



ROLE OF DEXMEDETOMIDINE IN GENERAL ANESTHESIA

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ABSTRACT

Dexmedetomidine is a highly selective alpha-2 adreno-receptor with maximum affinity to alpha-2A subunit. It has a property of hemodynamic stability, is a sedative /hypnotic, analgesic, sympatholytic, and anesthetic sparing drug. It is pharmacologically active D-enantiomer of medetomidine, assimilate an imidazoline structure. Dexmedetomidine has a selectivity for alpha-2:alpha-1 (1620:1) which is relatively high as compared to clonidine (220:1). It is 8 times more potent than clonidine. It provides a unique "conscious sedation" (i.e. patient appears to be asleep, but are readily arousable), reduces delirium and preserves respiratory function. Dexmedetomidine shows hypnotic action through activation of central pre and post synaptic alpha 2 receptors in locus coeruleus inducing a natural sleep state. Pharmacokinetic effect is similar in all age group. It is used in controlled hypotension as it is a near hypotensive agent. ATIPAMIZOLE is an antagonist for its sedative property. The main aim of this review article is to get knowledge about how Dexmedetomidine acts on different system to provide a desired effect during general anesthesia.

Keywords: Dexmedetomidine, Alpha-2 adrenergic agonist, Sedation, Anesthesia, Perioperative use

Chemical structure of Dexmedetomidine:

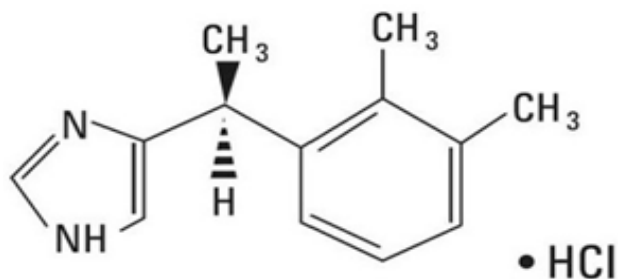


Figure: structure of Dexmedetomidine

INTRODUCTION

Dexmedetomidine is a potent, highly selective and specific alpha-2 adrenoreceptor agonist. It has 3 subunits: alpha 2A, alpha 2B and alpha 2C (alpha 2A being more selective). Alpha-2 adrenoreceptors are found in CNS, PNS, in effector organs such as liver, kidneys, pancreas, eyes, vascular smooth muscles and platelets [1]. Each receptor is responsible for specific action of alpha-2 agonist and it is mediated via G-coupled protein receptors [2].

Alpha-2A is responsible for sedation, analgesia and sympatholytic effect.

Alpha-2B shows vasoconstrictive cardiovascular effect (Initial Hypertension after rapid administration of alpha-2 adrenoreceptor agonist)[3, 4].

Alpha-2C shows anxiolytic effect modulates dopaminergic transmission, hypothermia and a variety of behavioral responses.

Dexmedetomidine was approved in the USA in 1999 for sedation and analgesia in the ICU. Compared to Clonidine, Dexmedetomidine is about eight times more specific for alpha-2 adrenoreceptors with an alpha-2: alpha-1 selectivity ratio of 1620:1.

PHARMACOKINETICS:

Dexmedetomidine has a rapid onset of action. An intravenous administration exhibits a rapid distribution half life (T_{1/2}) of 6 minutes and elimination half life of 2 hours [5, 6]. It has a steady state volume of distribution of 118L. Dexmedetomidine is metabolized almost completely by liver through Cytochrome-450 system and direct Glucoronidation. Metabolites are excreted in the urine (95%) and faeces.

94% of the Dexmedetomidine are bound to proteins. Dexmedetomidine should be cautiously used in patients with liver and renal impairment. It can cross the placenta so it can only be used during pregnancy if benefit overwhelms the potential risk.

For adult patient, loading dose of 0.5-1 microgram/kg over 10 minutes followed by a maintenance infusion of 0.2-0.7 microgram/kg/hour [1].

CLINICAL PHARMACOLOGY:

A) Sedative:

Dexmedetomidine produces subcortical form of sedation characterized by quick and easy arousal, resembling natural sleep. It acts through G-coupled protein receptor. On its activation, inhibits adenylyl cyclase. This enzyme is responsible for formation of cAMP(a second messenger) from ATP. Reduced cAMP

inside the cell favors anabolic pathways. Simultaneously there is an efflux of potassium ions through Calcium-activated potassium channels and inhibition of Calcium entry into Calcium channels in nerve terminals [7]. The change in membrane ion conductance cause hyperpolarization of a membrane suppressing neuronal firing in the Locus coeruleus of Pons as well as activity in the ascending noradrenergic pathway[6]. Concentration of 0.2-0.3 microgram/ml produces arousable sleep whereas concentration more than 1.9 microgram/ml produces unarousable sleep.

