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Dexmedetomidine: A Noble Drug for Analgesia and Sedation

Medical Science

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ABSTRACT

It has been decades since we are searching for a drug that can effectively manage peri operative requirements of analgesia and sedation and which has a better safety profile and physical properties and the search brings us close to the alpha-2 adrenergic agonist dexmedetomidine that appears to be fit. After its approval by FDA for clinical use dexmedetomidine usage has increased drastically and it appears to be the end of search for the most awaited wonder drug. This review will discuss its role in anesthesia practice as the major drug for various clinical conditions.

Introduction

Based on the actions, potency, specificity and efficacy of various naturally occurring or synthetic catecholamines, the adrenergic receptors are classified as alpha and beta type. Their activation produce different effect on different organ system which can be excitatory or inhibitory depending on the organ system involved (1, 2). These receptors are further subclassified into alpha1, alpha2 and beta1, beta2 and beta3 types. These receptor subtypes are present at pre, post and extra synaptic sites of sympathetic terminal (3). It is the unique property of alpha2 receptor that only the pre-synaptic subtype is of clinical importance and is known to regulate the noradrenaline and adenosine-tri-phosphate release via negative feedback mechanism (4). They are located in central nervous system, peripheral nervous system, vascular smooth muscles, platelets and various other organs such as liver, pancreas, kidney and eye. Post synaptic stimulation of these receptors include decreased salivation, secretion, bowel motility, inhibition of renin release, increased glomerular filteration and increased secretion of sodium and water in the kidney, decreased intraocular pressure, decreased insulin release from the pancreas. Locus ceruleus, an important modulator of wakefulness, is the major site for the hypnotic action of alpha2 receptor (5).

The alpha2 adrenergic agonist acts by decreasing the production of cAMP by inhibiting the adenylate cyclase enzyme which is achieved through activation of G protein which further activates the second messenger system. As a result of this, there occurs inward movement of excessive K+ ion and suppression of entry of calcium ions at nerve terminal leading to hyperpolarization of cell membrane thereby suppressing both neuronal firing and release of noradrenaline at the nerve terminals (6, 7).

Alpha2 adrenergic agonist drugs belonging to the imidazole class like clonidine and medetomidine have been in use since ages. The main limitation about these drugs in anesthesia use and critical care is non availability of parenteral preparations. Unreliable oral preparations are in use especially in veterinary medicine. Xylazine, detomidine and medetomidine are well accepted as anesthetics and sedatives in medium and large animals (8). Categorized as "centrally acting anti-hypertensive agent" this drug is also used in alcohol and opioid withdrawal without causing any dependence of its own, as a supportive treatment of myocardial ischemia and as an adjuvant to local anesthetics when used in neuraxial block (4, 9).

The most recent addition in this class is dexmedetomidine, a D-enantiomer of medetomidine which has been approved by FDA for usage in humans in 1999.

Pharmacology of Dexmedetomidine

This imidazole compound is an active D-enantiomer of medetomidine. It has an onset of 30 minutes when used singly. When used as an infusion, the standard loading dose is 1µg/kg over 10 minutes. Infusion dosing has been found to decrease the onset time. The duration of action is about 4 hours and an offset of 5 minutes. When compared with dexmedetomidine, Midazolam has an onset of 3-5 minutes, duration of action 1-2 hours and has an offset of about 2-6 hours.

Dexmedetomidine cause sedation, anxiolysis, analgesia, bradycardia and hypotension by acting on central receptors and its peripheral actions include decreased GI secretions and decreased GI motility, constriction of vascular and other smooth muscles, inhibition of Renin-Angiotensin (RA) system and decreased release of renin, increased Glomerular Filtration Rate (GFR), increased excretion of Na and water, decreased intra-ocular pressure and decreased insulin release.

Mechanism of Action

The alpha2 adrenoceptor agonist drug, dexmedetomidine has a unique mechanism for producing analgesia.

I) Mediated through G_1 protein controlled 'gating ' mechanism →hyper polarization → prevention of transmission of pain impulse
II) G0 protein controlled → N type voltage gated channels → Regulation of calcium channels.

This results in blockade of nerve terminal stimulation, transmission and propagation of signals at the spinal and supra spinal levels (10).

