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Role of Dexmedetomidine in Pediatric Intensive Care Practice: A Literature Review

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ABSTRACT

Dexmedetomidine is an α 2-adrenoceptor agonist with sedative, anxiolytic and analgesic properties.[1] This article reviews the use of dexmedetomidine in pediatric patients and its use in critical care. We will focus on the clinical experience of the drug in children and its role in sedation in Pediatric intensive care unit and for procedural sedation.

Introduction

Dexmedetomidine is an α2-adrenoceptor agonist used for its sedative, anxiolytic and analgesic properties. The US food and drug administration (FDA) first approved dexmedetomidine for use in adults in 1999[1] and in 2008 for sedation for surgical or medication procedures in adults without intubated airways outside the ICU.[2] 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).[2] In this review article we will focus on the pharmacology of the drug in children, our current state of knowledge, its use in children and its future perspective.

Dexmeditimodine formulation- Dexmedetomidine $C_{13}H_{16}N_2$ (sold under name of Precedex)

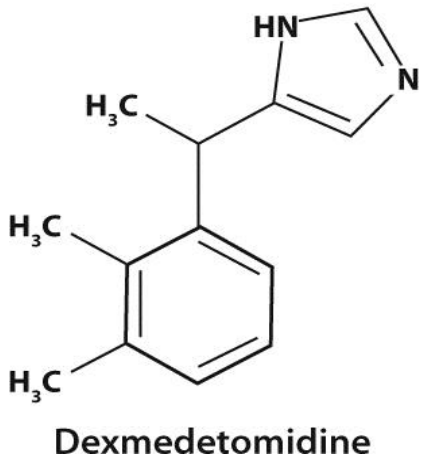

Figure 1. Chemical structure of Dexmedetomidine[4]-.

Mechanism of action- Dexmedetomidine is the S-enantiomer of medetomidine with increased specificity for the α2-adrenoceptor (α2:α1, 1620:1) compared to clonidine (α2:α1, 220:1). It exerts its effects by binding both central and peripheral α2-receptors. Receptor activation leads to alterations in ion channel conduction and cell hyperpolarization, resulting in inhibition of norepinephrine release.[1]

Clinical effects are related to the density of α2-receptors in various tissues throughout the body. The sedative and anxiolytic effects of dexmedetomidine result from binding of α2-adrenoceptors in the locus ceruleus in the pons. G-protein mediated inhibition of adenyl cyclase decreases cAMP production, preventing protein phosphorylation and altering ion channel conductance, thereby preventing norepinephrine release. This leads to downstream regulation of a sleep-promoting pathway involving inhibitory GABA neurotransmitters with resultant sedation and anxiolysis.[1]

Pharmacodynamics- Dexmedetomidine has effects on cerebral, respiratory, analgesic and cardiovascular systems.[3]

Pharmacokinetics- studies evaluating pharmacokinetics of dexmedetomidine in children are very limited.

Bioavailability- All of the studies have involved a brief exposure to dexmedetomidine. When administered IV, 93% of the dexmedetomidine is protein bound in children. When delivered by non-IV routes, the bioavailability of dexmedetomidine follows the order orogastric 16%, intranasal (IN) 65%, buccal 82%, and IM 104%.[2]

Distribution- 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.[4]

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Sedation	Provides sedation that permits arousal with gentle stimulation[3] When given via the orogastric route,2.6 μg/kg dexmedetomidine successfully sedated 80% of the children within 20 to 30 minutes. Transmucosal oral dexmedetomidine in a dose of 1 μg/kg administered 45 minutes preoperatively provided comparable anxiolysis and a similar response to parental separation as oral clonidine, 4 mg/kg administered 90 minutes preoperatively, and oral midazolam, 0.5 mg/kg administered 30 minutes preoperatively.[2]
Respiration	Lack of respiratory depression Blunts the CO_2 response curve Doesnot lead to extreme hypoxia or hypercapnia Respiratory rate, CO_2 tension, and oxygen saturation are maintained.
Anaesthesia	Adjunct to other drugs to improve sedation or anaesthesia Total IV anaesthesia described with dexmedetomidine and ketamine
Analgesia	Meta-analysis showed intraoperative drug was associated with reduced postoperative opioid consumption in the postanaesthetic care unit (PACU) and decreased pain intensity. Optimal dose was 0.5 μg/kg or more
Cardiovascular	Decreases heart rate in a dose dependent manner in children Conflicting data regarding safety in children with congenital heart disease.

