Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology

Joseph D. Tobias, MD

Objective: **To provide a general descriptive account of the end-organ effects of dexmedetomidine and to provide an evidence-based review of the literature regarding its use in infants and children.**

Data Source: **A computerized bibliographic search of the literature regarding dexmedetomidine.**

Main Results: **The end-organ effects of dexmedetomidine have been well studied in animal and adult human models. Adverse cardiovascular effects include occasional episodes of bradycardia with rare reports of sinus pause or cardiac arrest. Hypotension has also been reported as well as hypertension, the latter thought to be due to peripheral α_{2B} agonism with peripheral vasoconstriction. Although dexmedetomidine has no direct effects on myocardial function, decreased cardiac output may result from changes in heart rate or increases in afterload. There are somewhat conflicting reports in the literature regarding its effects on ventilatory function, with some studies (both human and animal) suggesting a mild degree of respiratory depression, decreased minute ventilation, and decreased response to CO_2 challenge whereas others demonstrate no effect. The central nervous system effects include sedation and analgesia with prevention of recall and memory at higher doses. Dexmedetomidine may also provide some neuroprotective activity during periods of ischemia. Applications in infants and children have included sedation during mechanical ventilation, prevention of emergence agitation following general anesthesia, provision of procedural sedation, and the prevention of withdrawal following the prolonged administration of opioids and benzodiazepines.**

Conclusions: **The literature contains reports of the use of dexmedetomidine in approximately 800 pediatric patients. Given its favorable sedative and anxiolytic properties combined with its limited effects on hemodynamic and respiratory function, there is growing interest in and reports of its use in the pediatric population in various clinical scenarios. (Pediatr Crit Care Med 2007; 8:115–131)**

Key Words: dexmedetomidine; α_2-adrenergic agonist; opioid tolerance and withdrawal; emergence delirium; procedural-sedation

Dexmedetomidine (Precedex, Hospira Worldwide, Lake Forest, IL) is the pharmacologically active dextro-isomer of medetomidine. It exerts its physiologic effects via α_2-adrenergic receptors. The α_2-adrenergic agonists are subclassified into three groups: imidazolines, phenylethylamines, and oxalozepines. Dexmedetomidine and clonidine are members of the imidazole subclass, which exhibits a high ratio of specificity for the α_2 vs. the α_1 receptor (Fig. 1). Clonidine exhibits an α_2:α_1 specificity ratio of 200:1 whereas that of dexmedetomidine is 1600:1, thereby making it a complete agonist at the α_2-adrenergic receptor (1). Dexmedetomidine has a short half-life (2–3 hrs vs. 12–24 hrs for clonidine) and is commercially available for intravenous administration. An epidural clonidine formulation, although not marketed for intravenous administration, has been used for this purpose in clinical practice without consequences. Dexmedetomidine's end-organ effects are mediated via postsynaptic α_2-adrenergic receptors and subsequent activation of a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein) (2), which results in inhibitory feedback and decreased activity of adenylyl cyclase (3). A reduction of intracellular cyclic adenosine monophosphate and intracellular cyclic adenosine monophosphate-dependent protein kinase activity results in the dephosphorylation of ion channels (4). Alterations in ion channel function, ion translocation, and membrane conductance lead to decreased neuronal activation and the clinical effects of sedation and anxiolysis (5). Centrally acting α_2-adrenergic agonists also activate receptors in the medullary vasomotor center, reducing norepinephrine with a resultant central sympatholytic effect leading to decreased heart rate (HR) and blood pressure (BP). As the central presynaptic α_{2A}-adrenergic receptor is a negative feedback receptor, agonists at this receptor result in decreased catecholamine release from the nerve terminal. Central nervous system stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus ceruleus in the brainstem play a prominent role in the sedation and anxiolysis produced by these agents. Decreased noradrenergic output from the locus ceruleus allows for increased firing of inhibitory neurons, most importantly the γ-aminobutyric acid system (6–8). Primary analgesic effects and potentiation of opioid-induced analgesia result from the activation of α_2-adrenergic receptors in the dorsal horn of the spinal cord and the inhibition of substance P release. These interactions with central nervous system and spinal cord α_2-adrenergic receptors mediate dexmedetomidine's primary physiologic effects including sedation, anxiolysis, analgesia, a decrease of the minimum alveolar con-

From the Departments of Anesthesiology and Pediatrics, University of Missouri, Columbia, MO.

