THE LANDMARK WORK OF Anand et al1,2 has documented the potential impact of anesthetic practice on morbidity and mortality after surgery for congenital heart disease. Nearly 20 years later, the anesthetic management of pediatric patients with congenital heart lesions is a delicate balance between the successful ablation of the harmful perioperative stress responses and the potential untoward sequelae of effective analgesia and sedation including prolonged ventilator dependence, adverse end-organ effects, and iatrogenic tolerance and dependency syndromes. Anesthesiologists remain intimately involved in the perioperative care of children undergoing cardiac surgery and continue to seek new modalities of perioperative analgesia and sedation in an attempt to limit these complications. Dexmedetomidine increasingly has been used by anesthesiologists and intensive care physicians to provide effective pain relief, sedation, and anxiolysis in critically ill infants and children while mitigating the adverse effects of ventilator and opioid dependency. Given its beneficial physiologic effects and limited adverse effect profile, there may be several potential applications for dexmedetomidine in the perioperative care of infants and children with congenital heart disease.

PHARMACOLOGY

Dexmedetomidine, a centrally acting \( \alpha_2 \)-adrenergic agonist, has similar physiologic properties to clonidine. However, when compared with clonidine, it has a higher selectivity ratio for the \( \alpha_2 \)- versus the \( \alpha_2 \)-adrenergic receptor than clonidine (1,600:1 vs 200:1, respectively) and a shorter half-life (2-3 hours vs 8-12 hours for clonidine). Dexmedetomidine acts through a G-coupled protein receptor, decreasing intracellular adenyl cyclase, cAMP, and cAMP-dependent protein kinase leading to dephosphorylation of ion channels. This results in reduced norepinephrine turnover and decreased central sympathetic outflow from the medullary vasomotor center with sympatholysis, decreased heart rate, and blood pressure. In addition, dexmedetomidine decreases renin and vasopressin levels, resulting in increased diuresis. The central stimulation of dexmedetomidine on parasympathetic outflow and inhibition of sympathetic outflow from the locus ceruleus lead to increased activity of inhibitory neurons of the \( \gamma \)-aminobutyric acid system, resulting in sedation and anxiolysis. Dexmedetomidine also inhibits the release of substance P from the dorsal horn of the spinal cord, leading to primary analgesic effects and potentiation of opioid-induced analgesia.3 Through these mechanisms, dexmedetomidine provides sedation and anxiolysis, lowers the minimum alveolar concentration for inhalation agents,4 decreases perioperative opioid requirements, decreases shivering responses,5 and reduces the incidence of emergence delirium/agitation.6 Currently, dexmedetomidine is Food and Drug Administration (FDA) approved only for short-term sedation (<24 hours) during mechanical ventilation of adult patients in an intensive care unit (ICU) setting. There is currently no FDA-approved usage in children. Despite this fact, there are more than 1,000 pediatric-aged patients reported in the literature who have received dexmedetomidine for a variety of clinical applications in and out of the operating room. The following discussion reviews the published reports of dexmedetomidine in infants and children with special emphasis on its use in patients with congenital heart disease.

CLINICAL EXPERIENCE WITH DEXMEDETOMIDINE

Previous reports in the pediatric population have shown the efficacy of dexmedetomidine as the sole agent for sedation during noninvasive radiologic procedures (computed tomography scan or magnetic resonance imaging). Although there are only 2 anecdotal reports in the literature of patients with congenital lesions undergoing imaging,7,8 4 prospective studies of infants and children have shown it to be an effective agent in achieving and maintaining sedation during noninvasive diagnostic imaging procedures. The patients studied maintained spontaneous ventilation and required fewer doses of rescue medication (additional doses of medication to maintain immobility) compared with other sedation regimens including propofol or midazolam-based techniques. Dexmedetomidine also was effective in patients when other agents (midazolam and/or chloral...
hydromorphone (10 minutes followed by a continuous infusion starting at 1 μg/kg/h). These studies showed that dexmedetomidine may offer favorable advantages over propofol in regards to its effects on cardiovascular and respiratory function. Koroglu et al. compared dexmedetomidine and propofol for sedation of children ranging in age from 1 to 7 years undergoing magnetic resonance imaging. After placement of an intravenous cannula using topical anesthetic cream, the patients were randomized to receive either dexmedetomidine (1 μg/kg followed by an infusion of 0.5 μg/kg/h) or propofol (3 mg/kg followed by an infusion of 100 μg/kg/h). Although both propofol and dexmedetomidine provided effective procedural sedation, more hemodynamic and respiratory effects were seen with propofol including tachycardia, decreased mean arterial pressure, and hypoxemia. Although likely to be of little clinical significance in the majority of patients, these differing effects may be of clinical consequence in patients with cyanotic congenital heart disease in whom a decrease in mean arterial pressure may increase right-to-left shunt or who may tolerate hypoxemia less easily than patients without comorbid diseases. Although there are limited data to date, the initial experience with dexmedetomidine has shown it to be safe and effective during magnetic resonance imaging.

