

# Dexmedetomidine in Children: Current Knowledge and Future Applications

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More than 200 studies and reports have been published regarding the use of dexmedetomidine in infants and children. We reviewed the English literature to summarize the current state of knowledge of this drug in children for the practicing anesthesiologist. Dexmedetomidine is an effective sedative for infants and children that only minimally depresses the respiratory system while maintaining a patent airway. However, dexmedetomidine does depress the cardiovascular system. Specifically, bradycardia, hypotension, and hypertension occur to varying degrees depending on the age of the child. Hypertension is more prevalent when larger doses of dexmedetomidine are given to infants. Consistent with its 2-hour elimination half-life, recovery after dexmedetomidine may be protracted in comparison with other sedatives. Dexmedetomidine provides and augments analgesia and diminishes shivering as well as agitation postoperatively. The safety record of dexmedetomidine suggests that it can be used effectively and safely in children, with appropriate monitoring and interventions to manage cardiovascular sequelae. (*Anesth Analg* 2011;113:1129–42)

Dexmedetomidine, an  $\alpha_2$  adrenergic agonist, was approved by the U.S. Food and Drug Administration in 1999 for sedation in adults whose airways were intubated in the intensive care unit (ICU) and in 2008 for sedation for surgical or medication procedures in adults without intubated airways outside the ICU.<sup>1</sup> However, the development of dexmedetomidine for use in children has been slow and unfocused. Currently, dexmedetomidine is not approved for use in children in any country. As an off-label medication, dexmedetomidine has been administered as an adjunct to anesthesia (general and regional) in and out of the operating rooms for both surgical and medical procedures in children and for sedation in the pediatric ICU (PICU). Its widest application in children has been for procedural sedation in radiology. In the past decade, the clinical applications of dexmedetomidine have been expanding with reports of its use as a premedication before anesthesia, as an adjunctive drug intraoperatively and postoperatively, to attenuate emergence complications including delirium, shivering, and pain in the perioperative period and for sedation, analgesia, hemodynamic management, and airway management in the ICU.<sup>2–30</sup> In some of these applications, the role of dexmedetomidine has been clearly defined, whereas in others, its role remains unclear.

Despite a wealth of clinical experience with dexmedetomidine, the pharmacokinetic and pharmacodynamic profiles of dexmedetomidine in children are incompletely understood. Our ability to expand the clinical applications

of dexmedetomidine in infants and children are limited by a dearth of comprehensive reviews of its pharmacology and clinical applications in children. This review is intended to provide a snapshot perspective of our current state of knowledge regarding dexmedetomidine and its use in children and to summarize the current pediatric applications of dexmedetomidine for the practicing clinician to focus future directions for this drug.

## PHARMACOKINETICS

A limited number of studies have investigated the pharmacokinetics of dexmedetomidine in children. All of the studies have involved a brief exposure to dexmedetomidine. When administered IV, 93% of the dexmedetomidine is protein bound in children.<sup>31</sup> In healthy children, the rapid ( $\alpha$ ) phase redistribution half-life is ~7 minutes, clearance is ~15 mL/kg/min, and the terminal ( $\beta$ ) elimination half-life is ~2 hours.<sup>31–33</sup> Dexmedetomidine is biotransformed in the liver to inactive metabolites, with 85% undergoing glucuronidation by UDP-glucuronyltransferase (UGT) and 15% by cytochrome P450 2A6.<sup>1,34–36</sup> A very small fraction of dexmedetomidine is excreted unchanged in urine and feces.

When delivered by non-IV routes, the bioavailability of dexmedetomidine follows the order orogastric 16%, intranasal (IN) 65%, buccal 82%, and IM 104%.<sup>37,38</sup>

A population pharmacokinetic analysis of pooled data from 4 pharmacokinetic studies using allometric size models and a maturation model generated age-dependent kinetic indices.<sup>39–41</sup> Population parameter estimates (between subject variability) using a 2-compartment model yielded an average clearance of 702 mL/min/70kg, ranging from 300 mL/min per 70 kg in term neonates to ~600 mL/min per 70 kg or 84.5% of mature clearance by 1 year of age<sup>39</sup> (Fig. 1). This maturation profile is very similar to those reported previously for paracetamol and morphine, drugs that are also cleared predominantly by glucuronide conjugation (UGT1A6 and UGT2B7).<sup>41,42</sup> Cytochrome P450 2A6 activity, which contributes only a small fraction of dexmedetomidine's metabolism, approaches adult activity by ~1 year of age.<sup>35,43,44</sup>

The pharmacokinetics of dexmedetomidine in pediatric subpopulations have also been studied, although only to a

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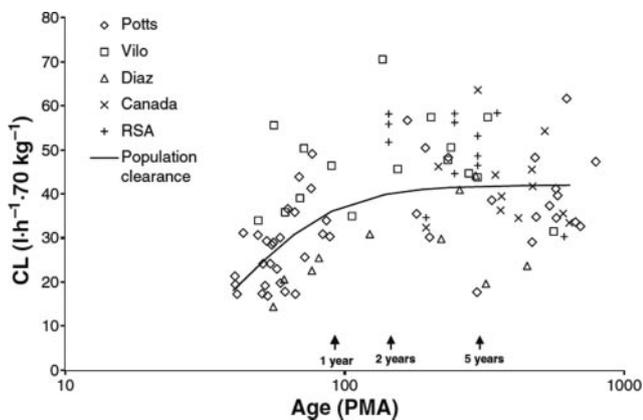
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**Figure 1.** Individual predicted dexmedetomidine clearances from the nonlinear mixed-effects modeling post hoc step, standardized to a 70-kg person using an allometric power model with an exponent of 3/4 ( $CL, l \cdot h^{-1} \cdot 70 \text{ kg}^{-1}$ ), are plotted against postmenstrual age on a log scale. The solid line represents the nonlinear relation between clearance and age. From Potts,<sup>39</sup> publisher permission obtained.

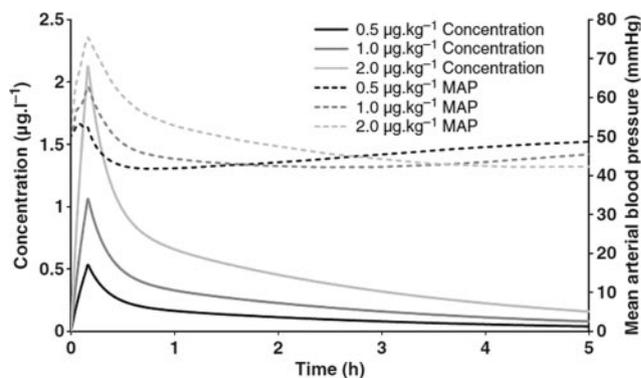
limited extent. In the immediate cardiac postsurgery period, the pharmacokinetic indices in infants and young children (1 to 24 months) are similar to those in healthy children. Clearance increases in parallel with age, although it lags behind children without cardiac disease by 27%.<sup>39</sup> Body weight and single-ventricle physiology correlate directly with clearance.<sup>45</sup> The reduced clearance of dexmedetomidine in this population may be attributed to depletion of substrate for glucuronide conjugation and decreased hepatic blood flow.<sup>46</sup> When administered as a single bolus dose to infants after cardiac surgery, the equilibration half-time ( $T_{1/2ke0}$ ) is 9.66 (165%) minutes.<sup>47</sup> These indices are unrelated to the child's age.

