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PHARMACOLOGICAL PROFILE OF DEXMEDETOMIDINE

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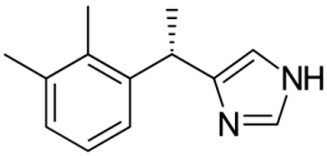
ABSTRACT Dexmedetomidine is a short-term sedative (<24 hours). α2-Adrenoceptor agonists have several beneficial actions during the perioperative period. They decrease sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery; reduce anesthetic and opioid requirements; and cause sedation and analgesia. This review discusses pharmacological profile of dexmedetomidine.

KEYWORDS : Dexmedetomidine, adverse effects, pharmacological action.

INTRODUCTION

Dexmedetomidine is a stereoisomer of medetomidine, with chemical formula 4-[(1S)-1-(2, 3-dimethylphenyl) ethyl]-1H-imidazole. It is a highly selective α2-adrenergic receptor (AR) agonist with a relatively highratioofα2/α1-activity.

Chemical formula



Pharmacokinetics

Absorption and distribution

Dexmedetomidine exhibits linear pharmacokinetics in the recommended dose range of 0.2 to 0.7 μg/kg/hr administered as intravenous infusion up to 24 hours. The distribution phase is rapid, with a half-life of distribution of approximately 6 minutes and elimination half-life of 2 hours. The steady-state volume of distribution is 118 L. The average protein binding is 94% and is constant across the different plasma concentrations and also similar in males and females.

It has negligible protein binding displacement by drugs commonly used during anesthesia.43 Context-sensitive half life ranges from 4 minutes after a 10-minute infusion to 250 minutes after an 8-hour infusion. Oral bioavailability is poor because of extensive first-pass metabolism. However, bioavailability of sublingually administered dexmedetomidine is high (84%), offering a potential role in pediatric sedation and premedication.[1]

Metabolism and excretion

Dexmedetomidine undergoes almost complete biotransformation through direct N-glucuronidation and cytochrome P-450 (CYP 2A6)-mediated aliphatic hydroxylation to inactive metabolites. Metabolites are excreted in the urine (about 95%) and in the feces (4%).[2]

Pharmacodynamics

Mechanism of action

α2-AR agonists produce clinical effects after binding to G-Protein-coupled α2-AR, of which there are three subtypes (α2A, α2B, and α2C) 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.45 Dexmedetomidine is 8 to 10 times more selective towards α2-AR than clonidine.46 Neither clonidine nor dexmedetomidine is totally selective for any one of the α2-AR subtypes, but dexmedetomidine seems to have higher α2A-AR and α2C-AR affinity than clonidine.[3]

Locus ceruleus of the brain stem is the principal site for the sedative action and spinal cord is the principal site for the analgesic action, both acting through α2A-AR. In the heart, the dominant action of α2-AR agonists is a decrease in tachycardia (through blocking cardioaccelerator nerve) and bradycardia via α2A-AR (through a vagomimetic action). In the peripheral vasculature, there is sympatholysis-mediated vasodilatation and smooth muscle cells receptor-mediated vasoconstriction.[4]

The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas.[2]

Systemic Effects

Cardiovascular system

Dexmedetomidine evokes a biphasic blood pressure response: A short hypertensive phase and subsequent hypotension. The two phases are considered to be mediated by two different α2-AR subtypes: the α-2B AR is responsible for the initial hypertensive phase, whereas hypotension is mediated by the α2A-AR.[5]

Central nervous system

Dexmedetomidine reduces cerebral blood flow and cerebral metabolic requirement of oxygen. Dexmedetomidine modulates spatial working memory, enhancing cognitive performance besides having sedative, analgesic, and anxiolytic action through the α2-AR.50 Studies suggest the likelihood of its neuroprotective action by reducing the levels of circulating and brain catecholamines and thus balancing the ratio between cerebral oxygen supplies, reducing excitotoxicity, and improving the perfusion in the ischemic penumbra. It reduces the levels of the glutamate responsible for cellular brain injury, especially in subarachnoid hemorrhage.[6] It has been shown to limit the morphologic and functional effects after ischemic (focal and global) and traumatic injury to the nervous system.

Respiratory effects

Dexmedetomidine effect on respiration appears to be similar in order of magnitude to those seen in the heavy sleep state.[7] Dexmedetomidine does not suppress respiratory function, even at high doses.[8]

Endocrine and renal effects

Dexmedetomidine activates peripheral presynaptic α2- AR, which reduces the release of catecholamines, and hence reduces sympathetic response to surgery.[9]

Clinical Applications of Dexmedetomidine

Premedication

Dexmedetomidine is used as an adjuvant for premedication, especially in patients susceptible topreoperative and perioperative stress because of its sedative, anxiolytic, analgesic, sympatho lytic, and stable haemodynamic profile.

Intraoperative use

Dexmedetomidine attenuates hemodynamic stress response to intubation and extubation by sympatholysis.[7]

Locoregional analgesia

Highly lipophilic nature of dexmedetomidine allows rapid absorption into the cerebrospinal fluid and binding to α2-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, caudal, or spinal).

Dexmedetomidine though enhances both central and peripheral neural blockade by local anesthetics[10]; however, the peripheral neural blockade is due to its binding to α2A-AR.[11]

Sedation in intensive care unit

Dexmedetomidine has become popular sedative agent in ICU, because of its ability to produce cooperative sedation, i.e., patients remain awake, calm, and are able to communicate their needs.

Procedural sedation

Dexmedetomidine is an attractive agent for short term procedural sedation. The usual dose of dexmedetomidine for procedural sedation is 1 μg/kg, followed by an infusion of 0.2 μg/kg/h. Its onset of action is less than 5 minutes and the peak effect occur within 15 minutes.

Analgesia

Dexmedetomidine activates α2-AR in the spinal cord reducing transmission of nociceptive signals like substance P. It has significant opioid sparing effect and is useful in intractable neuropathic pain.

Neurosurgery

Dexmedetomidine provides stable cerebral hemodynamics without sudden increase in ICP during intubation, extubation, and head pin insertion. It attenuates neurocognitive impairment (delirium and agitation) allowing immediate postoperative neurological evaluation.

Adverse Effects

The various reported side effects are hypotension, hypertension, nausea, vomiting, dry mouth, bradycardia, atrial fibrillation, pyrexia, chills, pleural effusion, atelectasis, pulmonary edema, hyperglycemia, hypocalcaemia, acidosis, etc. Rapid administration of dexmedetomidine infusion (Loading dose of 1 μg/ kg/ hr if given in less than 10 minutes) may cause transient hypertension mediated by peripheral α2B- AR vasoconstriction.45 But hypotension and bradycardia may occur with ongoing therapy mediated by central α2A-AR, causing decreased release of noradrenaline from the sympathetic nervous system. Long-term use of dexmedetomidine leads to super sensitization and upregulation of receptors; so, with abrupt discontinuation, a withdrawal syndrome of nervousness, agitation, headaches, and hypertensive crisis can occur.

CONCLUSION

Dexmedetomidine is clinically effective sedative.

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