The author has consulted for and received honoraria/speaking fees from Hospira.

DOI: 10.1097/01.PCC.0000257100.31779.41

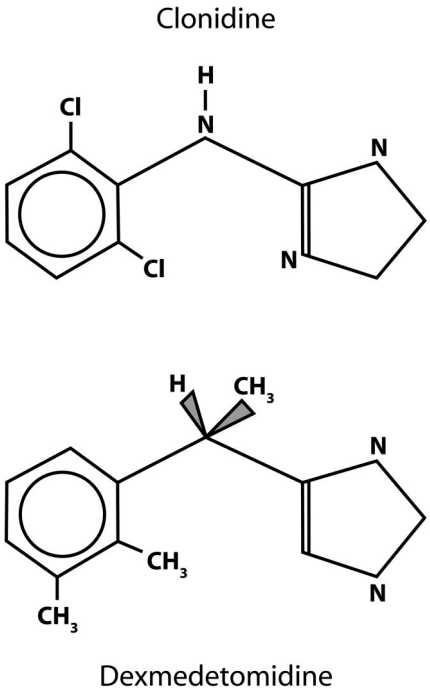

Figure 1. Representation of the chemical structure of clonidine and dexmedetomidine, α_2-adrenergic agonists of the imidazole subclass, which exhibit a high ratio of specificity for the α_2 vs. the α_1 receptor.

centration of inhalational anesthetic agents, decreased renin and vasopressin levels leading to diuresis, blunting of the sympathetic nervous system, and lowering of HR and BP (Fig. 2) (9, 10).

Currently, dexmedetomidine's only Food and Drug Administration (FDA)-approved indication is the provision of short-term sedation (<24 hrs) in adult patients in the intensive care unit (ICU) setting who are initially intubated and receiving mechanical ventilation (11). It is available in a water-soluble solution without the addition of lipid or propylene glycol and is not associated with pain following intravenous administration. There are no active or toxic metabolites. Given its favorable physiologic effects combined with a limited adverse effect profile reported to date, there is increasing use of this agent in the pediatric population. 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 in infants and children.

PHARMACOKINETICS

In healthy adult volunteers, dexmedetomidine's pharmacokinetic profile includes a rapid distribution phase (distribution half-life of 6 mins), an elimination half-life of 2 hrs, and a steady-state volume of distribution of 118 L (12). In the dosing range of 0.2–0.7 μg/kg/hr delivered via continuous intravenous infusion for up to 24 hrs, the pharmacokinetics are linear. Dexmedetomidine is 94% protein bound to serum albumin and α_1-glycoprotein. It undergoes hepatic metabolism with limited unchanged drug excreted in the urine or stool.

