazolam and morphine were used on day 4 and fentanyl/lorazepam again on day 5. The authors noted no tolerance as there was no difference in the midazolam doses on day 1 versus day 4 or the fentanyl doses on day 2 versus day 5. Additionally, no patient developed signs of withdrawal and they were discharged from the hospital sooner when compared with a cohort of five historical control patients (day 6-7 vs. day 8-10) who had received a midazolam infusion with as needed morphine for the entire 5-day course.

To date, there are limited reports in adult or pediatric patients regarding the use of dexmedetomidine for more than 24-48 hours as a sedative during mechanical ventilation. Shehabi et al¹¹⁰ retrospectively reviewed their experience with "long-term" dexmedetomidine infusions in 12 critically ill adult ICU patients. The median infusion time was 71.5 hours, with a range of 35 to 168 hours. Adequate sedation defined as a Ramsay sedation score of 2-5 was observed during 83% of the observation points. Sixteen of the patients required minimal supplementation sedation with midazolam (median dose of 4 mg/day) and 10 required minimal supplemental analgesia with morphine (median dose of 2 mg/day). They noted no evidence of hemodynamic rebound after abrupt cessation of dexmedetomidine. Hammer et al¹¹¹ reported the use dexmedetomidine for sedation for 4 days following tracheal resection in a 9-year-old boy. Dexmedetomidine was started when fentanyl and midazolam infusions in escalating doses were ineffective. Effective sedation was provided with a maximum dexmedetomidine dose of 0.5 mcg/kg/hr until postoperative day 4 when the patient was taken to the operating

room and his trachea was extubated.

Treatment of Withdrawal

Various scenarios may arise in the ICU setting in which the patient manifests withdrawal symptoms. Tolerance and subsequent withdrawal may be iatrogenic, related to the prolonged use of opioids, benzodiazepines, or other agents for the provision of sedation and analgesia during mechanical ventilation, or may be the result of the use of illicit medications, ethanol, tobacco, or cannabinoids. Regardless of the agent responsible for withdrawal symptoms, the literature has demonstrated the efficacy of α_2 -adrenergic agonists such as clonidine in the treatment of such problems. The potential efficacy of dexmedetomidine in treating these issues is supported by animal studies, and anecdotal clinical reports have shown this agent to be effective in treating withdrawal symptoms from various agents including opioids and benzodiazepines.¹¹²⁻¹¹⁶ The various anecdotal reports and case series have shown that dexmedetomidine is effective in both the adult and pediatric populations in the control of withdrawal that has occurred following the appropriate use of benzodiazepines and opioids for sedation in the ICU setting as well as withdrawal symptoms that have occurred from the use illicit substances including alcohol and cannabinoids. The advantages of dexmedetomidine over other α_2 -adrenergic agonists such as clonidine include its shorter half-life, allowing for easier titration and availability for IV administration.

Summary

Dexmedetomidine (Precedex) is an α_2 -adrenergic agonist that shares physiologic similarities with clonidine. It is currently approved by the FDA for continuous infusions for up to 24 hours in adult ICU patients who are initially intubated and receiving mechanical ventilation. As with any sedative agent, the potential exists for adverse end-organ effects, although the current literature suggests that these events are generally uncommon with dexmedetomidine. Reported adverse cardiovascular effects include occasional episodes of bradycardia, with rare reports of sinus pause or cardiac arrest. Hypotension has been reported, as well as hypertension, the latter caused by peripheral α_{2B} -agonism with peripheral vasoconstriction. Hypotension and bradycardia appear to be more common with the initial loading dose, in patients with comorbid cardiovascular disease, and when coadministered with other medications that have negative chronotropic effects. Although dexmedetomidine has no direct effects on myocardial function, decreased cardiac output may result from changes in HR and/or increases in afterload. Despite the potential for adverse consequences of the decreased HR and BP, preliminary perioperative data suggest a decreased incidence of ischemic episodes as well as the potential for decreased morbidity and mortality in patients with comorbid cardiovascular disease. Dexmedetomidine has been shown to modulate the sympathetic nervous system with blunting of the sympathetic stress response and decreased levels of endogenous epinephrine and norepinephrine. Animal data suggest an improvement of myocardial blood flow during ischemia as well as protection against postischemic depression of left ventricular function and catecholamine-induced arrhythmogenesis. Its effects on pulmonary vascular resistance remain somewhat controversial and require further study, although the preliminary data suggest the potential to increase pulmonary artery pressure and PVR via a mechanism similar to its effects on the peripheral vasculature and agonism at the α_{2B} -adrenergic receptor of the vasculature.

