

Dexmedetomidine: Applications in Pediatric Critical Care & Pediatric Anesthesiology

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Introduction

The α_2 -adrenergic agonists are sub-classified into 3 groups: imidazolines, phenylethylamines, and oxalozepines. Dexmedetomidine (Precedex[®], Hospira Worldwide Inc, Lake Forest, IL) and clonidine are members of the imidazole subclass which exhibits a high ratio of specificity for the α_2 versus the α_1 receptor. Clonidine exhibits an $\alpha_2:\alpha_1$ specificity ratio of 200:1 while that of dexmedetomidine is 1600:1 thereby making it a complete agonist at the α_2 -adrenergic receptor. Dexmedetomidine has a short half-life (2-3 hours vs. 12-24 hours for clonidine) and is commercially available for intravenous administration. Its physiologic effects are mediated via post-synaptic α_2 -adrenergic receptors and activation of a pertussis toxin-sensitive guanine nucleotide regulatory protein (G protein) resulting in decreased adenylyl cyclase activity. A reduction of intracellular cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase activity results in the dephosphorylation of ion channels. Alterations in ion channel function, ion translocation, and membrane conductance lead to decreased neuronal activation and the clinical effects of sedation and anxiolysis. 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). Central CNS 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 including γ -amino butyric acid (GABA). 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. A review of the end organ effects and adverse effect profile of dexmedetomidine has been recently reviewed and presented in the review article from Tobias which was published in *Pediatric Critical Care Medicine*. Dexmedetomidine's only FDA-approved indication is the provision of short term sedation (less than 24 hours) in adult patients in the ICU setting who are initially intubated and receiving mechanical ventilation. 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.

Pharmacokinetics

In healthy adult volunteers, dexmedetomidine's pharmacokinetic profile includes a rapid distribution phase (distribution half-life of 6 minutes); an elimination half-life of 2 hours; and a steady-state volume of distribution of 118 liters. In the dosing range of 0.2 to 0.7 $\mu\text{g}/\text{kg}/\text{hr}$ delivered via continuous intravenous infusion for up to 24 hours, 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. Data regarding dexmedetomidine pharmacokinetics in the pediatric population have been presented in one recent manuscript and 2 abstracts. All of these studies have demonstrated pharmacokinetics that are similar to those reported in the adult population. Petroz GC et al. randomized 36 children, ranging in age from 2 to 12 years, to receive dexmedetomidine infused for 10 minutes at 2, 4 or 6 $\mu\text{g}/\text{kg}/\text{hr}$ (0.33, 0.6 and 1 $\mu\text{g}/\text{kg}$). Using a two-compartment model, they reported 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 liter/kg, and a terminal elimination half-life of

1.8 hours. Rodarte et al. administered a continuous infusion in a dose ranging from 0.2-0.7 $\mu\text{g}/\text{kg}/\text{hr}$ for 8-24 hours to 10 children (0.3 to 7.9 years 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 liter/kg, clearance of 0.57 ± 0.14 liters/kg/hr (approximately 9.5 mL/kg/min), and a terminal elimination half-life of 2.65 ± 0.88 hours. They commented that their data demonstrated that the pharmacokinetics of dexmedetomidine in children were predictable and consistent with results similar to that reported in adults. The final pharmacokinetic study in children includes infants, ranging in age from 1 to 24 months, following surgery for congenital heart disease. The authors reported a median clearance of 27.2 mL/kg/min, peripheral volume of distribution of 2.5 liters/kg, and a terminal elimination half-life of 83 minutes. They concluded that infants appear to clear dexmedetomidine more quickly than adults or older children. Given its dependence on hepatic metabolism, a prolonged half-life and delayed elimination has been noted in adults with hepatic dysfunction. Additionally, prolonged sedation has been noted in patients with renal insufficiency which is postulated to result from an increased free fraction related to alterations in protein binding.