For more invasive procedures including cardiac catheterization, dexmedetomidine has not been effective uniformly when administered as a sole agent in either the pediatric or the adult population, a finding best explained by its limited analgesic properties for acute, painful stimuli. Munro et al. were the first to report their experience with dexmedetomidine for sedation during cardiac catheterization in pediatric patients. Their technique involved premedication with oral midazolam followed by inhalation induction with sevoflurane to facilitate the placement of vascular access. This was followed by discontinuation of the sevoflurane and the transition to intravenous dexmedetomidine administered as a bolus of 1 μg/kg administered over 10 minutes followed by a continuous infusion starting at 1 μg/kg/h. With this approach, 25% of the patients required supplementation with propofol secondary to movement during groin infiltration and catheter placement. A total of 60% required some type of rescue sedation during the procedure. No respiratory or cardiovascular events were noted. Given the significant need for rescue sedation, the study questions the efficacy of dexmedetomidine as the sole agent for sedation during cardiac catheterization.

Tosun et al. prospectively compared dexmedetomidine-ketamine with propofol-ketamine in 44 children (4 months-16 years) with acyanotic congenital heart disease undergoing cardiac catheterization. Ketamine (1 mg/kg) and dexmedetomidine (1 μg/kg) were administered over 10 minutes followed by an infusion of 0.7 μg/kg/h of dexmedetomidine and 1 mg/kg/h 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/h) and ketamine (1 mg/kg/h). Supplemental bolus doses of ketamine (1 mg/kg) were available as needed. Although sedation was managed effectively with both regimens, the authors concluded that the propofol-ketamine combination was superior. Patients sedated with ketamine-dexmedetomidine required more ketamine (2.03 ± 1.33 v 1.25 ± 0.67 mg/kg/h, p < 0.01), more frequently required supplemental doses of ketamine (10/22 v 4/22), and had longer recovery times (median time of 45 v 20 minutes, p = 0.01) than patients sedated with a propofol-ketamine combination. No clinically significant difference was noted in hemodynamic variables, although the heart rate was 10 to 20 beats/min lower throughout the procedure in patients receiving dexmedetomidine-ketamine. Systolic arterial blood pressure, oxygen saturation, and respiratory rate were not different between the 2 groups. The authors also reported the new onset of seizures during the maintenance sedation phase in 2 patients receiving the dexmedetomidine-ketamine combination. Neither of these patients had a previous neurologic history, and the authors commented that they could not determine the exact cause of the seizure activity.

The authors have reported the successful use of a combination of dexmedetomidine and ketamine in a prospective, open-label trial using these agents for sedation during cardiac catheterization in infants and children. Ketamine (2 mg/kg) and dexmedetomidine (1 μg/kg) mixed in the same syringe were administered over 2 to 4 minutes to provide the rapid onset of analgesia sedation before the placement of arterial and venous cannulae. After the initial invasive component of the procedure, dexmedetomidine was administered as an infusion (2 μg/kg/h for 30-60 minutes and then reduced to 1 μg/kg/h for the remainder of the procedure). Supplemental bolus doses of ketamine (1 mg/kg) were administered as needed. Rescue doses of ketamine rarely were needed and only when vascular cannulae needed to be changed. This approach used the complementary effects of the 2 agents and thereby avoided the potential adverse hemodynamic effects of the agents and avoided a slow onset that is sometimes observed when the loading dose is administered over 10 minutes. There were no significant cardiovascular events including hypertension, hypotension, or bradycardia. Arterial blood gas analysis obtained during the procedure revealed mild hypercarbia with a PaCO2 >45 mmHg in half of the patients. Additionally, upper airway obstruction that required repositioning of the airway occurred in 2 patients.

