JPPT

BRIEF REVIEW ARTICLE

Dexmedetomidine Use in Pediatric Intensive Care and Procedural Sedation

Marcia L. Buck, PharmD

Departments of Pharmacy Services and Pediatrics, University of Virginia Children's Hospital, Charlottesville, Virginia

OBJECTIVE Dexmedetomidine was approved by the Food and Drug Administration in 1999 for the sedation of adults receiving mechanical ventilation in an intensive care setting. It provides sedation with minimal effects on respiratory function and may be used prior to, during, and following extubation. Based on its efficacy in adults, dexmedetomidine is now being explored as an alternative or adjunct to benzodiazepines and opioids in the pediatric intensive care setting. This review describes the studies evaluating the safety and efficacy dexmedetomidine in infants and children and provides recommendations on dosing and monitoring.
METHODS The MEDLINE (1950-November 2009) database was searched for pertinent abstracts, using the key term dexmedetomidine. Additional references were obtained from the bibliographies of the articles reviewed and the manufacturer. All available English-language case reports, clinical trials, retrospective studies, and review articles were evaluated.
RESULTS Over two dozen case series and clinical studies have documented the utility of dexmedetomidine as a sedative in children requiring mechanical ventilation or procedural sedation. In several papers, dexmedetomidine use resulted in a reduction in the dose or discontinuation of other sedative agents. It may be of particular benefit in children with neurologic impairment or in those who do not tolerate benzodiazepines. The most frequent adverse effects reported with dexmedetomidine have been hypotension and bradycardia, in 10% to 20% of patients. These effects typically resolve with dose reduction.
CONCLUSIONS Dexmedetomidine offers an additional choice for the sedation of children receiving mechanical ventilation in the intensive care setting or requiring procedural sedation. While dexmedetomidine is well tolerated when used at recommended doses, it has the potential to cause hypotension and bradycardia and requires close monitoring. In addition to clinical trials currently underway, larger controlled studies are needed to further define the role of dexmedetomidine in pediatric intensive care.

KEYWORDS analgesia, child, dexmedetomidine, infant, intensive care, sedation

J Pediatr Pharmacol Ther 2010;15:17–29

INTRODUCTION

Dexmedetomidine is a selective alpha$_2$-adrenergic agonist. It is structurally related to clonidine (Figure), but has a much greater affinity for alpha$_2$-receptors over alpha$_1$-receptors (with a ratio of 1,600:1, compared to 200:1 for clonidine). Dexmedetomidine has activity at a variety of locations throughout the central nervous system. The sedative and anxiolytic effects of dexmedetomidine result primarily from its activity in the locus ceruleus of the brainstem. Stimulation of alpha$_2$-adrenergic receptors at this site reduces central sympathetic output, resulting in increased firing

see Editorial on page 4

ABBREVIATIONS BIS, Bispectral Index Monitor; EEG, electroencephalogram; IV, intravenous; MRI, magnetic resonance imaging; OSA, obstructive sleep apnea; PICU, Pediatric Intensive Care Unit

Address correspondence to: Marcia L. Buck, PharmD, FCCP, FPPAG, Department of Pharmacy Services, Box 800674, University of Virginia Health System, Charlottesville, VA 22908, email: mlb3u@virginia.edu

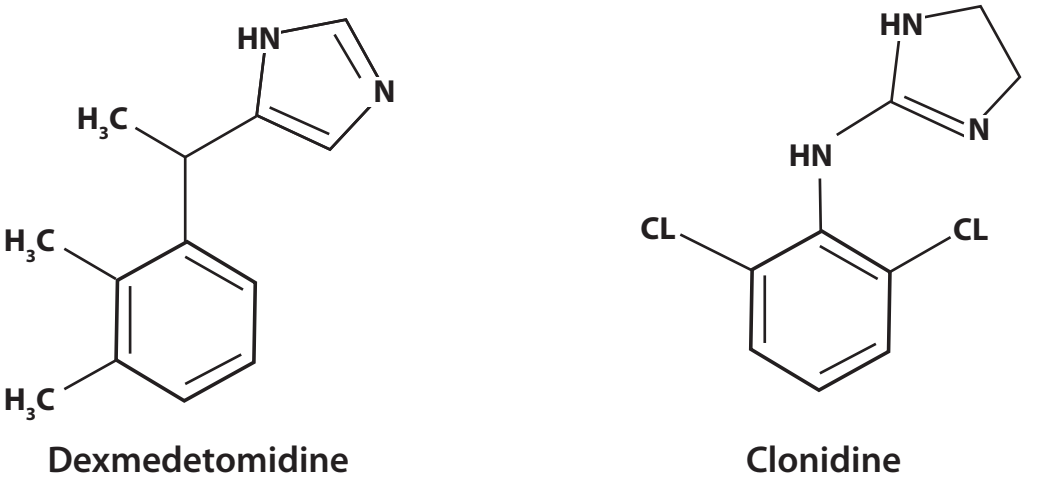

Figure. Comparison of Chemical Structure of Dexmedetomidine and Clonidine

of inhibitory neurons. The presence of dexmedetomidine at alpha$_2$-adrenergic receptors in the dorsal horn of the spinal cord modulates release of substance P and produces its analgesic effects.[1,2]

Dexmedetomidine was approved by the United States Food and Drug Administration on December 24, 1999, for the sedation of adults receiving mechanical ventilation in an intensive care setting. It received an additional indication for sedation of non-intubated patients prior to or during surgery or other medical procedures on October 17, 2008. At the recommended infusion rate of 0.2 to 0.7 mcg/kg/hr, dexmedetomidine provides sedation with minimal effects on respiratory function and may be used prior to, during, and following extubation. In clinical trials of adults, it produced the desired level of sedation in approximately 80% of patients, without the use of additional agents. In those receiving midazolam or morphine, it allowed the dose of each agent to be reduced.[1,2] Based on its efficacy in adults, dexmedetomidine is now being explored as an alternative or adjunct to benzodiazepines and opioids in the pediatric intensive care setting. Over two dozen case series and studies have been published evaluating the safety and efficacy of dexmedetomidine in infants and children. This review will summarize the current literature and provide recommendations for dexmedetomidine use in children.

