Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology

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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-

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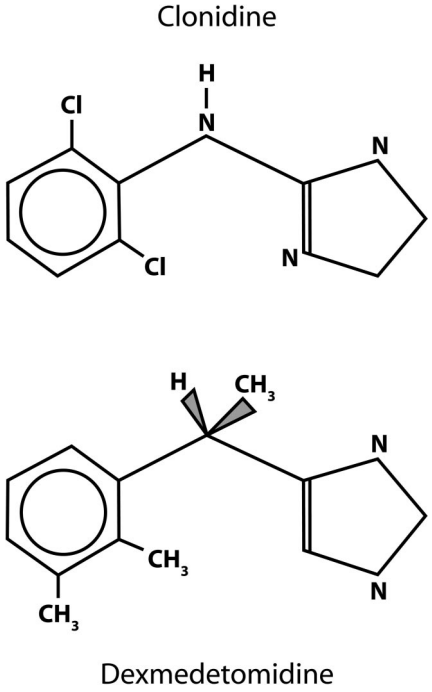

Figure 1. Representation of the chemical structure of clonidine and dexmedetomidine, α_2-adrenergic agonists of the imidazole subclass, which exhibit a high ratio of specificity for the α_2 vs. the α_1 receptor.

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.

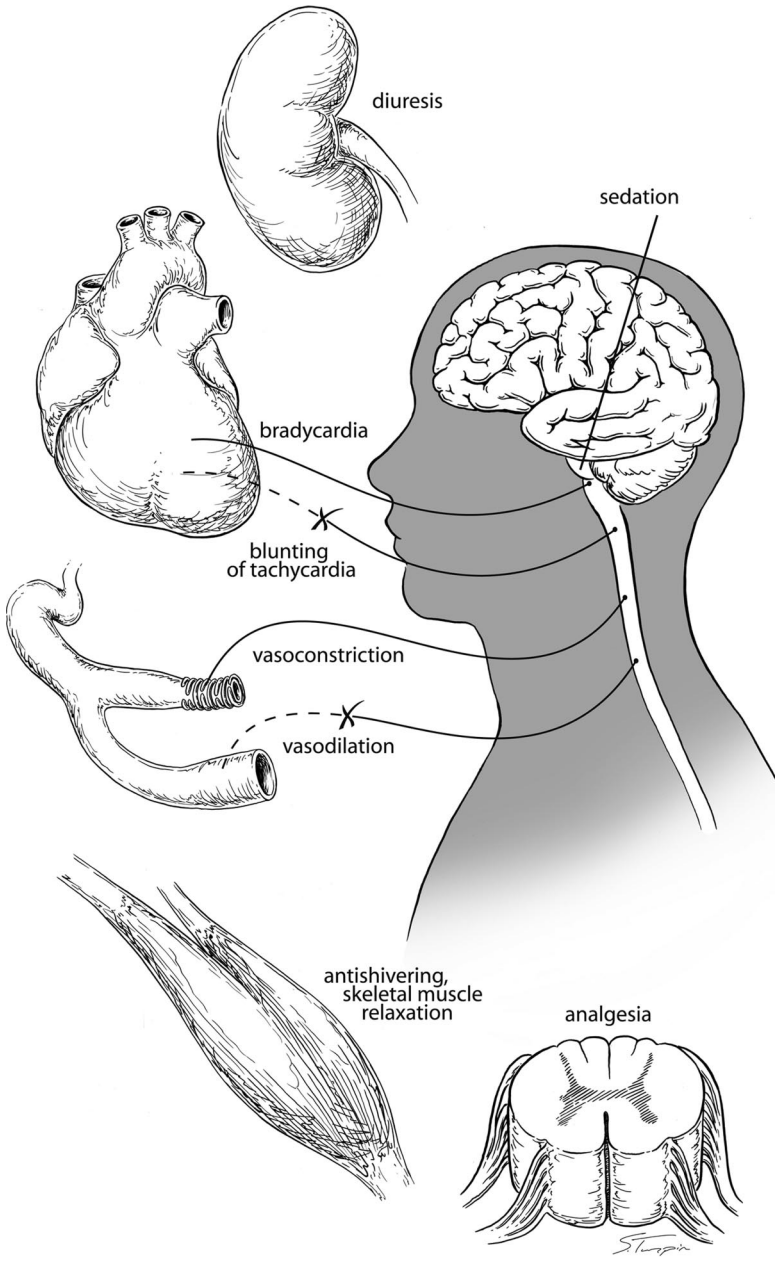

Figure 2. The physiologic end-organ effects of dexmedetomidine.

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

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, 41, 49, 50). In ten healthy adult male volunteers, sequential 40-min 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 (45). The visual analog sedation score (0 = very alert and 100 = very sedated) increased to 36 ± 27 and 62 ± 18 from a baseline of 0 with the first two targeted infusion levels (0.5 and 0.8 ng/mL). The two volunteers who received the highest incremental dose (calculated to achieve a plasma concentration of 8.0 ng/mL) were not arousable even with vigorous shaking. Picture recall and recognition were preserved during the lowest incremental infusion (0.5 ng/mL) but were 0% (0 of 10) and 20% (2 of 10), respectively, with the second and third infusion levels (0.8 and 1.2 ng/mL).

Dexmedetomidine's sedative response has been shown to have properties that parallel natural sleep (49, 50). Using functional magnetic resonance imaging (MRI), the blood oxygen level dependent signal, a correlate of local brain activity, changes with dexmedetomidine-induced sedation in a similar fashion to that seen during natural sleep (50). This is different from the pattern that occurs following the administration of midazolam. Using immunohistochemistry and *in situ* hybridization, dexmedetomidine has also been shown to induce a qualitatively similar pattern of *c*-fos expression in sleep-promoting brain nuclei of 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) (49). These effects were attenuated by atipamezole, an α_2-adrenergic antagonist, and did not occur in rats that lacked α_2-adrenergic receptors. These findings suggest a clinical advantage of dexmedetomidine with its pattern of sedation paralleling natural sleep when compared with other agents (barbiturates, benzodiazepines, and propofol) commonly used for ICU sedation. These agents disrupt the normal electroencephalographic patterns of sleep, and these effects may be responsible for the delirium seen in the ICU setting. Given that delirium has been shown to be an independent risk factor of mortality in the adult ICU setting, avoidance of the disruption of the natural sleep cycle may theoretically prevent such problems.