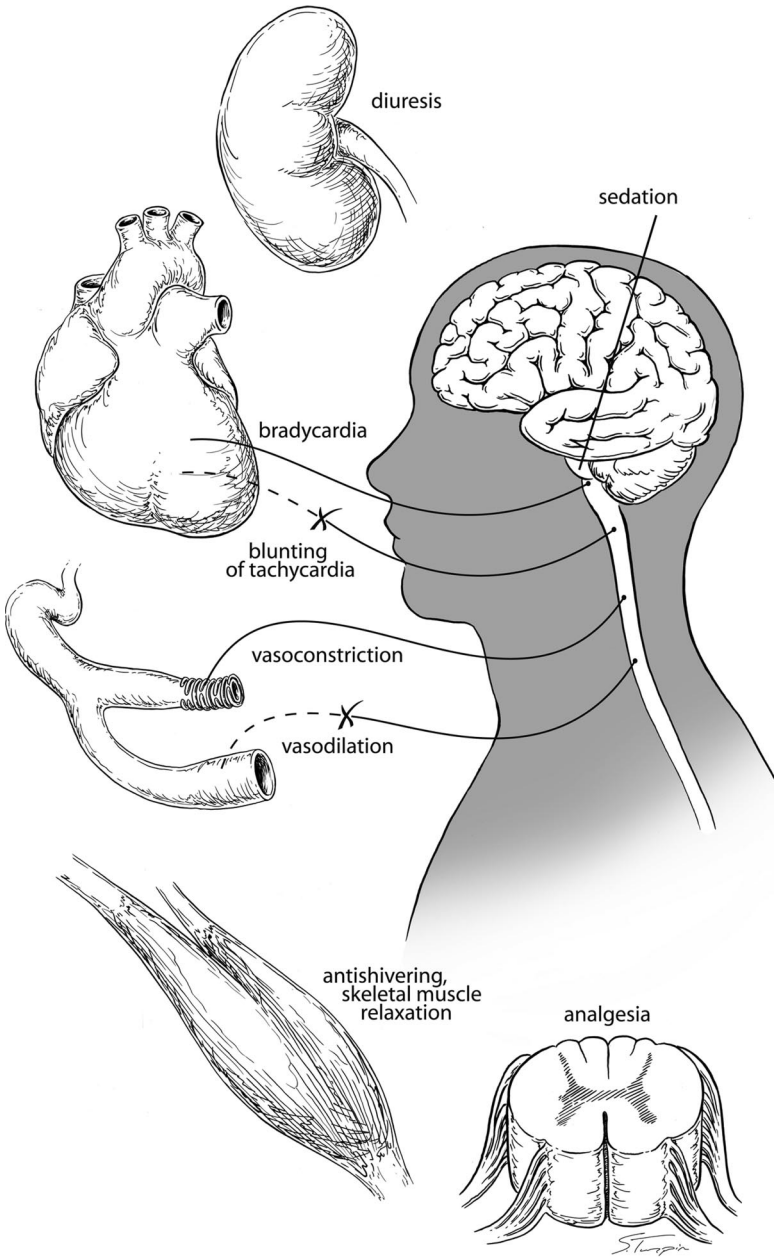

Figure 2. The physiologic end-organ effects of dexmedetomidine.

Cunningham et al. (13) evaluated dexmedetomidine pharmacokinetics following administration (0.6 μg/kg infused over 10 mins) in five adults with severe hepatic failure and compared the results with five age-matched controls with normal hepatic function. When compared with age-matched controls with normal hepatic function, there was an increased volume of distribution at steady state (3.2 vs. 2.2 L/kg, $p < .05$), an increased elimination half-life (7.5 vs. 2.6 hrs, $p < .05$), and a decreased clearance (0.32 vs. 0.64 L/hr/kg; $p < .05$) in patients with hepatic dysfunction. In a subsequent study in six adult patients with severe renal disease (24-hr creatinine clearance ≤30 mL/min) who were not receiving dialysis, there was no statistically significant difference between renal disease and control pa-

tients 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) (14). However, the elimination half-life was decreased with renal disease (113.4 ± 11.3 mins vs. 136.5 ± 13.0 mins, $p < .05$). Despite the shorter elimination half-life, there was prolonged sedation in patients with renal disease. The 1-hr postinfusion visual analog score of sedation (scale of 0 to 100) was 49.2 ± 25.4 in patients with renal disease compared with 26.2 ± 18.3 in patients with normal renal function ($p < .05$). The authors speculated that the increased sedation with renal failure resulted from decreased protein binding and an increased free fraction of the drug. Venn et al. (15) evaluated the impact of acute surgical intervention and critical illness on dexmedetomidine pharmacokinetics in ten adult patients following complex abdominal or pelvic surgical procedures. Dexmedetomidine administration included a loading dose of 0.4 μg/kg over 10 mins followed by an infusion of 0.7 μg/kg/hr. When compared with data from healthy volunteers, there was no difference in half-life, volume of distribution, or clearance.

Data regarding dexmedetomidine pharmacokinetics in the pediatric population have been presented in one recent manuscript and two abstracts (16–18). Petroz et al. (16) randomized 36 children, ranging in age from 2 to 12 yrs, to receive dexmedetomidine infused for 10 mins at 2, 4, or 6 μg/kg/hr (0.33, 0.6, and 1 μg/kg). Using a two-compartment model, they reported that the pharmacokinetics of dexmedetomidine in children are similar to adults with no dose-dependent kinetics, protein binding of 92.6%, weight-adjusted total body clearance of 13 mL/kg/min, a volume of distribution of the peripheral compartment of 1.0 L/kg, and a terminal elimination half-life of 1.8 hrs. Rodarte et al. (17) administered a continuous infusion in a dose ranging from 0.2 to 0.7 μg/kg/hr for 8–24 hrs to ten children (0.3–7.9 yrs of age) following cardiac procedures (n = 9) or craniofacial procedures (n = 1). Using a two-compartment model, they reported a volume of distribution of 1.53 ± 0.37 L/kg, a clearance of 0.57 ± 0.14 L/kg/hr (approximately 9.5 mL/kg/min), and a terminal elimination half-life of 2.65 ± 0.88 hrs. They commented that their data demonstrated that the pharmacokinetics of dexmedetomidine in children were predictable and consistent with results reported in adults. The final pharmacokinetic study in children included infants, ranging in age from 1 to 24 months, following surgery for congenital heart disease (18). The authors reported a median clearance of 27.2 mL/kg/min, peripheral volume of distribution of 2.5 L/kg, and terminal elimination half-life of 83 mins. They concluded that infants appear to clear dexmedetomidine more quickly than adults or older children.

