

Dexmedetomidine in Current Anaesthesia Practice- A Review

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ABSTRACT

Dexmedetomidine is an alpha 2 adrenergic receptor agonist, even ten times more selective than clonidine. It is a very versatile drug in anaesthesia practice, finding place in increasing number of clinical scenarios and is no more limited to intensive care unit (ICU) sedation. It is analgesic, has anaesthetic sparing effect, sympatholytic property, useful in other procedural sedation and also has cardiovascular stabilizing property. It reduces delirium and preserves respiratory function which adds benefits to its uses. The aim of this review is to make awareness of its role in present anaesthesia and discuss its limitations at the same time.

Keywords: Alpha 2 adrenergic agonist, Anaesthesia, Dexmedetomidine, Intensive care unit

INTRODUCTION

Dexmedetomidine is a highly selective alpha2 adrenoceptor (α 2-AR) agonist recently introduced to anaesthesia practice. It produces dose-dependent sedation, anxiolysis and analgesia (involving spinal and supraspinal sites) without respiratory depression [1,2]. Dexmedetomidine enhances anaesthesia produced by other anaesthetic drugs, causes perioperative sympatholysis and decreases blood pressure by stimulating central α 2 and imidazoline receptors [3,4]. It is the dextrorotatory S-enantiomer of medetomidine and is chemically described as (+)-4-(2, 3-dimethyl phenyl) ethyl-1 H-imidazole monohydrochloride with molecular weight as 236.7. The empirical formula is $C_{13}H_{16}HCl$.

PHARMACODYNAMICS

Dexmedetomidine is a relatively selective α 2 adrenoceptor agonist with a broad range of pharmacologic properties. Alpha2-AR agonists produce clinical effects after binding to G-Protein-coupled 2-AR, of which there are three subtypes (α 2A, α 2B, and α 2C) with each having different physiological functions and pharmacological activities. These receptor subtypes are found ubiquitously in the central, peripheral, and autonomic nervous systems, as well as in vital organs and blood vessels [5]. Dexmedetomidine is 8 to 10 times more selective towards α 2-AR than clonidine [6]. Alpha2 selectivity is observed following slow intravenous infusion of low and medium doses (10-300 mcg/kg). Both α 1 and α 2 activities are observed following slow intravenous infusion of high doses (>1000mcg/kg) or with rapid intravenous in animals. Sedative actions are believed to be mediated primarily by post-synaptic α 2-adrenoceptors. Dexmedetomidine has a low affinity for beta adrenergic, muscarinic, dopaminergic and serotonin receptors. It binds the α 2 receptors of locus ceruleus and spinal cord and causes sedation and analgesia respectively. Higher affinity to α 2 receptor selectively leads to vagomimetic action on heart (bradycardia) and vasodilatation. The role as an antishivering agent and diuretic is yet to be established [7].

PHARMACOKINETICS

Following intravenous administration, dexmedetomidine shows rapid distribution phase with a distribution half life of six minutes and a terminal elimination half life ($t_{1/2}$) of approximately two hours. Dexmedetomidine exhibits linear kinetics in the range between 0.2 - 0.7 micrograms (mcg)/kg/hr on i.v. infusion upto 24 h. In steady state, volume of distribution is about 118l. 94% is protein bound.

Oral bioavailability is poor because of extensive first pass metabolism. However, after sublingual & intranasal administration bioavailability is high (84%), giving it a potential role in paediatric sedation and premedication [8].

It undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine (95%) and faeces (4%) [9]. Biotransformation involves both direct glucuronidation (the major pathway) as well as cytochrome P450 mediated metabolism.

In subjects with varying degree of hepatic and renal impairment, clearance is lower than in normal subjects, it may need dose reduction. The pharmacokinetic profile of dexmedetomidine is not altered by age.

ADVERSE EFFECTS

The most frequently observed adverse effects include hypotension, hypertension, bradycardia, dry mouth and nausea. Other reported adverse effects include fever, rigors, cyanosis, muscle weakness. It may lead to arrhythmias, AV Block, cardiac arrest, T-wave inversion, tachycardia, angina pectoris, pulmonary edema, bronchospasm, respiratory depression, syncope, neuropathy, paresthesia, paresis, hyperkalaemia, lactic acidosis and hyperglycaemia.