Intracranial Pressure and Cerebral Perfusion Pressure. The effects of dexmedetomidine on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) were evaluated by Talke et al. (51) during the immediate postoperative period following transphenoidal resection of a pituitary tumor in adults. The dexmedetomidine infusion was started postoperatively and administered by a computer-controlled infusion to achieve a plasma concentration of 600 pg/mL. A lumbar intrathecal catheter was used to measure ICP. Although dexmedetomidine had no effect on ICP (highest ICP values in the dexmedetomidine patients were 19 and 20 mm Hg), CPP decreased from baseline of 95 ± 8 to a low of 78 ± 6 mm Hg ($p < .05$). Similar effects on ICP have been reported in an animal study with escalating doses of dexmedetomidine (20, 80, and 320 μg/kg) (52). Dexmedetomidine had no effect on ICP in the baseline state or in animals with intracranial hypertension (mean starting ICP of 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 (53).

Animal and human studies have demonstrated a reduction in cerebral blood flow (CBF) following dexmedetomidine (54, 55). Karlsson et al. (54) demonstrated a reduction of CBF in dogs anesthetized with 0.9% halothane; however, the authors could not determine whether dexmedetomidine directly constricted the cerebral vasculature or blunted the cerebral vasodilatation induced by halothane. Prielipp et al. (55) evaluated changes in CBF in nine healthy adult volunteers using positron emission tomography scanning. Dexmedetomidine dosing included a bolus dose of 1 μg/kg followed by an infusion of either 0.2 (low dose) or 0.6 (high dose) μg/kg/hr. Global CBF (mL/100 g/min) decreased from 91 mL/100 g/min at baseline to 64 mL/100 g/min and 61 mL/100 g/min with the low and high doses, respectively.

Seizure Threshold. Reports in the literature regarding the effects of dexmedetomidine on potential anticonvulsant or proconvulsant effects of dexmedetomidine are mixed (56–59). A lowering of the seizure threshold (proconvulsant effect) with doses of 100 and 500 μg/kg, but not 20 μg/kg, was noted in rats treated with the epileptogenic agent, pentylenetetrazol (56). The effect was blocked by atipamezole. The authors noted that their data were consistent with previous data demonstrating that medications which inhibit central noradrenergic transmission facilitate seizure expression. Dexmedetomidine (doses of 10 and 100 μg/kg, but not 1 μg/kg) also reduced the seizure threshold during enflurane anesthesia in cats (57). Anticonvulsant effects were demonstrated by other investigators (58, 59). Dexmedetomidine (20 μg/kg followed by an infusion of 1 μg/kg/min) increased the dose of cocaine required to cause seizures in Sprague-Dawley rats (58). With a cocaine infusion at 1.25 mg/kg/min, rats treated with dexmedetomidine manifested seizures at 49.3 ± 14.8 mins vs. 25.0 ± 7.7 mins in controls. In Sprague-Dawley rats, the dose of either levobupivacaine or bupivacaine required to induce seizures was higher in rats treated with dexmedetomidine than in controls (59).

Neuroprotection. Various animal models with complete and incomplete as well as transient and permanent ischemic injury have attempted to define dexmedetomidine's protective effects during central nervous system injury. Hoffman et al. (60) evaluated the effect of dexmedetomidine on neurologic and histopathologic outcome from incomplete cerebral ischemia in rats. Dexmedetomidine (10 or 100 μg/kg) was administered intraperitoneally, 30 mins before ischemia, produced by 30 mins of unilateral carotid occlusion combined with phlebotomy-induced hypotension. After 30 mins, the carotid occlusion was removed and the withdrawn blood reinfused. Dexmedetomidine blunted the endogenous release of epinephrine and norepinephrine and improved both histopathologic and neurologic outcome scores when compared with either controls or animals treated with both dexmedetomidine and atipamezole. Serum glucose concentrations were significantly higher in animals receiving dexmedetomidine, which the authors attributed to the α_2-adrenergic inhibition of insulin release.

In a subsequent study, dexmedetomidine (3 or 30 μg/kg) was administered either before and then for 48 hrs after the injury or only following the injury in gerbils exposed to 5 mins of bilateral carotid occlusion (61). Neuronal cells in the hippocampus (CA1 and CA3 regions) and

the dentate gyrus were examined 1 wk following the injury. When compared with controls, there was a significant decrease in the number of ischemic cells in the CA3 region of the hippocampus in rats that received 3 μg/kg but not 30 μg/kg of dexmedetomidine before the injury. No effect was noted with either dose if administered after the injury. In the dentate hilus, there were decreased numbers of ischemic cells in rats that received 3 μg/kg of dexmedetomidine before the injury and those that received 30 μg/kg of dexmedetomidine after the injury. The authors concluded that low-dose dexmedetomidine had neuroprotective effects if administration was started before the ischemic insult and continued for 48 hrs following it.

The same group of investigators evaluated dexmedetomidine in a model comparing transient (90 mins) and permanent ischemia using occlusion of the middle cerebral artery (62). Dexmedetomidine (bolus of 3 μg/kg followed by a 2-hr infusion of either 3 or 6 μg/kg/hr) was administered after middle cerebral artery occlusion. No effect was noted in the animals subjected to a permanent ischemic injury; however, the authors suggested that although not statistically significant, there was a trend toward decreased infarct size following transient ischemia with the higher dose of dexmedetomidine. Infarct volumes in the cortex and the brainstem were 20–30% less in dexmedetomidine-treated animals compared with the controls. In term, 5-day-old mice, dexmedetomidine decreased infarct size and histopathologic evidence of neuronal death induced by the intracerebral injection of the *N*-methyl-D-aspartate agonist, ibotenate (63). An *N*-methyl-D-aspartate agonist was chosen because of the evidence implicating glutamate as a causative agent in hypoxic-ischemic encephalopathy and periventricular white matter lesions in preterm infants.

The preliminary work assumed that dexmedetomidine's neuroprotective effect was the result of its blunting of endogenous catecholamine release during ischemia. Although dexmedetomidine suppresses plasma catecholamine concentrations following cerebral ischemia in rats, it does not alter brain norepinephrine or glutamate levels (64). Dexmedetomidine's neuroprotective effects may be mediated by a reduction in caspase-3 expression (a pro-apoptotic factor) and increased expression of active (autophosphorylated) focal adhesion kinase, a nonreceptor tyrosine kinase that plays a role in cellular plasticity and survival (65).

Miscellaneous CNS Effects. Additional effects on the central and peripheral nervous system include prevention of opioid-induced muscle rigidity and attenuation of shivering. Using hindlimb electromyographic activity, dexmedetomidine abolished increased electromyographic activity associated with alfentanil administration in rats (46). A decreased incidence of fentanyl-induced muscle rigidity during anesthetic induction was demonstrated following dexmedetomidine in adults undergoing coronary artery bypass grafting (15 of 40 or 37.5% vs. 33 of 40 or 82.5%) (66). In the same study, postoperative shivering occurred in 13 of 40 (32.5%) patients who received dexmedetomidine vs. 23 of 40 (57.5%) patients who received placebo. In healthy adult volunteers, the shivering threshold was 36.7 ± 0.3°C in control patients, 36.0 ± 0.5°C with dexmedetomidine ($p < .001$ compared with control), 35.5 ± 0.6°C with meperidine ($p < .001$ compared with control), and 34.7 ± 0.6°C with dexmedetomidine and meperidine ($p < .001$ compared with control) (67).

