PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the
University of Virginia Children's Hospital

Dexmedetomidine for Sedation in the Pediatric Intensive Care Setting
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D exmedetomine was approved by the Food and Drug Administration (FDA) on December 24, 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. In clinical trials of adults, dexmedetomidine produced the desired level of sedation in approximately 80% of patients with no additional agents. Concomitant use of dexmedetomidine also allowed for a reduction in the dose of midazolam or morphine.[1-3] Based on its efficacy in adults, dexmedetomidine is now being explored as a possible alternative or adjunct to benzodiazepines and opioids in the pediatric intensive care setting. This issue of *Pediatric Pharmacotherapy* will review the papers describing the efficacy and adverse effects of dexmedetomidine in children.

Mechanism of Action

Dexmedetomidine is a relatively selective $alpha_2$-adrenergic agonist. It is chemically related to clonidine, but has a much greater affinity for $alpha_2$-receptors over $alpha_1$-receptors (1,620:1 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 brain stem. Stimulation of $alpha_2$-adrenergic receptors at this site reduce central sympathetic output, resulting in increased firing 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.[1-3]

Clinical Experience in Children

A number of case reports, series, and small studies have been published describing the use of dexmedetomidine in infants and children. The initial reports of its utility in this population were published by Tobias, Berkenbosch, and Russo in two case series.[4,5] The first described their

experience with using dexmedetomidine during mechanical ventilation, in the operative setting, and for procedural sedation.[4] The second paper described dexmedetomidine use in five spontaneously breathing children requiring sedation.[5] Three were given a loading dose of 0.5 mcg/kg over 10 minutes followed by an intravenous (IV) infusion of 0.25 mcg/kg/hr, titrated to response. The remaining two patients, were given a single 0.5 mcg/kg bolus dose. All patients achieved adequate sedation and tolerated dexmedetomidine without adverse effects.

In 2004, these clinicians conducted a prospective randomized, open-label trial comparing midazolam and dexmedetomidine in children requiring mechanical ventilation.[6] Thirty children were randomized to either midazolam, with a 0.1 mg/kg loading dose followed by 0.1 mg/kg/hr, or dexmedetomidine low dose (0.25 mcg/kg loading dose followed by an infusion of 0.25 mcg/kg/hr) or high dose (0.5 mcg/kg followed by an infusion of 0.5 mcg/kg/hr). All infusions were titrated to maintain adequate sedation. No differences were noted in sedation scores or Bispectral Index Monitor (BIS) scores among the groups. The children in the high dose dexmedetomidine group required significantly fewer supplemental morphine doses than the children given midazolam. The total morphine use was also lowest in this group. 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.[6]

Additional evidence comes from a brief report of dexmedetomidine use in 48 pediatric patients treated at Phoenix Children's Hospital.[7] The patients (10 months-19 years of age) were given dexmedetomidine in an intensive care unit, for a variety of diagnoses, using a loading dose of 0.5 mcg/kg given over 15 minutes, followed by an

infusion of 0.25 to 1.25 mcg/kg/hr. The duration of infusion ranged from 12 to 144 hours. The most significant adverse effect was hypotension. The author found dexmedetomidine to be an effective sedative and recommended further research in the pediatric population.

In 2005, Berkenbosch, Wankum, and Tobias published a prospective case series of 48 children (mean age 6.9+3.7 years) receiving dexmedetomidine for procedural sedation.[8] 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 electroencephalogram, 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 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 beats/min, 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%). The authors concluded that dexmedetomidine was a useful alternative to traditional options for procedural sedation.[8]

Koroglu and colleagues reported similar success in their randomized trial comparing dexmedetomidine and midazolam for the sedation of 80 children (1-7 years of age) undergoing MRI.[9] The patients received a loading dose (1 mcg/kg dexmedetomidine or 0.2 mg/kg midazolam) given over 10 minutes, followed by an infusion (0.5 mcg/kg/hr dexmedetomidine or 6 mcg/kg/min midazolam). 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 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.

Similar benefits have been observed when dexmedetomidine was given as rescue therapy to five children who failed therapy with chloral hydrate and midazolam.[10] 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.[11-15] Dexmedetomidine has also been used for sedation after cardiac surgery, in the management of iatrogenic opioid and benzodiazepine withdrawal and cyclic vomiting syndrome.[16-18] While the results of these preliminary reports are promising, additional studies are needed to confirm their findings.

Pharmacokinetics
After IV administration, dexmedetomidine has a rapid distribution phase, with a 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, primarily by CYP2A6, and direct glucuronidation. The 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. Dose reduction may be needed in patients with hepatic dysfunction. The pharmacokinetic profile of dexmedetomidine has not been studied in children.[2,3]

Drug Interactions
Administration of dexmedetomidine with other sedatives and anesthetics typically produces a pharmacodynamic interaction resulting in enhanced sedative effects. As previously described, this additive effect is often used to reduce reliance on other agents. Although dexmedetomidine undergoes metabolism by cytochrome P450 enzymes, no drug interactions involving this pathway have been identified.[2,3]

During their study comparing midazolam and dexmedetomidine, Berkenbosch and Tobias observed a case of bradycardia in a 5 week old infant receiving both dexmedetomidine and digoxin.[19] 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 beats/min to 116 beats/min during administration of the loading dose, and continued to decline to the mid-90's, with periodic dips to 40 to 50 beats/min. 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.