Tolerability of dexmedetomidine hydrochloride was noted in healthy subjects who achieved plasma concentrations from 1.8 upto 13 times the upper boundary of therapeutic range. The most notable effect observed in those who achieved the highest plasma concentration was AV block which resolved spontaneously within one minute.

DRUG ABUSE AND DEPENDENCE

The dependence potential of dexmedetomidine has not been studied in human beings but studies in rodents and primates have demonstrated clonidine like withdrawal syndrome upon abrupt discontinuation. These symptoms include nervousness, headache and agitation accompanied or followed by a rapid rise in BP and elevated catecholamine levels in the plasma.

Dexmedetomidine can be readily reversed with the specific antagonist Atipamezole [10].

DRUG INTERACTION

In vitro studies indicated that clinically relevant cytochrome P 450 mediated drug interactions are unlikely. Co-administration of anesthetics, sedatives, hypnotics or opioids with dexmedetomidine hydrochloride is likely to lead to an enhancement of their effects. Hence, a reduction in dosage with these agents is required. Additionally, in situations where other vasodilators or negative chronotropic agents are used, co-administration of dexmedetomidine could have an additive pharmacodynamic effect and should be administered with caution and careful titration.

Route	Dose
Intravenous	loading dose of 1 mcg/kg over 10-20 minutes followed by a maintenance infusion in the range of 0.2- 0.7mcg/kg/hr. The rate of infusion can be increased in increments of 0.1mcg/kg/hr or higher.
Intramuscular	IM injection (2.5 mcg/kg) of dexmedetomidine has been used for premedication.
Spinal	0.1-0.2 mcg/kg
Epidural	1-2mcg/kg
Peripheral nerve block	1mcg/kg [11]
Buccal	1-2 mcg/kg [8,12]
Intranasal	1-2mcg/kg [12,13]

[Table/Fig-1]: Routes and dosages

DOSAGE AND ROUTES OF ADMINISTRATION [TABLE/FIG-1]

Dexmedetomidine Hydrochloride injections are available as Dexmedetomidine 50mcg/0.5ml, 100mcg/ml and 200mcg/2ml.

It should be used in controlled intravenous device when being used via intravenous route. The dose should be individualized and titrated to the desired clinical effect. Dose reduction is necessary in elderly patients or those with impaired hepatic or renal function.

CLINICAL APPLICATIONS

Premedication

As it is a sedative, anxiolytic, analgesic, sympatholytic and has stable hemodynamics, dexmedetomidine is used in premedication. It decreases oxygen consumption in intraoperative (upto 8%) and postoperative period (upto 17%) [14]. The dose for premedication is 0.33-0.67 mcg/kg i.v. or 2.5 µg/kg i.m. injection given 15 min before surgery.

Intensive care unit sedation

Dexmedetomidine is indicated for sedation in initially intubated and mechanically ventilated patients during treatment in intensive care setting. Dexmedetomidine currently is approved by FDA for use in ICU for not more than 24 hours; though many studies have reported its safe use for longer duration [15]. Dexmedetomidine has advantages for sedation in mechanically ventilated postoperative patients because it decreases requirement of opioids (>50%) and high PaO₂/FIO₂ with minimum respiratory depression. Dexmedetomidine is superior to midazolam and lorazepam for weaning because it shortens the time to extubate and stay in ICU [16,17].

Procedural sedation

Dexmedetomidine is indicated for sedation of non intubated patients prior to and/or during surgical and other procedures. It has been safely used in transesophageal echocardiography [18], colonoscopy [19], awake carotid endarterectomy [20], shockwave lithotripsy [15], vitreoretinal surgery [21], paediatric patients undergoing tonsillectomy [22]. The usual dose of dexmedetomidine for procedural sedation is 1 mcg/ kg, followed by an infusion of 0.2 mcg/kg/h. Its onset of action is less than 5 min and the peak effect occurs within 15 min. Dexmedetomidine provides a titratable form of hypnotic sedation that can be easily reversed by α_2 -AR antagonist atipamezole [10].

As an adjuvant in local & regional techniques

Highly lipophilic nature of dexmedetomidine allows rapid absorption into the cerebrospinal fluid and binding to α_2 -AR of spinal cord for its analgesic action. It prolongs the duration of both sensory and motor blockade induced by local anesthetics irrespective of the route of administration (e.g., epidural [23], caudal [24], or spinal [25]). It enhances both central and peripheral neural blockade by local anaesthetics [26] and has been successfully used in intravenous regional anesthesia (IVRA). Addition of 0.5 µg/kg dexmedetomidine

to lidocaine for IVRA improves quality of anesthesia and improves intraoperative-postoperative analgesia without causing side effects [27].