Applications in the Pediatric Population

The first two reports in the literature regarding the use of dexmedetomidine in pediatric patients were retrospective case series. The first of these described the use of dexmedetomidine use in 4 pediatric patients in various clinical scenarios including sedation during mechanical ventilation, combined with remifentanyl as an adjunct for controlled hypotension during posterior spinal fusion, and for procedural-sedation. Dexmedetomidine was effective in the first 2 scenarios; however, it was ineffective as the sole agent during upper gastrointestinal endoscopy. The second report outlined the use of dexmedetomidine in 3 patients in the Pediatric ICU setting and 2 in the post anesthesia care unit. In the PICU setting, dexmedetomidine was used for sedation during spontaneous ventilation without airway control in a 4-year-old with status asthmaticus whose agitation prevented the delivery of inhalational therapy, a 13-year-old who had significant anxiety following pectus excavatum surgery despite effective pain management with a thoracic epidural catheter, and a 17-year-old with withdrawal from the recreational use of illicit drugs. In the other 2 patients, a single bolus dose of dexmedetomidine (0.4-0.5 $\mu\text{g}/\text{kg}$) 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. The first study randomized 90 children to placebo or one of 2 doses of dexmedetomidine (0.15 $\mu\text{g}/\text{kg}$ or 0.3 $\mu\text{g}/\text{kg}$) which was administered following anesthetic induction with sevoflurane. The incidence of emergence delirium was 37% in the placebo group, 17% with 0.15 $\mu\text{g}/\text{kg}$ of dexmedetomidine and 10% with 0.3 $\mu\text{g}/\text{kg}$. Similar efficacy was reported in the 4 subsequent studies. Dexmedetomidine was administered in doses ranging from 0.5 to 1 $\mu\text{g}/\text{kg}$ as a bolus dose or an infusion of 0.2 $\mu\text{g}/\text{kg}/\text{hr}$ in one of the studies. These studies demonstrate an approximate 10-fold decrease in the incidence of emergence delirium when compared with placebo. One of the studies noted that both time to emergence (5.03 ± 2.3 vs. 3.30 ± 1.3 minutes, $p < 0.05$) and extubation (9.30 ± 2.9 vs. 7.20 ± 2.7 minutes, $p < 0.05$) were longer with dexmedetomidine versus placebo.

SEDATION IN THE PICU SETTING: To date, only one prospective, randomized trial has evaluated dexmedetomidine for sedation during mechanical ventilation in infants and children. 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 μ g/kg/hr or 0.5 μ g/kg/hr. 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 while the depth of sedation was compared using the Bispectral Index. Dexmedetomidine at 0.25 μ g/kg/hr was as effective as midazolam at 0.22 mg/kg/hr while the higher dose of dexmedetomidine (0.5 μ g/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 hours). Two of 10 patients receiving dexmedetomidine at 0.5 μ g/kg/hr had a Ramsay score of 1 at any time versus 6 or 10 patients receiving midazolam. There was a decrease in the number of Ramsay scores of 1 (5 with dexmedetomidine at 0.5 μ g/kg/hr versus 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 5 of the 6 patients who manifested a Ramsay score of 1 in either of the 2 dexmedetomidine groups (0.25 or 0.5 μ g/kg/hr) were less than 12 months of age. Although there is likely significant clinical experience with the use of dexmedetomidine for longer than 24 hours as a sedative during mechanical ventilation, the only information currently available in the literature in children is anecdotal.

In another report from the PICU setting, Chrysostomou et al. retrospectively reviewed their experience with dexmedetomidine infusions following cardiac and thoracic surgical procedures in 38 patients with a mean age of 8 ± 1 years. Seven patients (18%) were less than 1 year 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 μ g/kg/hr (0.32 ± 0.15 μ g/kg/hr). The infusion was continued for 3 to 26 hours (14.7 ± 5.5 hours) at 0.1-0.75 μ g/kg/hr (0.3 ± 0.05 μ g/kg/hr). There was mild to moderate sedation 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 hours of the dexmedetomidine infusion. There was a trend toward a requirement for a higher dexmedetomidine infusion and more rescue doses in patients less than 1 year of age compared to those more than 1 year of age (0.4 ± 0.13 versus 0.29 ± 0.17 μ g/kg/hr). Bradycardia occurred in 1 patient, 15 minutes after starting the dexmedetomidine infusion and resolved with its discontinuation. Transient hypotension was noted in 6 patients (15%) and resolved with decreasing the dexmedetomidine infusion in 3 and with discontinuation of the infusion in 3.

PROCEDURAL SEDATION (NON-INVASIVE PROCEDURES): There is increasing interest and a growing number of reports of regarding the use of dexmedetomidine for non-invasive procedural-sedation. Preliminary data were provided by Nichols et al. who used dexmedetomidine for "rescue sedation" during radiologic imaging (CT and MR) in 5 patients, ranging in age from 11 months to 16 years, when a combination of chloral hydrate and midazolam were ineffective. This has been followed by prospective trials evaluating the efficacy of dexmedetomidine in the clinical scenario. Koroglu et al. randomized 80 children (1-7 years of age) to dexmedetomidine or midazolam during