Biotransformation- Dexmedetomidine is biotransformed in the liver to inactive metabolites, with 85% undergoing glucuronidation by UDP-glucuronyl transferase (UGT) and 15% by cytochrome P450 2A6.[2] It is extensively metabolized through both the cytochrome P450 enzyme system, by aliphatic hydroxylation via CYP2A6, and direct glucuronidation. N-glucuronidation produces inactive metabolites, while aliphatic hydroxylation produces active 3hydroxy-dexmedetomidine, which then undergoes glucuronidation and 3-carboxy-dexmedetomidine.

N-methylation produces active 3-hydroxy-N-methyl-dexmedetomidine, 3-carboxy-N-methyl- dexmedetomidine, and dexmedetomidine-N-methyl-O-glucuronide.[4] A very small fraction of dexmedetomidine is excreted unchanged in urine and feces.[2]

Elimination- In healthy children, the rapid phase redistribution half-life is 7 minutes, clearance is 15 mL/kg/min, and the terminal elimination half-life is 2 hours.[2] These metabolites are eliminated in the urine (95%) and feces (4%).[4]

Use in pregnancy- Literature suggests that dexmedetomidine doesn't cross uteroplacental barrier due to its high placental extraction but as its use in labor analgesia/as an adjunct to general anesthesia still remains off label, the concerned Anesthesiologist must select the patient carefully and should be able to justify its use. One should try to avoid the use of dexmedetomidine in presence of bradyarrhythmias, severe left ventricular/biventricular dysfunction and hypovolemic states.[5]

Use in setting of hepatic and renal insufficiency- According to the manufacturer, clearance of this agent was 53%, 64%, and 74% lower in adult patients with mild, moderate, and severe hepatic impairment (Child-Pugh Classification), respectively, compared with healthy subjects. Therefore, dose reduction should be considered for patients with hepatic dysfunction.[6] Dexmedetomidine is primarily eliminated as metabolites by the kidney, with no unchanged drug found in the urine. The pharmacokinetics (PKs) did not significantly change in patients with severe renal dysfunction (creatinine clearance <30 mL/min) compared with healthy adults. However, the metabolites may accumulate in patients with renal dysfunction with long-term administration. The PKs and effects of the metabolites are unknown in patients with impaired renal function. Thus, the manufacturer recommends consideration of reduced doses in these patients. Specific dose reductions in hepatic and renal dysfunction have not been established, thus additional studies in both adult and pediatric patients are needed.[6]

Clinical trials in pediatrics[6]- there have been many case reports, few case series and few randomized controlled studies in pediatrics, here we are short listing the studies in intensive care in pediatrics**.**

Author	Study design	Pt age; number; Use	Dose of dexmedetomidine	Duration of drug; concurrent sedative used	Efficacy	Adverse effects
Tobias et al[7]	Prospective randomized	2mo to 8.2 yr; 30; Mechanical ventilation	Loading dose (LD)- 0.25-0.5 μg/kg then continuous infusion (CI) 0.28±0.07-0.68±0.15 μg/kg/h	24h; morphine	No difference in Ramsay sedation scale (RSS), PICU sedation score, bispectral index (BIS)	Severe bradycardia (n=1) [concurrent digoxin use]; not significant BP differences, lower heart rate in dex group
Tobias et al[8]	Case report	5week; 1; Mechanical ventilation	Loading dose 0.5 μg/kg then continuous infusion 0.44 μg/kg/h	13h; morphine	NA	Bradycardia (HR decreased from 133 to 116 bpm during loading dose, then to 90 bpm over 13 h; events of 40–50 bpm were observed), drug was discontinued