During pediatric cardiac surgery, an adjuvant dexmedetomidine infusion has been shown to reduce plasma concentrations of various perioperative stress hormone responses. Mukhtar et al. randomized 30 infants and children to placebo or dexmedetomidine (bolus of 1 μg/kg over 10 minutes followed by infusion of 0.5 μg/kg/h). Dexmedetomidine was administered after anesthetic induction, endotracheal intubation, and placement of arterial and venous cannulae. The induction and maintenance of anesthesia included fentanyl, pancuronium, and isoflurane. Increases in plasma levels of cortisol, glucose, epinephrine, and norepinephrine were greater in the placebo group than the dexmedetomidine group. In addition, lower nitroprusside infusions were required after bypass in the dexmedetomidine group. No adverse events were noted.

Clinical studies in adults have shown that the perioperative administration of α2-adrenergic agonists may modify the incidence of adverse cardiovascular events including myocardial ischemia and tachycardia. Additionally, the lowering of heart rate and myocardial oxygen consumption by dexmedetomidine may provide beneficial effects in patients with coronary artery disease. Talke et al. randomized 24 adult patients undergoing vascular surgery to placebo or 1 of 3 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 hour before anesthetic induction and continued for 48 hours. 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 (average of 23 minutes per hour) when compared with the low-dose (9 min/h, \( p = 0.006 \)), medium-dose (0.5 min/h, \( p = 0.004 \)), and high-dose (2.3 min/h, \( p = 0.004 \)) dexmedetomidine groups.\(^{14,17} \) 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 \( \beta \)-adrenergic blockade.\(^{18} \)

Animal studies have shown direct myocardial preservation with dexmedetomidine through lowering stress responses,\(^{19,20} \) lowering anti-ischemic responses (such as lactate production),\(^{21} \) raising resistance to arrhythmia formation,\(^{22} \) and promoting protective mechanisms during periods of hypoxia and reoxygenation.\(^{23} \) Such data have resulted in an increase use of dexmedetomidine for the management of adults undergoing cardiac and vascular surgery.

The potential benefits and efficacy of dexmedetomidine in providing postoperative sedation in infants and children with congenital heart disease undergoing mechanical ventilation also have been shown. Chrysostosmou et al\(^{24} \) retrospectively reviewed their experience with postoperative dexmedetomidine infusion in pediatric patients undergoing cardiac and thoracic surgery. Dexmedetomidine was administered after the surgical procedure as a continuous infusion of 0.1 to 0.5 \( \mu \)g/kg/h and continued for 3 to 26 hours. In these 38 patients, the authors reported successful postoperative sedation in 93% of patients with absent or minimal pain scores at 83% of the assessment points. Furthermore, they reported that 87% of patients were easily weaned and extubated while on dexmedetomidine. Adverse events related to the dexmedetomidine infusion were bradycardia (1 patient) and transient hypotension (6 patients). Bradycardia resolved with discontinuation of the infusion, whereas the hypotension was treated with reduction of infusion rate in 3 patients and discontinuation of infusion in the remaining three.

Dexmedetomidine has been used to treat iatrogenic withdrawal and facilitate weaning of opioid and benzodiazepine medications in pediatric patients including those with cardiac disease. Baddigam et al\(^{25} \) and Finkel et al\(^{26} \) provided anecdotal evidence for the efficacy of dexmedetomidine in controlling withdrawal symptoms in infants and children after cardiac surgery and heart transplantation. These findings agree with larger published series in children that show dexmedetomidine to be effective in controlling withdrawal syndromes and facilitating the reduction of opioid and benzodiazepine agents.\(^{27} \)

**ADVERSE EFFECTS OF DEXMEDETOMIDINE**

As with any sedative agent, the potential exists for adverse end-organ effects. Although reported adverse events with dexmedetomidine are relatively uncommon, there is a potential for cardiovascular, respiratory, and central nervous system effects. Potential cardiac and hemodynamic effects include bradycardia, sinus arrhythmias, and hypotension. Bradycardia and hypotension occur most often during the initial loading dose\(^{28} \) in patients with comorbid disease (such as conduction abnormalities)\(^{29,30} \) and when dexmedetomidine is coadministered with other negative inotropic agents (propofol, volatile anesthetic agents, and digoxin).\(^{4,31} \) In addition to its potential to cause bradycardia and hypotension, another area of concern in the pediatric patient with congenital heart disease is the effect on pulmonary vascular resistance. To date, there remain limited data regarding the potential effects of dexmedetomidine on the pulmonary vascular bed. Ebert et al\(^{32} \) evaluated the hemodynamic effects of dexmedetomidine in 10 healthy adult volunteers and found that, with increasing dexmedetomidine infusion rates and higher plasma concentrations (>1.9 ng/mL), the concentration required to prevent recall in 100% of patients, there were progressive increases in mean arterial pressure and systemic vascular resistance as well as pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (PAP). The PAP increased 44% from baseline, whereas the PVR increased 155% from baseline. Kastner et al\(^{33} \) evaluated the hemodynamic effects of dexmedetomidine in 6 healthy adult sheep. After the induction of general anesthesia, instrumentation, and 1 hour of stabilization time, dexmedetomidine in a dose of 2 \( \mu \)g/kg was administered over 1 minute. There were significant yet transient increases in mean arterial pressure, systemic vascular resistance, PAP, and PVR that subsided over 3 to 5 minutes. Similar results have not been reported in children and adults undergoing diagnostic cardiac catheterization.