MR imaging. Dexmedetomidine was administered as a loading dose of 1 $\mu\text{g}/\text{kg}$ over 10 minutes followed by an infusion of 0.5 $\mu\text{g}/\text{kg}/\text{hr}$ while midazolam was administered as a loading dose of 0.2 mg/kg followed by an infusion of 6 $\mu\text{g}/\text{kg}/\text{hr}$. The quality of sedation was better and the need for rescue sedation was less (8 of 40 versus 32 of 40) with dexmedetomidine compared to midazolam. Similar efficacy was reported by Berkenbosch et al. in an open label trial during MRI in 48 pediatric patients ranging in age from 5 months to 16 years. Dexmedetomidine was administered as a loading dose of 0.5 $\mu\text{g}/\text{kg}$ over 5 minutes and repeated as needed to achieve the desired level of sedation. Following this, a continuous infusion was started at a rate in $\mu\text{g}/\text{kg}/\text{hr}$ which was equivalent to the loading dose. The mean loading dose was 0.92 ± 0.36 $\mu\text{g}/\text{kg}$ followed by an infusion of 0.69 ± 0.32 $\mu\text{g}/\text{kg}/\text{hr}$. 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 prior to dexmedetomidine than in those who received dexmedetomidine as a primary agent (117 ± 41 versus 69 ± 34 minutes). A subsequent study by the same investigators randomized 60 children to dexmedetomidine or propofol during MR imaging. The agents were equally effective in providing sedation. Induction time, recovery time, and discharge times were shorter with propofol while 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 4 children receiving propofol versus 0 receiving dexmedetomidine.

The largest experience with dexmedetomidine for procedural sedation comes from the Boston Children's Hospital. In a retrospective review of prospective data from their QA database, Mason et al. presented data regarding dexmedetomidine for sedation in 62 children during radiological imaging. Dexmedetomidine was administered as a loading dose of 2 $\mu\text{g}/\text{kg}$ over 10 minutes and repeated as needed to achieve effective sedation. The loading dose was followed by an infusion, starting at 1 $\mu\text{g}/\text{kg}/\text{hr}$. The mean loading dose was 2.2 $\mu\text{g}/\text{kg}$ with 52 patients requiring only the initial dose of 2 $\mu\text{g}/\text{kg}$ for completion of the scan. The time to achieve sedation varied from 6 to 20 minutes. Although HR and BP decreased in all patients, no treatment was necessary and no value was less than the 5th percentile for age. No effects on respiratory function were noted. Two patients manifested significant agitation during the administration of the loading dose and were switched to other sedative agents (propofol or pentobarbital). The ongoing experience from the Boston Children's Hospital has suggested that higher loading and infusion doses (up to 3 $\mu\text{g}/\text{kg}$) are needed to achieve a rapid onset and a high efficacy rate. Despite the use of higher doses and a more rapid infusion rate (3 $\mu\text{g}/\text{kg}$ over 10 minutes), no significant increase in adverse effects has been noted. Anecdotal case reports have also demonstrated the efficacy of dexmedetomidine for sedation during cardiac MR imaging and radiation therapy.

PROCEDURAL SEDATION (INVASIVE PROCEDURES): There have been mixed results when using dexmedetomidine for invasive procedures. Although Tobias et al. reported that dexmedetomidine was not effective for upper GI endoscopy in an 11-year-old boy, Jooste et al. reported successful sedation with dexmedetomidine during fiberoptic intubation in 2 pediatric patients, both of whom were 10 years 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. However, Jalowicki et al. found dexmedetomidine to be ineffective during colonoscopy, associated with a high incidence of adverse effects, and to delay discharge in adults and therefore abandoned the study before completion.

Similar issues were reported when comparing dexmedetomidine with midazolam for monitored anesthesia care in adults during cataract surgery.

In the first prospective evaluation of dexmedetomidine as the lone agent during an invasive procedure in infants and children, Munro et al. 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 minutes followed by an infusion of 1 µg/kg/hr titrated up to 2 µg/kg/hr as needed). Five patients (25%) moved during local infiltration of the groin which did not require treatment or interfere with cannulae placement. Twelve (60%) of patients received a propofol bolus during the procedure for movement, an increasing BIS number, or anticipation of a stimulus.

Anecdotal experience suggests that a combination of dexmedetomidine with ketamine may be effective for painful invasive procedures. Scher and Gitlin 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. compared dexmedetomidine-ketamine with propofol-ketamine for sedation during cardiac catheterization in children with acyanotic congenital heart disease undergoing cardiac catheterization. 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, $P < 0.01$), more supplemental doses of ketamine (10/22 vs. 4/22), and had longer recovery times (median time of 45 vs. 20 minutes, $p = 0.01$) than patients sedated with a propofol-ketamine combination. No clinically significant differences were noted in hemodynamic and respiratory parameters. During the maintenance sedation phase, 2 patients receiving the dexmedetomidine-ketamine combination had convulsions. Neither had a history of previous neurological 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 while ketamine may prevent the bradycardia and hypotension which has been reported with dexmedetomidine. 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 minutes.

