A Narrative Review on Dexmedetomidine

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Abstract
Dexmedetomidine is an easily adaptable anesthetic agent that can be used in a wide range of perioperative procedures with distinct sedative, analgesic, and sympatholytic effects. Significant benefits can be gained in the perioperative care of surgical patients, especially those with cardiovascular concerns or a history of opioid use, because of its capacity to provide arousable sedation, lower opioid doses, and preserve hemodynamic stability. Dexmedetomidine's clinical relevance is further expanded by its neuroprotective properties, particularly in neurosurgery and trauma settings. Although it is usually well accepted, its usage requires close observation to prevent adverse effects including bradycardia and hypotension. Thus, Dexmedetomidine is a useful addition to the anesthesiologist's armamentarium for incorporation into perioperative care procedures.

Keywords: Anesthetic agent, Analgesia, Dexmedetomidine , Sedative, Sympatholytic

Introduction

In the perioperative context, dexmedetomidine, a highly selective α2-adrenergic agonist, has become a useful anesthetic with a variety of uses. This drug is an appealing option for doctors to manage different stages of the surgical process because of its unique mix of sedative, analgesic, and sympatholytic characteristics. Its unique therapeutic effects, including as drowsiness, analgesia, and hemodynamic stability without considerable respiratory depression, are attributed to its strong selectivity for α2-adrenergic receptors. Dexmedetomidine's significance in contemporary perioperative medicine is expected to be strengthened as research into its full potential continues to broaden its application in a variety of clinical contexts [1-3].

History

Since the initial discovery of α2-adrenoceptor agonists like clonidine, the list of uses for this family of medications has kept growing. Dexmedetomidine, the most recent member of this category, was licensed in December 1999 and used as a short-term (less than 24 hours) sedative for patients in intensive care units who were on mechanical ventilation. In 2008 it was authorized in the United States for the sedation

of patients who are not intubated before to or during surgery. However, in 2011the European Union approved it for use in sedating intensive care unit patients who need a certain amount of sedation when they are responsive to verbal cues[4-6].

Structure and properties

The S enantiomer of medetomidine, a sedative and analgesic used in veterinary medicine, is called dexmedetomidine. It is a derivative of imidazole. (S)-4-[1-(2,3-dimethyl phenyl) ethyl] is the chemical name.-3H-imidazole, which has the chemical formula C13H16N2 and a molecular weight of 236.74, and a pKa of dexmedetomidine-7.1. It comes in a transparent isotonic solution with 100 mcg per milliliter and 9 mg of sodium chloride per milliliter of water. It is also freely soluble in water. It comes in a 1 ml ampoule with 100 µg/ml of a transparent, isotonic, preservative-free solution with a pH of 4.5-7 [7-9].

Mechanism of action

Dexmedetomidine is an agonist of the α2 receptor that is very selective. There are several of these pre- and post-synaptic receptors in the central and peripheral nervous systems. α-2A, α-2B, and α-2C are the three different types of α-adrenergic receptors. By centrally stimulating α-2 adrenergic receptors, dexmedetomidine increases the inhibitory neuron firing action, which results in a sedative and sympatholytic effect. Vasoconstriction is a result of postsynaptic α-2 receptor stimulation in the peripheral vascular system [10].

Table 1: Routes of administration of dexmedetomidine with dosages [11]

Route	Dose
Intravenous	1 µg/kg as a loading dose spread out over 10–20 minutes, followed by a maintenance infusion of 0.2–0.7 µg/kg/h. Increments of 0.1 µg/kg/h or more can be used to increase the infusion rate.
Intramuscular	2.5 µg/kg for premedication.
Spinal	0.1-0.2 µg/kg

Epidural	1-2 µg/kg
Peripheral nerve block	1 µg/kg
Buccal	1-2 µg/kg
Intranasal	1-2 µg/kg

Pharmacokinetics

Absorptionand distribution

Dexmedetomidine is most frequently administered intravenously, although it can also be administered by other means. The benefit of this is that it prevents the high peak plasma levels (0.3–1.5 ng/mL) that are visible following intravenous delivery. With a bioavailability of only 16%, there is an increase in first pass metabolism following oral ingestion. Dexmedetomidine is significantly (94%) protein bound to α1-glycoprotein and serum albumin. It has a distribution volume of 1.31–2.46 L/kg [3,12,13].

Metabolism and elimination

The hepatic extraction ratio for the liver's metabolism of dexmedetomidine is 0.7. Metabolites include N-methyl O-glucuronide dexmedetomidine, 3-hydroxy, 3-carboxy, 3-hydroxy N-methyl, and 3-carboxy N-methyl. There are no clinical effects of the metabolites. Only when creatinine clearance is less than 30 milliliters per minute does the kidneys' excretion of the metabolite require a dose decrease; however, hepatic impairment may require a half dose reduction [3].