Miscellaneous End-Organ Effects

Gastrointestinal Motility. Using radiolabeled sodium chromate in a whole animal model (rat), Asai et al. (68) evaluated the effects of clonidine, dexmedetomidine, and morphine on gastrointestinal transit time and gastric emptying. Although all three drugs strongly inhibited gastrointestinal transit time in a dose-dependent manner, morphine's effect on gastric emptying was greater than that of either clonidine or dexmedetomidine, which only weakly inhibited gastric emptying time. Gastric emptying evaluated as the percentage of radioactivity that had entered the small intestine at 30 mins was 88.2% in the control group, 70.9% with clonidine, 78% with dexmedetomidine, and 23% with morphine. Herbert et al. (69) compared the effects of clonidine and dexmedetomidine in an *in vitro* model using an isolated segment of guinea pig ileum with an assessment of the pressure required to induce peristalsis. Inhibition of gastrointestinal motility, defined by the requirement for an increased pressure to stimulate peristalsis, was increased with both clonidine and dexmedetomidine; however, the effect was markedly greater with dexmedetomidine.

Adrenocortical Function. As demonstrated by the classic problems with etomidate, compounds that contain an imidazole ring can inhibit hydroxylase enzymes involved in the production of adrenocorticosteroids. As dexmedetomidine contains an imidazole ring, there are theoretical concerns regarding its effects on steroidogenesis. In a series of *in vitro* and *in vivo* animal studies, the effects of dexmedetomidine on steroidogenesis, binding to glucocorticoid receptors, and adrenocorticotrophic hormone (ACTH)-stimulated release of corticosterone were investigated (70). In the concentrations that are used clinically, there was no evidence to suggest that dexmedetomidine depressed adrenocortical function to the extent that occurs with etomidate. However, the studies did demonstrate that high doses of dexmedetomidine are capable of inhibiting steroidogenesis. In 20 adult patients who required sedation during mechanical ventilation randomized to receive either propofol or dexmedetomidine, there was no difference in cortisol, ACTH, prolactin, and glucose concentrations between the two groups (71). However, some of the dexmedetomidine patients had abnormal ACTH stimulation tests, although these were attributed to their acute surgical illness and not dexmedetomidine. None of the patients were felt to be at risk for adrenocortical failure or manifested clinical symptoms of adrenal dysfunction. The failure to meet the criteria for an acceptable ACTH stimulation test varied according to the criteria used. If an acceptable response following ACTH administration was a peak cortisol concentration ≥400 nmol/L, nine of ten patients had a normal response. If the peak cortisol level following ACTH administration was increased to ≥550 nmol/L, eight of ten had a normal response. However, if there was a requirement to increase the serum cortisol by 200 nmol/L from baseline following ACTH, only five of ten patients met the criterion. 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 had been reported with etomidate.

White Blood Cell Function and Inflammatory Response. In an *in vitro* study, dexmedetomidine was shown to have no effect on white blood cell chemo-

taxis, phagocytosis, or superoxide anion production leading (72). The authors concluded that there is no concern with its use in patients with acute infectious processes (72). They also noted that their data did not demonstrate any beneficial effects in disease processes that involve auto-tissue injury due to neutrophils. Despite this, other data suggest that dexmedetomidine may modify the inflammatory response. In the study by Venn et al. (71), in which patients were randomized to receive either propofol or dexmedetomidine, 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 (72). Additional work has demonstrated that dexmedetomidine may blunt the systemic inflammatory response during endotoxemia (73). In a study that randomized rats to one of four groups (endotoxin administration, saline control, dexmedetomidine, or endotoxin and dexmedetomidine), the mortality rates at 8 hrs after endotoxin administration 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 into 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 investigated the effects of dexmedetomidine on neuromuscular blockade (74, 75). In a rat model, vecuronium was administered by continuous infusion to produce a steady-state depression of the first twitch (T1) of the train-of-four to 53 ± 2% of baseline (74). Dexmedetomidine (10, 30, or 100 μg/kg) had no effect on the T1 height during the initial 30 mins following administration. After 30 mins, there were minor differences between the groups; however, the authors concluded that these effects were unlikely to be of clinical significance. Similar findings were reported by Talke et al. (75) in ten healthy adult volunteers anesthetized with alfentanil and propofol. Rocuronium was administered by continuous infusion to produce a 50% decrease from baseline of the T1 of the train-of-four, followed by dexmedetomidine administered by a computer-controlled infusion to a plasma concentration of 0.6 ng/mL. There was a statistically significant decrease in the T1 height from 51 ± 2% to 44 ± 9% ($p < .0001$) and an increase in plasma rocuronium concentrations. The authors concluded that dexmedetomidine's effects on neuromuscular function are related to alterations of rocuronium pharmacokinetics and not a direct effect on the neuromuscular junction. The authors also emphasized that the effect is small and unlikely to be of clinical significance.

CLINICAL APPLICATIONS

Preliminary Reports

The two initial reports regarding the use of dexmedetomidine in pediatric patients were retrospective case series (76). The first report, involving four pediatric patients, outlined dexmedetomidine use to provide sedation during mechanical ventilation, dexmedetomidine combined with remifentanil as an adjunct for controlled hypotension during posterior spinal fusion, and dexmedetomidine for procedural sedation (76). Although dexmedetomidine was effective in the first two scenarios, dexmedetomidine was ineffective as the sole agent during upper gastrointestinal endoscopy. The second report outlined the use of dexmedetomidine in three patients in the pediatric ICU setting and two in the postanesthesia care unit (77). In the pediatric ICU setting, dexmedetomidine was used for sedation during spontaneous ventilation without airway control in a 4-yr-old with status asthmaticus whose agitation prevented the delivery of inhalational therapy, a 13-yr-old who had significant anxiety following pectus excavatum surgery despite effective pain management with a thoracic epidural catheter, and a 17-yr-old with withdrawal from the recreational use of illicit drugs. In the other two patients, a single bolus dose of dexmedetomidine (0.4–0.5 μg/kg) controlled postoperative emergence delirium and postoperative shivering.