END-ORGAN EFFECTS OF DEXMEDETOMIDINE

Cardiovascular and Hemodynamic Effects

Heart Rate, Blood Pressure, Cardiac Output, and Myocardial Contractility. Hypotension and bradycardia have been reported in adult patients, especially in the presence of comorbid cardiac disease, when administered with other medications that possess negative chronotropic effects or following large or rapid bolus doses. In healthy adult volunteers, there is a biphasic effect following dexmedetomidine with an initial increase in systolic blood pressure (sBP) and a reflex decrease in HR followed by a stabilization of sBP and HR at values below the baseline (19). Stimulation of peripheral postsynaptic α_{2B}-adrenergic receptors results in vasoconstriction and the initial increase in sBP, whereas the eventual decrease in BP and HR results from central presynaptic α_{2A}-adrenergic receptor stimulated sympatholysis.

In healthy, adult volunteers, dexmedetomidine doses of 0.25, 0.5, 1.0 and 2.0 μg/kg administered over 2 mins resulted in a decrease from baseline of the mean arterial pressure (MAP) at 60 mins of 14%, 16%, 23%, and 27% (19). Following a dose of 1 μg/kg, cardiac output, measured by thoracic bioimpedance, was 81 ± 13% of baseline at 1 min, 88 ± 14% of baseline at 10 mins, and 91 ± 11% of baseline at 60 mins. With a dose of 2 μg/kg, cardiac output was 58 ± 32% of baseline at 1 min, 76 ± 33% of baseline at 10 mins, and 85 ± 28% of baseline at 60 mins.

The potential for adverse hemodynamic effects with dexmedetomidine in patients with comorbid features is illustrated in an adult ICU population of 98 cardiac and general surgery patients who received dexmedetomidine for sedation during mechanical ventilation (11). Dexmedetomidine was dosed as a bolus dose of 1 μg/kg over 10 mins followed by an infusion of 0.2–0.7 μg/kg/hr. Hypotension (MAP ≤60 mm Hg or a ≥30% decrease from baseline) occurred in 18 of 66 patients. Eleven of the episodes occurred during the bolus. Hypertension was noted in six of the 66 patients during the loading dose. Although no morbidity or mortality was noted, the infusion was temporarily (n = 3) or permanently (n = 3) discontinued, and treatment with atropine (n = 2) or temporary cardiac pacing (n = 4) was necessary.

Bradycardia and sinus arrest have been reported with dexmedetomidine (20, 21). In a study combining dexmedetomidine with propofol to induce anesthesia, two of the first four patients had brief and self-limited sinus arrest after laryngoscopy (20). Dexmedetomidine was administered as a bolus dose of 1 μg/kg over 15 mins followed by an infusion of 0.4 μg/kg/hr resulting in the administration of an average dose of 1.47 μg/kg before anesthetic induction with propofol. The protocol was amended (decrease of the dexmedetomidine dose to 0.7 μg/kg over 15 mins followed by an infusion of 0.27 μg/kg/hr), and no subsequent problems were noted.

We reported bradycardia in a 5-wk-old infant with trisomy 21 who was receiving dexmedetomidine for sedation during mechanical ventilation (22). Concomitant medications included digoxin for the treatment of chronic congestive heart failure due to an unrepaired atrioventricular canal defect. Twelve hours after the initiation of the dexmedetomidine infusion, the infant's HR decreased to 40–50 beats/min with a stable BP. The dexmedetomidine infusion was discontinued without other therapy, and the HR returned to baseline within 60 mins.