There are somewhat conflicting reports in the literature regarding the effects of dexmedetomidine on ventilatory function, with some studies (both human and animal) suggesting some degree

of respiratory depression with mild increases of PaCO₂ (4-5 mm Hg), decreased minute ventilation, and decreased response to CO₂ challenge during performance of CO₂ response curves following bolus doses of 1 or 2 mcg/kg. Additionally, there is one case report of postoperative apnea that may be linked to dexmedetomidine. Despite these reports, other animal and human studies have shown no effect on respiratory function, and one anecdotal adult report outlines the maintenance of spontaneous ventilation with doses up to 10 mcg/kg/hr. Dexmedetomidine has been shown to protect against bronchoconstriction from a provocative inhalational challenge in an animal model.

The CNS effects include sedation and analgesia with prevention of recall and memory at higher doses. These effects are mediated via its central mechanism of action in the locus ceruleus. Animal data suggest that dexmedetomidine may induce a sleep-like state with electroencephalographic characteristics of nonrapid eye movement sleep. These properties may allow avoidance of the interruption of normal sleep cycles that is seen with other sedative agents and perhaps a decreased incidence of ICU delirium, thereby giving dexmedetomidine a significant advantage of other commonly used agents such as benzodiazepines.¹¹⁷

Despite its lack of direct effects on ICP, its hemodynamic effects may result in a decreased CPP. Both animal and human studies have demonstrated cerebral vasoconstriction with a decrease of CBF. Mixed results have been noted in animal studies regarding the anticonvulsant or proconvulsant effects of dexmedetomidine, with studies suggesting a proconvulsant effect when coadministered with either enflurane or pentylene-tetrazol and an anticonvulsant effect when seizures are provoked by either cocaine or local anesthetic agents. Another intriguing CNS effect of dexmedetomidine is its potential neuroprotective activity during periods of ischemia. Although there are some discrepancies in the literature related to the mechanism of ischemia, its duration, the animal model used, and the dosing regimen of dexmedetomidine, the majority of the data tend to support the potential neuroprotective effects of dexmedetomidine when given prior to a transient ischemic injury. The neuroprotective effect appears to be lost if dexmedetomidine is given after the ischemic injury or with a permanent versus a transient injury. It has also been shown that this effect is provided despite the fact that serum glucose concentrations may increase following dexmedetomidine administration because of decreased endogenous insulin release. Although the neuroprotective effects were originally ascribed to control of the catecholamine surge that occurs with ischemia, this mechanism has now been questioned, with recent evidence favoring increased expression of active FAK, a nonreceptor tyrosine kinase that plays a role in cellular plasticity and a reduction in caspase-3 expression.

Although not FDA-approved for other clinical scenarios, given its beneficial physiologic effects and its limited adverse effect profile, there are numerous additional applications of dexmedetomidine that have been reported in the literature. It has seen great use in the perioperative arena, with several clinical trials demonstrating significant benefits from its preoperative, intraoperative, or postoperative administration, including preoperative sedation, prevention of opioid-induced muscle rigidity, reduction of intraoperative requirements for both inhalational and intravenous anesthetic agents, blunting of the surgical stress response with decreased endogenous catecholamine release, control of the hemodynamic response to endotracheal intubation, and decreased perioperative tachycardia. Preliminary data suggest that the control of perioperative tachycardia may result in a decreased incidence of perioperative cardiovascular morbidity in patients with coronary artery disease. It has been used for monitored anesthetic care in combination with regional anesthetic techniques. Postoperative benefits include a decreased incidence of postanesthesia shivering, a

decreased incidence of emergence delirium in pediatric patients after general anesthesia with sevoflurane or desflurane, and the potentiation of opioid and epidural analgesia.