The peripheral neural blockade is due to its binding to α_2 A-AR [26]. Dexmedetomidine added to levobupivacaine for axillary brachial plexus block shortens the onset time and prolongs the duration of the block and postoperative analgesia [28].

Intraarticular use

Intraarticular dexmedetomidine in patients undergoing arthroscopic knee surgery improves the quality and duration of postoperative analgesia [29,30].

Controlled hypotension.

Dexmedetomidine is an effective and safe agent for controlled hypotension mediated by its central and peripheral sympatholytic action. Its easy administration, predictability with anaesthetic agents, and lack of toxic side effect while maintaining adequate perfusion of the vital organs makes it a near-ideal hypotensive agent [31].

Attenuation of response to tracheal intubation and extubation

Dexmedetomidine attenuates hemodynamic stress response to intubation and extubation by its sympatholytic property [32-35]. As respiratory depression is absent, it can be continued at extubation period unlike other drugs. Dexmedetomidine, at IV doses of 0.33 to 0.67 µg/kg given 15 min before surgery attenuates the hemodynamic response to endotracheal intubation.

Anaesthetic sparing effect

When used intraoperatively in lower concentration, requirement of other anaesthetic agents is reduced. Fewer interventions are required for the treatment of tachycardia. Incidence of myocardial ischemia is also reduced. However, side effects like hypotension and bradycardia may occur, needing intervention.

Cardiovascular stabilizing effect

The cardiovascular effects of dexmedetomidine have been well studied in animal and adult human models. Growing experience, mostly in the pediatric population, has demonstrated the potential therapeutic applications of dexmedetomidine in the acute treatment of arrhythmias. Additionally, its use during cardiac surgery has been associated with a decreased incidence of postoperative ventricular and supraventricular tachyarrhythmias. Dexmedetomidine may be useful for the treatment of the deleterious cardiovascular effects of acute cocaine intoxication and overdose [36].

Cardiac surgery

Dexmedetomidine in addition to blunting the hemodynamic response to endotracheal intubation also reduces the extent of myocardial ischemia during cardiac surgery [37]. Dexmedetomidine has been successfully used to manage patients with pulmonary hypertension undergoing mitral valve replacement, with reduction in pulmonary vascular resistance, pulmonary artery pressure, and pulmonary capillary wedge pressures [38]. It is useful in off-pump Coronary Artery Bypass Grafting (CABG), vascular surgery, thoracic surgery and conventional CABG.

Neurosurgery

Besides providing cerebral hemodynamic stability, dexmedetomidine also prevents sudden increase in intracranial pressure during intubation, extubation and head pin insertion. This fact can be exploited in neuroanaesthesia. It attenuates neurocognitive impairment (delirium and agitation) allowing immediate postoperative neurological evaluation. It exerts its neuroprotective effects through several mechanisms which make the usage of this drug very promising during cerebral ischemia [39]. It does not interfere with neurological monitors [38] and has an upcoming role in "functional"

neurosurgery. It has been used in awake craniotomy for the resection of tumours or epileptic foci in eloquent areas, and the implantation of deep brain stimulators for Parkinson's disease [38]. It allowed for a reduction or elimination of other sedatives, and it was particularly useful in children with chronic neurologic impairments.

In Obese patients

Dexmedetomidine does not cause respiratory depression. This fact can be utilized in sedating morbidly obese patient; thereby avoiding respiratory depression caused by narcotics [40].

Dexmedetomidine is also useful as anesthetic adjuvant in Bariatric surgery and sleep apnea patients.

Use in MRI and CT scan

High dose dexmedetomidine (3mcg/kg IV load over 10 minutes with an infusion of 1 mcg/kg/hour) has been used successfully for sedation of children undergoing MRI. Using this dose, Mason et al., [41] noted bradycardia and a 20% drop in blood pressure with minimal change in respiratory parameters.

Awake Intubation

Dexmedetomidine used for securing the airway with a fiberoptic intubation [42].

Monitored Anaesthesia Care

Dexmedetomidine has been used for sedation for monitored anesthesia care in gynaecological, urological, burns patients and trauma patients.