In a study of 192 patients with American Society of Anesthesiologists ratings of 1 or 2, randomized to receive either intramuscular dexmedetomidine and intravenous saline, intramuscular dexmedetomidine and intravenous fentanyl, or intramuscular midazolam and intravenous fentanyl, followed by maintenance anesthesia (70% nitrous oxide in 30% oxygen, fentanyl, and either enflurane or isoflurane), intraoperative bradycardia and hypotension were significantly more common in the patients who received dexmedetomidine compared with those receiving midazolam (23). In one patient, bradycardia (HR 35 beats/min) required pharmacologic therapy. Khan et al. (24),

in a 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 concentration group and seven in the concentration group. Interventions including crystalloid, crystalloid and methoxamine, or atropine were necessary in five patients. The majority of the hemodynamic events (75%) occurred at an end-tidal isoflurane of ≥1%.

In a cohort of 80 children, ranging in age from 1 to 12 yrs, no clinically significant hypotension or bradycardia occurred with the intraoperative administration of dexmedetomidine (0.5 μg/kg) during anesthesia at 1 minimum alveolar concentration with either desflurane or sevoflurane (25). However, there was a greater decrease in HR in patients anesthetized with sevoflurane compared with those receiving desflurane (104 ± 16 vs. 120 ± 17 beats/min, $p < .01$).

Lowering of HR and thereby myocardial oxygen consumption may provide beneficial effects in patients with coronary artery disease. Talke et al. (26) randomized 24 adult patients undergoing vascular surgery to placebo or one of three plasma concentrations of dexmedetomidine: 0.15 ng/mL (low dose), 0.3 ng/mL (medium dose), or 0.45 ng/mL (high dose). Dexmedetomidine was started 1 hr before anesthetic induction and continued for 48 hrs. Although there was an increased intraoperative need for atropine and/or phenylephrine with dexmedetomidine, no such difference was noted postoperatively. In the placebo group, there was an increased incidence of tachycardia (23 mins/hr) when compared with the low-dose (9 mins/hr, $p = .006$), medium-dose (0.5 mins/hr, $p = .004$), and high-dose (2.3 mins/hr, $p = .004$) dexmedetomidine groups. In an anecdotal report, the negative chronotropic effect of dexmedetomidine was used as a therapeutic maneuver during off-pump coronary artery bypass surgery when tachycardia was unresponsive to β-adrenergic blockade (27).

The potential for significant negative chronotropic effects appears to be greater when dexmedetomidine is administered with medications that have negative chronotropic effects (propofol, succinylcholine, digoxin, pyridostigmine) or during vagotonic procedures (laryngoscopy) (20–22). Animal studies have not demonstrated direct effects on myocardial contractility or intracellular calcium regulation (28). When studied in an isolated right ventricular papillary muscle preparation, dexmedetomidine had no effect on the amplitude and time variables of isometric, isotonic, or zero-loaded-clamped twitches and intracellular calcium currents (28).

Sympathetic Nervous System and Endogenous Catecholamine Release. Biochemical data from a cohort of eight adult postoperative patients demonstrate the sympatholytic effects of dexmedetomidine (29). Following a 60-min dexmedetomidine infusion administered by a computer-controlled infusion protocol 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/min, and sBP decreased from 158 ± 23 to 140 ± 23 mm Hg. The same investigators evaluated changes in plasma and urinary catecholamines in 41 adult patients undergoing vascular surgery (30). Dexmedetomidine was started intraoperatively and continued for the first 48 postoperative hours. When compared with patients receiving dexmedetomidine, plasma norepinephrine concentrations were two to three times higher at the time of tracheal extubation and at 60 mins after arrival in the postanesthesia care unit than in the control group. Urinary normetanephrine levels increased significantly in the placebo group, whereas no change was noted in patients receiving dexmedetomidine.

A similar sympatholytic effect has been demonstrated following the intraoperative administration of dexmedetomidine to pediatric patients undergoing cardiopulmonary bypass and surgery for congenital heart disease (31). Muktar et al. (31) randomized 30 infants and children to placebo or dexmedetomidine (bolus of 10 μg/kg over 10 mins followed by an infusion of 0.5 μg/kg/hr), which was administered after anesthetic induction and placement of arterial and venous cannulae. Although plasma cortisol, norepinephrine, epinephrine, and glucose concentrations increased in both the dexmedetomidine and the placebo groups after sternotomy and following cardiopulmonary bypass, the increase was significantly less in patients receiving dexmedetomidine. Additionally, when weaning from cardiopulmonary bypass, less sodium nitroprusside was required in patients receiving dexmedetomidine (0.3 ± 0.36 vs. 1.3 ± 0.68 μg/kg/min, $p < .05$). No adverse effects were noted.