Prevention of Emergence Delirium Following Anesthesia

Five prospective, randomized trials detail the successful use of dexmedetomidine to prevent emergence delirium following general anesthesia in a total of 288 pediatric patients (Table 1) (78–82). The first of these studies randomized 90 children to placebo, dexmedetomidine 0.15 μg/kg, or dexmedetomidine 0.3 μg/kg following anesthetic induction with sevoflurane (78). The incidence of emergence delirium was 37% in the placebo group, 17% with 0.15 μg/kg of dexmedetomidine, and 10% with 0.3 μg/kg. Similar efficacy was reported in the other four studies using dexmedetomidine in doses ranging from 0.5 to 1 μg/kg as a bolus dose or an infusion of 0.2 μg/kg/hr (79–82). These studies note up to an eight- to ten-fold decrease in the incidence of emergence delirium when compared with placebo. Dexmedetomidine was effective regardless of the anesthetic used (sevoflurane or desflurane) and the type of surgical procedure. Although four of the studies reported no difference in time to emergence and tracheal extubation (78, 79, 81, 82), Guler et al. (80) noted that both time to emergence (5.03 ± 2.3 vs. 3.30 ± 1.3 mins, $p < 0.05$) and time to extubation (9.30 ± 2.9 vs. 7.20 ± 2.7 mins, $p < .05$) were longer with dexmedetomidine vs. placebo.

Sedation in the Pediatric ICU (Mechanical Ventilation and Spontaneous Ventilation)

There is currently only one prospective, randomized trial evaluating dexmedetomidine for sedation during mechanical ventilation in infants and children (Table 2). Thirty infants and children requiring sedation during mechanical ventilation were randomized 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 μg/kg/hr or 0.5 μg/kg/hr (83). Morphine (0.1 mg/kg) was provided as needed with an increase of the midazolam or dexmedetomidine infusion in 20% increments if necessary. The efficacy of the sedation regimens was assessed using the Ramsay sedation score and the need for supplemental morphine, whereas the depth of sedation was compared using the Bispectral Index. Dexmedetomidine at 0.25 μg/kg/hr was as effective as midazolam at 0.22 mg/kg/hr, whereas the higher dose of dexmedetomidine (0.5 μg/kg/hr) was more effective. With the higher dose of dexmedetomidine, although sedation scores and the Bispectral Index were equivalent, there was a decreased need for supplemental morphine (0.28 ± 0.12 vs. 0.74 ± 0.5 mg/kg/24 hrs). Two of ten patients receiving dexmedetomidine at 0.5 μg/kg/hr had a Ramsay score of 1 at any time vs. six of ten patients receiving midazolam. There was a decrease in the

Table 1. Dexmedetomidine to prevent emergence delirium following general anesthesia

Author and Reference	Type of Study and No. of Patients	Dexmedetomidine Dosing	Findings
Ibacache et al. (78)	Prospective, randomized trial, n = 90	Placebo or one of two doses of dexmedetomidine (0.15 or 0.3 μg/kg) following the induction of general anesthesia.	No difference in the time to awakening and tracheal extubation. The incidence of emergence delirium with sevoflurane was 37% in the placebo group, 17% with 0.15 μg/kg dexmedetomidine, and 10% with 0.3 μg/kg.
Hanafy et al. (79)	Prospective, randomized trial, n = 46	Placebo or dexmedetomidine (0.5 μg/kg) following the induction of general anesthesia.	Dexmedetomidine patients were less likely to exhibit agitation, were less likely to require treatment for agitation, and had lower pain scores. There was no difference in recovery time.
Guler et al. (80)	Prospective, randomized trial, n = 60	Placebo or dexmedetomidine (0.5 μg/kg) prior to emergence.	Dexmedetomidine patients had a decreased incidence of severe agitation, pain, and coughing during recovery. Times to tracheal extubation and emergence were longer with dexmedetomidine.
Shukry et al. (81)	Prospective randomized trial, n = 50	Placebo or dexmedetomidine (infusion of 0.2 μg/kg/hr) started after anesthetic induction and continued for 15 mins into the recovery phase.	The incidence and the number of episodes of emergence delirium were decreased with dexmedetomidine compared with placebo. There were no differences in pain scores and the times to tracheal extubation and discharge from the recovery room.
Isik et al. (82)	Prospective randomized trial, n = 42	Placebo or dexmedetomidine (1 μg/kg) after the induction of general anesthesia for magnetic resonance imaging.	No differences in hemodynamic variables. Times to removal of the laryngeal mask airway and eye opening with verbal stimuli were shorter with placebo. No difference in recovery room and hospital discharge time. The incidence of emergence agitation was 4.8% with dexmedetomidine and 47.6% with placebo.

number of Ramsay scores of 1 (five with dexmedetomidine at 0.5 μg/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 μg/kg/hr) were <12 months of age.

One retrospective case series and two other case reports detailed the use of dexmedetomidine for sedation during mechanical ventilation (Table 2) (84–86). The first of these outlined the use of dexmedetomidine as part of a rotating sedation regimen in an attempt to prevent the development of tolerance and withdrawal during prolonged sedation regimens (84). The second remains the only report of the administration of a dexmedetomidine infusion for >24 hrs for sedation during mechanical ventilation in a child (85). The final of these reports details the use of dexmedetomidine to transition from fentanyl/midazolam sedation before extubation in a 12-yr-old who was status post heart transplantation and required mechanical ventilation for respiratory failure (86).

In another potential application for the pediatric ICU setting, Chrysostomou et al. (87) retrospectively reviewed their experience with dexmedetomidine infusions following cardiac and thoracic surgical procedures in 38 patients with a mean age of 8 ± 1 yrs. Seven patients (18%) were <1 yr of age and 33 (87%) were extubated and breathing spontaneously. The dexmedetomidine infusion without a loading dose was started following the surgical procedure at 0.1–0.5 μg/kg/hr (0.32 ± 0.15 μg/kg/hr). The infusion was continued for 3–26 hrs (14.7 ± 5.5 hrs) at 0.1–0.75 μg/kg/hr (0.3 ± 0.05 μg/kg/hr). Mild to moderate sedation was achieved 93% of the time and no to mild pain 83% of the time. Forty-nine doses of rescue agents were required for either sedation or analgesia (1.3 ± 0.26 boluses per patient). Twenty-nine (60%) were required during the first 5 hrs of the dexmedetomidine infusion. There was a trend toward a requirement for a higher dexmedetomidine infusion and more rescue doses in patients <1 yr of age compared with those >1 yr of age (0.4 ± 0.13 vs. 0.29 ± 0.17 μg/kg/hr). Bradycardia occurred in one patient, 15 mins after starting the dexmedetomidine infusion, and resolved with its discontinuation. Transient hypotension was noted in six patients (15%) and resolved with decreasing the dexmedetomidine infusion in three and with discontinuation of the infusion in three.

