Review Article

Indian Journal of Anaesthesia and Analgesia
Volume 3 Number 1, January - April 2016
DOI : https: / / dx.doi.org / 10.21088 / ijaa.2349.8471.3116.8

Current Role of Dexmedetomidine in Pediatric Cardiac Anesthesia

Manjula Sarkar*, Pushkar M. Desai**

Abstract

Dexmedetomidine is a novel drug which is a selective α2-adrenoceptor agonist. It has unique properties of producing sedation, anxiolysis, amnesia and analgesia but at the same time without respiratory depression.

It provides a unique "conscious sedation" (patients appear to be asleep, but are readily roused), analgesia, without respiratory depression. It decreases central nervous system (CNS) sympathetic outflow in a dose dependent manner and has analgesic effects best described as opioid-sparing. There is increasing evidence of its organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection and renoprotection.

This article is intended to highlight special situations in cardiac anesthesia (especially paediatric) where dexmedetomidine plays a crucial role.

Keywords: Dexmedetomidine; Cardiac Anesthesia; Pediatric.

Dexmedetomidine is a novel drug which is a selective α2-adrenoceptor agonist. It has unique properties of producing sedation, anxiolysis, amnesia and analgesia but at the same time without respiratory depression [1,2].

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History

Dexmedetomidine was approved by the United States Food and Drug Administration (FDA) in 1999 only for short-term sedation / analgesia (< 24 hours) in the intensive care unit (ICU). Its unique properties make it as an attractive agent during perioperative period. In 2008 it was again additionally recommended in non-intubated patients as premedication during surgery or other medical procedures for sedation [4]. It is also approved in Europe for conscious sedation in adult ICU patients [5]. However, it is still not approved for use in pediatric patients but several case reports suggest its successful use without any evidence of adverse effects. Its use in pediatric population has expanded in preventing emergence delirium, to facilitate radiological and cardiac catheterization procedural sedation as well as in opioid withdrawal management [6].

Pharmacology

Dexmedetomidine is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1 H-imidazole monohydrochloride. Dexmedetomidine is an active D-enantiomer of medetomidine, the methylated derivative of etomidine. It incorporates an imidazoline structure, thus having an agonist effect on imidazoline receptors. Dexmedetomidine is chemically related to clonidine, but is approximately eight times more specific for α-2 adrenoceptors with α-2: α-1 selectivity ratio of 1620:1, compared with 200:1 for clonidine, especially for the 2a subtype, which makes dexmedetomidine more effective than clonidine for sedation and analgesia [7]. It has a pH in the range of 4.5-7. It is water soluble with pKa of 7.1. Its effects are dose-dependently reversed by administration of a selective á-2 antagonist, such as atipamezole [3].

Systemic Effects and Mechanism of Action

Hypnotic effect : It is mediated

Author's Affiliation:
*Professor **3rd Year Resident, Dept. of Anesthesia, Seth GS Medical College and KEM Hospital, Parel, Mumbai, Maharashtra, India.

Corresponding Author:
Manjula Sarkar, MD, Professor, Dept. of Anesthesia, Seth GS Medical College and KEM Hospital, Parel, Mumbai, Maharashtra, India.
E-mail: drmanjusarkar@gmail.com

by the hyperpolarization of noradrenergic neurons in the locus ceruleus of the brain stem. α-2 adrenergic receptor activation inhibits adenylyl cyclase reducing cyclic AMP (cAMP). At the same time, efflux of potassium through calcium-activated potassium channels occurs and inhibition of calcium entry into nerve terminals occurs [8]. This hyperpolarization of the neuronal membrane suppresses neuronal firing in the locus ceruleus as well as activity in the ascending noradrenergic pathway [9].

Dexmedetomidine inhibits norepinephrine release from the neurons in locus ceruleus. Loss of inhibitory control over the ventrolateral preoptic nucleus (VLPO) releases GABA and galanin, which further inhibits locus ceruleus. This decreases release of histamine, and the reduced occupancy of the histamine receptors on the cells of the subcortical areas induces a hypnotic state [10. Suppression of locus ceruleus results in decreased heart rate (HR) and systemic vascular resistance (SVR) [4].

Analgesic Effects

Activation of α2B-adrenoceptors in the dorsal horn of the spinal cord inhibits substance P release producing analgesia [11,12].

Cardiovascular Effects

Activation of peripheral α2b receptors results in vasoconstriction and the initial increase in systolic blood pressure, whereas the eventual decrease in blood pressure and heart rate results from central presynaptic α 2a receptor stimulated sympatholysis in the central nervous system, causing a decrease in norepinephrine release. Bradycardia is caused by both a reflex response at the sinus node to peripheral vasoconstriction and the decrease in sympathetic outflow from the central nervous system [8,13].

Respiratory Effects

Some studies have demonstrated respiratory depression with mild increases of PaCO2 (4-5 mm Hg), decreased minute ventilation, decreased response to carbon dioxide challenge using carbon dioxide response curves, or upper airway obstruction following bolus doses [14].

In contrast to infusions of opioids, benzodiazepines, or propofol, dexmedetomidine can safely be infused through tracheal extubation and beyond [3].

No adverse effects on the pulmonary vasculature have been reported including patients with preexisting pulmonary hypertension [15].

Organ Protection

Dexmedetomidine has been shown to exhibit myocardial protection, neuroprotection and renal protective properties. Perioperative infusion appears to benefit the perioperative hemodynamic management of surgical patients undergoing vascular surgery [16].

In one study, dexmedetomidine attenuated hypoxic-ischemic brain injury in developing brain and significant improvement in functional neurological outcomes after brain injury was also demonstrated [17].

Dexmedetomidine decreases renal cortical release of norepinephrine and exerts a diuretic effect too. There is experimental evidence that dexmedetomidine attenuates murine radiocontrast nephropathy by preserving cortical blood flow [18.19].