Additional clinical applications include prevention or treatment of substance withdrawal, both iatrogenic and that related to illicit drug abuse, and for the provision of procedural-sedation during nonpainful radiologic imaging. However, the current literature suggests that it is not effective as a sole agent for painful procedures. For that indication, there may be a role for the combination of dexmedetomidine with analgesic agents such as ketamine for painful procedures. When used in this combination, the adverse effects of the two medications (salivation, hypertension, tachycardia, and emergence hallucinations with ketamine and hypotension and bradycardia with dexmedetomidine) may be avoided.

Dexmedetomidine is available in a 2-mL vial of a 100 mcg/mL solution. For continuous infusions, it is generally reconstituted in normal saline to a 4 mcg/mL solution, which can be administered via a peripheral or central vein. Acquisitions costs vary from \$50-\$80 per vial. Given its favorable sedative and anxiolytic properties combined with its limited effects on hemodynamic and respiratory function, there is growing interest in its use in various clinical scenarios and patient populations. It appears to be an agent that may be well suited in several areas for the care of the adult and pediatric trauma patient.

References

1. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of selectivity, specificity, and potency of medetomidine as an alpha₂-adrenoceptor agonist. *Eur J Pharmacol* 1998;150:9-14.
2. Correa-Sales C, Reid K, Maze M. Pertussis toxin mediated ribosylation of G proteins blocks the hypnotic response to an alpha₂ agonist in the locus cereleus of the rat. *Pharmacol Biochem Behav* 1992;43:723-7.
3. Correa-Sales C, Nacif-Coelho C, Reid K, Maze M. Inhibition of adenylate cyclase in the locus cereleus mediates the hypnotic response to an alpha₂ agonist in the rat. *J Pharmacol Exp Ther* 1992;263:1046-50.
4. Nacif-Coelho C, Correa-Sales C, Chang LL, Maze M. Perturbation of ion channel conductance alters the hypnotic response to the alpha₂ adrenergic agonist dexmedetomidine in the locus cereleus of the rat. *Anesthesiology* 1994;81:1527-34.
5. Sculptoreanu A, Scheuer T, Catterall WA. Voltage-dependent potentiation of L-type Ca²⁺ channels due to phosphorylation by cAMP-dependent protein kinase. *Nature* 1993;364:240-3.
6. Correa-Sales C, Rabin BC, Maze M. A hypnotic response to dexmedetomidine, an alpha₂ agonist is mediated in the locus cereleus in rats. *Anesthesiology* 1992;76:948-52.
7. Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. *Anesthesiology* 1989;71:75-9.
8. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha₂-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003;98:428-36.
9. Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg* 2000;90:699-705.
10. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans: I Sedation, ventilation, and metabolic rate. *Anesthesiology* 1992;77:1125-33.
11. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. *Anaesthesia* 1999;54:1136-42.
12. Dyck JB, Shafer SL. Dexmedetomidine pharmacokinetics and pharmacodynamics. *Anesth Pharm Rev* 1993;1:238-245.
13. Cunningham FE, Baughman VL, Tonkovich L, et al. Pharmacokinetics of dexmedetomidine in patients with hepatic failure (abstract). *Clin Pharmacol Ther* 1999;65:128.
14. De Wolf AM, Fragen RJ, Avram MJ, et al. The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. *Anesth Analg* 2001;93:1205-9.
15. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. *Br J Anaesth* 2002;88:669-75.