PHARMACOKINETICS

After intravenous (IV) administration, dexmedetomidine has a rapid distribution phase, with a distribution half-life of approximately 6 minutes in adults. It is extensively distributed, with a volume of distribution of 118 L and protein binding of 94%. Dexmedetomidine exhibits linear kinetics over the recommended dosage range of 0.2 to 0.7 mcg/kg/hr. It is extensively metabolized through both the cytochrome P450 enzyme system, by aliphatic hydroxylation via CYP2A6, and direct glucuronidation. N-glucuronidation produces inactive metabolites, while aliphatic hydroxylation produces active 3-hydroxy-dexmedetomidine, which then undergoes glucuronidation, and 3-carboxy-dexmedetomidine. N-methylation produces active 3-hydroxy-N-methyl-dexmedetomidine, 3-carboxy-N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl-O-glucuronide. These metabolites are eliminated in the urine (95%) and feces (4%). Dexmedetomidine has a terminal elimination half-life of approximately 2 hours and a clearance of 39 L/hr in adults. Dose reduction is recommended for patients with hepatic dysfunction.[2]

The pharmacokinetic profile of dexmedetomidine in children has been assessed in several studies.[3-7] In 2006, a two-center study evaluated the pharmacokinetics and pharmacodynamics of dexmedetomidine in children undergoing surgery.[3] Thirty-six children between 2 and 12 years of age were assigned to receive dexmedetomidine infusions of 2, 4, or 6 mcg/kg/hr for 10 minutes or placebo. Plasma protein binding

of dexmedetomidine was 92.6 ± 0.7%. The estimated central volume of distribution was 0.81 L/kg, with a peripheral volume of distribution of 1 L/kg. The estimated systemic clearance rate was 0.013 L/kg/min, with a terminal half-life of 1.8 hours. In a second pharmacokinetic study, 10 children ranging in age from 4 months to 7.9 years who received dexmedetomidine during postoperative mechanical ventilation were assessed.[4] They were given an IV loading dose of 1 mcg/kg, followed by an infusion of 0.2 to 0.7 mcg/kg/hr. Treatment continued for an average duration of 18.8 hours (range 8-24 hours). The average volume of distribution at steady state was 2.53 ± 0.37 L/kg, with an average clearance of 0.57 ± 0.14 L/hr/kg and a terminal elimination half-life of 2.65 ± 0.88 hours. The authors of both of these studies concluded that dexmedetomidine pharmacokinetic parameters in children were similar to those of adults.

The following year, a third dexmedetomidine study evaluated the effects of age on pharmacokinetic parameters.[5] Eight children between 28 days to 23 months of age and another eight between 2 and 11 years of age were studied after receiving a single 1 mcg/kg IV dose of dexmedetomidine for procedural sedation. Clearance was not significantly different between the groups, 17.4 mL/kg/min in the younger children and 17.3 mL/kg/min in the older children, but the median volume of distribution at steady state was significantly larger in the younger children (3.8 L/kg versus 2.2 L/kg, $p<0.05$). Elimination half-life was also significantly longer in the younger children, with a median of 139 minutes compared to 96 minutes in the older subjects ($p<0.05$). An additional study, a population pharmacokinetic analysis using nonlinear mixed effects modeling, was published in 2008.[6] One hundred forty-eight observations were obtained from 45 children, 4 days to 14 years of age, who received dexmedetomidine after cardiac surgery. A two-compartment model with first order elimination was chosen based on the best fit of these data. Clearance was estimated at 39.2 L/hr per 70 kg (CV 30.36%) and central volume of distribution at 36.9 L per 70 kg (CV 69.49%). The authors estimated that clearance rates in neonates were approximately one-third of adult values, but reached 87% of adult values by 1 year of life. The differences in the results of these four studies may be partially explained by the age distribution of the samples. The minimum age in the first study was 2 years and only three patients less than 1 year of age were included in the second study, which may have prevented the authors from detecting the slower clearance in younger children observed in two subsequent papers. A recent pooled analysis of the data from all four pediatric dexmedetomidine pharmacokinetic studies confirms this observation.[7] The authors also identified another difference in clearance: patients who were receiving a dexmedetomidine infusion after cardiac surgery had a significantly slower clearance than those who received short-term procedural sedation. As a result of these data, it appears that dexmedetomidine infusion rates should be titrated with both patient age and clinical status in mind.

ADVERSE EFFECTS

The most significant adverse reactions associated with dexmedetomidine are hypotension and bradycardia, resulting from its sympatholytic activity. In clinical trials of adults, 25% of patients receiving dexmedetomidine experienced hypotension, compared to 13% of patients given placebo. Bradycardia was seen in 5% of treated patients versus 3% of controls.[2] Both hypotension and bradycardia have been reported in several pediatric studies, although rarely have the changes been clinically significant or required intervention to correct. However, dexmedetomidine should be used with caution in patients already at risk for arrhythmias or hemodynamic instability. In a study of 12 children undergoing ablation of supraventricular accessory pathways, administration of dexmedetomidine (1 mcg/kg IV loading dose followed by an infusion of 0.7 mcg/kg/hr) resulted in a significant decrease in heart rate and transient hypertension.[8] Both sinus node and atrioventricular node function were affected. The authors recommended that dexmedetomidine not be used during cardiac electrophysiologic studies. Another recent paper cited the use of therapeutic hypothermia as a potential contributing factor in two children who developed clinically significant bradycardia after receiving dexmedetomidine infusions of 0.5 to 1 mcg/kg/hr.[9] Both patients recovered after discontinuation of therapy. In most cases, dexmedetomidine-induced hypotension or bradycardia resolves with dose reduction and administration of IV fluid boluses.