Procedural Sedation (Noninvasive Procedures)

Reports of dexmedetomidine for noninvasive procedural sedation are summarized in Table 3. Preliminary data were provided by Nichols et al. (88), who used dexmedetomidine for "rescue sedation" during radiologic imaging (computed tomography and MRI) in five patients ranging in age from 11 months to 16 yrs when a combination of chloral hydrate and midazolam was ineffective. Four prospective trials have evaluated the efficacy of dexmedetomidine for sedation during noninvasive radiologic imaging (89–92).

Koroglu et al. (89) randomized 80 children (1–7 yrs of age) to dexmedetomidine or midazolam during MRI. Dexmedetomidine was administered as a loading dose of 1 μg/kg over 10 mins followed by an infusion of 0.5 μg/kg/hr, whereas midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 μg/kg/hr. 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.

Table 2. Dexmedetomidine for sedation in the pediatric intensive care unit

Author and Reference	Type of Study and No. of Patients	Dexmedetomidine Dosing	Findings
Tobias and Berkenbosch (83)	Prospective randomized trial, n = 30	Midazolam at 0.1 mg/kg/hr vs. dexmedetomidine at either 0.25 or 0.5 μg/kg/hr with doses of morphine as required.	Dexmedetomidine at 0.25 μg/kg/hr was as effective as midazolam at 0.22 mg/kg/hr, whereas dexmedetomidine at 0.5 μg/kg/hr was more effective. Patients receiving dexmedetomidine at 0.5 μg/kg/hr had a decreased need for supplemental morphine (0.28 ± 0.12 vs. 0.74 ± 0.5 mg/kg/24 hrs), and fewer patients manifested a Ramsay score of 1 (two of ten vs. six of ten).
Wheeler et al. (84)	Retrospective case report, n = 2, compared with historical controls, n = 5	Rotating sedation (continuous infusion of midazolam, fentanyl, or dexmedetomidine) in patients who required sedation for 5 days.	Patients who received the rotating sedation regimen did not develop tolerance or manifest withdrawal symptoms and were discharged earlier (days 6–7 vs. 8–10 days) when compared with patients who received a single agent for 5 days.
Hammer et al. (85)	Case report, n = 1	Continuous infusion of 0.2–0.5 μg/kg/hr.	Dexmedetomidine infusion provided effective sedation during mechanical ventilation when escalating doses of midazolam and fentanyl were ineffective.
Chrysostomou et al. (86)	Case report, n = 1	Dexmedetomidine infusion of 0.2 μg/kg/hr to start; later increased to 0.4 μg/kg/hr.	12-year-old status post cardiac transplantation with respiratory failure. Infusion started 20 hrs prior to tracheal extubation and continued for 6 hrs afterward to provide sedation and allow for transition from fentanyl/midazolam sedation to spontaneous ventilation in a patient who had failed two previous attempts at extubation.
Chrysostomou et al. (87)	Retrospective review, n = 38	Cohort of patients following cardiac surgery. No loading dose. Initial infusion started at 0.32 ± 0.15 μg/kg/hr followed by a mean infusion at 0.3 ± 0.05 μg/kg/hr.	Mild to moderate sedation achieved 93% of the time, whereas no to mild pain was reported 83% of the time. A total of 49 rescue doses of a sedative or analgesic were required (1.3 ± 0.26 boluses per patient). Bradycardia occurred in one patient and resolved with its discontinuation. Transient hypotension was noted in six patients (15%) and resolved with decreasing the dexmedetomidine infusion in three and with discontinuation in three.

Similar efficacy was reported by Berkenbosch et al. (90) in an open-label trial during MRI in 48 pediatric patients ranging in age from 5 months to 16 yrs. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg over 5 mins and repeated as needed to achieve the desired level of sedation. Following this, a continuous infusion was started at a rate in μg/kg/hr, which was equivalent to the loading dose. Fifteen patients had failed chloral hydrate and/or midazolam, and 33 patients received dexmedetomidine as the primary agent. The mean loading dose was 0.92 ± 0.36 μg/kg followed by an infusion of 0.69 ± 0.32 μg/kg/hr. Effective sedation was achieved in all patients, and the scan was completed without other agents. Recovery time was longer in patients who had received other agents before dexmedetomidine than in those who received dexmedetomidine as a primary agent (117 ± 41 vs. 69 ± 34 mins).

A second study by Koroglu et al. (91) randomized 60 children to dexmedetomidine or propofol during MRI. Dexmedetomidine was administered as a loading dose of 1 μg/kg over 10 mins followed by an infusion of 0.5 μg/kg/hr, whereas propofol was administered as a loading dose of 3 mg/kg followed by an infusion of 100 μg/kg/hr. Although equally effective in providing sedation, induction time, recovery time, and discharge times were shorter with propofol. Adverse effects including hypotension and oxygen desaturation were more common with propofol. Oxygen desaturation requiring intervention (chin lift, discontinuation of the infusion, and supplemental oxygen) occurred in four children receiving propofol vs. none of those receiving dexmedetomidine.

In a retrospective review of prospective data from their quality assurance database, Mason et al. (92) presented data regarding dexmedetomidine for sedation in 62 children during radiologic imaging. Dexmedetomidine was administered as a loading dose of 2 μg/kg over 10 mins and repeated to achieve effective sedation, after which an infusion was started at 1 μg/kg/hr. The mean loading dose was 2.2 μg/kg, with 52 patients requiring only the initial dose of 2 μg/kg. The time to achieve sedation was 9.9 ± 2.4 mins (range 6–20 mins). Sinus arrhythmias were noted in ten patients (16%). Although HR and BP decreased in all patients, no treatment was necessary and no value was less than the fifth percentile for age. No changes were observed in end-tidal CO_2, and no patient developed oxygen desaturation while breathing room air. Two patients manifested significant agitation during the administration of the loading dose and were switched to other sedative agents (propofol or pentobarbital).

Anecdotal case reports have also demonstrated the efficacy of dexmedetomidine for sedation during cardiac MRI and radiation therapy (93–96). A final report regarding the use of dexmedetomidine for noninvasive procedural sedation describes the combination of dexmedetomidine and ketamine for three patients with trisomy 21 and obstructive sleep apnea requiring sedation during static and dynamic cine MRI (97). Effective sedation was provided by an initial bolus dose of ketamine (1 mg/kg) and dexmedetomidine (1 μg/kg) followed by a continuous infusion of dexmedetomidine (1 μg/kg/hr).