DOSAGE [12]

ICU Sedation

Adult Patients

Loading dose of 1 ìg / kg over 10 min

Maintenance infusion generally initiated at 0.4 μg / kg / h

Titrate to desired clinical effect with doses ranging from 0.2 to 0.7 μg / kg / h

More than 65 years old / impaired hepatic or renal function:

A dose reduction should be considered

Sedation for Surgical or other Procedures

Adult Patients

Loading dose of 1 μg / kg over 10 min

Maintenance infusion generally initiated at 0.6 ìg / kg / h

Titrate to desired clinical effect with doses ranging from 0.2 to 1 μg / kg / h

Adult patients undergoing less invasive procedures:

Loading infusion of 0.5 μg / kg given over 10 min may be suitable

More than 65 years old / impaired hepatic or renal function:

A dose reduction should be considered

Awake fiberoptic intubation:

Loading infusion of 1 μg / kg over 10 min

Maintenance infusion of 0.7 μg/kg/h until the endotracheal tube is secured.

Literature Review of Dexmedetomidine Use in Paediatric Cardiac Anesthesia

As an adjunct: Dexmedetomidine has been proved as a useful adjunct in cardiac anesthesia. It is shown that an infusion of dexmedetomidine @ 0.2-0.4 μg/kg/hr during perioperative period decreases extubation time and the length of ICU stay [20]. Recent metaanalysis in 2003 concluded that the use of α-2 adrenergic agonists reduced mortality and incidence of myocardial infarction following vascular surgery. It also reduced ischemic episodes during cardiac surgery [21].

Decreased heart rate, SVR and antiarrhythmic properties of dexmedetomidine contribute to better management of pediatric cardiac surgical patients postoperatively.

Attenuation of Sympathoadrenal Stress Response

A study conducted at our institute [22] in 60 pediatric patients between five to seven years of age undergoing cardiac surgery, dexmedetomidine when used as an adjunct to general anesthesia, we found that it considerably reduces anesthetic requirement and attenuates surgical stress response in the form of reduced incidence of hyperglycemia.

Pulmonary Hypertension

Regarding pulmonary hypertension, dexmedetomidine has been successfully used in patients undergoing mitral valve replacement in which it decreased fentanyl requirements, attenuated the increase in systemic vascular resistance index and pulmonary vascular resistance index after sternotomy and also decreased mean arterial pressure, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure, in comparison with the values in the placebo group [23].

Few centres in India are using dexmedetomidine along with fentanyl in order to prevent episodes of pulmonary hypertensive crisis intraoperatively.

Tobias et al. [24], in a prospective, randomized trial, found that dexmedetomidine at a dose of 0.5 μg/kg/hr provided more effective sedation than midazolam. This was demonstrated by the need for fewer bolus doses of morphine, a decrease in the 24h requirements for supplemental morphine, as well as a decrease in the total number of assessment points with a Ramsay sedation score of 1 (inadequate sedation) and the number of patients who had a Ramsay score of 1.

Chrysostomou et al [25], in a retrospective study of 38 spontaneously breathing and mechanically ventilated children undergoing cardiothoracic surgery, found that dexmedetomidine provided adequate sedation 93% of the time and adequate analgesia 83% of the time. Side effects included hypotension (15%) and transient bradycardia in one patient.

Antiarrythmic Actions

Numerous case reports and research work have demonstrated anti arrhythmic properties of dexmedetomidine. High dose of dexmedetomidine upto 3 μg/kg/hr successfully reverted junctional ectopic tachycardia (JET) to sinus rhythm (SR) in an infant undergoing intracardiac repair of Tetralogy of Fallot (TOF) [26]. In a recent randomized trial, dexmedetomidine exerts its effectiveness in preventing occurrence of postoperative JET following complete surgical repair of TOF [27]. Chrysostomou C et al concluded that dexmedetomidine decreased incidence of atrial, junctional, ventricular and supraventricular tachyarrhythmias after congenital cardiac surgery[28].

Refractory Arrhythmia

Few case reports have demonstrated successful use of dexmedetomidine in restoring sinus rhythm when other antiarrhythmic drugs were not effective [29,30).

Electrophysiological Studies and Intervention

Dexmedetomidine depressed sinus and atrioventricular nodefunction resulting into bradycardia during electrophysiological study in paediatric patients [31]. But, one should keep in mind that the changes in PR interval, QRS interval etc were related to changes in heart rate only [32].

Prevention of Delirium

Dexmedetomidine has been also used to provide sedation in the postanesthesia care unit following sevoflurane anesthesia to decrease the incidence of agitation in the pediatric population, and to allow intubation in a sedated pediatric patient.

Cardiac Catheterization

It is successfully used for procedural sedation in cardiac catheterization laboratory[33].

Robert Mester et al [34]suggested that a

combination of ketamine and dexmedetomidine provides effective sedation for cardiac catheterization in infants and children without significant effects on cardiovascular or ventilatory function.

Neuroprotection

Neurological injury is a common and frequent problem encountered in paediatric cardiac population. Dexmedetomidine has generated a lot of enthusiasm because of its neuroprotective properties. Various animal studies have shown neuroprotection exhibited by dexmeddetomidine [35,36]. Sato et al [37] found improved short-term neurologic outcome with combination of hypothermia and dexmedetomidine therapy.

Overall, dexmedetomidine is an attractive agent both during perioperative and ICU settings. Its opioid-sparing properties, minimal respiratory depression; preserved gut motility; prevention of postoperative nausea, vomiting and shivering; and potential neuroprotection, cardioprotection and renoprotection make it as an invaluable anesthetic agent in pediatric cardiac and also during general anesthesia.

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