In specific clinical scenarios such as hemorrhage, hypovolemia, or congestive heart failure, there is the potential for dexmedetomidine's sympatholytic effect to be detrimental by offsetting the protective function of the sympathetic nervous system. In an animal model, Blake et al. (32) evaluated the effects of dexmedetomidine on the BP response during incremental decreases in intravascular blood volume induced by a gradual inflation of an inferior vena cava cuff. In control animals, the gradual reduction of intravascular volume resulted in a progressive increase in HR with peripheral vasoconstriction to maintain MAP until cardiac index was approximately 40% of baseline, at which time there was failure of vasoconstriction and a decrease in MAP. Dexmedetomidine, administered intravenously or directly into the fourth ventricle of the central nervous system, resulted in a decrease of HR and MAP from baseline and an earlier decompensation during inflation of the inferior vena cava cuff. Similar findings were reported in rabbits treated with doxorubicin to induce a chronic congestive heart failure and then subjected a reduction of intravascular volume by inflation of an inferior vena cava cuff (33).

Myocardial Oxygen Consumption and Perioperative Ischemia. Clinical studies in adults have shown that the perioperative administrative of α_2-adrenergic agonists may modify the incidence of adverse cardiovascular events including myocardial ischemia (34, 35). In an animal model of coronary artery stenosis, dexmedetomidine reduced blood flow in the nonischemic myocardium and in the ischemic epicardial layer; however, there was no effect on blood flow in the ischemic mid-myocardial and subendocardial layers, thereby increasing the ischemic-nonischemic blood flow ratio (36). Myocardial oxygen demand also decreased with dexmedetomidine, thereby further reducing the ischemic myocardium's oxygen deficiency

Similar findings were reported by Willigers et al. (37) in their animal model using graded coronary stenosis to produce lactate release from the poststenotic myocardium. Lactate production occurred in zero of eight dogs receiving

dexmedetomidine compared with four of seven in the control group ($p = .03$). With dexmedetomidine, lactate release was 46% less during emergence from anesthesia, and the endocardial/epicardial blood flow ratio increased by 35% compared with the control group. Decreased levels of plasma epinephrine (158 vs. 1909 pg/mL) and norepinephrine (126 vs. 577 pg/mL) and decreased HR (123 ± 6 vs. 160 ± 10 beats/min) were noted. The authors postulated that this may account for the anti-ischemic effect of dexmedetomidine.

Additional potentially protective effects of dexmedetomidine on myocardial performance include preservation of myocardial dysfunction following ischemia and prevention of catecholamine-induced arrhythmogenesis (38, 39). Hypoxia followed by reoxygenation exposes the myocardium to an oxidative stress, resulting in tissue injury/death and myocardial dysfunction. In rats exposed to 60 mins of hypoxia, dexmedetomidine administered before but not after hypoxia significantly improved left ventricular-developed pressure after reoxygenation (38). The effect was blocked by 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 μg/kg/min in control animals vs. 6 μg/kg/min in animals receiving dexmedetomidine) (39).

Pulmonary Vascular Resistance. There is limited information regarding dexmedetomidine's effects on the pulmonary vasculature and pulmonary vascular resistance (PVR). In six instrumented sheep, dexmedetomidine (2 μg/kg over 1 min) transiently increased mean pulmonary artery pressure (MPAP) and PVR (40). PVR increased from a baseline of 81 ± 16 dynes·sec·cm^{-5} to a maximum of 141 ± 27 dynes·sec·cm^{-5}, whereas MPAP increased from 15 ± 1 to 18 ± 0 mm Hg. MAP also increased (86 ± 2 to 93 ± 6 mm Hg), as did systemic vascular resistance (1416 ± 83 to 1889 ± 64 dynes·sec·cm^{-5}). There was no change in pulmonary artery occlusion pressure. Similar transient pulmonary hemodynamic changes have been reported in healthy human volunteers with graded dexmedetomidine infusions to a plasma concentration of 1.9 ng/mL (19). Given the potential impact of these findings, especially in patients with elevated MPAP or PVR, future studies are needed to define these effects.