16. Bloor BC, Ward DS, Belleville JP, et al. Effects of intravenous dexmedetomidine in humans, II: Hemodynamic changes. *Anesthesiology* 1992;77:1134-1142.
17. Peden CJ, Cloote AH, Stratford N, Prys-Roberts C. The effect of intravenous dexmedetomidine premedication on the dose requirement of propofol to induce loss of consciousness in patients receiving alfentanil. *Anaesthesia* 2001;56:408-413.
18. Ingersoll-Weng E, Manecke GR, Thistlethwaite PA. Dexmedetomidine and cardiac arrest. *Anesthesiology* 2004;100:738-739.
19. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. *Pediatr Crit Care Med* 2003;4:203-5.
20. Scheinin H, Jaakola ML, Sjovald S, et al. Intramuscular dexmedetomidine as premedication for general anaesthesia. A comparative multicenter study. *Anesthesiology* 1993;78:1065-1075.
21. Khan ZP, Munday IT, Jones RM. Effects of dexmedetomidine on isoflurane requirements in health volunteers. 1: Pharmacodynamic and pharmacokinetic interactions. *Br J Anaesth* 1999;83:372-380.
22. Talke P, Li J, Jain U, et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. *Anesthesiology* 1995;82:620-635.
23. Ruesch S, Levy JH. Treatment of persistent tachycardia with dexmedetomidine during off-pump cardiac surgery. *Anesth Analg* 2002;95:316-318.
24. Housmans PR. Effects of dexmedetomidine on contractility, relaxation, and intracellular calcium transients of isolated ventricular myocardium. *Anesthesiology* 1990;73:919-922.
25. Talke P, Richardson CA, Scheinin M, Fisher DM. Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. *Anesth Analg* 1997;85:1136-42.
26. Talke P, Chen R, Thomas B, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesth Analg* 2000;90:834-839.
27. Blake DW, Ludbrook J, Van Leeuwen AF. Dexmedetomidine and haemodynamic responses to acute central hypovolaemia in conscious rabbits. *Clin Exp Pharm Physiol* 2000;27:801-809.
28. Blake DW. Dexmedetomidine and hemodynamic responses to simulated hemorrhage in experimental heart failure. *Anesth Analg* 2000;91:1112-1117.
29. Talke P, Li J, Jain U, et al. The study of Perioperative Ischemia Research Group. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. *Anesthesiology* 1995;82:620-633.
30. Oliver MF, Goldman L, Julian DG, Holme I. Effect of mivazerol on perioperative cardiac complications during non-cardiac surgery in patients with coronary artery disease: the European Mivazerol Trial (EMIT). *Anesthesiology* 1999;91:951-961.
31. Roekaerts PMH, Prinzen FW, De Lange S. Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs. *Br J Anaesth* 1996;77:427-429.
32. Willigers HM, Prinzen FW, Roekaerts PM, et al. Dexmedetomidine decreases perioperative myocardial lactate release in dogs. *Anesth Analg* 2003;96:657-664.
33. Guo H, Takahashi S, Cho S, et al. The effects of dexmedetomidine on left ventricular function during hypoxia and reoxygenation in isolated rat hearts. *Anesth Analg* 2005;100:629-635.
34. Kamibayashi T, Mammoto T, Hayashi Y, et al. Further characterization of the receptor mechanism involved in the antidysrhythmic effect of dexmedetomidine on halothane/epinephrine dysrhythmias in dogs. *Anesthesiology* 1995;83:182-9.
35. Kastner SBR, Kull S, Kutter APN, et al. Cardiopulmonary effects of dexmedetomidine in sevoflurane-anesthetized sheep with and without nitric oxide inhalation. *Am J Vet Res* 2005;66:1496-1502.
36. Ebert T, Hall J, Barney J, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000;93:382-394.
37. Bol CJG, Danhoff M, Stanski DR, Mandema JW. Pharmacokinetic-pharmacodynamic characterization of the cardiovascular, hypnotic, EEG, and ventilatory responses to dexmedetomidine in the rat. *J Pharm Exper Ther* 1997;283:1051-1058.
38. Nguyen D, Abdul-Rasool I, Ward D, et al. Ventilatory effects of dexmedetomidine, atipamezol, and isoflurane in dogs. *Anesthesiology* 1992;76:573-579.
39. Nishida T, Nishimura M, Kagawa K, et al. The effects of dexmedetomidine on the ventilatory response to hypercapnia in rabbits. *Intensive Care Med* 2002;28:969-975.
40. Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: Crossover comparison of the respiratory effects of dexmedetomidine and remifentanyl in healthy volunteers. *Anesthesiology* 2004;101:106-7.
41. Furst SR, Weinger MB. Dexmedetomidine, a selective α_2 -agonist, does not potentiate the cardiorespiratory depression of alfentanil in the rat. *Anesthesiology* 1990;72:882-888.