## PHYSIOLOGIC EFFECTS

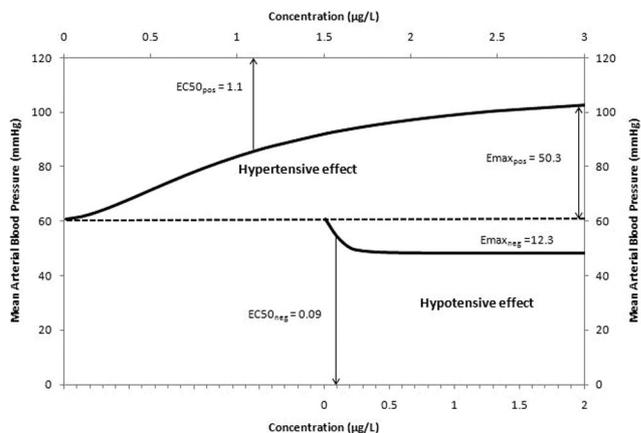
### Cardiovascular

The cardiovascular effects of dexmedetomidine are mediated via adrenoreceptors in both the central and peripheral nervous systems. In children, large doses of dexmedetomidine cause peripheral vasoconstriction, which may lead to transient systemic hypertension, whereas low doses cause central sympatholysis, which can lead to systemic hypotension (Figs. 2 and 3).<sup>31,47</sup> If an initial loading dose of dexmedetomidine is not administered or if the loading dose is infused slowly (i.e., over 10 minutes), the severity of the hypotension after dexmedetomidine is attenuated. In such cases, systolic blood pressure decreases up to 30% from baseline,<sup>31</sup> although hypertension has occurred.<sup>31</sup> Similar concerns regarding the hypotension after dexmedetomidine were reported in adult ICUs. In a small retrospective cohort study, careful titration of the dose of dexmedetomidine (adjustments to the rate could not be undertaken <30 minutes from the previous adjustment, and the circulatory indices had to exceed prescribed thresholds to adjust the dose) and omission of the initial loading dose attenuated the frequency of hypotension 4-fold, although the incidence of bradycardia did not change.<sup>48</sup>

In healthy children, the severity of the hypotension varies directly with the dose of dexmedetomidine. When a

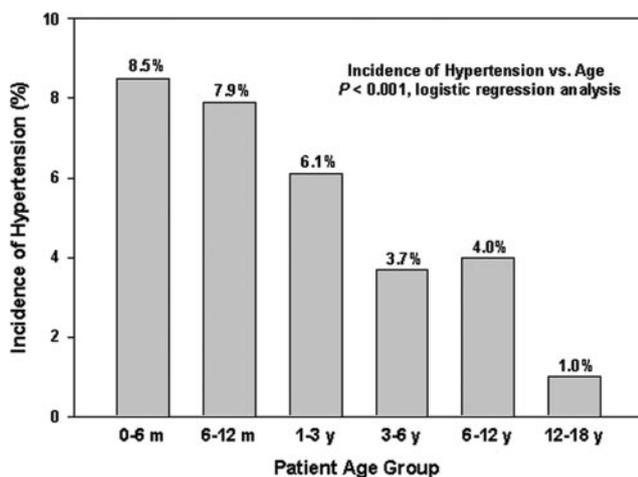


**Figure 2.** Simulated concentration-response and response-time curve for a typical 1-year-old (10 kg) child after a 0.5, 1, and 2  $\mu\text{g} \cdot \text{kg}^{-1}$  slow bolus of dexmedetomidine. The solid lines represent dexmedetomidine concentrations, and the dashed lines represent mean arterial blood pressure (MAP). Pharmacokinetic and pharmacodynamic parameters for the simulation are those determined from this study. This figure illustrates that doses that produce plasma concentrations  $>0.5 \mu\text{g}/\text{L}$  are associated with an increase in MAP above baseline. Plasma concentrations  $>1 \mu\text{g}/\text{L}$  are associated with an increase in MAP that is  $>20\%$  from baseline. From Potts,<sup>47</sup> publisher permission obtained.



**Figure 3.** The mean age of this cohort of children was 2.67 years (range 4 days–14 years). Parameter estimates were derived for an effect compartment concentration-response relationship using a composite Emax model. The combined effect of the composite Emax model on MAP is presented in this figure, which illustrates the combined hyper- and hypotensive effect of dexmedetomidine. The solid arrow indicates the concentration at which the hypertensive effect begins; the dashed arrow indicates the concentration producing a 20% increase in MAP from baseline. Reproduced with permission from Potts et al.<sup>47</sup>

loading dose between 0.5 and 1  $\mu\text{g}/\text{kg}$  dexmedetomidine is administered over  $\sim 10$  minutes as the sole sedative, systolic blood pressure decreases as the dose increases, reaching a maximum decrease of 30% from baseline at 1  $\mu\text{g}/\text{kg}$ .<sup>31</sup> When a small loading dose of 0.5  $\mu\text{g}/\text{kg}$  dexmedetomidine is infused over 5 minutes during 1 minimum alveolar concentration sevoflurane or desflurane, systolic blood pressure decreases only 10%.<sup>49</sup> When IV ketamine (2 mg/kg) and dexmedetomidine (1  $\mu\text{g}/\text{kg}$ ) are administered over several minutes followed by an IV infusion of dexmedetomidine, systolic blood pressure does not change significantly from baseline.<sup>50</sup> Larger doses of dexmedetomidine, 2 to 3  $\mu\text{g}/\text{kg}/\text{h}$ , cause more profound decreases in



**Figure 4.** Three-thousand five-hundred twenty-two children received dexmedetomidine per protocol: initial bolus of 3  $\mu\text{g}/\text{kg}$  dexmedetomidine over 10 minutes, followed by a continuous infusion of 2  $\mu\text{g}/\text{kg}/\text{h}$  to maintain a Ramsay Sedation Score (RSS) of 4. If at any point during the sedation, the child failed to achieve or maintain RSS 4, this bolus could be repeated up to 2 more times. The most frequent incidence of hypertension occurred in children <1 year of age who received more than 1 bolus ( $P < 0.001$ ). From Mason,<sup>53</sup> publisher permission obtained.

systolic blood pressure (with a 24% incidence of hypotension) as the dose increases, particularly in young infants.<sup>51,52</sup>

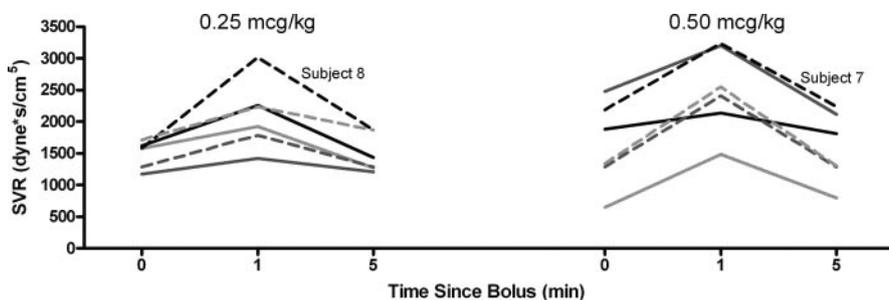
There are limited reports of dexmedetomidine-induced hypertension in children. In a retrospective review of dexmedetomidine as the sole sedative for radiological procedures, hypertension occurred more frequently after  $\geq 2$  boluses of 3  $\mu\text{g}/\text{kg}$  (infused over 10 minutes) IV dexmedetomidine than after 1 bolus and in younger (<1 year) children rather than in older children.<sup>53</sup> At these doses, the frequency of the hypertension is greatest in infants (<6 months of age), at 8.5%, and decreases with increasing age (Fig. 4). The episodes of hypertension reported were transient, resolving spontaneously within 30 minutes. Nonetheless, a positive relationship between the dose of dexmedetomidine and either the frequency or severity of the hypertension have not been a consistent finding in children.<sup>53</sup>