Respiratory Effects

Ventilation. The ventilatory effects of increasing doses of dexmedetomidine (0.25, 0.5, 1, and 2 μg/kg over 2 mins) have been evaluated in healthy adult volunteers by measurement of oxygen saturation, $Paco_2$, CO_2 response curves with CO_2 rebreathing, and respiratory inductance plethysmography (10, 41). With doses of 1 or 2 μg/kg, $Paco_2$ increased significantly with a maximum effect noted 10 mins following the dose. The mean $Paco_2$ increase from baseline was 5.0 and 4.2 mm Hg with the 1.0 and 2.0 μg/kg doses, respectively. The effect persisted for 60 mins following 1 μg/kg and for 105 mins following 2 μg/kg. Following 2.0 μg/kg, minute ventilation decreased from 8.7 ± 0.7 to 6.3 ± 1.5 L/min ($p < .05$). The decrease resulted predominantly from a decreased tidal volume with less effect on respiratory rate. Significant changes were also noted using CO_2 response curves, as minute ventilation at an end-tidal CO_2 of 55 mm Hg was depressed following the both the 1- and 2-μg/kg doses. The authors also noted short episodes of apnea and irregular breathing in some subjects, which occurred more commonly with the two highest doses (seven of ten patients with 2 μg/kg and five of six patients with 1 μg/kg vs. one of six with either 0.5 μg/kg or 0.25 μg/kg). Respiratory inductance plethysmography was used to demonstrate that these problems were obstructive and not central. Although oxygen saturation decreased with the obstructive episodes, the average room air oxygen saturation remained >95% following all doses of dexmedetomidine. The oxygen saturation decrease was greatest at 10 mins following 1 μg/kg (decrease from 98.5 ± 0.7% to 96.2 ± 1.3%) and at 60 mins following 2 μg/kg (decrease from 98.3 ± 0.8% to 95.4 ± 1.2%). Similar respiratory effects have been demonstrated in experimental animals although a paradoxic effect has been noted with more of an effect on ventilation with 1 vs. 10 μg/kg in one study and 10 or 30 μg/kg vs. 50 μg/kg in another (42–44).

Conflicting results were reported when comparing the respiratory effects of dexmedetomidine with remifentanil in six healthy adult volunteers (45). When compared with baseline, a remifentanil infusion to achieve a stepwise plasma concentration of 1, 2, 3, and 4 ng/mL resulted in respiratory depression manifested as a decrease in respiratory rate and minute ventilation, increased $Paco_2$, blunting of the CO_2 response curve, and apnea with oxygen desaturation. During stepwise 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, and no change in the end-tidal CO_2 when compared with baseline values. With dexmedetomidine, some patients demonstrated a periodic increase in minute ventilation during CO_2 response curves (hypercapnic arousal) that correlated with changes in the Bispectral Index. The authors noted that similar changes occur during natural sleep and that these findings may result from dexmedetomidine's mechanism of action in the locus ceruleus and its convergence on the natural sleep pathway. The authors concluded that dexmedetomidine stands apart from other sedatives in that it appears to be clinically safe from a respiratory point of view even in doses high enough to cause unresponsiveness. Similar findings were reported from an evaluation of the respiratory effects of dexmedetomidine (10 and 30 μg/kg) and alfentanil in an animal model (rats) (46). Neither dose of dexmedetomidine had an effect on Pao_2, $Paco_2$, or pH, whereas the administration of alfentanil resulted in a decrease in pH and Pao_2 and an increase in $Paco_2$. Dexmedetomidine had no additional effect when administered after alfentanil, and in fact, dexmedetomidine in a dose of 30 μg/kg decreased the acidosis and hypercapnia that occurred following alfentanil. Despite these findings, monitoring of respiratory function during the administration of dexmedetomidine in high-risk patients or those receiving other agents that may depress respiratory function appears warranted given the recent report of central apnea after a general anesthetic that included dexmedetomidine (47).

Airway Reactivity. In mongrel dogs, the intravenous but not the inhalational administration of dexmedetomidine has been shown to prevent histamine-induced bronchoconstriction (48). Bronchoconstriction was provoked with aerosolized histamine, and its effect on airway caliber was evaluated using high-resolution computed tomography with an evaluation of airway cross-sectional area. Aerosolized histamine constricted the airways to 66 ± 27% of baseline compared with 87 ± 30.4% of baseline when

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.