TREATMENT OF WITHDRAWAL: Regardless of the agent responsible for withdrawal, the potential role of dexmedetomidine in treating such problems is supported by animal studies, case reports in adults and children, and one retrospective case series in infant. We have previously reported our experience with the use of dexmedetomidine to control withdrawal in 7 infants ranging in age from 3 to 24 months. 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 ≥ 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 2 patients who had received the highest

doses of fentanyl (8.5 ± 0.7 versus 4.6 ± 0.5 $\mu\text{g}/\text{kg}/\text{hr}$, $p < 0.0005$). Withdrawal was controlled and subsequent Finnegan scores were ≤ 7 .

INTRAOPERATIVE APPLICATIONS: In addition to the anecdotal report outlining the use of dexmedetomidine combined with remifentanyl to provide controlled hypotension during posterior spinal fusion, there are 2 reports describing the successful intraoperative use of dexmedetomidine for awake neurosurgical procedures in pediatric patients. Ard et al. used dexmedetomidine to provide sedation during awake craniotomy in 2 patients, both of whom were 12 years old. Anesthesia for skin incision, craniotomy and dural opening were provided by sevoflurane, fentanyl and nitrous oxide via a laryngeal mask airway (LMA). Dexmedetomidine ($0.1-0.3$ $\mu\text{g}/\text{kg}/\text{hr}$) 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 LMA was removed. Similar success was reported by Everett et al. in 2 additional pediatric patients undergoing awake craniotomy, both of whom were 16 years of age.

MISCELLANEOUS APPLICATIONS: Additional reports from the literature have described various other potential applications of dexmedetomidine in the pediatric population. Khasawinah et al. reported the successful use of dexmedetomidine in 3 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. evaluated the potential efficacy of oral dexmedetomidine in 13 patients ranging in age from 4 to 14 years. Oral dexmedetomidine in doses ranging from 1.0 to 4.2 $\mu\text{g}/\text{kg}$ was used as premedication prior to inhalational anesthetic induction or to facilitate IV cannula placement prior to procedural sedation in 9 patients with neurobehavioral disorders. Effective sedation was achieved in 11 of the 13 patients. An anecdotal report in a 14-year-old suggests the potential efficacy of dexmedetomidine in the treatment of chronic regional pain (CRPS) syndrome type I. Finally, dexmedetomidine may be an effective agent to control shivering following general anesthesia. Dexmedetomidine (0.5 $\mu\text{g}/\text{kg}$ over 3-5 minutes) was administered in a prospective, open label fashion to 24 children ranging in age from 7 to 16 years of age. Shivering behavior ceased within 5 minutes with a mean onset time of 3.5 ± 0.9 minutes.

Summary

Dexmedetomidine (Precedex[®]) is an α_2 -adrenergic agonist which shares physiologic similarities with clonidine. It is currently approved by the FDA for continuous infusions for up to 24 hours in adult ICU patients who are initially intubated and receiving mechanical ventilation. 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 various clinical scenarios within the pediatric population. 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, such adverse effects have the potential for significant morbidity or even mortality in critically ill infants and children. Of concern in infants and children following cardiovascular surgery are animal data suggesting that the rapid administration of dexmedetomidine may increase pulmonary artery pressure and pulmonary vascular resistance. To date, the literature contains reports of its use in approximately 1000 pediatric patients. Given its favorable sedative and anxiolytic properties combined with its limited effects on hemodynamic and

respiratory function, there is growing interest in its use in the pediatric population in various clinical scenarios.

Suggested Readings

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Questions

1. Dexmedetomidine's central mechanism of sedation is mediated via the:
 - a. Locus ceruleus
 - b. Hypothalamus
 - c. Reticular activating system
 - d. Cerebral cortex
 - e. Dorsal roof of the spinal cord

2. Potential adverse effects of dexmedetomidine include all of the following except:
 - a. Hypotension
 - b. Bradycardia
 - c. Hypertension
 - d. Salivation
 - e. Respiratory depression

3. Rapid administration of dexmedetomidine may result in:
 - a. Hypertension
 - b. Nystagmus
 - c. Tachycardia
 - d. A decrease in PVR
 - e. Shivering

4. Which of the following is an FDA-approved indication for dexmedetomidine:
 - a. Emergence delirium
 - b. Treatment of withdrawal
 - c. Sedation of adults during mechanical ventilation
 - d. Treatment of shivering
 - e. Procedural sedation during MR imaging

5. Dosing of dexmedetomidine should be adjusted in:
 - a. Infants
 - b. Patients with hepatic insufficiency
 - c. Patients with hypertension
 - d. Patients with ARDS
 - e. None of the above