Adverse Reactions
The most significant adverse reactions associated with dexmedetomidine are hypotension and bradycardia, resulting from its sympatholytic activity. In clinical trials of adults, 28% of patients receiving dexmedetomidine experienced hypotension, compared to 13% of patients given placebo. Bradycardia was seen in 7% of treated patients versus 3% of controls. While a reduction in the infusion rate or administration of IV fluids is often adequate to alleviate these symptoms, administration of atropine may be necessary in cases of significant bradycardia. Transient hypertension has been reported with the administration of the loading dose due to initial peripheral vasoconstriction. In clinical trials, the rate of hypertension was similar in treated patients and controls (16% compared to 18%). Hypertension rarely requires intervention beyond slowing the infusion rate.[2,3]

Other adverse reactions reported with dexmedetomidine during clinical trials included nausea (11%), fever (5%), vomiting (4%), hypoxia (4%), tachycardia (3%), and anemia (3%). It is recommended that dexmedetomidine be used with caution in patients with advanced heart block or severe ventricular dysfunction, as well as in hypovolemic patients or those with chronic hypertension.[2,3]

Dosing Recommendations
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. In adults, dexmedetomidine may be initiated with a loading dose of 1 mcg/kg given over 10 minutes, but many pediatric centers are reducing or omitting the loading dose in an effort to avoid cardiovascular instability.

Dexmedetomidine may be prepared as a 2 mcg/mL solution with normal saline or further diluted. It is compatible with a wide range of IV fluids and drugs frequently used in the pediatric intensive care setting, including:[2]

amiodarone	lorazepam
ampicillin	magnesium
cefazolin	methylprednisolone
cisatracurium	midazolam
dexamethasone	milrinone
dobutamine	morphine
dopamine	nitroglycerine
epinephrine	norepinephrine
esmolol	ondansetron
famotidine	pancuronium
fentanyl	phenylephrine
furosemide	piperacillin-tazobactam
gentamicin	potassium chloride
heparin	propofol
isoproterenol	sodium bicarbonate
labetolol	vancomycin
lidocaine	vecuronium

Dexmedetomidine is incompatible with amphotericin and diazepam. A complete list of compatibility information is provided by the manufacturer in the product labeling.[2]

Length of Infusion
Although it has not been well studied, it is possible that abrupt cessation of dexmedetomidine may produce withdrawal symptoms similar to those seen with clonidine withdrawal (ie, agitation, irritability, headache, and rebound hypertension). For that reason, the manufacturer recommends that dexmedetomidine not be used for more than 24 hours.[2]

In 2004, Shehabi and colleagues published the results of a prospective, open-label trial of dexmedetomidine given for periods greater than 24 hours.[20] Twenty adults received dexmedetomidine for a median time of 71.5 hours (range of 35 to 168 hours). No loading dose was given, and the infusion was titrated to maintain a Ramsay sedation score of 2 to 4. After abrupt discontinuation of dexmedetomidine, the mean increase in systolic blood pressure was 7% (occurring 5 hours after stopping the infusion), with a mean increase in heart rate of 11% (at 14 hours after cessation).

In clinical practice, treatment for periods longer than 24 hours has been reported to be well tolerated. In an observational study of 136 patients at 10 institutions, Dasta and colleagues reported that a third of the patients received dexmedetomidine for a period greater than 24 hours.[21] In those patients, the average length of treatment was 54 hours, with a range of 24.5 to 123.5 hours. There were no reports of rebound symptoms. Limited data are available regarding prolonged administration to children. As described earlier, Serlin reported use up to 144

hours.[7] In 2005, Hammer and colleagues reported the successful use of dexmedetomidine for 4 days in a child after tracheal reconstruction for subglottic stenosis.[22]

Availability and Cost

Dexmedetomidine (Precedex®; Hospira, Inc.) is available in a 100 mcg/mL concentration in a 2 mL preservative-free vial.[2] The average wholesale price is approximately $55.00 per vial. For comparison, a 5 mg vial of midazolam is approximately $5.00.

Summary

Dexmedetomidine offers an additional choice for the sedation of children receiving mechanical ventilation or requiring procedural sedation. 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. While dexmedetomidine appears to be well tolerated, it has the potential to cause significant hypotension and should be used only in carefully monitored situations. Additional controlled studies are needed to define the role of dexmedetomidine in the sedation of infants and children.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 12/16/05:

1. Sodium tetradecyl sulfate (Sotradecol®) was added to the Inpatient Formulary.
2. Fondaparinux (Arixtra®) was added for the prevention of deep vein thrombosis (DVT) and treatment of DVT and pulmonary embolism. It is restricted to use by Hematology.
3. A new formulation of sildenafil (Revatio®) was added with restriction to patients with pulmonary hypertension.
4. Lopinavir/ritonavir (Kaletra®) tablets were added to the Formulary; the capsules will not be available after March.
5. Alendronate/cholecalciferol (Fosamax plus D®) was added to the Outpatient Formulary.
6. Tinzaparin (Innohep®), a low molecular weight heparin, was added to the Outpatient Formulary with restriction to Hematology.