42. Ho AMH, Chen S, Karmakar MK. Central apnoea after balanced general anaesthesia that included dexmedetomidine. *Br J Anaesth* 2005;95:773-775.
43. Groeben H, Mitzner W, Brown RH. Effects of the α_2 -adrenoceptor agonist dexmedetomidine on the bronchoconstriction in dogs. *Anesthesiology* 2004;100:359-363.
44. Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic-anesthetic action in rats via activation of central alpha-2 adrenoceptors. *Anesthesiology* 1989;71:75-79.
45. Nelson LE, Lu J, Guo T, et al. The α_2 -adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. *Anesthesiology* 2003;98:428-436.
46. Talke P, Tong C, Lee HW, et al. Effect of dexmedetomidine on lumbar cerebrospinal fluid pressure in humans. *Anesth Analg* 1997;85:358-364.
47. Zornow MH, Scheller MS, Sheehan PB, Strant MAP, Matsumoto M. Intracranial pressure effects of dexmedetomidine in rabbits. *Anesth Analg* 1992;75:232-237.
48. Vartiainen J, MacDonald E, Urtri A, et al. Dexmedetomidine-induced ocular hypotension in rabbits with normal or elevated intracranial pressure. *Invest Ophthalmol Vis Sci* 1992;33:2019-2023.
49. Karlsson BR, Forsman M, Roald OK, et al. Effect of dexmedetomidine, a selective and potent α_2 -agonist, on cerebral blood flow and oxygen consumption during halothane anaesthesia in dogs. *Anesth Analg* 1990;71:125-129.
50. Prielipp RC, Wall MH, Tobin JR, et al. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. *Anesth Analg* 2002;95:1052-1059.
51. Mirski MAZ, Rossell LA, McPherson RW, et al. Dexmedetomidine decreases seizure threshold in a rat model of experimental generalized epilepsy. *Anesthesiology* 1994;81:1422-1428.
52. Miyazaki Y, Adachi T, Kurata J, et al. Dexmedetomidine reduces seizure threshold during enflurane anaesthesia in cats. *Br J Anaesth* 1999;82:935-937.
53. Whittington RA, Virag L, Vulliamoz Y, et al. Dexmedetomidine increases the cocaine seizure threshold in rats. *Anesthesiology* 2002;97:693-700.
54. Tanaka K, Oda Y, Funao T, et al. Dexmedetomidine decreases the convulsive potency of bupivacaine and levobupivacaine in rats: involvement of α_2 -adrenoceptor for controlling convulsions. *Anesth Analg* 2005;100:687-696.
55. Hoffman WE, Kochs E, Werner C, et al. Dexmedetomidine improves neurologic outcome from incomplete ischemia in the rat. Reversal by the α_2 -adrenergic antagonist atipamezole. *Anesthesiology* 1991;75:328-332.
56. Kuhmonen J, Pokorny J, Miettinen R, et al. Neuroprotective effects of dexmedetomidine in the gerbil hippocampus after transient global ischemia. *Anesthesiology* 1997;87:371-377.
57. Kuhmonen J, Haapalinna A, Sivenius J. Effects of dexmedetomidine after transient and permanent occlusion of the middle cerebral artery in the rat. *J Neural Transm* 2001;108:261-271.
58. Laudénbach V, Mantz J, Lagercrantz H, et al. Effects of α_2 -adrenoceptor agonists on perinatal excitotoxic brain injury. *Anesthesiology* 2002;96:134-141.
59. Engelhard K, Werner C, Kaspar S, et al. Effect of the α_2 -agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. *Anesthesiology* 2002;96:450-457.
60. Dahmani S, Rouelle D, Gressens P, et al. Effects of dexmedetomidine on hippocampal focal adhesion kinase tyrosine phosphorylation in physiologic and ischemic conditions. *Anesthesiology* 2005;103:969-977.
61. Jalonen J, Hynynen M, Kuitunen A, et al. Dexmedetomidine as an anesthetic agent in coronary artery bypass grafting. *Anesthesiology* 1997;86:331-345.
62. Doufas AG, Lin CM, Suleman MI, et al. Dexmedetomidine and meperidine actively reduce the shivering threshold in humans. *Stroke* 2003;34:1218-1223.
63. Asai T, Mapleson WW, Power I. Differential effects of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat. *Br J Anaesth* 1997;78:301-307.
64. Herbert MK, Roth-Goldbrunner S, Holzer P, et al. Clonidine and dexmedetomidine potentially inhibit peristalsis in the guinea pig ileum in vitro. *Anesthesiology* 2002;97:1491-1499.
65. Maze M, Virtanen R, Daunt D, et al. Effects of dexmedetomidine, a novel imidazole sedation-anesthetic agent, on adrenal steroidogenesis: in vivo and in vitro studies. *Anesth Analg* 1991;73:204-208.
66. Venn RM, Bryant A, Hall GM, et al. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in postoperative patients needing sedation in the intensive care unit. *Br J Anaesth* 2001;86:650-656.