Table 3. Dexmedetomidine for noninvasive procedural sedation in infants and children

Author and Reference	Type of Study and No. of Patients	Dexmedetomidine Dosing	Findings
Koroglu et al. (89)	Prospective, randomized trial, n = 80	Dexmedetomidine (loading dose of 1 μg/kg over 10 mins → an infusion of 0.5 μg/kg/hr) vs. midazolam (loading dose of 0.2 mg/kg followed by an infusion of 6 μg/kg/hr).	The quality of sedation during radiologic imaging was better and the need for rescue sedation was less (eight of 40 vs. 32 of 40) with dexmedetomidine compared with midazolam.
Berkenbosch et al. (90)	Prospective, open-label trial, n = 48	Loading dose of 0.5 μg/kg over 5 mins, repeated as needed to achieve an acceptable level of sedation. Continuous infusion equal to loading dose.	Dexmedetomidine was effective either after other agents had failed (n = 15) or as a primary agent (n = 33) for radiologic imaging. Sedation initiated with 0.92 ± 0.36 μg/kg followed by an infusion of 0.69 ± 0.32 μg/kg/hr.
Koroglu et al. (91)	Prospective, randomized trial, n = 60	Dexmedetomidine (loading dose of 1 μg/kg over 10 mins → an infusion of 0.5 μg/kg/hr) vs. propofol (3 mg/kg followed by an infusion of 100 μg/kg/hr).	Onset of sedation, recovery, and discharge times were significantly shorter with propofol. Hypotension and oxygen desaturation noted with propofol but not dexmedetomidine.
Mason et al. (92)	Prospective, open-label trial, n = 62	Dexmedetomidine (loading dose of 2 μg/kg over 10 mins and repeated as needed followed by an infusion of 1 μg/kg/hr).	Effective sedation in all but two patients who required alternative sedation when they became increasingly agitated during the loading dose.
Shukry and Ramadhyani (93)	Case report, n = 1	Loading dose of 1 μg/kg → infusion of 0.7–0.8 μg/kg/hr.	Dexmedetomidine as sole agent for sedation during radiation therapy in nine of 12 procedures, with additional sedation (propofol 5–10 mg) required in three.
Young (94)	Case report, n = 1	Loading dose of 1 μg/kg → infusion of 0.5 μg/kg/hr.	Additional propofol (5 mg) needed after loading dose to induce somnolence otherwise effective sedation was achieved.
Fahy and Okumura (95)	Case report, n = 1	Infusion of 0.3–0.7 μg/kg/hr for first course of therapy. Loading dose of 1 μg/kg → infusion up to 1.4 μg/kg/hr for second course.	In both cases, propofol (20 μg/kg/hr) required to provide effective sedation.
Kunisawa and Iwasaki (96)	Case report, n = 1	Premedication with diazepam and atropine orally followed by dexmedetomidine (1 μg/kg → 0.7 μg/kg/hr).	Successful sedation. Patient was not fully awake for 210 mins.
Luscri and Tobias (97)	Case series, n = 3	Loading dose of ketamine (1 mg/kg) and dexmedetomidine (1 μg/kg) → infusion of 1 μg/kg/hr.	One patient required a repeat of the bolus doses of ketamine and dexmedetomidine and an increase of the infusion to 2 μg/kg/hr. Brief episode of upper airway obstruction in one patient, which responded to repositioning of the airway. The maximum end-tidal CO_2 values were 49, 53, and 52 mm Hg in the three patients.

Procedural Sedation (Invasive Procedures)

There have been mixed results when using dexmedetomidine for invasive procedures (Table 4). Although Tobias and Berkenbosch (76) reported that dexmedetomidine was not effective for upper gastrointestinal endoscopy in an 11-yr-old boy, Jooste et al. (98) reported successful sedation with dexmedetomidine during fiberoptic intubation in two pediatric patients, both of whom were 10 yrs old, who presented for operative procedures and evidence of cervical spinal cord compromise. Similar success with dexmedetomidine for sedation during fiberoptic intubation of the trachea has been reported in adults (99, 100).

In the first prospective evaluation of dexmedetomidine as the lone agent during an invasive procedure in infants and children, Munro et al. (101) reported their experience with dexmedetomidine during cardiac catheterization. Following premedication with midazolam and the placement of intravenous access with the inhalation of sevoflurane, the inhalational anesthetic agent was discontinued and dexmedetomidine administered (1 μg/kg over 10 mins followed by an infusion of 1 μg/kg/hr titrated up to 2 μg/kg/hr as needed). The average maintenance infusion rate was 1.15 ± 0.29 μg/kg/hr (range, 0.6–2.0 μg/kg/hr). Five patients (25%) moved during local infiltration of the groin, which did not require treatment or interfere with cannulae placement. Twelve (60%) patients received a propofol bolus during the procedure for movement, an increasing Bispectral Index number, or anticipation of a stimulus. No adverse hemodynamic or respiratory effects were noted.

Table 4. Dexmedetomidine for invasive procedural sedation in children

Author and Reference	Type of Study and No. of Patients	Dexmedetomidine Dosing	Findings
Tobias and Berkenbosch (76)	Case report, n = 1	Dexmedetomidine 0.6 μg/kg → 0.5 μg/kg/hr. BIS number decreased to 89. Bolus repeated. BIS number decreased to 42.	With the introduction of the endoscope into the patient's mouth, the BIS number increased to 98 and the patient became distressed. Procedure completed with midazolam/ketamine sedation.
Jooste et al. (98)	Case report, n = 2	Incremental doses of midazolam to 0.1 mg/kg followed by dexmedetomidine (1 μg/kg → 0.7 μg/kg/hr). The sedation regimen was supplemented with topical anesthesia of the airway using 1% lidocaine.	Adequate sedation to allow for fiberoptic intubation of the trachea without patient movement or coughing in two 10-year-old pediatric patients with cervical spine abnormalities and cervical spinal cord compromise.
Munro et al. (101)	Prospective, open-label trial, n = 20	Dexmedetomidine (1 μg/kg over 10 mins followed by an infusion of 1 μg/kg/hr and titrated up to 2 μg/kg/hr as needed).	Average dexmedetomidine infusion rate of 1.15 ± 0.29 μg/kg/hr (range, 0.6–2.0 μg/kg/hr). Five patients (25%) moved during local infiltration of the groin. Twelve (60%) received a propofol bolus during the procedure for movement, an increasing BIS number, or anticipation of a stimulus. No adverse hemodynamic or respiratory effects noted.
Tosun et al. (105)	Prospective, randomized trial, n = 44	Ketamine (1 mg/kg) + dexmedetomidine (1 μg/kg) administered over 10 mins followed by dexmedetomidine (0.7 μg/kg/hr) and ketamine (1 mg/kg/hr) or propofol (1 mg/kg) and ketamine (1 mg/kg) followed by propofol (100 μg/kg/hr) and ketamine (1 mg/kg/hr). Supplemental ketamine (1 mg/kg) as needed.	Patients sedated with ketamine and dexmedetomidine required more ketamine and had longer recovery times (median time of 45 vs. 20 mins) than patients sedated with propofol and ketamine. No clinically significant difference was noted in hemodynamic and respiratory variables. Convulsions occurred during the maintenance sedation phase in two patients receiving the dexmedetomidine-ketamine combination; however, the exact etiology could not be determined.