Heart rate (HR) also decreases up to 30% from awake measurements after an initial loading dose of dexmedetomidine, 0.5 to 1  $\mu\text{g}/\text{kg}/\text{h}$ , over 10 minutes in children.<sup>31,52</sup> When a similar loading dose is followed by a continuous infusion of 0.5  $\mu\text{g}/\text{kg}/\text{h}$ , the HR decreases an initial 30% during sevoflurane and 15% with desflurane anesthesia and then levels off, infrequently decreasing further or to bradycardia.<sup>49</sup> These HR responses were not attenuated by pretreating the children with IV glycopyrrolate (5  $\mu\text{g}/\text{kg}$ ).<sup>49</sup> Interestingly, HR does not decrease after a loading dose of the combination ketamine (2 mg/kg) and dexmedetomidine (1  $\mu\text{g}/\text{kg}$ ), followed by an infusion of dexmedetomidine (2  $\mu\text{g}/\text{kg}$  and then 1  $\mu\text{g}/\text{kg}$ ).<sup>50</sup> Preservation of the HR in the latter case may be attributed to the offsetting sympathetic effects of ketamine and dexmedetomidine.<sup>50</sup> Large doses of dexmedetomidine (2 to 3  $\mu\text{g}/\text{kg}/\text{h}$  followed by a continuous infusion of 2  $\mu\text{g}/\text{kg}/\text{h}$ ) produce a 16% incidence of

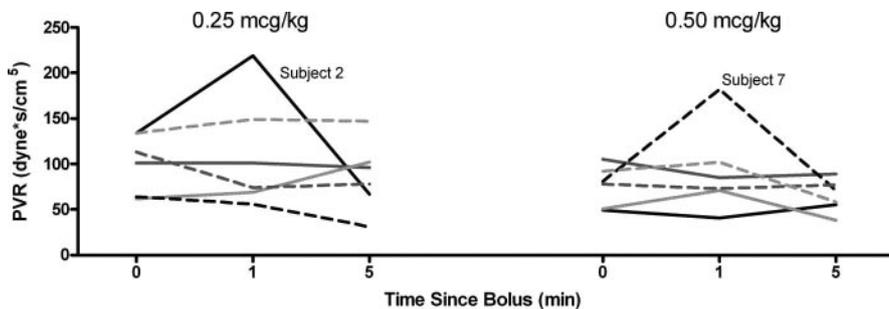
bradycardia, with HRs as low as 30 beats per minute (bpm), and proportionally more bradycardia in younger infants than in older children.<sup>52</sup> In that study, the age-specific baseline HRs were based on published "age-adjusted awake heart rates"<sup>54</sup> and bradycardia was defined as a >20% decrease in HR below the minimum age-adjusted HR.<sup>52</sup> Children who developed bradycardia maintained their systolic blood pressure within normal limits. As a result, the authors did not believe that the slow HRs posed a substantive threat to the children and therefore did not treat them.

Treating dexmedetomidine-induced bradycardia with glycopyrrolate yielded an unexpected response beyond the increase in HR. Evidence from an anecdotal report suggests that IV glycopyrrolate (5  $\mu\text{g}/\text{kg}$ ) causes profound, albeit transient, systemic hypertension when it is administered to treat dexmedetomidine-induced bradycardia.<sup>55</sup> The mechanism for the hypertensive response to the glycopyrrolate remains unclear. Other interventions to treat dexmedetomidine-induced bradycardias have not been investigated. However, if bradycardia occurs in the presence of marked hypotension, then aggressive intervention is recommended to prevent end-organ ischemic damage. Such intervention should include but is not limited to stopping the dexmedetomidine infusion, stimulating the child with verbal and tactile stimulation, and perhaps the administration of  $\beta$ -agonists and/or inotropes. Current evidence suggests that caution should be exercised when administering anticholinergics to treat isolated dexmedetomidine-associated bradycardia in children.

In children with congenital heart disease and those in the ICU immediately after cardiothoracic surgery, an initial loading dose of dexmedetomidine 1  $\mu\text{g}/\text{kg}$  IV infused over 10 minutes followed by an infusion of 1  $\mu\text{g}/\text{kg}/\text{h}$  decreases the HR  $\sim 18\%$ .<sup>56</sup> Despite the slow HR, normal sinus rhythm was maintained, and the electrocardiogram intervals were unaffected (with QTc intervals unchanged).<sup>56</sup> However, bradycardia (to HR values in the 40 to 50 per minute range) has been reported after a sedative dose of dexmedetomidine in an infant receiving digoxin after atrioventricular (AV) canal repair.<sup>57</sup> The mechanism for the bradycardia is believed to be direct suppression of the sinus or AV nodes, or both.<sup>58</sup> In a retrospective review of 14 children who were sedated with dexmedetomidine (0.3 to 0.4  $\mu\text{g}/\text{kg}/\text{h}$ ) after Fontan procedures, 6 of 9 children triggered cardiac pacing (threshold set to a HR <90 per minute) that in several cases continued for up to 90 minutes after dexmedetomidine was discontinued.<sup>59</sup> In children who were sedated with dexmedetomidine for electrophysiology studies of atrial and junctional tachyarrhythmias, 28% developed complications: 1 developed transient complete AV heart block, 4 developed hypotension that responded to IV fluids and calcium,<sup>60</sup> and 9 children required AV pacing to optimize their hemodynamics.<sup>60</sup> Bradycardia is an ongoing concern with this drug, particularly in young children whose cardiac output depends on an adequate HR. HR must be continuously monitored when dexmedetomidine sedation is administered to younger age infants and to children taking  $\beta$ -blockers and other medications that slow the HR, those with congenital heart disease and those with cardiac conduction defects.



**Figure 5.** Systemic vascular resistance (SVR) versus time for 2 doses of dexmedetomidine. SVR increased at 1 minute but recovered to baseline by 5 minutes. From Jooste,<sup>68</sup> publisher permission obtained.



**Figure 6.** Pulmonary vascular resistance (PVR) versus time for 2 doses of dexmedetomidine. PVR is preserved with time with both doses, except for 1 child in each group. From Jooste,<sup>68</sup> publisher permission obtained.

In addition to its chronotropic effects, dexmedetomidine may directly affect conduction paths through the sinoatrial and AV nodes. In children with supraventricular accessory pathways who underwent ablation of the pathways during sedation with dexmedetomidine, conduction through the sinus and AV nodes was depressed, as evidenced by an increase in the duration of the sinus cycle, increase in the recovery time of the sinus node and a prolongation of the PR interval.<sup>58</sup> Dexmedetomidine has been used to treat junctional ectopic tachycardia and re-entrant supraventricular tachycardia in a small group of children, with mixed success.<sup>60</sup> These data suggest that dexmedetomidine may affect cardiac conduction in children, particularly those with cardiac disease, and that these children should be closely and carefully monitored.

Bradycardia has also been described after moderate hypothermia in 2 children who were sedated with dexmedetomidine (0.7 and 1  $\mu\text{g}/\text{kg}/\text{h}$  infusions) and remifentanyl infusions after closed head injury.<sup>61</sup> The bradycardias (as low as 35 bpm) resolved spontaneously with discontinuation of the dexmedetomidine.