Large-dose dexmedetomidine has been used by some clinicians to increase the rate of successful procedural sedation, but this regimen has resulted in increased numbers of patients with adverse hemodynamic effects.[10] A recent retrospective study of 747 children evaluated the safety and efficacy of large-dose therapy, with IV loading doses of 2-3 mcg/kg followed by infusions of 1-2 mcg/kg/hr. While the authors achieved adequate sedation in 97% of their patients, there was a 16% incidence of bradycardia. The rate of bradycardia was no different in patients who received additional pentobarbital when compared to those given dexmedetomidine alone (13% compared to 16%, p=0.57). None of the patients with bradycardia required intervention. However, the same authors later reported three cases of significant bradycardia, defined as a heart rate less than 20% of the lowest age-adjusted normal value, in children receiving their large-dose regimen for procedural sedation.[11] Per protocol at the institution, the patients were treated with glycopyrrolate 5 mcg/kg given IV, but immediately developed hypertension. As a result of this exaggerated response, the authors recommend that anticholinergics such as glycopyrrolate not be used in the management of dexmedetomidine-induced bradycardia.

Transient hypertension has been reported with the administration of the loading dose due to initial vasoconstriction caused by stimulation of peripheral postsynaptic alpha$_{2B}$-adrenergic receptors. In clinical trials of adults, the rate of hypertension was similar in treated patients and controls (12% compared to 19%).[2] Clinically significant hypertension has been reported in isolated pediatric cases,[12] but has not been common in larger case series.[13] Management consists of slowing the infusion rate, but rarely is discontinuation of treatment necessary. Other adverse reactions reported with dexmedetomidine during premarketing clinical trials in adults included nausea (9%), vomiting (4%), fever (4%), hypoxia (4%), hypovolemia, atelectasis, and dry mouth (each 3%), tachycardia, pleural effusions, hypoxia, chills, anemia, and agitation (each 2%). There have been rare reports of arrhythmias, including sinus arrest, associated with dexmedetomidine administration. It is recommended that this drug be used with caution in patients with a history of atrioventricular nodal block or severe ventricular dysfunction, as well as in hypovolemic patients or those with chronic hypertension.[2]

DRUG INTERACTIONS

Administration of dexmedetomidine with other sedatives and anesthetics typically produces a pharmacodynamic interaction resulting in enhanced sedation. This additive effect often allows for a reduction in the dose of sedative agents with a more significant adverse effect profile, such as benzodiazepines. Although dexmedetomidine undergoes metabolism by cytochrome P450 enzymes, no drug interactions involving this pathway have been identified. Dexmedetomidine does not alter responsiveness to nondepolarizing neuromuscular blocking agents.[2]

The ability of dexmedetomidine to produce hypotension or bradycardia may be magnified by administration with other drugs capable of producing those effects. In a study comparing midazolam and dexmedetomidine, the authors observed a case of bradycardia in a 5-week-old infant receiving both dexmedetomidine and digoxin.[14] The patient had an atrioventricular septal defect and was given dexmedetomidine (0.5 mcg/kg loading dose followed by an infusion of 0.44 mcg/kg/hr) during mechanical ventilation for an acute respiratory syncytial virus infection. The patient continued to receive her home dose of digoxin (10 mcg twice daily) during hospitalization. The patient's heart rate decreased from 133 bpm to 116 bpm during administration of the loading dose. It continued to decline to the mid-90's, with periodic dips to 40 to 50 bpm. Heart rate returned to baseline within 1 hour of discontinuing dexmedetomidine. The authors theorized that the drugs produced bradycardia through an additive increase in vagal tone.

CLINICAL EXPERIENCE IN CHILDREN

Preliminary Experience

Initial reports of the use of dexmedetomidine as a sedative in the pediatric population were published in two case series from the same institution.[15,16] The first, published in 2002, described experience with dexmedetomidine in two children during mechanical ventilation, in one child during surgery, and in one other for procedural sedation.[15] Infusion rates ranged from 0.25 to 0.7 mcg/kg/hr. Although dexmedetomidine produced mild decreases in heart rate and

blood pressure in three patients, no intervention was required. Three patients achieved adequate sedation, but an 11-year-old boy undergoing endoscopy required the addition of midazolam and ketamine before his procedure could be performed. Their second paper described dexmedetomidine use in five additional children.[16] Three were given an IV loading dose of 0.5 mcg/kg over 10 minutes followed by an infusion of 0.25 mcg/kg/hr, titrated to response. The two remaining patients were given a single 0.5 mcg/kg IV bolus dose. All of the patients achieved the desired level of sedation. As in their initial case series, the children tolerated dexmedetomidine without significant adverse effects. Based on the successful use of dexmedetomidine in these two case series, the authors concluded that this agent deserved further study as a sedative for children.

Use during Mechanical Ventilation

In 2004, the same clinicians conducted a prospective randomized open-label trial comparing midazolam and dexmedetomidine in children requiring mechanical ventilation.[17] Thirty children were randomized to either midazolam, with a 0.1 mg/kg IV loading dose followed by 0.1 mg/kg/hr, or dexmedetomidine small-dose (0.25 mcg/kg IV followed by an infusion of 0.25 mcg/kg/hr) or large-dose (0.5 mcg/kg IV followed by an infusion of 0.5 mcg/kg/hr). Three sedation scoring tools, the Ramsay score, a pediatric intensive care unit (PICU) sedation score, and a score assessing response to tracheal suctioning, were used to evaluate the patients, as well as Bispectral Index Monitor (BIS). The BIS score represents a processed electroencephalogram (EEG) measurement ranging from 0 (isoelectric EEG) to 100 (fully awake). No differences were noted in sedation scores or BIS scores among the groups. Mean BIS numbers were 57 ± 8 for the midazolam group, 51 ± 12 for the small-dose dexmedetomidine group, and 60 ± 10 for the large-dose dexmedetomidine group. The children in the large-dose dexmedetomidine group required significantly fewer supplemental morphine doses than the children given midazolam and had a lower total morphine dose. The number of inadequately sedated children was also lower in the two dexmedetomidine groups than in the midazolam group. Based on their results, the authors suggest that dexmedetomidine at a dose of 0.25 mcg/kg/hr was approximately equivalent to midazolam given at a rate of 0.22 mg/kg/hr, and that a higher infusion rate (0.5 mcg/kg/hr) may be more effective.