Post operative analgesia

Dexmedetomidine also provides intense analgesia during the postoperative period. In one study, by Venn RM et al., [43], the postoperative analgesic requirements were reduced by 50% in cardiac patients and the need for rescue midazolam for sedation was diminished by 80%.

Obstetric use

There are no adequate and well controlled studies in pregnant women. It should be used only if benefits outweigh the potential risk to the foetus.

Dexmedetomidine has high lipophilicity and so it passes through placenta but it disappears very fast [44]. Mahdy et al., found that after intrathecal dexmedetomidine injection there were significantly longer sensory and motor block times than patients in control and fentanyl group and there were no adverse effects on mothers or babies in any group [45]. Fyreface-Ogan et al., found no significant differences in the APGAR score, pH of umbilical venous blood, baseline fetal heart rate and minimal change of maternal blood pressure after intrathecal administration of dexmedetomidine. The maximum sensory level reached by dexmedetomidine and fentanyl were almost the same [46]. A valid index of fetal welfare has been reported in a metanalysis study of neonatal acid-base data with its uses in different anaesthesia comparing umbilical artery or vein pH and base umbilical artery acid- base status [47].

It is not known if dexmedetomidine hydrochloride is excreted in human milk. It should be used with caution in lactating woman.

Paediatric Use

Although dexmedetomidine is not currently approved by the Food and Drug Administration (FDA) for the pediatric population, findings have shown it to be effective in various clinical scenarios for sedation [48]. Dexmedetomidine has been found to be useful in sedation during mechanical ventilation, prevention of emergence delirium, after general anaesthesia and procedural sedation during noninvasive radiological procedures [49]. Munro et al., [50] reported dexmedetomidine as the primary agent for sedation during cardiac catheterization in infants and children. Kristin et al., [51] suggested that invasive procedures can successfully be performed in

spontaneously breathing infants and toddlers with congenital heart disease using dexmedetomidine 1-3 mcg/ kg alone or in addition to low dose ketamine. High dose dexmedetomidine (3mcg/kg IV load over 10 minutes with an infusion of 1 mcg/kg/hour) has been used successfully for sedation of children undergoing sedation for MRI [52,53].

Use in the Elderly

In patients more than 65 y of age, a higher incidence of bradycardia and hypotension was observed following dexmedetomidine administration. Hence a dose reduction is needed and renal function should be monitored.

Pain and Palliative Care

Dexmedetomidine may also offer a new paradigm in the pharmacologic treatment of symptoms of distress (intractable pain, agitation or delirium) at the end of life. Recently, the FDA has approved to examine the use of dexmedetomidine in treating cancer patients at the end of life who are suffering from intractable pain, agitation or delirium [54]. It has significant opioid sparing effect and is useful in intractable neuropathic pain [55].

Other uses

Cervical spine surgery and other spine surgery, Evoked potential study and Head injury. It has been used in the treatment of alcohol and drug withdrawal of narcotics, benzodiazepines, alcohol and recreational drugs. Dexmedetomidine is effective in preventing ethanol-induced neurodegeneration. It used in the management of tetanus in ICU. It may be used as an antishivering agent.

PRECAUTIONS

Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are recommended during i.v. infusion of dexmedetomidine in preexisting severe bradycardia (heart block) or ventricular dysfunction (ejection fraction <30) including decompensated congestive heart failure. Hypovolemic patients need fluid supplementation because they are prone to hypotension under dexmedetomidine therapy.

Elderly and diabetics are more prone to hypotension as it decreases sympathetic nervous activity. However, dexmedetomidine may lack amnesic properties, as a small number of patients during the study were able to recall their ICU stay and found the experience very stressful [43]. Dexmedetomidine may cause reduced lacrimation. Lubrication of patient's eye should be considered to avoid corneal dryness when using dexmedetomidine.

Limiting its usefulness is the caution that the drug cannot be bolused due to concerns about peripheral α_2 -receptor stimulation with resulting hypotension and bradycardia, combined with its current high cost relative to generic medications such as propofol, fentanyl and midazolam which can achieve similar clinical effects.

CONCLUSION

Dexmedetomidine is a very useful addition to the family of drugs used in anaesthesia. It can be exploited in a wide range of use as discussed above at the same time requiring vigilance during its use. High cost is its limiting factor.

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