67. Nishina K, Akamatsu H, Mikawa K, et al. The effects of clonidine and dexmedetomidine on human neutrophil function. *Anesth Analg* 1999;88:452-458.
68. Taniguchi T, Kidani Y, Kanakura H, et al. Effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. *Crit Care Med* 2004;32:1322-1326.
69. Weinger MB, Partridge BL, Henry AF. Dexmedetomidine does not modify the neuromuscular blocking action of vecuronium in the anaesthetized rat. *Br J Anaesth* 1995;74:455-457.
70. Talke PO, Caldwell JE, Richardson CA, et al. The effects of dexmedetomidine on neuromuscular blockade in human volunteers. *Anesth Analg* 1999;88:633-639.
71. Jaakola ML, Kanto J, Scheinin H, et al. Intramuscular dexmedetomidine premedication – an alternative to midazolam-fentanyl in elective hysterectomy. *Acta Anaesthesiol Scand* 1994;38:238-243.
72. Scheinin B, Lindgren L, Randell T, et al. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and preoperative fentanyl. *Br J Anaesth* 1992;68:126-131.
73. Jaakola ML. Dexmedetomidine premedication before intravenous regional anesthesia in minor outpatient hand surgery. *J Clin Anesth* 1994;6:204-211.
74. Aho M, Lehtinen AM, Erkola O, et al. The effect of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991;74:997-1002.
75. Khan ZP, Munday IT, Jones RM, et al. Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 1: Pharmacodynamic and pharmacokinetic interactions. *Br J Anaesth* 1999;83:372-380.
76. Aho M, Erkola O, Kallio A, et al. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. *Anesth Analg* 1992;75:940-946.
77. Fragen RJ, Fitzgerald PC. Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years. *J Clin Anesth* 1999;11:466-470.
78. Aantaa R, Kanto J, Scheinin M, et al. Dexmedetomidine, an α_2 -adrenergic agonist, reduces anesthetic requirements for patients undergoing minor gynecologic surgery. *Anesthesiology* 1990;73:230-235.
79. Bührer M, Mappes A, Lauber R, et al. Dexmedetomidine decreases thiopental dose requirement and alters distribution pharmacokinetics. *Anesthesiology* 199;80:1216-1227.
80. Dutta S, Karol MD, Cohen T, et al. Effect of dexmedetomidine on propofol requirements in healthy subjects. *J Pharm Sci* 2001;90:172-181.
81. Arain SR, Ebert TJ. The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth Analg* 2002;95:461-466.
82. Ard J, Doyle W, Bekker A. Awake craniotomy with dexmedetomidine in pediatric patients. *J Neurosurg Anesth* 2003;15:263-266.
83. Bekker A, Kaufman B, Samir H, et al. The use of dexmedetomidine infusion for awake craniotomy. *Anesth Analg* 2001;92:1251-1253.
84. Ramsay MA, Luteran DL. Dexmedetomidine as a total intravenous anesthetic agent. *Anesthesiology* 2004;101:787-790.
85. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine – a novel α_2 -adrenoceptor agonist – in healthy volunteers. *Pain* 1991;46:281-285.
86. Unlugenc H, Gunduz M, Guler T, et al. The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. *Eur J Anaesth* 2005;22:386-391.
87. Arain SR, Ruehlow RM, Uhrich TD, et al. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg* 2004;98:153-158.
88. Aho MS, Erkola OA, Scheinin H, et al. Effect of intravenously administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesth Analg* 1991;73:112-118.
89. Wahlander S, Frumento RJ, Wagener G, et al. A prospective, double-blind, randomized, placebo-controlled study of dexmedetomidine as an adjunct to epidural analgesia after thoracic surgery. *J Cardiothor Vasc Anesth* 2005;19:630-635.
90. Ibacache ME, Munoz HR, Brandes V, et al. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. *Anesth Analg* 2004;98:60-63.
91. Hanafy MA, El-Zahaby HM, Swellam AM. The effect of dexmedetomidine on the emergence agitation associated with desflurane anaesthesia in children. *Eg J Anaesth* 2004;20:135-140.