Another early retrospective study described the use of dexmedetomidine in 65 pediatric patients (mean age 5 years) with burns.[18] The infusion was initiated at 0.2 mcg/kg/hr and titrated to an average dose of 0.5 mcg/kg/hr. Twenty-six patients received an IV loading dose of 1 mcg/kg. The average duration of therapy was 11 days. All patients were considered adequately sedated, based on clinical impression, even those who had previously failed treatment with opioids and benzodiazepines. Similar efficacy rates were reported from a retrospective study of 38 children given dexmedetomidine after cardiac or thoracic surgery.[19] After an initial dose of 0.32 ± 0.15 mcg/kg/hr, patients were titrated to a mean dose of 0.3 ± 0.05 mcg/kg/hr (range 0.1-0.75 mcg/kg/hr). There was a trend towards larger dose requirements in patients less than 1 year of age, with a mean of 0.4 ± 0.13 mcg/kg/hr compared to 0.29 ± 0.17 mcg/kg/hr in older children (p=0.06). The desired level of sedation was achieved in 93% of patients; analgesia was adequate in 83%. Six patients (15%) had hypotension; three patients responded to dose reduction and three cases resolved with discontinuation. One patient developed bradycardia. These early studies prompted many institutions to consider a role for dexmedetomidine in their pediatric patients requiring mechanical ventilation.

Dexmedetomidine may have a unique role in the sedation of children with neurologic impairment who require mechanical ventilation. It is often difficult to achieve adequate sedation in these patients, and the use of large-dose therapies may increase the risk of adverse effects. Benzodiazepines, among the most common sedatives used in pediatric patients, may produce paradoxical agitation or hypotension. The benefits of dexmedetomidine in these patients has been suggested in several papers, beginning with a case series of 5 children with trisomy 21 published in 2007.[20] The patients ranged from 2 months to 3 years of age, and all were receiving mechanical ventilation after cardiac surgery. Dexmedetomidine, administered at infusion rates of 0.2 to 2.5 mcg/kg/hr, provided adequate sedation even after discontinuation of fentanyl and midazolam. Therapy was generally well tolerated, with only one patient experiencing transient hypotension

and bradycardia with an infusion rate of 0.7 mcg/kg/hr. None of the patients experienced paradoxical agitation and all were successfully extubated on therapy.

In 2008, a prospective observational study described dexmedetomidine use in 17 infants and children (ages 1 month to 17 years) requiring mechanical ventilation, including ten children with neurologic impairment.[13] Twenty treatment courses were evaluated. In 15 cases, dexmedetomidine was initiated to minimize the use of midazolam prior to extubation. In the remaining cases, it was chosen as an alternative sedative in patients unable to tolerate midazolam. The average dose at initiation was 0.2 ± 0.2 mcg/kg/hr; no loading doses were given. The maximum dose was 0.5 ± 0.2 mcg/kg/hr, with an average duration of therapy of 32 hours (range 3 to 75 hours). Ten treatment courses exceeded 24 hours. Mean arterial pressures and heart rate were not significantly different before and 1 hour after starting therapy. These values were also assessed at discontinuation and 12 hours later to assess for withdrawal or rebound hypertension, but no differences were observed. One patient developed transient hypotension during the study. None of the patients, including those with neurologic impairments, developed paradoxical agitation. There were no cases of withdrawal. The authors concluded that careful patient selection and a conservative approach to dosing resulted in successful introduction of dexmedetomidine into their PICU.

Three additional retrospective studies were published in 2009.[21-23] The first compared dexmedetomidine to standard analgesic/sedative combinations in 14 children after Fontan surgery.[21] The patients, all between 14 months and 11 years, received either dexmedetomidine (0.1-1 mcg/kg/hr) or standard therapy with a combination of midazolam, propofol, buprenorphine, and/or pentazocine. Doses were adjusted to maintain target pediatric sedation scores. The five children who received standard therapy developed respiratory depression, while the nine patients given dexmedetomidine had no evidence of respiratory depression (defined as a $PaCO_2$ > 42 mm Hg). All of the patients had cardiac pacing wires in place throughout the study, set to activate at a heart rate less than 90 bpm. Six of the nine children given dexmedetomidine developed bradycardia and were paced, compared to none in the standard treatment group. Duration of mechanical ventilation and length of stay were not significantly different between the groups. No withdrawal or rebound was observed in the dexmedetomidine group. The authors concluded that the lack of respiratory depression with dexmedetomidine may decrease the risk for elevated pulmonary vascular resistance and improve cardiac function, making it a useful option for sedation after Fontan surgery.

In the largest retrospective study to date, the records of 121 children (2 months to 21 years) who received dexmedetomidine while undergoing mechanical ventilation were evaluated.[22] The average effective dose was 0.55 mcg/kg/hr, with a range of 0.15 to 0.7 mcg/kg/hr. Therapy was adjusted based on COMFORT scores, a system incorporating signs and symptoms of both pain and agitation. Dexmedetomidine was the sole sedative in 18 patients. The remaining patients received combination therapy with opiates and/or benzodiazepines. The addition of dexmedetomidine resulted in a dose reduction of 42% and 36% in the patients treated with benzodiazepines and opiates, respectively. The average length of therapy was 25.8 hours, with a range of 20 minutes to 60 hours. Hypotension and/or bradycardia requiring intervention occurred in 27% of patients. In 10%, adverse effects led to the discontinuation of the drug. The authors concluded that the use of dexmedetomidine allowed reductions in the doses of opiates and benzodiazepines for most patients, but that close hemodynamic monitoring was necessary to identify adverse effects.