Cardiac arrest has been reported in adults during dexmedetomidine sedation,<sup>62–67</sup> although similar reports in children have been exceedingly infrequent. Bradycardia and a 10-second asystole were reported in an 18-year-old after double-lung transplant during sedation with an opioid and dexmedetomidine.<sup>67</sup> Normal sinus rhythm was restored when dexmedetomidine was discontinued.

The effects of dexmedetomidine on pulmonary artery pressure in children are incompletely understood. During isoflurane anesthesia for routine surveillance after heart transplant, a rapid IV infusion of 0.25 or 0.5  $\mu\text{g}/\text{kg}$  dexmedetomidine increased both systemic and pulmonary pressures transiently, the increases in the former being larger than those in the latter. Pressures returned to normal within 5 minutes of discontinuation of the dexmedetomidine (Figs. 5 and 6).<sup>68</sup> After cardiac surgery, dexmedetomidine mini-

mally affected the pulmonary artery pressure, and ventricular function remains unchanged.<sup>69</sup>

### Respiratory

One of dexmedetomidine's key advantages over other sedation medications is that it maintains ventilation and airway patency in the presence of increasing sedation. Respiratory rate and hemoglobin oxygen saturation are unchanged after 1  $\mu\text{g}/\text{kg}$  dexmedetomidine infused over 10 minutes.<sup>31</sup> In children anesthetized with sevoflurane or desflurane, a slow infusion of IV dexmedetomidine (0.5  $\mu\text{g}/\text{kg}$ ) maintained the end-tidal  $\text{Pco}_2$  during spontaneous respiration.<sup>49</sup> In a retrospective review of children who were sedated with either dexmedetomidine or a sedative regimen (propofol, midazolam, pentazocine, and buprenorphine) after Fontan surgery, carbon dioxide tension was unchanged after dexmedetomidine in comparison with the sedative regimen.<sup>59</sup>

Upper airway patency is maintained during dexmedetomidine sedation in children. In a magnetic resonance imaging (MRI) study of healthy children who breathed spontaneously during dexmedetomidine (1 or 3  $\mu\text{g}/\text{kg}/\text{h}$ ), the cross-sectional areas of the nasopharynx and retroglottal space were only modestly reduced in comparison with baseline, and respiratory indices were maintained.<sup>70</sup> In a retrospective review of children with obstructive sleep apnea who were sedated with dexmedetomidine during MRI, airway patency during sedation with dexmedetomidine was maintained with less artificial airway support than that during sedation with propofol.<sup>71</sup>

### Central and Peripheral Nervous Systems

#### Cerebral Hemodynamic and Metabolic Effects

In adults, dexmedetomidine decreases cerebral blood flow in proportion to a decrease in cerebral metabolic rate, suggesting that cerebral oxygen supply and demand are

matched during dexmedetomidine sedation.<sup>72–74</sup> Dexmedetomidine infusions do not affect intracranial or lumbar cerebrospinal fluid pressure or cerebral perfusion pressure in adults, even in those with severe head injury (Glasgow Coma Scale  $\leq 8$ ).<sup>75,76</sup> Similar data in children have not been forthcoming.

When administered via the neuraxial route, dexmedetomidine confers some analgesic and antinociceptive actions in animals, adults, and children.<sup>77–81</sup> In rabbits, epidurally administered dexmedetomidine showed evidence of neurotoxicity to white matter,<sup>82</sup> although this has not been validated in other models. The potential to cause neurotoxicity is also a concern when drugs are administered via the IN route. This latter route gives direct access to brain tissue via the cribriform plate in the roof of the nose. Until the conflicting neurotoxicity data are clarified, caution should be exercised when administering dexmedetomidine via the neuraxial and IN routes.

Evidence suggests that during cerebral ischemia in animals, dexmedetomidine may be neuroprotective.<sup>77,83–85</sup> Further study is required in children to validate this finding in humans.

#### **Effect on Apoptosis and Cerebral Ischemia**

Dexmedetomidine attenuates isoflurane-induced apoptosis in neonatal rats by blocking caspase-3 activation, B cell lymphoma-2 protein family, and phosphorylated extracellular signal-regulate kinase protein expression,<sup>86,87</sup> although it does not completely protect against isoflurane-induced neuronal injury. The clinical implications and application of animal studies for the developing human fetus, neonate, and child have yet to be elucidated.

#### **Effect on Neurological Activity: Motor- and Sensory-Evoked Potentials**

Studies have documented that dexmedetomidine preserves both somatosensory and motor-evoked potentials, making it a suitable adjunctive sedative for surgeries that require these monitors.<sup>8,12,88,89</sup> When used in combination with opioids, propofol, or both, dexmedetomidine facilitates neurophysiological monitoring for scoliosis surgery as well as for the placement of deep brain stimulators in children.<sup>8,14</sup>

#### **Sedative and EEG Effects**

Dexmedetomidine affects sedation through selective binding to the  $\alpha_2$  adrenoceptors in the locus coeruleus in the central nervous system. Sedation mediated through the locus coeruleus closely mimics endogenous sleep, as evidenced by studies in rats.<sup>90</sup> In children, the electroencephalogram (EEG) during dexmedetomidine sedation resembles that of natural nonrapid eye movement sleep.<sup>91,92</sup> Hence, this medication seems particularly appropriate for EEG studies in children with seizure disorders. The plasma concentrations of dexmedetomidine that confer sedation in adults,  $>0.6 \mu\text{g/L}$ , are thought to also hold true in children.<sup>39,93</sup>

#### **Miscellaneous Effects**

##### **Autonomic Nervous System**

Preliminary evidence suggests that autonomic activity during dexmedetomidine sedation in adults is suppressed to a similar extent as propofol at the same depth of anesthesia.<sup>94</sup> In adults, a single prospective study concluded that dexmedetomidine decreased autonomic activity to a similar

degree as did fentanyl, as reflected in the tone entropy and spectral analysis of HR.<sup>95</sup> Comparable data are not available in children.

#### **Effect on Thermal Regulation**

Dexmedetomidine interferes with thermoregulation by diminishing shivering, vasoconstriction, and nonshivering thermogenesis. Dexmedetomidine attenuates shivering in children, an effect thought to be mediated via a dose-dependent decrease in thermoregulatory vasoconstriction and shivering thresholds.<sup>96</sup> In an open-label prospective study in 24 children  $>7$  years of age who shivered after general anesthesia,  $0.5 \mu\text{g/kg}$  IV dexmedetomidine stopped the shivering in all of the children within 5 minutes, without recurrence.<sup>97</sup> Infants, however, depend more on nonshivering thermogenesis than on shivering and vasoconstriction.<sup>98–101</sup> In addition to the above effects of dexmedetomidine on vasoconstriction and shivering, activation of hypothalamic  $\alpha_2$  adrenergic receptors decrease centrally mediated metabolic heat production. Furthermore, dexmedetomidine inhibits lipolysis via postsynaptic  $\alpha_2$  receptors, thereby interfering with nonshivering thermogenesis in infants, creating the potential for developing hypothermia. It is therefore not surprising to read of a 2-day-old neonate who developed bradycardia that was unresponsive to atropine (75 bpm) and hypothermia ( $33^\circ\text{C}$  axillary) in the postoperative period while being sedated with dexmedetomidine and receiving epidural analgesia, without support from external warming devices. Reducing the dexmedetomidine infusion from 1 to  $0.2 \mu\text{g/kg/h}$  and applying an external heat source (as in a radiant overhead warmer) restored the infant's temperature to  $37.6^\circ\text{C}$  within 3 hours, without sequelae.<sup>102</sup> It would seem prudent to recommend external warming devices for all children sedated with dexmedetomidine, particularly neonates and infants.