Tobias et al [9]	Case series	10 wk to 14 y; 4; Mechanical vntilation, intraoperatively for controlled hypertension, invasive procedure	LD 0.5–0.6 μg/kg (n = 3) then CI 0.25–0.7 μg/kg/h	0–24 h; morphine (2 pts)	Effective sedation and anxiolysis,improved RSS and BIS for ,mechanical ventilation (n = 2), achieved desired MAP without reflex tachycardia (n=1)	NS changes in BP or HR noted, other than controlled hypotension in 1 pt
Hammer et al[10]	Case reprot	9y; 1; Mechanical ventilation	CI- 0.2–0.5 μg/kg/h	4 d; CI midazolam,fentanyl	Pt more cooperative, pain score 0–2	Stable HR and BP
Tobias et al[11]	Case series	4-17y; 5; withdrawal, post anesthesia emergence delirium and shivering, non-invasive procedure	LD 0.5 μg/kg (n = 3) then CI 0.25 μg/kg/h (SD 0.5 μg/kg)[n = 2]	0–40 h; CI midazolam, morphine prn (1 pt)	Effective anxiolytic in spontaneously breathing pts (n = 2); controlled symptoms of withdrawal (n = 1); ceased emergence agitation and shivering (n = 2)	None reported
Enomoto et al[12]	Case report	9 mo; 1 Mechanical ventilation	CI 0.4–1.4 μg/kg/h	>2 mo; CI midazolam, fentanyl. Discontinued Dex. Changed to ketamine, then Dex restarted once drug- induced hepatitis was ruled out due to unattainable sedation	Adequate sedation, pt comfortable	Discontinuation because of hepatic insufficiency later attributed to CMV infection; no other adverse effects were reported.
Tobias JD[13]	Retrospective	3-24 mo; 7; Opioid withdrawal	LD 0.5 μg/kg then CI 0.5–0.7 μg/kg/h	NA; CI midazolam, fentanyl	Finnegan score ≤7, controlled signs and symptoms of withdrawal	HR and RR decreased with bolus dose ($p < 0.02$) without exceeding limit for age
Finkel JC et al[14]	Case report	8mo; 1; Opioid and benzodiazepine withdrawal	LD 1 μg/kg then CI 0.2–0.7μg/kg/h, bolus 1 μg/kg q6h prn if BIS >80 or arterial BP >20% over baseline if at maximum CI rate	7d, none	Target BIS 60–80 reached with titration of CI	No rebound effects; hemodynamically stable
Finkel JC et al[15]	Case report	2d; 1; Sedation and analgesia	LD 1 μg/kg over 10 min followed by CI 0.4–1 μg/kg/h	7 d; continuous ropivacainemand fentanyl epidural	Adequate sedation	Hypothermia-induced bradycardia noted at h4 of CI, resolved (at h12) after decreased rate to 0.4 μg/kg/h, temporary discontinuation of fentanyl infusion, addition of radiant warmer at h9. Given naloxone and atropine without resolution of symptoms