The most recent retrospective study[23] was a continuation of an earlier project evaluating dexmedetomidine after cardiac surgery.[19] The authors evaluated 80 infants and children who received dexmedetomidine as a single agent or in combination with other agents. Sedation and pain scores were gauged as adequate in 94% and 90% of the patients, respectively. Systolic blood pressure decreased from a mean of 89 ± 15 mm Hg to 85 ± 11 mm Hg ($p=0.05$) and heart rate declined from 149 ± 22 bpm to 129 ± 16 bpm ($p<0.001$) during treatment, but the authors acknowledged the difficulty in assessing postoperative hemodynamic changes from those associated with dexmedetomidine. An association was noted, however, between larger doses and the development of bradycardia. The cumulative results of these case series and studies suggest

that dexmedetomidine has a role in the sedation of infants and children requiring mechanical ventilation in the intensive care setting; but as with all other sedative/analgesic agents, close monitoring is vital to minimize adverse effects. Larger prospective trials, currently in development, should further our knowledge of optimal dosing and monitoring techniques.

Use for Procedural Sedation

Dexmedetomidine has significant advantages as a procedural sedative. Its limited effect on respiratory drive and its relatively short half-life make it a useful tool for the management of pediatric patients. In 2005, a prospective case series of 48 children (mean age 6.9 ± 3.7 years) receiving dexmedetomidine for procedural sedation was published.[24] Thirty-three patients received dexmedetomidine as their primary sedative, while the remaining patients were treated after failing midazolam and/or chloral hydrate. The majority of the patients were sedated for a magnetic resonance imaging (MRI) study, with the remaining patients having an EEG, a nuclear medicine study, or a combination of studies. Of note, more than 20% of the patients had an underlying neurologic disorder. Dexmedetomidine was given with a loading dose of 0.92 ± 0.36 mcg/kg (range 0.3-1.92 mcg/kg) given IV over 10 minutes, followed by an infusion of 0.69 ± 0.32 mcg/kg/hr (range 0.25-1.14 mcg/kg/hr). The mean duration of the procedure was 47 ± 16 minutes, with a mean recovery time of 84 ± 42 minutes. All studies were performed successfully. There were significant decreases from baseline in blood pressure and heart rate (19.0 ± 18.4 mm Hg and 12.9 ± 12.3 bpm, respectively), but parameters remained within normal limits for age. There were also minor decreases in respiratory rate (3 ± 3.5 breaths/min) and oxygen saturation (2.6 ± 2%). Dexmedetomidine was judged by the authors to be both a safe and effective means of providing procedural sedation.

Similar results were noted in a randomized trial comparing dexmedetomidine and midazolam for the sedation of 80 children between 1 and 7 years of age who were undergoing MRI.[25] The patients received a loading dose (dexmedetomidine 1 mcg/kg or midazolam 0.2 mg/kg given IV over 10 minutes), followed by an infusion (dexmedetomidine 0.5 mcg/kg/hr or midazolam 6 mcg/kg/min). Inadequate sedation was defined as movement resulting in difficulty completing the study and the need for rescue sedation. All patients successfully completed the study. Adequate sedation was obtained in 80% of the dexmedetomidine group, compared to only 20% of the midazolam group. The requirement for rescue sedation was significantly lower in the dexmedetomidine group. Heart rate and mean blood pressure declined in both groups, although no child experienced clinically significant bradycardia or hypotension. Respiratory depression was not observed in any of the children receiving dexmedetomidine, but desaturation was noted in three children given midazolam followed by rescue propofol. As in the previous paper, the authors suggest that dexmedetomidine may be a useful alternative to traditional agents for procedural sedation in infants and children.

Several small clinical trials have compared dexmedetomidine to propofol for pediatric procedural sedation.[26-28] In 2005, 60 children undergoing MRI were randomized to receive either dexmedetomidine (1 mcg/kg IV loading dose followed by 0.5 mcg/kg/hr infusion) or propofol (3 mg/kg IV loading dose followed by 100 mcg/kg/min infusion).[26] Adequate sedation occurred in 83% of the dexmedetomidine patients and 90% of the propofol patients. The onset of sedation, recovery time, and discharge time were all significantly shorter in the propofol group. More of the patients in the propofol group experienced adverse effects, with a lower mean arterial pressure, heart rate, and respiratory rate. Oxygen desaturations were reported in four propofol patients but none of the children receiving dexmedetomidine. Overall, both drugs were acceptable means of providing sedation, but neither offered a distinct advantage.

A second comparison of dexmedetomidine and propofol was published in 2008.[27] Forty children between 1 and 10 years of age were randomized to receive either the combination of midazolam (0.1 mg/kg IV) and dexmedetomidine (1 mcg/kg IV followed by 0.5 mcg/kg/hr) or propofol (250-300 mcg/kg/min) for sedation during MRI. Previous experience with dexmedetomidine as a single agent had led the authors to add midazolam to enhance the level of sedation produced. Both treatment arms provided adequate sedation, but time to full responsiveness in the midazolam-dexmedetomidine group was longer by an average of 15 minutes ($p<0.05$). Heart

Table. Dexmedetomidine Compatibility with Common ICU Medications[2]