## **CLINICAL APPLICATIONS**

### **Preoperative**

Dexmedetomidine has been used as a premedication in children for anxiolysis and analgesia and to maintain hemodynamic stability during induction of anesthesia. When given via the orogastric route,  $2.6 \mu\text{g/kg}$  dexmedetomidine successfully sedated 80% of the children within 20 to 30 minutes.<sup>3</sup> Transmucosal oral dexmedetomidine in a dose of  $1 \mu\text{g/kg}$  administered 45 minutes preoperatively provided comparable anxiolysis and a similar response to parental separation as oral clonidine,  $4 \text{ mg/kg}$  administered 90 minutes preoperatively, and oral midazolam,  $0.5 \text{ mg/kg}$  administered 30 minutes preoperatively.<sup>5</sup> Recovery and discharge times were similar among the 3 groups.<sup>5</sup> Mean arterial blood pressure, HR, and postoperative pain scores after both dexmedetomidine and clonidine were reduced similarly.<sup>5</sup> Larger doses of transmucosal oral dexmedetomidine, 3 to  $4 \mu\text{g/kg}$ , given 1 hour preoperatively, provided as effective sedation and comparable separation from parents as diazepam suppository ( $0.7 \text{ mg/kg}$ ), although the former achieved a greater level of sedation (a higher Ramsay Sedation Score) than did the latter.<sup>103</sup>

IN dexmedetomidine  $1 \mu\text{g/kg}$  sedates 50%–60% of children within 1 hour.<sup>104</sup> IN dexmedetomidine  $0.5$  and  $1 \mu\text{g/kg}$  1 hour preoperatively provides more anxiolysis at

the time of separation from the parents than oral midazolam in a dose of 0.5 mg/kg 30 minutes preoperatively.<sup>7</sup> Moreover, dexmedetomidine 1 µg/kg provides deeper sedation during induction of anesthesia than oral midazolam.<sup>7</sup> Dexmedetomidine premedication decreases HR 11% after 0.5 µg/kg and 16% after 1 µg/kg within 60 minutes from their respective baseline values. IN dexmedetomidine 2 µg/kg given to children with burn injuries 30 to 45 minutes before separation from their parents provided comparable quality of the separation, induction, and emergence to oral midazolam (0.5 mg/kg).<sup>6</sup> Dexmedetomidine premedication was more likely to provide effective sleep before entering the operating suite for anesthetic induction.<sup>6</sup> The slow onset of maximal sedation after IN dexmedetomidine premedication, 1 hour, is ~5-fold greater than the 10 to 15 minutes required for oral midazolam in doses of 0.75 to 1 mg/kg.

### Intraoperative Applications

Maintaining a steady respiratory drive during sedation is a key advantage of dexmedetomidine that distinguishes it from other sedatives. This quality makes it suitable for the management of the difficult airway in children<sup>11,16</sup> and in children with obstructive sleep apnea. Case reports describe excellent conditions for successful laryngoscopy, rigid bronchoscopy, and tracheal extubation when an infusion of dexmedetomidine 2.5 µg/kg/h is combined with propofol (200 to 250 µg/kg/min) and supplemented with boluses of dexmedetomidine (0.25 to 1 µg/kg) for tracheal reactivity.<sup>15</sup> Although case reports in children suggest advantages with dexmedetomidine for bronchoscopy, recent large, randomized studies in adults have not demonstrated a significant difference in incidence of adverse events, patient, or anesthesiologist satisfaction in the ease and experience of performing an awake fiberoptic intubation with dexmedetomidine versus midazolam.<sup>105</sup>

Sedation with dexmedetomidine to secure the airway via fiberoptic bronchoscopy has been reported in both anecdotal reports as well as in 2 randomized studies in adults.<sup>105,106</sup> In both studies, supplemental midazolam (1 mg total dose) was administered to some patients to achieve sufficient sedation to successfully complete the fiberoptic tracheal intubation. This approach has direct application for adolescents and mature children with unstable cervical spines or with difficult airways who either refuse general anesthesia or should not be anesthetized owing to preexisting conditions. However, no prospective studies in children have reported the use of dexmedetomidine for securing the airway in children.

In children with large anterior mediastinal masses, dexmedetomidine 2 µg/kg IV followed by an infusion of 2 µg/kg/h supplemented with ketamine and small doses of propofol and midazolam maintain spontaneous respiration and permit minor procedures to be completed without compromising either respiration or cardiac output.<sup>13</sup>

### Craniotomy-Awake-Surgery

Dexmedetomidine has been used for awake craniotomies, supplanting the older regimen of droperidol and fentanyl. With an IV infusion of 0.1 to 0.3 µg/kg/h, dexmedetomidine permits removal of laryngeal mask airways, spontaneous ventilation, and reliable responses to commands

during functional mapping.<sup>9</sup> In adolescents and adults, dexmedetomidine has been used for awake craniotomies to facilitate cortical mapping to identify motor and speech areas.<sup>10,17,21</sup> Dexmedetomidine preserves epileptiform activity in children with seizure disorders, making it an effective sedative to identify the regions of cortex that are responsible for seizures and to resect those foci.<sup>20,91</sup>

### Cardiac Surgery

In children (1 to 6 years) undergoing cardiac surgery, dexmedetomidine 0.5 µg/kg IV followed by an infusion of 0.5 µg/kg/h attenuates the hemodynamic and neuroendocrine (epinephrine, norepinephrine, blood glucose, plasma cortisol) responses at time of incision, time of sternotomy, and after bypass.<sup>19</sup> These findings are consistent with data in adults in whom a single dose of 2 µg/kg dexmedetomidine before surgery reduces the isoflurane requirements, the hemodynamic responses to intubation and extubation, and the neuroendocrine markers (plasma norepinephrine and epinephrine).<sup>18</sup>

### Blunting Physiologic Responses and Controlled Hypotension

Dexmedetomidine attenuates the hemodynamic responses to stimulation and reduces the arterial blood pressure, HR, and intraocular pressure in adults when administered before the stimulating procedure or intervention.<sup>107-109</sup> For example, dexmedetomidine has been used to induce hypotension in adults to decrease surgical bleeding.<sup>110,111</sup> Thus far, induced hypotension to reduce bleeding has not been reported in children, apart from a single report of an adolescent who received 0.2 to 0.7 µg/kg/h dexmedetomidine to maintain a mean arterial blood pressure of 55 to 65 mm Hg during an anterior spinal fusion.<sup>112</sup> Until the effects of dexmedetomidine on cardiac function, cerebral blood flow, and cerebral perfusion pressure in children have been elucidated, this indication for dexmedetomidine should be approached with caution.

### Regional Anesthesia

The effects of neuraxial dexmedetomidine have been studied in children, albeit to a limited extent. There is sufficient published literature to dispel any concern regarding the neurotoxicity of clonidine, but the same does not hold true for dexmedetomidine. Hence, the authors caution against the use of neuroaxial dexmedetomidine in children until further data clarify any potential neurotoxic effects.

