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Original Research Paper

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DEXMEDETOMIDINE REVIEW

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ABSTRACT Dexmedetomidine is a new and attractive drug, which is being used in many clinical scenarios. Dexmedetomidine is a potent, highly selective -2 adrenoceptor agonist, with sedative, analgesic, anxiolytic, sympatholytic, and opioid-sparing properties. Initially used for ICU sedation, but now used in different clinical conditions. Dexmedetomidine emerged as a one of the versatile drug in anaesthesia and intensive care. The common side effects include hypotension and bradycardia. Its use is not recommended in patients with advanced heart block and with ventricular dysfunction.

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

Dexmedetomidine

It is newer more selective α2 agonist (dexmedetomidine hydrochloride is the S-enantiomer of medetomidine), having 8 times more affinity than clonidine for α2 receptors. It was approved by the Food and Drug Administration (FDA) in 1999 for use in humans for short term sedation in intensive care unit. Initially used for sedation and analgesia in intensive care, its use has been extended to other various clinical situations as well as in regional anaesthesia as a useful adjunct.[1]

Chemical formula

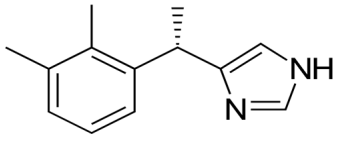
$C_{13}H_{16}N_2HCl$

It has a molecular weight of 236.7 g/mol. Dexmedetomidine hydrochloride is a white powder that is freely soluble in water and has a pKa of 7.1. It is supplied as a clear, colourless, isotonic solution with a pH of 4.5 to 7.0. Each ml contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative free and contains no additives or chemical stabilizers.

IUPAC Name

(+)-4-(S)-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazolemono hydrochloride.

Molecular Structure



Mechanism of Action

It acts by binding to G-protein coupled α2 adrenergic receptors, which are found in central, peripheral and autonomic nervous systems and also in various vital organs and blood vessels throughout the body.[2] There are three subtypes of these receptors namely α-2A, α-2B and α-2C each having different functions and activities. Dexmedetomidine is considered to have more affinity for α-2A and α-2C receptors as compared to clonidine.[3]

The site of action for sedative effects of dexmedetomidine is locus ceruleus and is mediated by hyperpolarization of noradrenergic neurons thus inhibiting noradrenaline release and inhibiting activity in descending medulla-spinal noradrenergic pathways.[4,5]

Analgesic effects are mainly mediated by α-2C and α-2A receptors present on the neurons of superficial dorsal horn in laminsa II, by inhibiting the release of pro-nociceptive transmitters namely substance P and glutamate and by hyperpolarization of spinal interneurons.[6]

Activation of post-synaptic α-2 receptors lead to sympatholysis and results in hypotension and bradycardia; thus, helps in attenuating the stress response. Other useful actions of dexmedetomidine include decreased salivation, increased glomerular filtration, decreased intraocular pressure, decreased shivering threshold, decreased bowel motility and decreased insulin release from pancreas.[7]

Pharmacokinetics

Absorption: Dexmedetomidine has poor bioavailability due to extensive first pass metabolism; however, sublingual route has high bioavailability of about 84%.[8] It exhibits linear pharmacokinetics over a dose range of 0.2-0.7 μg/kg/h intravenous infusion.

DISTRIBUTION

It is rapidly distributed with a volume of distribution being 118 litres and has an elimination half life of 2 h. It is 94% protein bound and does not displaces most of the protein bound drugs used commonly in anaesthesia and intensive care. The context sensitive half life varies from 4 mins for a 10 mins infusion to 250 mins for an 8 hrs infusion.

Metabolism and Excretion

Dexmedetomidine undergoes complete biotransformation by glucuronidation and by cytochrome P-450 mediated aliphatic hydroxylation to inactive metabolites. These metabolites are excreted in the urine (95%) and in feces (4%). The dose needs to be adjusted in patients with hepatic failure towing to lower rates of metabolism.

Systemic effects of Dexmedetomidine

Cardiovascular system

The effects of dexmedetomidine on blood pressure are biphasic with an initial transient rise with a reflex fall in heart rate. brought about by stimulation of α-2B subtypes of receptors present in vascular smooth muscles. This is followed by fall in blood pressure and heart rate due to inhibition of central sympathetic outflow and stimulation of pre-synaptic α-2 receptors cause decreased release of nor-adrenaline leading to further fall in the blood pressure.[9,10]

These hemodynamic effects; however, may be deleterious in patients with fixed stroke volume, on rate reducing drugs such as beta blockers, digitalis, etc and in hypovolemic patients.

Central nervous system

Dexmedetomidine causes a reduction in cerebral blood flow and cerebral metabolic demand of oxygen with a slight reduction in intracranial pressure. It has found to have neuroprotective effects by reducing the circulating and cerebral catecholamines; thus, reducing the excitotoxicity and improving the blood supply to the ischemic cerebral tissues. It also reduces the levels of glutamate, which is found to enhance the cellular brain injury especially in subarachnoid hemorrhage.[11]

Respiratory system

Dexmedetomidine does not have any depressant effects on respiratory function even at higher doses with no impairment of ventilation or gas exchange; however, may produce mild hypercapnia.[12,13] It is considered to be a good sedating agent with good cardiovascular stability; thus, facilitating weaning in patients on prolonged ventilatory support with failed previous attempts.

Endocrine and renal system

Dexmedetomidine causes suppression of stress response to surgery by activation of peripheral α-2 receptors and reducing the release of catecholamines. It is found to have no inhibitory effects on steroidogenesis when used for short term sedation by intravenous infusion.[14,15]

Uses

The major clinical role of dexmedetomidine in anaesthesiology and intensive care practice, which has been established, can be summarized as:

1. Sedation in critically ill patients.
2. Procedural sedation.
3. Perioperatively because of its anxiolytic, analgesic, sympatholytic and sedative effects, has found its application in premedication, prevention of stress response to laryngoscopy and prevention of emergence delirium.
4. As adjuvant in various regional blocks.
5. As post-operative adjunct and analgesic.

Adverse effects

The common side-effects include hypotension, bradycardia, dry mouth, nausea. Long-term infusions of dexmedetomidine may result in up regulation of receptors leading to the development of withdrawal syndrome on abrupt discontinuation manifesting as nervousness, agitation, headaches and hypertensive crisis.[16] Its use is not recommended in patients with advanced heart block and with ventricular dysfunction.

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