Solutions		
0.9% sodium chloride in water 5% dextrose in water		
Medications		
alfentanil	dolasetron	milrinone
amikacin	dopamine	mivacurium
aminophylline	droperidol	morphine
amiodarone	enalaprilat	nalbuphine
ampicillin	ephedrine	nitroglycerin
ampicillin/sulbactam	epinephrine	norepinephrine
atracurium	erythromycin	ofloxacin
atropine	esmolol	ondansetron
azithromycin	etomidate	pancuronium
aztreonam	famotidine	phenylephrine
bretylium	fenoldopam	piperacillin
bumetanide	fentanyl	piperacillin/tazobactam
butorphanol	fluconazole	potassium chloride
calcium gluconate	furosemide	procainamide
cefazolin	gatifloxacin	prochlorperazine
cefepime	gentamicin	promethazine
cefoperazone	glycopyrrolate	propofol
cefotaxime	granisetron	ranitidine
cefotetan	haloperidol	remifentanil
cefoxitin	heparin	rocuronium
ceftazidime	hydrocortisone	sodium bicarbonate
ceftizoxime	hydromorphone	sodium nitroprusside
ceftriaxone	hydroxyzine	succinylcholine
cefuroxime	isoproterenol	sufentanil
chlorpromazine	ketorolac	sulfamethoxazole-trimethoprim
cimetidine	labetalol	theophylline
ciprofloxacin	levofloxacin	thiopental
cisatracurium	lidocaine	ticarcillin
clindamycin	linezolid	ticarcillin/clavulanate
dexamethasone	lorazepam	tobramycin
digoxin	magnesium	vancomycin
diltiazem	methylprednisolone	vecuronium
diphenhydramine	metoclopramide	verapamil
dobutamine	metronidazole	

rate was transiently slower than baseline in the midazolam-dexmedetomidine group, but never fell below 60 bpm. Systolic blood pressure was higher in the patients who received dexmedetomidine, but no interventions for either adverse effect were necessary. Neither group showed evidence of respiratory compromise. The authors concluded that dexmedetomidine, when used with midazolam, provided adequate sedation for MRI procedures in pediatric patients, but the combination resulted in more cases of prolonged recovery, bradycardia, and hypotension.

Another paper comparing dexmedetomidine with propofol was published in 2009.[28] This retrospective study evaluated 52 children given dexmedetomidine (median IV loading dose 2 mcg/kg with an infusion of 2 mcg/kg/hr) and 30 children given propofol (median IV loading dose 1 mg/kg with an infusion of 200 mcg/kg/min) for sedation during MRI. Forty-one patients in the dexmedetomidine group and 26 patients in the propofol group had a previous diagnosis of obstructive sleep apnea (OSA). There were 23 patients with trisomy 21 in the dexmedetomidine group and 17 in the propofol group. An interpretable study was obtained in 98% of the dexmedetomidine group and 100% of the propofol group. Thirty percent of the children in the propofol group required an artificial airway, compared to only 12% of the dexmedetomidine patients. Significantly more patients with OSA in the propofol group required an artificial airway, 56% compared to 7% in the dexmedetomidine group (p=0.02). Both drugs were well tolerated; bradycardia was reported more frequently in the dexmedetomidine patients, while hypotension was more common in the propofol group. Neither group required intervention. The authors concluded that dexmedetomidine was an acceptable alternative to propofol for pediatric MRI sleep studies, and may be a better alternative in children with OSA. Taking the results of these comparison trials as a whole, dexmedetomidine appears to provide a useful alternative to propofol for procedural sedation in children, with a longer time to recovery, but a lower incidence of adverse effects.

When used in combination with other agents, dexmedetomidine may also be useful in the sedation of children undergoing cardiac catheterization. A recent paper described the results of 16 infants and children who received ketamine and dexmedetomidine prior to diagnostic or therapeutic catheterization.[29] Patients were given a 2 mg/kg IV bolus of ketamine, along with a dexmedetomidine 1 mcg/kg IV loading dose followed by an infusion of 2 mcg/kg/hr for 30 minutes. At that point, the infusion was reduced to 1 mcg/kg/hr. Supplemental ketamine doses were given as needed. After the initial drug doses, heart rate decreased by an average of 7 ± 5 bpm. Two patients required an earlier reduction in the infusion rate to 1 mcg/kg/hr because of bradycardia. No significant changes in blood pressure or respiratory rate were noted. None of the patients experienced apnea, but $PaCO_2$ increased above 45 mm Hg in seven patients. Three patients required a supplemental dose of ketamine. Based on their experience, the authors concluded that the dexmedetomidine-ketamine combination was a useful regimen for procedural sedation during pediatric cardiac catheterization.

Additional papers have investigated the use of dexmedetomidine specifically for procedural sedation in children with trisomy 21, autism, and other behavioral and neurologic conditions.[30-32] A case series of three children with trisomy 21 demonstrated effective sedation during MRI with a combination of ketamine and dexmedetomidine.[30] Two other papers have added further support for the use of dexmedetomidine in this patient population. In 2008, a retrospective study was published describing 42 children between 2 and 11 years of age who received dexmedetomidine for sedation during EEG analysis.[31] Eighteen of the children were given oral dexmedetomidine at a dose of 2.9-4.4 mcg/kg prior to the placement of intravenous access. Forty children received a dexmedetomidine loading dose (average total dose 2.1 ± 0.8 mcg/kg, given IV as 0.5 to 1 mcg/kg increments every 3 to 5 minutes). A maintenance infusion was then started, with an average dose of 1.5 ± 0.2 mcg/kg/hr. The average time to sedation was 50 ± 12 min with oral dosing and 14 ± 8 min with IV dosing. All patients were considered to have effective sedation and no additional agents were required. All of the patients had transient decreases in heart rate and blood pressure; six had more than a 30% decrease in blood pressure compared to baseline. All received fluid boluses and two required a dose reduction. Oxygen saturation remained above 92% in all patients. Recovery was uneventful in

all of the patients, with no cases of agitation or paradoxical excitement.

A second retrospective study evaluated 315 children with autism or other neurobehavioral disorders receiving dexmedetomidine for procedural sedation.[32] The mean total dexmedetomidine dose used was 2.6 ± 1.6 mcg/kg. Ten percent of the children were treated with dexmedetomidine alone; the others received dexmedetomidine with midazolam. The mean induction time was 7.8 ± 3.5 minutes. The authors found no difference in dosing requirements between the children with autism and those with other conditions. Children 3 years of age or younger required doses that were, on average, 20% larger than those of the older children. All but four of the procedures were able to be successfully completed. Hypotension and bradycardia occurred in 9.5% and 20.3% of patients, respectively. As in the studies conducted in children receiving mechanical ventilation, dexmedetomidine appears to be an effective sedative for infants and children with neurologic impairment.