92. Guler G, Akin A, Tosum Z et al. Single-dose dexmedetomidine reduces agitation and provides smooth extubation after pediatric adenotonsillectomy. *Pediatr Anesth* 2005;15:762-766.
93. Nichols DP, Berkenbosch JW, Tobias JD. Rescue sedation with dexmedetomidine for diagnostic imaging: a preliminary report. *Pediatr Anesth* 2005;15:199-203.
94. Koroglu A, Demirbilek S, Teksan H, et al. Sedative, hemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. *Br J Anaesth* 2005;94:821-824.
95. Berkenbosch JW, Wankum P, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. *Pediatr Crit Care Med* 2005;6:435-439.
96. Shukry M, Ramadhani U. Dexmedetomidine as the primary sedative agent for brain radiation therapy in a 21-month old child. *Pediatr Anesth* 2005;15:241-242.
97. Young ET. Dexmedetomidine sedation in a pediatric cardiac patient scheduled for MRI. *Can J Anaesth* 2005;52:730-732.
98. Fahy CJ, Okumura M. Sedation for paediatric stereotactic radiosurgery: the dexmedetomidine experience. *Anaesth Intensive Care* 2004;32:809-811.
99. Tobias JD, Berkenbosch JW. Initial experience with dexmedetomidine in paediatric-aged patients. *Paediatr Anaesth* 2002;12:171-175.
100. Jalowiecki P, Rudner R, Gonciarz M, et al. Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. *Anesthesiology* 2005;103:269-273.
101. Scher CS, Gitlin MC. Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fiberoptic intubation. *Can J Anesth* 2003;50:607-610.
102. Luscri N, Tobias JD. Monitored anesthesia care with a combination of ketamine and dexmedetomidine during magnetic resonance imaging in three children with trisomy 21 and obstructive sleep apnea. *Pediatr Anesth* 2006;16:782-6.
103. Levänen J, Mäkelä ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. *Anesthesiology* 1995;82:1117-1125.
104. Triltsch AE, Welte M, von Homeyer P, et al. Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized double blind, placebo-controlled phase II study. *Crit Care Med* 2002;30:1007-1014.
105. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *Br J Anaesth* 2001;87:684-690.
106. Herr DL, Sum-Ping J, England M. ICU sedation after coronary artery bypass graft surgery: Dexmedetomidine-based versus propofol-based sedation regimens. *J Cardiothor Vasc Anesth* 2003;17:576-584.
107. Corbett SM, Rebuck JS, Greene CM, et al. Dexmedetomidine does not improve patient satisfaction when compared with propofol during mechanical ventilation. *Crit Care Med* 2005;33:940-945.
108. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. *South Med J* 2004;97:451-5.
109. Wheeler A, Bothwell M, Tobias JD. Prevention of medication withdrawal following laryngotracheoplasty. *Am J Pain Manage* 2005;15:15-21.
110. Shehabi Y, Ruettimann U, Adamson H, et al. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intensive Care Med* 2004;30:2188-2196.
111. Hammer GB, Philip BM, Schroeder AR, et al. Prolonged infusion of dexmedetomidine for sedation following tracheal resection. *Pediatr Anesth* 2005;15:616-620.
112. Maccioli GA. Dexmedetomidine facilitates drug withdrawal. *Anesthesiology* 2003;98:575-577.
113. Multz AS. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. *Anesth Analg* 2003;96:1054-1055.
114. Finkel JC, Elrefai A. The use of dexmedetomidine to facilitate opioid and benzodiazepine detoxification in an infant. *Anesth Analg* 2004;98:1658-1659.
115. Finkel JC, Johnson YJ, Quezado ZMN. The use of dexmedetomidine to facilitate acute discontinuation of opioids after cardiac transplantation in children. *Crit Care Med* 2005;33:2110-2112.
116. Baddigam K, Russo P, Russo J, et al. Dexmedetomidine in the treatment of withdrawal syndromes in cardiothoracic surgery patients. *J Intensive Care Med* 2005;20:118-123.
117. Pandharipande P, Shintaine A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology* 2006;104:21-26.