BIS, Bispectral Index.

However, dexmedetomidine has failed as the sole agent for sedation in other scenarios in the adult population. Jalowiecki et al. (102) found dexmedetomidine to be ineffective during colonoscopy, to be associated with a high incidence of adverse effects, and to delay discharge in adults, and the authors therefore abandoned the study before completion. Similar issues were encountered when dexmedetomidine was compared with midazolam for monitored anesthesia care in adults during cataract surgery (103).

Given its limited analgesic effects, dexmedetomidine may not be the ideal agent for painful procedures. Anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be effective in such scenarios. Scher and Gitlin (104) reported the successful use of dexmedetomidine (bolus of 1 μg/kg followed by an infusion of 0.7 μg/kg/hr) and ketamine (15 mg followed by an infusion of 20 mg/hr) for procedural sedation (awake fiberoptic intubation in an adult patient). Tosun et al. (105) compared a dexmedetomidine-ketamine combination with a propofol-ketamine combination in 44 children (4 months to 16 yrs) with acyanotic congenital heart disease undergoing cardiac catheterization. Ketamine (1 mg/kg) and dexmedetomidine (1 μg/kg) were administered over 10 mins followed by an infusion at 0.7 μg/kg/hr of dexmedetomidine and 1 mg/kg/hr of ketamine. In the other arm of the study, propofol (1 mg/kg) and ketamine (1 mg/kg) were administered as the loading dose followed by an infusion of propofol (100 μg/kg/hr) and ketamine (1 mg/kg/hr). Supplemental ketamine (1 mg/kg) was given as needed. Although sedation was managed effectively with both regimens, patients sedated with ketamine-dexmedetomidine required more ketamine (2.03 ± 1.33 vs. 1.25 ± 0.67 mg/kg/hr, $p < .01$) and more supplemental doses of ketamine (10/22 vs. four of 22) and had longer recovery times (median time of 45 vs. 20 mins, $p = .01$) than patients sedated with a propofol-ketamine combination. No clinically significant differences were noted in hemodynamic and respiratory variables. During the maintenance sedation phase, two patients receiving the dexmedetomidine-ketamine combination had convulsions. Neither had a history of previous neurologic problems, and the authors could not determine the cause of the seizure activity.

Despite the limited data, the combination of dexmedetomidine with ketamine makes pharmacologic sense as the two medications have the potential to balance the hemodynamic and adverse effects of the other. Dexmedetomidine may prevent the tachycardia, hypertension, salivation, and emergence phenomena from ketamine, whereas ketamine may prevent the bradycardia and hypotension that have been reported with dexmedetomidine (106). Additionally, ketamine as part of the sedation induction may speed the onset of sedation and eliminate the slow onset time when dexmedetomidine is used as the sole agent and the loading dose is administered over 10 mins.

Table 5. Anecdotal reports of dexmedetomidine to control withdrawal in infants and children

Authors and Reference	Patient Demographics	Dexmedetomidine Dosing Regimen
Finkel and Elrefai (115)	8-month-old infant with Hurler syndrome who required prolonged sedation during mechanical ventilation. Using a Bispectral Index monitor, the authors titrated the dexmedetomidine infusion after discontinuation of midazolam and fentanyl infusions.	Dexmedetomidine (0.2–0.7 μg/kg/hr) was continued for 7 days and then tapered over a 24-hr period. This allowed for withdrawal of benzodiazepines and opioids.
Baddigam et al. (116)	17-year-old with infected aortic valve. History of cannabinoid, tobacco, ethanol, and other substance abuse. Manifested withdrawal symptoms during postoperative period.	Dexmedetomidine, loading dose of 0.5 μg/kg → infusion of 0.25 μg/kg/hr, controlled the withdrawal behavior (diaphoresis, agitation, tachycardia, and hypertension).
	4-month-old infant, status post repair of congenital heart disease. Withdrawal behavior after fentanyl sedation during mechanical ventilation.	Dexmedetomidine, loading dose of 0.5 μg/kg → infusion of 0.25 μg/kg/hr, controlled withdrawal behavior. Dexmedetomidine weaned over 48–72 hrs.
	55-day-old infant, status post palliation of congenital heart disease. Withdrawal behavior after fentanyl for sedation during mechanical ventilation.	Dexmedetomidine, loading dose of 0.5 μg/kg → infusion of 0.25 μg/kg/hr, controlled withdrawal behavior.
Finkel et al. (117)	Two pediatric patients (6-month-old and 7-year-old) who were status post cardiac transplantation. Withdrawal behavior following the prolonged administration of opioids and benzodiazepines.	Dexmedetomidine, loading dose of 1 μg/kg → infusion of 0.8–1.0 μg/kg/hr, controlled the withdrawal behavior. Dexmedetomidine infusions administered and then weaned for a total duration of use of 8 and 16 days in the two patients.

Intraoperative Applications

In addition to the report of Tobias and Berkenbosch (76), which reported the use of dexmedetomidine combined with remifentanil to provide controlled hypotension during posterior spinal fusion, two other reports have described the intraoperative use of dexmedetomidine, both of which entail its use for awake neurosurgical procedures in pediatric patients (107, 108). Ard et al. (107) used dexmedetomidine to provide sedation during awake craniotomy in two patients, both of whom were 12 yrs old. Anesthesia for skin incision, craniotomy, and dural opening were provided by sevoflurane, fentanyl, and nitrous oxide via a laryngeal mask airway. Dexmedetomidine (0.1–0.3 μg/kg/hr) provided sedation during the tumor resection and provided an awake and cooperative patient to allow identification of critical language areas. For this part of the procedure, the other anesthetic agents were discontinued and the laryngeal mask airway was removed. Similar success was reported by Everett et al. (108) in two additional pediatric patients undergoing awake craniotomy, both of whom were 16 yrs of age.