Dexmedetomidine has also been used to provide sedation for children in a wide variety of other settings. Additional reports have documented the utility of dexmedetomidine in children requiring fiberoptic intubation and in children undergoing awake craniotomy, sevoflurane anesthesia, stereotactic radiosurgery, and radiation therapy.[33-37] Dexmedetomidine has also been used for sedation during hypercyanotic spells in a neonate with tetralogy of Fallot, in the management of an infant undergoing iatrogenic opioid and benzodiazepine withdrawal, and in children and adolescents with cyclic vomiting syndrome.[38-40]

DOSING AND ADMINISTRATION

Based on the reports available to date, the recommended adult dosage range of 0.2 to 0.7 mcg/kg/hr may also be used in children.[13,15-40] Dexmedetomidine may be initiated with a loading dose of 1 mcg/kg given over 10 minutes, but some pediatric centers reduce or omit the loading dose in an effort to avoid bradycardia and hypotension. The infusion should be titrated to patient response, with a suggested maximum dose of 2 mcg/kg/hr. Dexmedetomidine (Precedex; Hospira, Worldwide Inc.) is available in a 100 mcg/mL concentration in a 2 mL preservative-free vial. It may be prepared as a 2 to 4 mcg/mL solution using normal saline. It is compatible with a wide range of IV fluids and drugs frequently used in the pediatric intensive care setting (Table). Dexmedetomidine is not compatible with amphotericin and diazepam. The compatibility of dexmedetomidine with blood products has not been studied.[2]

WITHDRAWAL

Although not well studied, abrupt cessation of dexmedetomidine may produce withdrawal symptoms similar to those seen with clonidine withdrawal, including agitation, irritability, headache, and rebound hypertension. In clinical practice, infusions have often been continued for longer than 24 hours without adverse effects. In 2005, the successful use of dexmedetomidine for a 4-day period in a child requiring mechanical ventilation following tracheal reconstruction for subglottic stenosis was described.[41] Additional experience comes from the series of 65 children given dexmedetomidine during mechanical ventilation after burn injury.[18] There were no reports of withdrawal or rebound, despite an average duration of 11 days and a range of 2 to 50 days. In 2009, a retrospective study of 54 children given dexmedetomidine after cardiac surgery also found no adverse effects with prolonged use.[42] The mean duration of administration was 16.7 hours, with a range from 1 to 112.5 hours. None of the patients exhibited withdrawal or rebound effects.

Conversely, a case report from 2007 describes tachycardia, hypertension, and emesis after abrupt discontinuation of a dexmedetomidine infusion in a 2-year-old boy.[43] He had been treated for 6 days following a Glenn procedure, with dexmedetomidine doses ranging from 0.3 to 0.8 mcg/kg/hr. Reinstitution of therapy, with subsequent weaning by 0.1 mcg/kg/hr every 8 hours, resulted in resolution of all symptoms. While the majority of pediatric reports to date have failed to demonstrate significant withdrawal effects, the potential for this response, with its significant implications in patients with underlying cardiovascular instability, warrants close monitoring at the conclusion of therapy. In patients treated for extended periods, it may be useful to slowly taper the dose to minimize the risk for withdrawal.[44]

SUMMARY

Dexmedetomidine offers an additional choice for the sedation of children receiving mechanical ventilation in the intensive care setting or requiring procedural sedation. Its benefits include limited effects on respiratory drive, a relatively short half-life, no significant drug interactions, and a generally mild adverse effect profile. It may be particularly useful in children with underlying neurologic disorders, who often develop agitation or adverse hemodynamic and respiratory effects with opioids or benzodiazepines. Dexmedetomidine appears to be well tolerated when used at recommended doses, but it has the potential to cause significant hypotension and bradycardia and should be used only when the patient can be appropriately monitored. While the case series and studies published to date suggest that this agent is appropriate for pediatric use, additional studies, including prospective clinical trials currently underway, are needed to further define the role of dexmedetomidine in pediatric intensive care.

DISCLOSURE The author declares no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

REFERENCES

1. Munoz R, Berry D. Dexmedetomidine: promising drug for pediatric sedation? Pediatr Crit Care Med 2005;6:493-494.
2. Precedex [package insert]. Lake Forest, IL: Hospira, Inc.; October 2008. Available at: http://www.precedex.com. Accessed September 25, 2009.
3. Petroz GC, Sikich N, James M, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. Anesthesiology 2006;105:1098-1110.
4. Diaz SM, Rodarte A, Foley J, et al. Pharmacokinetics of dexmedetomidine in postsurgical pediatric intensive care unit patients: preliminary study. Pediatr Crit Care Med 2007;8:419-424.
5. Vilo S, Rautiainen P, Kaisti K, et al. Pharmacokinetics of intravenous dexmedetomidine in children under 11 years of age. Br J Anaesth 2008;100:697-700.
6. Potts AL, Warman GR, Anderson BJ. Dexmedetomidine disposition in children: a population analysis. Paediatr Anaesth 2008;18:722-730.
7. Potts AL, Anderson BJ, Warman GR, et al. Dexmedetomidine pharmacokinetics in pediatric intensive care - a pooled analysis. Paediatr Anaesth 2009;19:1119-1129.
8. Hammer GB, Drover DR, Cao H, et al. The effects of dexmedetomidine on cardiac electrophysiology in children. Anesth Analg 2008;106:79-83.
9. Tobias JD. Bradycardia during dexmedetomidine and therapeutic hypothermia. J Intensive Care Med 2008;23:403-408.
10. Mason KP, Zurakowski D, Zgleszewski SE, et al. High dose dexmedetomidine as the sole sedative for pediatric MRI. Paediatr Anaesth 2008;18;403-411.
11. Mason KP, Zgleszewski S, Forman RE, et al. An exaggerated hypertensive response to glycopyrrolate therapy for bradycardia associated with high-dose dexmedetomidine. Anesth Analg 2009;108:906-908.
12. Erkonen G, Lamb F, Tobias JD. High-dose dexmedetomidine-induced hypertension in a child with traumatic brain injury. Neurocrit Care 2008;9:366-369.
13. Buck ML, Willson DF. Use of dexmedetomidine in the pediatric intensive care unit. Pharmacotherapy 2008;28:51-57.
14. Berkenbosch JW, Tobias JD. Development of bradycardia during sedation with dexmedetomidine in an infant concurrently receiving digoxin. Pediatr Crit Care Med 2003;4:203-205.
15. Tobias JD, Berkenbosch JW. Initial experience with dexmedetomidine in paediatric-aged patients. Paediatric Anaesth 2002;12:171-175.
16. Tobias JD, Berkenbosch JW, Russo P. Additional experience with dexmedetomidine in pediatric patients. South Med J 2003;96:871-875.
17. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J 2004;97:451-455.