When 1 µg/kg dexmedetomidine is combined with 2.5 mg/kg bupivacaine for caudal analgesia in children, dexmedetomidine decreases the sevoflurane requirements, the incidence of emergence agitation, and the need for adjuvant analgesics postoperatively in comparison with bupivacaine alone. Intraoperative hemodynamics are similar in the 2 treatment groups.<sup>78</sup>

Epidural dexmedetomidine and clonidine appear to be equally effective. In a double-blind study in children undergoing lower abdominal surgery, bupivacaine (2.5 mg/kg) combined with either 2 µg/kg clonidine or dexmedetomidine for epidural analgesia, yielded similar analgesia, duration of action, and hemodynamic sequelae.<sup>79</sup> As cautioned above, the potential neurotoxicity of dexmedetomidine has not been dispelled.

## Postoperative Applications

Prophylactic dexmedetomidine reduces the incidence of emergence delirium after sevoflurane anesthesia in children.<sup>22–25,29,113</sup> Doses of IV dexmedetomidine up to 0.5  $\mu\text{g}/\text{kg}$  at the end of surgery reduce the incidence of emergence delirium one-third to one-half that observed in the controls, from 47% to ~17%.<sup>22,24,113</sup> A dose of dexmedetomidine of 1  $\mu\text{g}/\text{kg}$  IV reduces the incidence of emergence delirium by 90% of that in controls, to 4.8%.<sup>25</sup> An infusion of dexmedetomidine of 0.2  $\mu\text{g}/\text{kg}/\text{h}$  reduces the incidence of delirium by 50%, from 61% to 26%.<sup>29</sup>

The opioid-sparing effects of dexmedetomidine in children are incompletely understood. Dexmedetomidine 1  $\mu\text{g}/\text{kg}$  and morphine IV 100  $\mu\text{g}/\text{kg}$  exhibit comparable morphine-sparing effects after tonsillectomy and adenoidectomy.<sup>26</sup> Dexmedetomidine, 2 or 4  $\mu\text{g}/\text{kg}$ , increases the morphine-free interval as well as the total postoperative morphine dose in comparison with IV fentanyl, 1 or 2  $\mu\text{g}/\text{kg}$ .<sup>30</sup> In children with obstructive sleep apnea undergoing tonsillectomy and adenoidectomy, intraoperative dexmedetomidine decreased the postoperative pain scores, the number of rescue doses of morphine, and the incidence of severe emergence agitation in comparison with fentanyl.<sup>27</sup>

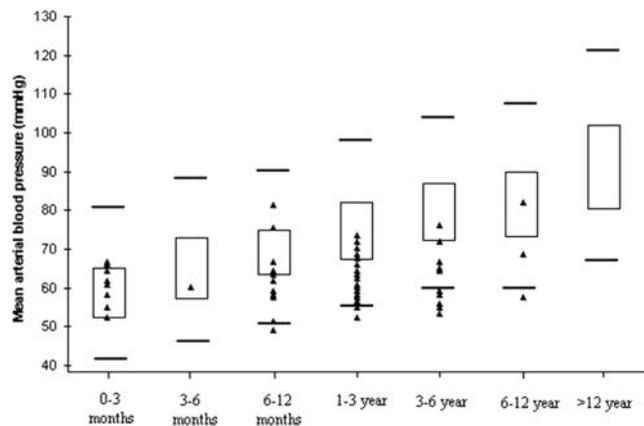
## Dosing Overdose

Two overdoses with dexmedetomidine have been reported in children, one a 10-fold overdose with 10  $\mu\text{g}/\text{kg}$  IV infusion over 10 minutes, and the second, a 60-fold overdose with 60  $\mu\text{g}/\text{kg}/\text{h}$  infusion. Neither case manifested cardiorespiratory instability, although recovery was protracted in both cases (for 2 hours).<sup>114,115</sup>

## Sedation Outside of the Operating Room

The largest experience with dexmedetomidine as a sedative for children outside the operating room has been in MRI. Although initial reports suggested that dexmedetomidine at 1  $\mu\text{g}/\text{kg}$  IV initial loading dose over 10 minutes followed by 0.5  $\mu\text{g}/\text{kg}/\text{h}$  provided effective sedation for MRI scans, these data could not be corroborated. The current evidence suggests that to provide sedation in >90% of children with dexmedetomidine, either supplemental sedatives must be coadministered with the dexmedetomidine (e.g., IV midazolam) or the bolus or infusion rate of dexmedetomidine must be more rapid than that reported initially.<sup>116–118</sup>

Two approaches have been pursued to provide effective sedation with dexmedetomidine for the majority of children who require MRI. In the first, a single IV dose of midazolam was coadministered with the loading dose of dexmedetomidine (1  $\mu\text{g}/\text{kg}$ ) that was followed by a continuous infusion of 0.5  $\mu\text{g}/\text{kg}/\text{h}$  dexmedetomidine. One hundred percent of the 20 children successfully completed the MRIs, although early recovery after dexmedetomidine was delayed in comparison with propofol.<sup>119</sup> In the second approach, effective sedation was achieved using larger boluses and infusions of dexmedetomidine, repeating the bolus if necessary and supplementing with small doses of adjuvant sedatives (pentobarbital) if dexmedetomidine failed to achieve adequate sedation conditions.<sup>51–53,70,71,120</sup> An initial loading dose of 2 to 3  $\mu\text{g}/\text{kg}$  IV dexmedetomidine could be repeated twice, followed by an infusion of up to 2  $\mu\text{g}/\text{kg}/\text{h}$ .<sup>52,120</sup> These doses were



**Figure 7.** Mean arterial blood pressure (MAP) for all 65 children in the cohort. Boxes represent normal age-adjusted range, and horizontal bars denote 20% above and below the highest and lowest values, respectively, of normal age-adjusted MAP values (6 magnetic resonance imaging, 3 computed tomography). From Mason,<sup>122</sup> publisher permission obtained.

administered by a registered nurse for computed tomography (CT) and MRI studies under the supervision of an anesthesiologist.

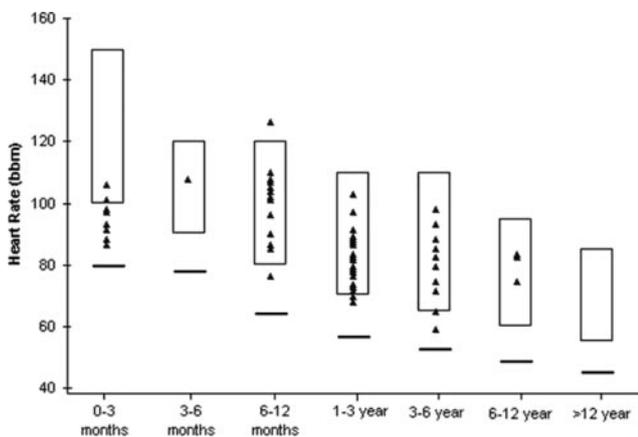
Most children who require MRI and CT scans require deep sedation or general anesthesia, and many of the children are neurocognitively impaired. The dose regimen for dexmedetomidine in children with autism undergoing primarily MRI scans is 1.4  $\mu\text{g}/\text{kg}$  IV loading dose followed by an infusion of 1.1  $\mu\text{g}/\text{kg}/\text{h}$ .<sup>121</sup> However in that study, 90% of the children received supplemental midazolam to complete the scan; 60% received IV midazolam, 0.08 mg/kg, and 40% received oral midazolam, 0.45 mg/kg. Intramuscular dexmedetomidine (2.4 to 2.9  $\mu\text{g}/\text{kg}$ ) has also been administered for sedation for MRI and CT scans with 100% success, recovery times of ~20 minutes, and hypotension in 14%.<sup>122</sup> There were no cases of hypertension or bradycardia (Figs. 7 and 8).<sup>122</sup>

In children with polysomnogram-confirmed sleep apnea, dexmedetomidine 2  $\mu\text{g}/\text{kg}$  IV loading dose followed by an infusion of 2  $\mu\text{g}/\text{kg}/\text{h}$  provided adequate sedation for MRI.<sup>71</sup> In this retrospective study, fewer instances of airway support during dexmedetomidine were required in comparison with propofol.