Physiological effects

α-2 receptors mediate the sedative, anxiolytic, and sympatholytic actions. This happens when the G-protein inhibits the postsynaptic receptors' L-type calcium channels in the pons' locus ceruleus. These channels are unable to conduct impulses; instead, voltage-gated calcium-activated potassium channels conduct the impulses. However, α-2 antagonists such atipamezole can easily reverse these effects. It generates analgesia through an α-2 receptor found in the locus ceruleus and spinal cord. The modification of the spinal cord-dorsal horn, which has more α-2 receptors, releases substance P, which has an analgesic effect. Dexmedetomidine has no effect on cognitive performance. It generates less neuronal hyperpolarization through the opening of chloride channels than propofol and thiopentone [10].

System wise effects:

Cardiovascular system: A brief hypertension phase and subsequent hypotension are the two phases of the biphasic blood pressure response that dexmedetomidine generates. The α-2A receptor mediates hypotension, while the α-2B receptor causes the early hypertensive phase. It has a sympatholytic effect by lowering catecholamine release in the autonomic ganglia and peripheral nerves. Myocardial contractility, cardiac output, and systemic blood pressure are all indirectly reduced along with systemic vascular resistance [14].

Central nervous system: Although dexmedetomidine lowers cerebral blood flow and oxygen metabolism, its impact on intracranial pressure (ICP) is still unclear [15]

Respiratory system: Even at high dosages, dexmedetomidine does not impair respiratory function. When administered to post-operative ICU patients who are breathing on their own, it has no negative effects on gas exchange or respiratory rate. It may make weaning and extubation easier for trauma/surgical intensive care unit patients who have failed prior weaning attempts due to agitation and hyperdynamic cardiopulmonary response since it helps maintain sedation without hemodynamic instability or respiratory drive depression [16-18].

Endocrine and renal system: Dexmedetomidine decreases catecholamine release and, consequently, the sympathetic reaction to surgery by activating peripheral presynaptic α2-adrenergic receptors [19].

Clinical Properties

Analgesia: Dexmedetomidine has strong analgesic properties that can lessen the requirement for opioids throughout the recovery phase. This is particularly helpful for individuals for whom opioid-sparing measures are essential, like those who have a history of opioid misuse or specific comorbidities who should not take high doses of opioids. By effectively reducing the need for opioids and relieving pain, dexmedetomidine can help reduce the risk of opioid-related adverse effects like constipation, respiratory depression, and dependence. Its analgesic properties can also help patients recover more quickly, have lower pain scores, and spend less time in the hospital[20].

Sympatholytic effect: Dexmedetomidine's impact is crucial for preserving hemodynamic stability during surgery. It can lessen the circulatory response to surgical stress by decreasing sympathetic output, which lowers the risk of perioperative tachycardia and hypertension. Patients with cardiovascular risk factors, such as heart failure, coronary artery disease, or hypertension, benefit most from this feature. Dexmedetomidine can therefore enhance overall surgical results and help avoid harmful cardiovascular events [21].

Neuroprotection: Dexmedetomidine may provide neuroprotective advantages in specific clinical settings, such as neurosurgery or in traumatic brain injury patients. Neuroanesthesia is particularly interested in its capacity to lower intracranial pressure and cerebral blood flow without sacrificing cerebral oxygenation. Dextmedetomidine may help prevent harm to brain tissue before and after surgery by lowering excitotoxicity and regulating the inflammatory response. Furthermore, after surgery, its neuroprotective actions might help to enhance neurological outcomes and lower the prevalence of cognitive impairment[22].

Sedation: Dexmedetomidine is frequently used for sedation in the intensive care unit (ICU) and during surgery. Compared to conventional sedatives, its distinct profile of sedative effects encourages a more cooperative or "arousable" sedation. This unique feature makes it easier to wake up patients and engage them as needed, which is especially useful in situations where patient involvement is required. Effective sedation that preserves the patient's capacity to obey vocal instructions might improve patient compliance and comfort while possibly lowering the risk of delirium and other issues related to deep sedation [23].