18. Walker J, MacCallum M, Fischer C, et al. Sedation using dexmedetomidine in pediatric burn patients. J Burn Care Res 2006;27:206-210.
19. Chrysostomou C, Di Filippo S, Manrique A, et al. Use of dexmedetomidine in children after cardiac and thoracic surgery. Pediatr Crit Care Med 2006;7:126-131.
20. Kalyanaraman M, Costello JL, Starr JP. Use of dexmedetomidine in patients with trisomy 21 after cardiac surgery. Pediatr Cardiol 2007;28:396-399.
21. Tokuhira N, Atagi K, Shimaoka H, et al. Dexmedetomidine sedation for pediatric post-Fontan procedure patients. Pediatr Crit Care Med 2009;10:207-212.
22. Czaja AS, Zimmerman JJ. The use of dexmedetomidine in critically ill children. Pediatr Crit Care Med 2009;10:381-386.
23. Chrysostomou C, Sanchez De Toledo J, Avolio T, et al. Dexmedetomidine use in a pediatric cardiac intensive care unit: can we use it in infants after cardiac surgery? Pediatr Crit Care Med 2009;10:654-660.
24. Berkenbosch JW, Wankum PC, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. Pediatr Crit Care Med 2005;6:435-439.
25. Koroglu A, Demirbilek S, Teksan H, et al. Sedative, haemodynamic and respiratory effects of dexmedetomidine in children undergoing magnetic resonance imaging examination: preliminary results. Br J Anaesth 2005;94:821-824.
26. Koroglu A, Teksan H, Sagir O, et al. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. Anesth Analg 2006;103:63-67.
27. Heard C, Burrows F, Johnson K, et al. A comparison of dexmedetomidine-midazolam with propofol for maintenance of anesthesia in children undergoing magnetic resonance imaging. Anesth Analg 2008;107:1832-1839.
28. Mahmoud M, Gunter J, Donnelly LF, et al. A comparison of dexmedetomidine with propofol for magnetic resonance imaging sleep studies in children. Anesth Analg 2009;109:745-753.
29. Mester R, Easley B, Brady KM, et al. Monitored anesthesia care with a combination of ketamine and dexmedetomidine during cardiac catheterization. Am J Therapeut 2008;15:24-30.
30. Luscri N, Tobias JD. Monitored anesthesia care with a combination of ketamine and dexmedetomidine during magnetic resonance imaging in three children with trisomy 21 and obstructive sleep apnea. Paediatr Anaesth 2006;16:782-786.
31. Ray T, Tobias JD. Dexmedetomidine for sedation during electroencephalographic analysis in children with autism, pervasive developmental disorders, and seizure disorders. J Clin Anesth 2008;20:364-368.
32. Lubisch N, Roskos R, Berkenbosch JW. Dexmedetomidine for procedural sedation in children with autism and other behavior disorders. Pediatr Neurol 2009;41:88-94.
33. Jooste EH, Ohkawa S, Sun LS. Fiberoptic intubation with dexmedetomidine in two children with spinal cord impingements. Anesth Analg 2005;101:1238-1248.
34. Ard J, Doyle W, Bekker A. Awake craniotomy with dexmedetomidine in pediatric patients. J Neurosurg Anesth 2003;15:263-266.
35. Ibacache ME, Munoz HR, Brandes V, et al. Single-dose dexmedetomidine reduces agitation after sevoflurane anesthesia in children. Anesth Analg 2004;98:60-63.
36. Fahy CJ, Okumura M. Sedation for paediatric stereotactic radiosurgery: the dexmedetomidine experience. Anaesth Intensive Care 2004;32;809-811.
37. Shukry M, Ramadhyani U. Dexmedetomidine as the primary sedative agent for brain radiation therapy in a 21-month old child. Paediatr Anaesth 2005;15;241-242.
38. Senzaki H, Ishido H, Iwamoto Y, et al. Sedation of hypercyanotic spells in a neonate with tetrology of Fallot using dexmedetomidine. J Pediatr (Rio J) 2008;84:377-380.
39. Finkel JC, Elrefai A. The use of dexmedetomidine to facilitate opioids and benzodiazepine detoxification in an infant. Anesth Analg 2004;98:1658-1659.

40. Khasawinah TA, Ramirez A, Berkenbosch JW, et al. Preliminary experience with dexmedetomidine in the treatment of cyclic vomiting syndrome. Am J Therapeut 2003;10:303-307.
41. Hammer GB, Philip BM, Schroeder AR, et al. Prolonged infusion of dexmedetomidine for sedation following tracheal resection. Paediatr Anaesth 2005;15;616-620.
42. Bejian S, Valasek C, Nigro JJ, et al. Prolonged use of dexmedetomidine in the pediatric cardiothoracic intensive care unit. Cardiol Young 2009;19:98-104.
43. Weber MD, Thammasitboon S, Rosen DA. Acute discontinuation syndrome from dexmedetomidine after protracted use in a pediatric patient. Paediatr Anaesth 2007;18:87-88.
44. Enomoto Y, Kudo T, Saito T, et al. Prolonged use of dexmedetomidine in an infant with respiratory failure following living donor transplantation. Paediatr Anaesth 2006;16:1285-1288.