Walker J et al[16]	Retrospective	0.6-17y; 65; Inadequate sedation with opioids and benzodiazepins in burn ICU patients	LD 1 μg/kg (n = 26) then CI initially 0.2 μg/kg/h, titrated to range of 0.1–2 μg/kg/h	11±10 (2–50) d; CI opioid and benzodiazepine (specific agents NA)	Maintained or decreased dose of concurrent opioids; achieved adequate sedation	NS episodes of bradycardia or hypertension; no respiratory effects; no changes in blood glucose levels (n = 21)
Mukhtar AM et al[17]	Prospective randomized Placebo-contolled	1-6y; 30; Stress response during cardiac surgery	LD 0.5 μg/kg then CI 0.5 μg/kg/h	Until end of CPB; NA	Plasma cortisol, epinephrine, norepinephrine, and blood glucose levels significantly lower in Dex group after sternostomy and CPB; significantly smaller dose of sodium nitroprusside required with Dex	Significant decrease in HR and MAP from baseline (desired)b
Chrysostomou C et al[18]	Retrospective	8±1.1y; 38; Sedation in CCU	Initial CI 0.32±0.15 μg/kg/h, then 0.3±0.05 μg/kg/h	14.7±5.5 h; CI opioids and/or benzodiazepine (NA)±prn midazolam, lorazepam, fentanyl, morphine, hydromorphone, or chloral hydrate	Mild to moderate sedation (93%), mean ICU sedation score 1.3±0.6, mean pain score 1.5±0.9 (FLACC and NVAS)	Transient hypotension (15%); transient hypertension (5%); bradycardia (n = 1)
Finkel JC et al[19]	Case series	6mo,7y; 2; Opioid withdrawal	LD 1 μg/kg then CI 0.5–1 μg/kg/h	5 and 16 d; CI midazolam, fentanyl, prn methadone, lorazepam, fentanyl or midazolam	Maintained University of Michigan Sedation Score ≤ 2	No hemodynamic instability or rebound hypertension
Baddingam K et al[20]	Case series	55d, 4mo,17y; withdrawal	LD 0.5 μg/kg then CI 0.25 μg/kg/h	18 h to 8 d; CI midazolam(n = 1), morphine prn (n = 1), CI fentanyl (n = 1), midazolam prn (n = 2), CI propofol (n = 1), hydromorphone PCA (n = 1), lorazepam prn (n = 1)	Withdrawal behavior decreased or controlled	None reported
Czaja SA et al[21]	Retrospective observational study	2mo-21 yrs; 121; Mechanical vntilation	Average dose was CI-0.55 μg/kg/hr (range 0.15–0.70 μg/kg/hr)	25.8 hrs(20 mins to 60 hours); Morphine and lorazepam(n=103)	Reduction in benzodiazepine and opiate dose by at least 20% with the dexmedetomidine infusion (70% and 73%patients, respectively	Hypotension and/or bradycardia in 33 of 121 (27%) patients. Discontinuation in 12 of 121 (10%) patients.
Wang SS et al[22]	Prospective, randomized controlled	3-6 yrs; 40; Anaesthesia induction and intubation	intranasal DEX 1 μg/kg (group D1) or 2 μg/kg (group D2) 30 min before anesthesia induction	Single dose; Sevoflurane	2 μg/kg DEX deeper sedation and less anxiety by the assessments of the alertness scale, behavior score, and BIS scores	None reported

Drug dosage- dose of dexmedetomidine for various procedure[23]-

Table 3. Summary of various dosing regimens and routes of administration for perioperative dexmedetomidine.

Application	Route	Dose range
Preoperative applications		
Anxiolysis	Buccal	1μg/kg^{-1}
	Intranasal	0.5–2 μg/kg^{-1}
Intraoperative applications		
Airway procedures	I.V.	Loading dose: 0.5–2 μg kg^{-1} over 10 min followed by an infusion of 0.5–3 μg kg^{-1} h^{-1}
Neurosurgical procedures		
Posterior spine fusions	I.V.	0.1–0.5 μg kg^{-1} h^{-1} (a target plasma concentration of 0.4 ng ml^{-1})
Brain tumour and epileptic seizure	I.V.	0.1–0.5 μg kg^{-1} h^{-1}
Cardiac surgery	I.V.	0.5 μg kg^{-1} bolus and 0.5 μg kg^{-1} h^{-1} infusion Applications to benefit the recovery period
Adenotonsillectomy	I.V.	0.5–1 μg kg^{-1}
Postoperative shivering	I.V.	0.5 μg kg^{-1}
Postoperative emergence agitation	I.V.	0.2–1 μg kg^{-1}