Treatment of Withdrawal

Regardless of the agent responsible for withdrawal, the potential role of dexmedetomidine in treating such problems is supported by animal studies (109–112), case reports in adults and children (113–117), and one retrospective case series in infants (Table 5) (118). The largest series reported in either the adult or pediatric population regarding the use of dexmedetomidine to control withdrawal is a retrospective review of seven infants ranging in age from 3 to 24 months (118). The patients had received a continuous fentanyl infusion supplemented with intermittent doses of midazolam for during mechanical ventilation. Withdrawal was documented by a Finnegan score $\geq$12. Dexmedetomidine was administered as a loading dose of 0.5 μg/kg/hr followed by an infusion of 0.5 μg/kg/hr. The loading dose was repeated and the infusion increased to 0.7 μg/kg/hr in the two patients who had received the highest doses of fentanyl (8.5 $\pm$ 0.7 vs. 4.6 $\pm$ 0.5 μg/kg/hr, $p < .0005$). Withdrawal was controlled, and subsequent Finnegan scores were $\leq$7.

Miscellaneous Applications

Four additional reports have appeared in the literature describing the use of dexmedetomidine in the pediatric population (119–122). Khasawinah et al. (119) reported the successful use of dexmedetomidine in three patients to control the signs and symptoms of cyclic vomiting syndrome, a disorder thought to be related to alterations in the central control of the sympathetic nervous system, which manifests as recurrent bouts of vomiting. Zub et al. (120) evaluated the potential efficacy of oral dexmedetomidine in 13 patients ranging in age from 4 to 14 yrs. Oral dexmedetomidine in doses ranging from 1.0 to 4.2 μg/kg was used as premedication before inhalational anesthetic induction or to facilitate intravenous cannula placement before procedural sedation in nine patients with neurobehavioral disorders. Effective sedation was achieved in 11 of the 13 patients. An anecdotal report in a 14-yr-old suggested the potential efficacy of dexmedetomidine in the treatment of chronic regional pain syndrome type I (121). The final report in the pediatric population describes the postoperative administration of dexmedetomidine to control shivering following general anesthesia (122). Dexmedetomidine (0.5 μg/kg over 3–5 mins) was administered in a prospective, open-label fashion to 24 children ranging in age from 7 to 16 yrs of age. Shivering behavior ceased within 5 mins with a mean onset time of 3.5 $\pm$ 0.9 mins.

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 hrs in adult ICU patients who are initially intubated and receiving mechanical ventilation. To date, there are no FDA-approved indications for its use in children, but with ongoing encouragement from the medical community, it is hoped that the manufacturers will seek FDA approval for

Table 6. Potential adverse effect profile of dexmedetomidine

Cardiovascular
Bradycardia or sinus pause/arrest
Hypotension
Decreased cardiac output
Hypertension
Sinus arrhythmia
Decreased central sympathetic nervous system activity
Increased pulmonary vascular resistance and pulmonary artery pressure (single animal study)
Respiratory
Increased resting $Paco_2$
Decreased minute ventilation at rest and during CO_2 challenge
Irregular breathing pattern
Apnea (obstructive)
Central nervous system
Ineffective sedation and/or analgesia
Paradoxical agitation
Potentiation of neuromuscular blockade (clinically insignificant)
Proconvulsant effect (animal study)
Decreased cerebral perfusion due to effect on mean arterial pressure

Table 7. Reported applications of dexmedetomidine in pediatric patients

Sedation during mechanical ventilation
Adjunct for controlled hypotension during orthopedic surgery
Procedural sedation
Upper gastrointestinal endoscopy (not effective as sole agent)
Noninvasive radiologic imaging
Radiation therapy
Cardiac catheterization (as sole agent and with ketamine)
Fiberoptic tracheal intubation
Treatment of substance withdrawal (iatrogenic and from illicit drug use)
Sedation in the pediatric intensive care unit during spontaneous ventilation without endotracheal intubation
Treatment and prevention of emergence delirium following general anesthesia
Treatment of shivering following general anesthesia
Provision of postoperative sedation and analgesia awake craniotomy
Part of an intraoperative anesthetic technique for awake craniotomy
Oral administration as a premedicant for the operating room or prior to procedural sedation
Treatment of cyclic vomiting syndrome
Intravenous regional anesthesia in the treatment of chronic regional pain syndrome type I

various clinical scenarios within the pediatric population (123).

As with any sedative agent, the potential exists for adverse end-organ effects with dexmedetomidine. Although the current literature suggests that these events are relatively uncommon with dexmedetomidine, the hemodynamic or respiratory effects should they occur have the potential for significant morbidity or even mortality in critically ill infants and children (Table 6). Potential cardiovascular effects include 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} agonist with peripheral vasoconstriction. Hypotension and bradycardia occur more commonly with the initial loading dose, with comorbid cardiovascular disease, and when coadministered with other medications that have negative chronotropic effects. A single animal study (n = 6) suggested that MPAP and PVR may be transiently elevated following dexmedetomidine. There are conflicting reports in the literature regarding effects on ventilatory function, with some studies (both human and animal) demonstrating respiratory depression with mild increases of $Paco_2$ (4–5 mmHg), decreased minute ventilation, decreased response to CO_2 challenge using CO_2 response curves, or upper airway obstruction following bolus doses of 1 or 2 μg/kg. Despite these reports, other animal and human studies have suggested no effect on respiratory function. Although dexmedetomidine has no direct effect on ICP, its hemodynamic effects may decrease 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. As with any agent used for sedation and/or analgesia, failures will occur, and at times it may be necessary to switch to alternative agents. Despite these concerns, anecdotal evidence demonstrates the potential safety of this drug even when drug errors occur such as infusing the medication in μg/kg/min instead of μg/kg/hr (124). If there is a concern regarding the potential adverse effect profile of dexmedetomidine in critically ill infants and children, various precautions should be considered including omitting the loading dose, using a lower loading dose, administering the loading dose over a longer period of time, and using a continuous infusion starting at the lower end of the recommended dosing range.

Dexmedetomidine is available as a 2-mL, 100-μg/mL solution that can be diluted in 50 mL of saline to provide a 4-μg/mL solution that can be administered via a peripheral or central vein. Acquisition costs vary from $50 to $80 per vial. To date, the literature contains reports of its use in approximately 800 pediatric patients. Given is favorable sedative and anxiolytic properties combined with its limited effects on hemodynamic and respiratory function, there is growing interest in the use of dexmedetomidine in the pediatric population in various clinical scenarios, including sedation during mechanical ventilation, procedural sedation, the treatment of withdrawal, and prevention of emergence agitation (Table 7). It may also be an effective agent for the provision of sedation and anxiolysis in situations where the maintenance of spontaneous ventilation is required, and therefore it may play a role in combination with regional anesthetic techniques or patient-controlled analgesia following major surgical procedures. Although dexmedetomidine may not be effective as the sole agent, there may be a role for the combination of dexmedetomidine with analgesic agents such as ketamine for painful invasive procedures.

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