B) Analgesic:

Dexmedetomidine binds to CNS and spinal alpha-2 receptors. Pain transmission is suppressed by hyperpolarization of interneurons, reduction of release of substance P and glutamate [8].

C) CVS Effect:

Dexmedetomidine shows biphasic hemodynamic effects. i.e. hypotension at low plasma concentration(both loading and maintenance dose in excess of 0.7 microgram/kg/hour) [9] and hypertension at higher plasma concentration (dose of 1-4 microgram/kg) [8, 10]. The reason for hypertension is activation of alpha-2B receptor in vascular smooth muscles causing peripheral vasoconstriction leading to hypertension. This is accompanied by quick decrease in Heart Rate due to baroreflex [8]. After few minutes, when plasma concentration of Dexmedetomidine decreases, the vasoconstriction attenuates, as it also activates alpha-2 receptors in the vascular endothelial cells (alpha-2A), which results in vasodilation [11] [12]. Together with pre-synaptic alpha-2 adrenoreceptors inhibiting sympathetic release of catecholamines and increased vagal activity, results in hypotensive phase.

D) Respiratory System Effect:

With therapeutic concentration upto 2.4 ng/ml, minimal respiratory depression is seen with a preservation of ventilatory response to CO₂ [13-15]. The ventilatory frequency increases with increasing doses, which is compensated for slight decreased Tidal Volume. Hypercapnic arousal phenomena of Dexmedetomidine sedation is similar to those during natural sleep [15]. The hypercapnic ventilator response is known to decrease with age [16]. Therefore elderly patient are more vulnerable to respiratory depression than young healthy volunteers.

E) CNS Effects:

The primary site of action of alpha-2 agonist is Locus Coeruleus. This is why Dexmedetomidine produces different type of sedation compared to benzodiazepines and propofol. Recent data suggests the neuroprotective effect of Dexmedetomidine by involving I1-imidazoline receptors in brainstem and hippocampus [17].

F) Renal System:

Alpha-2 adrenoreceptors stimulation reduces efferent sympathetic outflow of renal nerves which in turn decreases Anti Diuretic Hormone [18].

G) Endocrine System:

Effect of Dexmedetomidine on endocrine system is due to decrease catecholamines which attenuates the response to stress by inhibiting the secretion of ACTH and cortisol [18]. Stimulation of alpha-2 adrenoreceptor agonist located on cells of Islet of Langerhans can temporarily inhibit the release of insulin with detectable clinical hyperglycemia [19].

H) Other Systems:

Decrease salivation, decrease secretion and bowel motility in GIT, decrease IOP, decrease platelet aggregation and decrease shivering threshold by 2 degree Celsius [20].

CLINICAL APPLICATION:

The sedative, anxiolytic and sympatholytic properties of Dexmedetomidine make it a drug of choice for premedication. It decreases the tachycardia response to Endotracheal intubation at a dose of 0.25-1 microgram/kg [8-10, 21]. It reduces perioperative sympathetic stimulation and minimizes postoperative pain.

Unlugenc et al [22] gave 1 microgram/kg dose of Dexmedetomidine within 10 minutes of induction of anesthesia and has found a marked reduction in heart rate within 10 minutes.

Yuen et al [23] evaluated the intranasal Dexmedetomidine for premedication in children as compared to oral midazolam. They concluded that use of 0.5 or 1 microgram/kg intranasal Dexmedetomidine produces more sedation than 0.5 mg/kg oral midazolam, but with similar and acceptable cooperation.

It is a useful adjuvant during intraoperative use of general anesthesia. Dexmedetomidine provides hemodynamic stability and reduces the requirement of other anesthetic drugs such as Isoflurane [24-26] Sevoflurane [27, 28], Propofol [29-31], Thiopental [32-35] and Fentanyl [36].

An opioids- sparing effect is described when using Dexmedetomidine perioperatively [22, 37, 38]. This might be beneficial in reducing post-operative nausea or ventilator depression as seen with opiates. It improves quality of recovery and facilitates post-operative GI motility.

SIDE EFFECTS:

- 1) Bradycardia
- 2) Hypotension
- 3) Hypertension
- 4) Dry mouth
- 5) Nausea

6) Hyperglycemia

ANTAGONIST:

Injection ATIPAMEZOLE at the dose of 15-150 microgram/kg I/V reverses the effect of Dexmedetomidine.

CONCLUSION

Dexmedetomidine has a unique feature of sedation, sympatholysis, analgesia, hemodynamic stability and minimal respiratory depression. It has become a frequently used drug in anesthetic armamentarium. Dexmedetomidine provides a special type of sedation from which patient can be readily arousable when required. . Dexmedetomidine reduces the requirement of other anesthetic and analgesic drugs, facilitates a magnificent recovery. Hepatic failure, Hypovolemic shock and Heart block are the absolute contraindications of Dexmedetomidine.

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