Dexmedetomidine has been administered via the transmucosal oral (buccal) route for sedation for radiological studies. In infants and children between 4 months and 19 years, 2 to 3  $\mu\text{g}/\text{kg}$  transmucosal dexmedetomidine successfully sedated only 60% of the children within 28 minutes and failed to sedate 35%, despite repeat dosing.<sup>123</sup>

Intravenous dexmedetomidine has successfully sedated >95% of children undergoing CT imaging after a bolus dose of 2  $\mu\text{g}/\text{kg}$  and a 1  $\mu\text{g}/\text{kg}/\text{h}$  infusion, repeated boluses, and supplemented with small doses of pentobarbital as needed.<sup>51,120,124</sup> Bradycardia, hypotension, and sinus arrhythmias have been described with these doses, although they have not required treatment.<sup>51–53,70,91,120</sup>

Dexmedetomidine administered via both the oral and parenteral routes appears suited for sedation for EEG because of its action on the  $\alpha_2$  receptor in the locus ceruleus.<sup>91,125</sup> The EEG during dexmedetomidine sedation



**Figure 8.** Sixty-five consecutive children (21 undergoing magnetic resonance imaging [MRI], and 44 undergoing computed tomography [CT] imaging) received IM dexmedetomidine. Children sedated for MRI received a larger total dose of dexmedetomidine, mean 2.9  $\mu\text{g}/\text{kg}$  (range 1.6 to 4) in comparison with children in the CT group, mean 2.4  $\mu\text{g}/\text{kg}$  (range 1 to 6) ( $P \leq 0.01$ ). Boxes represent normal age-adjusted range for heart rates, and the horizontal bars denote 20% below the lowest value of normal age-adjusted heart rate. From Mason,<sup>122</sup> publisher permission obtained.

is similar to stage 2 of natural nonrapid eye movement sleep.<sup>91</sup> In a retrospective comparison of IV dexmedetomidine ( $\leq 2 \mu\text{g}/\text{kg}$  bolus,  $\leq 2 \mu\text{g}/\text{kg}/\text{h}$  infusion) and propofol for pediatric magnetoencephalography, dexmedetomidine did not interfere with the ability to detect EEG activity.<sup>126</sup>

Dexmedetomidine has been described for sedation for interventional procedures including central line placement, bronchoscopy, chest tubes, and lithotripsy. Dexmedetomidine provides effective sedation after a bolus of 1.5  $\text{m}/\text{kg}$  (with a range of 1 to 3  $\mu\text{g}/\text{kg}$ ) during spontaneous respiration. It should be noted that 50% of the children required supplemental ketamine (0.7  $\text{mg}/\text{kg}$ ).<sup>127</sup> For children who are scheduled for lithotripsy, 1  $\mu\text{g}/\text{kg}$  IV dexmedetomidine combined with 1  $\text{mg}/\text{kg}$  ketamine preserved hemodynamics, provided effective sedation, and facilitated a more rapid recovery than did midazolam sedation combined with ketamine.<sup>128</sup> The combination of ketamine and dexmedetomidine may provide the key to maintaining respiratory drive as well as preserving hemodynamics in infants and children.

When dexmedetomidine is used as the sole sedative for cardiac catheterization in children, the success rate is disappointing.<sup>50,129,130</sup> With a loading dose of 1  $\mu\text{g}/\text{kg}$  IV dexmedetomidine followed by an infusion of 1 to 2  $\mu\text{g}/\text{kg}/\text{h}$ , most children required supplemental sedation with either ketamine or propofol (1  $\text{mg}/\text{kg}$ ) to maintain adequate sedation and immobility.<sup>50,130</sup> When the regimen of dexmedetomidine and ketamine was compared with propofol and ketamine for cardiac catheterization, all of the studies were completed successfully. Although the respiratory indices in the 2 groups were similar, those who received dexmedetomidine exhibited reduced HRs, more supplemental ketamine, and a prolonged recovery time (49.54 vs 23.16 minutes).<sup>129</sup>

Dexmedetomidine may have clinical applications for pediatric dentistry, although experience in young children is limited. In a case series, children who required moderate

sedation in the dental clinic received IN dexmedetomidine 2  $\mu\text{g}/\text{kg}$  followed 30 minutes later by IN sufentanil 1  $\mu\text{g}/\text{kg}$ .<sup>131</sup> The mean time to the onset of sedation after this regimen was  $\sim 45$  minutes, and the time to recovery was 52 minutes. Although the quality of the sedation was better than that after oral midazolam, both the onset of and recovery from IN sedation were slower than after oral midazolam.

The combination of dexmedetomidine with an adjunctive anesthetic/analgesia such as propofol or fentanyl provides excellent sedation for upper and lower gastrointestinal endoscopy in adults. However, dexmedetomidine proved to be less effective when compared with a propofol/fentanyl combination for endoscopic retrograde cholangiopancreatography, demonstrating comparatively less analgesia and more agitation.<sup>132</sup> Whether supplementing propofol with dexmedetomidine confers any advantage in children undergoing endoscopy procedures remains unclear. In adults, both dexmedetomidine and propofol reduce lower esophageal sphincter pressure similarly without changing the gastroesophageal pressure gradient.<sup>133</sup> In children, dexmedetomidine 1  $\mu\text{g}/\text{kg}$  bolus with 0.5  $\mu\text{g}/\text{kg}/\text{h}$  infusion does not reduce the plasma concentration of propofol required to produce a targeted clinical effect in children undergoing esophagogastroduodenoscopy.<sup>134</sup> Additional studies are required to determine whether larger plasma concentrations of dexmedetomidine shift the propofol response curve and confer an advantage in children undergoing gastrointestinal procedures. The value and benefit of supplementing or replacing propofol with dexmedetomidine for pediatric gastroenterology procedures have not been established.

#### Intensive Care Unit

Dexmedetomidine has been an effective sedative in infants and children in the PICU in numerous reports, including prospective trials up to 3 days.<sup>135-138</sup> In these studies, dexmedetomidine spared the doses of benzodiazepines and opioids, although bradycardia and hypotension were notable in 27% of children. Interestingly, HR did not decrease significantly during dexmedetomidine administration, with only 1 child developing bradycardia. That episode of bradycardia resolved with discontinuation of dexmedetomidine.<sup>139</sup> After cardiac and thoracic surgery, dexmedetomidine sedation yielded hypotension in only 15% of children.<sup>139</sup> These episodes were treated successfully by either reducing or stopping the dexmedetomidine infusion. That the dose requirements for IV and inhaled medications are greater in younger-age subjects<sup>140,141</sup> is consistent with the dose requirements for benzodiazepines and opioids during dexmedetomidine sedation in children  $<1$  year of age in comparison with older children.<sup>139</sup> In a retrospective study from the PICU, arterial blood pressure and HR were maintained during dexmedetomidine infusions for up to 15 days.<sup>142</sup> In the 29 children in that study, one-third received an initial loading dose, whereas the remaining two-thirds received only a continuous infusion. These data suggest that dexmedetomidine may be administered to those children who are at risk for hypotension and bradycardia, provided the dosing regimens are adjusted to the child's cardiovascular state.