Other uses

Table 4. Current common perioperative and periprocedural applications of dexmedetomidine in children[23]

Application	Advantage
Preoperative applications	
Anxiolysis	Easy and quick arousal from sedation Minimal respiratory depression Attenuates sympathetic haemodynamic response
Intraoperative applications	
Airway procedures	Obtunds airway reflexes while maintaining
Rigid bronchoscopy	stable haemodynamic and respiratory
Drug-induced sleep endoscopy	profiles in spontaneously
ventilating children Magnetic resonance imaging sleep studies Provides sedative properties paralleling natural sleep Open thyroplasty	
Anterior mediastinal mass biopsy Difficult intubation	
Neurosurgical procedures Posterior spine fusions	Lowers requirements for propofol and inhalation agents Facilitates intraoperative wake-up tests
Brain tumour and epileptic seizure	Preserves epileptiform activity
foci resection	Allows comfortable and cooperative sedation
Cardiac surgery	Blunts sympathetic response, provides analgesia and sedation in the postoperative period, and expedites extubation
Painful procedures	
Extracorporeal shock-wave lithotripsy Burn dressing change	Combining ketamine and dexmedetomidine in these procedures provides sedation, analgesia, amnesia, and haemodynamic stability
Lumbar puncture Bone marrow biopsy Central venous line placement Chest tube insertion	
Applications to benefit the recovery period	
Adenotonsillectomy	May reduce the incidence of severe emergence agitation, opioid requirements, and episodes of oxygen desaturation in children with obstructive sleep apnoea
Postoperative shivering Postoperative emergence agitation	

Drug interaction - Administration of dexmedetomidine with other sedatives and anesthetics typically produces a pharmacodynamic interaction resulting in enhanced sedation. This additive effect often allows for a reduction in the dose of sedative agents with a more significant adverse effect profile, such as benzodiazepines.[4]

Dexmedetomidine does not alter responsiveness to nondepolarizing neuromuscular blocking agents. The ability of dexmedetomidine to produce hypotension or bradycardia may be magnified by administration with other drugs capable of producing those effects. In a study comparing midazolam and dexmedetomidine, the authors observed a case of bradycardia in a 5-week-old infant receiving both dexmedetomidine and digoxin.[4]

Adverse reactions- The most significant adverse reactions associated with dexmedetomidine are hypotension and bradycardia, resulting from its sympatholytic activity. Both hypotension and bradycardia have been reported in several pediatric studies, although rarely have the changes been clinically significant or required intervention to correct. However, dexmedetomidine should be used with caution in patients already at risk for arrhythmias or hemodynamic instability.[4]

Transient hypertension has been reported with the administration of the loading dose due to initial

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

In a study done by Sperotto el al[24] all the adverse events were hemodynamic: 15 patients (31.9%) experienced isolated bradycardia, one patient (2.1%) experienced isolated hypotension, whereas six patients (12.8%) experienced both. an intervention (dose reduction) was required in 33% of AEs, but no treatment.[24]

Conclusion

Dexmedetomidine is relatively safe and easy to use drug, it can be used as an adjunctive drug for sedation in pediatric intensive care unit and for procedural sedation. Its benefits include limited effects on respiratory drive, a relatively short half-life, no significant drug interactions, and a generally mild adverse effect profile.[4] It can be a very helpful sedative agent in patients with neurological disorders with refractory seizures and where other first line drugs are contraindicated or have an adverse profile due to younger age. The adverse effects that have been reported uptil date are mainly hemodynamic. These adverse effects were dose dependent and were reversed back just by merely reducing the dose. This drug has a very wide window of opportunity but more pediatric studies are required, exploring its uses in difficult sedation and its interactions with other sedative agents. Secondly the effect of drug on developing brain is to be studied and whether there is neurotoxicity associated with it or what is the depth is a further area of research. Thirdly in depth knowledge of pharmacological profile of the drug in pediatrics is to be considered.

Conflict of interest- None

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