Reports on the respiratory effects of dexmedetomidine remain conflicted. In a cohort of adults, Hall et al\(^{34} \) noted no clinically significant changes in the end-tidal carbon dioxide, oxygen saturation, and respiratory rate with dexmedetomidine administered as a bolus of 0.6 \( \mu \)g/kg followed by an infusion of 0.2 to 0.6 \( \mu \)g/kg/h. However, Belleville et al\(^{35} \) reported that dexmedetomidine in a dose of 2 \( \mu \)g/kg resulted in a rightward shift and depression of the slope of the CO\(_2\) response curve. They also showed a decreased ventilatory response to a CO\(_2\) challenge (end-tidal carbon dioxide = 55 mmHg). As mentioned earlier, in the authors’ study of pediatric cardiac patients undergoing cardiac catheterization, there was a statistically significant rise in PaCO\(_2\), with half of the patients showing a PaCO\(_2\) >45 mmHg, although no clinical consequences were noted. These findings combined with the potential for transient upper airway obstruction that may occur in patients receiving dexmedetomidine while spontaneously ventilating without an artificial airway necessitate that continuous anesthesia monitoring and skilled personnel are available for each patient receiving dexmedetomidine.

Potential central nervous system adverse effects include potential changes in cerebral perfusion pressure, cerebral blood blood flow, and effect on seizure threshold. Observed decreases in cerebral perfusion pressure are primarily mediated through decreases in systemic blood pressure and not in alterations in cerebral vascular resistance or intracranial pressure. Animal studies have shown conflicting reports on both proconvulsant and anticonvulsant properties. There are no human reports to date.
THE AUTHORS’ EXPERIENCE WITH DEXMEDETOMIDINE

The authors have used dexmedetomidine safely in caring for children throughout the perioperative period of their cardiac surgery. The authors’ experience using dexmedetomidine for nonpainful procedures (such as cardiac magnetic resonance imaging and computed tomography scans) and for invasive procedures (cardiac catheterization) have been similar to the published data presented. The authors’ current dosing guidelines are provided in Table 1. During cardiac surgery, an infusion of 0.5 \( \mu g/kg/h \) is typically started after intubation and appropriate vascular access but before skin incision. The dexmedetomidine infusion is typically maintained throughout the procedure (including bypass and transport to the intensive care unit). In the intensive care unit, infusions can be maintained safely through extubation or stopped prior to extubation depending on the clinical scenario. For those intensive care unit patients requiring increasing sedation, a bolus of 0.5 \( \mu g/kg \) administered over 10 minutes followed by an infusion starting at 0.3 to 0.5 \( \mu g/kg/h \) have been found to be effective in the majority of children. If additional sedative effect is needed, repeating a slow bolus and/or increasing the rate by 0.2 to 0.3 \( \mu g/kg/h \) is typically sufficient. Although not currently FDA approved for more than 24 hours, there are a few reports of prolonged infusions (>24 hours duration) in children. Walker et al. retrospectively studied their dexmedetomidine sedation in difficult-to-sedate pediatric burn patients. The mean duration of treatment was 11 days with a range of 2 to 50 days. Infusion rates varied 0.1 to 2 \( \mu g/kg/h \). Additional anecdotal information suggests that patients may require escalating dosages over time to provide adequate sedation.

CONCLUSION

There is a growing body of evidence supporting the safety and benefit of dexmedetomidine in managing pediatric cardiac patients. Critics of dexmedetomidine usage in children often identify the lack of pharmacologic data, FDA approval, and limited understanding of all the adverse effects of this agent. However, these issues can only be addressed by a medical community active in advancing the care of children. When
starting at a lower continuous infusion rate. Future studies in infants and children that evaluate the short- and long-term benefits of adjuvant dexmedetomidine administration may provide the greatest information and support for its integration into the routine perioperative care of infants and children with congenital heart disease.

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