

Summarised Pharmacological Views on Dexmedetomidine

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Introduction

Dexmedetomidine is selective alpha two adrenergic agonist like clonidine, but it is eight times more selective alpha two agonist than clonidine. Dexmedetomidine produces sedation and anxiolysis effect and it has analgesic effect like opioids but no respiratory depression, which makes it best for procedural sedation. Dexmedetomidine can be used for awake fiberoptic intubation, as it does not cause respiratory depression [1]. Atipamezole is a synthetic alpha two adrenergic receptor antagonist, which is used to treat over dose of dexmedetomidine. Dexmedetomidine is sold under the trade name called precedex, dexdomitor and dexdor. Case Study on dexmedetomidine is going on as it is new medicine which came in the market after 1999.

Mechanism of action

Adrenergic receptors are of two types: alpha and beta.

Alpha adrenergic receptors are subdivided into alpha 1 and alpha 2. stimulation of alpha receptors produces excitatory effects, alpha two receptors are located on the presynaptic membrane in the brain and postsynaptic membrane in the pancreatic islets and platelets. Stimulation of alpha two receptors on presynaptic membrane inhibits the release of nor adrenaline [2].

All the alpha receptors are G- protein coupled receptors including alpha two receptors. G Proteins are bound to inner face of the plasma membrane. It has three subunits viz., alpha, beta and gamma. When the ligand binds to the g protein coupled receptor, the associated g protein gets activated. This in turn activates adenylyl cyclase or phospholipase C to generate the respective second messengers. G protein acting via second messengers to bring a chain of intracellular changes. Thus, G- protein acts as mediator between receptors and second messenger.

Second messengers are cAMP, IP3, DAG, Ca⁺⁺ and cGMP

Sedation and analgesic effect of dexmedetomidine are mediated by hyperpolarization/depolarization of neurotransmitter system,

which inhibits neuronal activity in the nucleus in the pons of brain stem and inhibits release of nor epinephrine and descending medullo spinal noradrenergic pathway. Suppression of inhibitory control stimulates neurotransmitters that decrease histamine secretion producing hypnosis without respiratory depression. As we said dexmedetomidine inhibits the descending medullispinal noradrenergic pathway, it influences or modulates nociceptive neurotransmission, which prevents propagation of pain signal that brings analgesia. Dexmedetomidine causes hypotension and bradycardia, which is good to reduce the stress response of surgery by sympatholytic effect caused by activation of alpha two receptors in post synaptic membrane. In addition to hypotension and bradycardia, activation of alpha two receptors in postsynaptic membrane also reduces salivary secretion, increase glomerular filtration rate, decrease intra ocular pressure and shivering. Dexmedetomidine may cause transient hypertension which is due to peripheral vasoconstriction, which is seen mostly during loading time, This is one of adverse effect of dexmedetomidine.

Pharmacokinetics

Dexmedetomidine can be administered by many routes, but most commonly administered by IV route. The bioavailability of dexmedetomidine is poor because of vast first pass metabolism. Dexmedetomidine is well absorbed via intra-nasal route and buccal mucosa, hence it helps to use in un-cooperative children. Dexmedetomidine is retained in plasma (albumin & alpha 1 glycoprotein), hence the volume of distribution is small. Dexmedetomidine can cross blood brain barrier and placental barrier and the half life of dexmedetomidine is two hours. Dexmedetomidine is metabolised by liver through xenobiotic metabolism and cytochrome P450. It is excreted via urine.

Pharmacodynamics

Pharmacodynamics is the study of actions of the drugs on the body and their mechanisms of action. Drugs produce their effects by interacting with the physiological systems of the organisms, by such interaction, drugs merely modify the rate of functions of the various system, here we will discuss the actions of dexmedetomidine on different physiological systems of the organisms.

Respiratory system

Dexmedetomidine is not respiratory depressant and it does not cause bronchodilation as well, but it may produce mild hypercapnia and mechanism behind this is unknown.

Central Nervous System

Dexmedetomidine reduces cerebral blood flow, but it is not proven that it has effects on ratio of cerebral oxygen supply to cerebral oxygen demand (ration of cerebral blood flow to cerebral metabolic rate) and more research study is required on this.

Cardiovascular system

Alpha adrenergic receptors are present in smooth muscles of certain blood vessels. Dexmedetomidine stimulates the alpha two adrenergic receptors and prevents the release of nor adrenaline from nerve ending, whereby it reduces heart rate and blood pressure and dexmedetomidine also works post-synaptic ally to reduce blood pressure and heart rate.

Renal system

Dexmedetomidine maintains adequate cardiovascular stability (c.o constant), which in turn increases urine output.

Doses and considerations.

ICU Sedation (ADULT): Generally, initiate at 1mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hour.

Procedural Sedation (ADULT): Generally initiate 1mcg/kg over 10 minutes, followed by a maintenance infusion dose of 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hour.

Age more than 65 years and patient with impaired liver should be given consideration while giving dexmedetomidine. (Table-1)

Indications	Adult doses
Initial procedural sedation.	1mcg/kg over 10 mins.
Maintenance	0.2 to 1 mcg/kg/hr
Initial ICU sedation	1 mcg/kg over 10 mins.
Maintenance	0.2 to 0.7 mcg/kg/hr (it is adjusted to achieve desired level of sedation)
Intra-nasal dose for children	1 to 2 mcg/kg
Premedication	0.33 to 0.67 mcg/kg iv.

Adverse effects

Adverse effects include: bradycardia, hypotension, hypertension, dry mouth, nausea, fever and muscle weakness.

Applications of dexmedetomidine

- There are many places where we can dexmedetomidine viz in premedication, it can be used as sedative, anxiolytic, analgesic. It reduces oxygen consumption during intraoperative and postoperative period.
- ICU sedation- it is used for intubated and mechanically ventilated patients.
- Procedural sedation- TEE, colonoscopy, awake carotid endarterectomy, shockwave lithotripsy, vitreoretinal surgery, paediatric patient undergoing tonsillectomy.
- As adjuvant in local and regional techniques- it prolongs the duration of sensory and motor blockade induced by local, spinal, epidural and caudal Anesthesia.
- Intra articular use- for patient undergoing, arthroscopic knee surgery, it improves the quality and duration of post op analgesia.
- Awake fiberoptic intubation.
- Cardiac surgery.
- Neurosurgery- prevents sudden increase in ICP during intubation, extubation. etc.
- Bariatric surgery.
- MRI and CT scan.

Conclusion

Dexmedetomidine is one of the best choice for procedural sedation, as it does not cause respiratory depression, other than that it gives good analgesia, and it blends increased heart rate due surgical stress. We don't need to use opioids for post-operative pain as it provides analgesia for long hours.

References

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