### **Dexmedetomidine and Withdrawal**

Intravenous and subcutaneous dexmedetomidine have been used to treat, prevent, or facilitate withdrawal from benzodiazepines or opioids in children.<sup>143–145</sup> In adults, the beneficial effects of dexmedetomidine appear to plateau.<sup>146</sup> Whether a similar plateau effect occurs in children has not been established.

Rebound hypertension has not been a consistent finding after discontinuing chronic dexmedetomidine administration in children, although rebound hypertension and tachycardia have been reported after discontinuing 7 days of dexmedetomidine sedation in a child after a Fontan procedure.<sup>147</sup> Alternatively, dexmedetomidine for up to 50 days has been administered as an adjunct to benzodiazepines and opioids in children with burns and for 2 months in an infant after liver transplant, without evidence of tachyphylaxis or rebound hypertension upon discontinuation.<sup>148,149</sup> In the absence of well-designed studies, it is difficult to determine whether rebound hypertension is a substantive risk after chronic dexmedetomidine infusions in children.

### **Cyclical Vomiting**

Cyclical vomiting is a chronic recurrent disorder of unknown etiology that is resistant to treatment. In an anecdotal report of 3 children with cyclical vomiting who were resistant to in-hospital therapy with chlorpromazine, diphenhydramine, and lorazepam, an IV bolus of either 0.25 or 0.5  $\mu\text{g}/\text{kg}$  dexmedetomidine, followed by a continuous infusion of 0.25  $\mu\text{g}/\text{kg}/\text{h}$ , resolved the cyclical vomiting for as long as 18 hours.<sup>150</sup>

### **Palliative Care**

There has been little movement to exploit the analgesic properties of dexmedetomidine until now. Recent interest from palliative care providers suggests that dexmedetomidine may provide a bridge to wean or reduce the patients' dependency on opioids and for end-of-life therapy.<sup>151,152</sup> This application has been applied only in adults.

## **FUTURE APPLICATIONS AND DIRECTION**

On the basis of this review, we advise caution regarding the future applications of dexmedetomidine in pediatric anesthesia and sedation. Although dexmedetomidine is available for off-label use in children, we posit that 3 key issues will limit the scope of use and application of this medication in children: (1) there are no specific indications for its use in children; (2) there is a dearth of research on the pharmacology, pharmacodynamics, and physiologic effects of dexmedetomidine in children, particularly in areas outside of the intensive care unit; and (3) the hemodynamic, analgesic, and recovery profile of dexmedetomidine may challenge its use in young infants and ambulatory surgery. We believe that the lack of focus and clarity in defining these issues has contributed to the inertia that has stalled the addition of dexmedetomidine to hospital formularies, which in turn has limited our access to this medication.

As a premedication, dexmedetomidine does not hold great promise. Its slow and unpredictable onset and maintenance of anxiolysis, regardless of route of administration, together with its prolonged offset make it an unsuitable substitute for oral midazolam.

As a sedative, dexmedetomidine holds the most promise: it maintains spontaneous respiration and preserves oxygenation and ventilation, at depths of sedation that range from moderate to deep sedation. The respiratory-sparing effects of dexmedetomidine may be most effectively exploited if it were used as a singular sedative for ICU. In this regard, it may be particularly suited for use by nonanesthesiologists, after appropriate education and training in the recognition and treatment of hemodynamic sequelae. Further investigation of its role in children with obstructive sleep apnea who are at risk for propofol, inhaled anesthesia, or opioid-associated implications is warranted.

Dexmedetomidine does not reliably induce amnesia, which precludes its use as the primary or sole anesthetic or sedative during surgical and painful procedures that require amnesia. The effect of dexmedetomidine on memory and amnesia in the pediatric population is undetermined. Until we are certain that dexmedetomidine creates anterograde amnesia, adjunctive benzodiazepines should be considered if amnesia is a requisite. Drug combinations, although synergistic with respect to analgesia and sedation, may exacerbate the side effects of dexmedetomidine. The physiological responses to such drug combinations must be carefully defined.

Dexmedetomidine is neither a complete anesthetic nor a complete analgesic. Its role as an adjunct for total IV anesthesia holds very realistic and practical promise. In particular, dexmedetomidine may play an integral role during neurosurgery and during spinal surgery with monitoring evoked potentials.

The risk of apoptosis in young children remains a subject of interest to pediatric anesthesiologists. Among the anesthetics implicated in causing apoptosis in infant rodents, only dexmedetomidine and possibly xenon have been deemed to be "safe."<sup>86,153</sup> If the human studies on apoptosis substantiate a risk of neurocognitive dysfunction after anesthesia in young children, dexmedetomidine may prove to be pivotal in providing safe anesthesia to this age group.

The role of dexmedetomidine in the PICU and in critically ill patients remains to be determined. Recent studies in adults suggest that dexmedetomidine decreases the vasopressor and opioid requirements after cardiac surgery as well as after major abdominal surgery.<sup>154–157</sup> Although dexmedetomidine decreases the postoperative opioid requirements for up to 7 days, there is no evidence that this is a dose-dependent analgesic effect.<sup>158</sup> There have been some promising reports in adults that dexmedetomidine can decrease ICU delirium, shorten the duration of intubation in comparison with benzodiazepines, and improve 28-day mortality rates in tracheally intubated, septic patients.<sup>155,159–161</sup> Similar studies are required to determine whether these same benefits can be achieved in children.

We envision only a limited role for dexmedetomidine in mainstream pediatric anesthesia because its dose is limited by its prolonged half-life and the frequency of circulatory side effects. The incidence and severity of the circulatory effects increase as the number of bolus doses increases in the infant. The role of IV hydration in attenuating or preventing hemodynamic effects remains to be elucidated. If pretreatment with balanced salt solution boluses attenuates

the magnitude of the circulatory changes, then a broader role for dexmedetomidine in children may be possible. In this era of ambulatory surgery, the role of sedatives with half-lives of 2 to 3 hours is, by definition, quite limited. Small doses and brief exposures may reduce the risk of a prolonged recovery and delayed discharge from the recovery room and hospital. In target populations that include the morbidly obese, difficult airways, and obstructive sleep apnea, dexmedetomidine may be the optimal sedative.

Several deficiencies apparent in the development of dexmedetomidine have hampered identifying its role in pediatric anesthesia. A structured dosing regimen for dexmedetomidine in infants and children has not been forthcoming. The current dosing is empirical and is based for the most part on studies in adults. In the United States, a pediatric indication for dexmedetomidine has not been forthcoming. Future roles for dexmedetomidine in children could include sedation to simulate natural sleep for sleep studies and diagnostic EEGs. The most significant role of dexmedetomidine will be in the ICU should it show demonstrable benefits on morbidity and mortality in infants and children. It remains our primary concern that dexmedetomidine has not been carefully and methodically studied in terms of its pharmacologic and physiologic effects in infants and children. It remains an orphan drug in children and may—if large, randomized, prospective studies are not performed—never achieve a proper indication for its use in children. ■■

#### DISCLOSURES

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**Contribution:** This author helped write the manuscript.

**Attestation:** Keira P. Mason approved the final manuscript.

**Name:** Jerrold Lerman, MD, FRCPC, FANZCA.

**Contribution:** This author helped write the manuscript.

**Attestation:** Jerrold Lerman approved the final manuscript.

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