Antidote

Alpha-2 adrenergic receptor antagonist atipamezole has shown promise as a dexmedetomidine counteragent. Atipamezole is a useful treatment for dexmedetomidine-induced problems since it has been demonstrated to quickly reverse the sedative and cardiovascular effects of the drug. Atipamezole acts quickly; its effects peak within 15 minutes, allowing for a timely reversal of dexmedetomidine's effects and the restoration of normal physiological processes, including awareness and cardiovascular stability. This reversal is especially helpful in surgical situations where a quick recovery from sedation is crucial, including in the post-anesthesia care unit (PACU) or when someone overdoses on dexmedetomidine.Atipamezole has been shown in studies to efficiently counteract the sedative and hypotensive effects of dexmedetomidine, facilitating a speedier recovery and discharge of patients from the PACU. With its quick onset of action and brief duration of impact, atipamezole's pharmacokineticswhich include rapid absorption and a short elimination half-lifemake it appropriate for prompt clinical intervention [8,16,24,25]

Adverse effects:

Although dexmedetomidine is usually well tolerated, adverse consequences are possible. Bradycardia and hypotension, which are associated with its sympatholytic activity, are frequent side effects hence it must be used with caution in patients with pre-existing heart block, low ejection fraction, congestive heart failure, elderly patients, hypovolemic patients. Usually dosage-dependent, these symptoms can be controlled with supportive measures or dose modifications. For example, substantial

hypotension can be countered by lowering the infusion rate or by giving fluids and vasopressors. Less frequently, during loading doses, individuals may have nausea, dry mouth, reduced lacrimation and brief hypertension [26].

Clinical Uses:

In the operating room:

- Premedication: Dexmedetomidine's sedative, anxiolytic, analgesic, sympatholytic, and steady hemodynamic characteristics make it ideal adjuvant for premedication. Dosage: Intravenous administration of 0.33 to 0.67 mg/kg 15 minutes prior to surgery; this dose reduces the risk of bradycardia and hypotension [8].
- Dexmedetomidine is a safe and efficient medication for controlled hypotension when used in conjunction with general anesthesia. The hemodynamic stress response to intubation and extubation is also lessened by it. Additionally, it can be applied to fiberoptic intubation while awake. Because it doesn't produce respiratory depression, it can be used to sedate individuals who are extremely fat, preventing narcotic-induced respiratory depression [27,28].
- Because dexmedetomidine is highly lipophilic, it can be quickly absorbed into the cerebrospinal fluid and bind to the spinal cord's α2-adrenergic receptor to produce analgesia as an adjuvant to regional anesthesia. Regardless of the method of administration, it extends the duration of sensory and motor blockage brought on by local anesthetics. It has been effectively utilized in intravenous regional anesthesia (IVRA) and improves both central and peripheral neuronal blocking by local anesthetics. For IVRA, adding 0.5 μg/kg dexmedetomidine to lidocaine enhances intraoperative-postoperative analgesia and anesthesia quality without producing adverse effects [11,29].
- **Monitored anaesthesia care**: In gynecological, urological, burn, and trauma patients, dexmedetomidine has been utilized as a sedative for controlled anesthesia care [30].
- **Post-operative uses:**Additionally, dexmedetomidine produces strong analgesia in the postoperative phase, which lessens the need for opioids and other sedative drugs, lowers the risk of postoperative delirium, and promotes early mobilization. It is linked to decreased nausea and vomiting, which lowers the morbidity rate following surgery [31].

All things considered, dexmedetomidine's adaptability as an anesthetic and its advantageous pharmacological profile have made it a useful tool for perioperative care.

Non-operating room anesthesia

- **Procedural sedation**: Patients who are not intubated can be sedated with dexmedetomidine prior to, during, and/or after surgery. Shockwave lithotripsy,

awake carotid endarterectomy, colonoscopy, vitreoretinal surgery, and pediatric patients have all been safely treated with it. Dosage: 0.2 µg/kg/h infusion after a loading dose of 1 µg/kg. It takes less than five minutes to start working, and within fifteen minutes, the maximum effect is achieved [32].

- **Acute or chronic pain:**Dexmedetomidine can also be used to treat end-of-life distress symptoms, such as delirium, agitation, or intractable pain. It helps with intractable neuropathic pain and has a notable opioid-sparing effect [33].

In the intensive care unit

- Sedation: In the critical care unit, dexmedetomidine is prescribed for sedation in patients who are initially intubated and on mechanical ventilation [34].

Conclusion

A unique blend of sedative, analgesic, and sympatholytic qualities makes dexmedetomidine a very adaptable anesthetic drug that can be used in a variety of perioperative settings. Significant benefits can be gained in the perioperative care of surgical patients, especially those with cardiovascular concerns or a history of opioid use, because to its capacity to provide arousable sedation, lower opioid doses, and preserve hemodynamic stability. Dexmedetomidine's clinical relevance is further expanded by its neuroprotective properties, particularly in neurosurgery and trauma situations. Although it is usually well accepted, its usage requires close observation to prevent adverse effects including bradycardia and hypotension, especially in individuals with liver impairment. Dexmedetomidine's safety profile is improved by the availability of atipamezole as an antidote, which enables quick and efficient reversal of its sedative and cardiovascular effects.Given its many advantages and the growing body of research proving its efficacy, dexmedetomidine is a useful tool for anesthesiologists and should be further investigated and incorporated into perioperative care procedures.

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