The main centre, Locus Coeruleus, regulates the supra spinal analgesic and sedative action by modulating the descending noradrenergic pathway. These pathways share a common output area with central opioid pathway.

The spinal level acts by closing the gates for the stimuli from peripheral Aδ and C fibers at the dorsal horn and also by inhibiting the substance P release. They seem to act through substantia gelatinosa (Lamina II in grey matter) (11).

Dexmedetomidine has been shown to cause less respiratory depression and resembles the physiological sleep (12). This property is not seen with clonidine and seems to be mediated by alpha2 subunit (13). Another unique and desirable property of dexmedetomidine is easy arousablity (14). These properties have proved this drug to be near ideal for analgesia and sedation (15, 16).

Action on cardiovascular system

It has got no direct effect on heart. When used repeatedly or in large doses, it has been associated with a transient rise in blood pressure (BP) and significant bradycardia for around 10 minutes. It causes stimulation of alpha2B receptors in the peripheral smooth muscles thus leading to peripheral vasoconstriction and rise in BP (17). This is followed by a fall in BP and normalization of bradycardia. This action has been attributed to direct inhibition of central alpha2 agonist effect (18) or by decreasing release of nor adrenaline by stimulation of presynaptic alpha2 receptors (19). Significant postoperative bradycardia is found in nearly 40% of the patients receiving high dose (20). These patients can be treated with glycopyrollate (0.1-0.2mg), atropine (0.5-1.0mg), ephedrine (25-50mg) or intra vascular volume infusion (21).

Metabolism

Liver is the main organ of biotransformation and excretion of dexmedetomidine with minimal unchanged fraction and nearly 95% of its byproducts are excreted through kidney. The metabolites are pharmacologically inert. Patients with liver dysfunction may have adverse effect on drug clearance but renal impairment has no effect (4).

An ideal intravenous sedative and analgesic should have the following properties:

- Water soluble.
- Simple and easily available
- No need for any special license for procurement
- Painless injection
- Compatible and non reactive with other drugs
- High potency and efficacy
- High precision, predictability and reproducibility
- Minimal respiratory side effects, should suppress airway reflexes
- Minimal and manageable cardiovascular side effects
- Rapidly metabolized with no active metabolites and no effect on liver and renal dysfunction
- Rapid and predictable reversal of effects

Indication and Dosage

The main indications of dexmedetomidine are sedation and analgesia. It can be used in following conditions:

- As premedication and sedation in short procedures. It is used as an initial loading dose of 1- 6 μg/kg given as slow infusion over 10 minutes. A response of 3 on Mackenzie's Sedation assessment score (awakening responses to calling with closed eyes) and maintained on 0.2-0.7 μg/kg/hr (22)
- To attenuate the stress induced sympathetic response to laryngoscopy, endotracheal intubation and surgical incision (0.2-0.7 μg/kg/hr)
- As an intra-operative analgesic as an alternative to opioids
- As an adjuvant to anaesthetic agents or as an individual analgesic/anaesthetic
- As post-operative analgesic.
- As a sole sedative and analgesic in critically ill patients on ventilator (14).
- As a neuro-protective agent by decreasing cerebral blood flow without affecting cerebral metabolic rate (CMRO2) or intra cranial pressure (ICP) (23).
- As a sole sedative agent with local anesthetic agents in a high risk patient for axillo-femoral bypass graft (24)
- As an adjuvant to the local anaesthetics like bupivacaine when injected via intra-thecal route in urological and gynaecological surgeries (25, 26)
- For intra articular administration in various orthopedic conditions(27)
- As anti-shivering agent for thermoregulation.

Conclusion

Dexmedetomidine has revolutionized the way of giving intra-venous anaesthesia. Pre-operative sedation and anxiolytic effect have made it the almost ideal premedication in anesthesia practice. The viewpoint of providing intra and post- operative analgesia, without any significant side-effects has changed. It has entered into critical care setting as a novel analgesic and sedative with minimal morbidity and dependence on the ventilator. The newer routes of administration other than the conventional intra-venous route such as neuraxial, regional has taken the drug on a newer level. The safety profile of this drug along with its ability to provide the desired effects has made it the most promising recent advance in anesthesia.

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