A review on Dexmedetomidine: Present and Future

Zeinab Hamed Sawan, Hosam Mohamed Soliman, Ahmed Ezzat Attia Mostafa, Rania Ahmed Kamel
Department of Anesthesia, Intensive Care and Pain management, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author: Ahmed EzzatAttiaMostafa,**
E-mail: midozewil@gmail.com

Abstract:

Dexmedetomidine is a potent, highly selective α-2 adrenoceptor agonist, with sedative, analgesic, anxiolytic, sympatholytic, and opioid-sparing properties. Dexmedetomidine induces a unique sedative response, which shows an easy transition from sleep to wakefulness, thus allowing a patient to be cooperative and communicative when stimulated. Dexmedetomidine may produce less delirium than other sedatives or even prevent delirium. The analgesic effect of dexmedetomidine is not strong; however, it can be administered as a useful analgesic adjuvant. As an anesthetic adjuvant, dexmedetomidine decreases the need for opioids, inhalational anesthetics, and intravenous anesthetics. The sympatholytic effect of dexmedetomidine may provide stable hemodynamics during the perioperative period. Dexmedetomidine-induced cooperative sedation with minimal respiratory depression provides safe and acceptable conditions during neurosurgical procedures in awake patients and awake fiberoptic intubation. Despite the lack of pediatric labelling, dexmedetomidine has been widely studied for pediatric use in various applications. Most adverse events associated with dexmedetomidine occur during or shortly after a loading infusion. There are some case reports of dexmedetomidine-related cardiac arrest following severe bradycardia. Some extended applications of dexmedetomidine discussed in this review are promising, but still limited, and further research is required. The pharmacological properties and possible adverse effects of dexmedetomidine should be well understood by the anesthesiologist prior to use. Moreover, it is necessary to select patients carefully and to determine the appropriate dosage of dexmedetomidine to ensure patient safety.

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Indications:

Dexmedetomidine (Precedex), a pharmacologically active dextroisomer of medetomidine, is a selective α2-adrenergic receptor agonist. The food and drug administration (FDA) approved indications for dexmedetomidine are sedation of intubated and mechanically ventilated patients in the intensive care unit (ICU) and peri-procedural (or peri-operative) sedation of non-intubated patients. Over time, usage has expanded to off-label uses, including treatment and prevention of delirium, adjunctive analgesia, therapy for insomnia in the ICU, and treatment of alcohol withdrawal**(1).**

Dexmedetomidine can markedly reduce the anesthetic requirements of inhaled and intravenous anesthetics. It can also decrease

the dose of opioids required, perioperatively and postoperatively, in patients undergoing a variety of surgical procedures. This opioid-sparing effect of dexmedetomidine decreases opioid use and thereby reduces the risk of opioid-induced respiratory depression in bariatric patients or those with significant respiratory disease **(2).**

MechanismofAction:

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist (selectivity ratio for α2: α1 is 1600:1). The sympatholytic effect of dexmedetomidine made it attractive to be used as a hypotensive drug during surgery because of decrease in heart rate (HR) and cardiac output with no decrease in stroke volume unless the plasma concentrates reaches above 5.1 µg/mL. The cardiovascular effects of dexmedetomidine begin with initial hypertension following the administration ofa loading dose, due to the activation of α 2B receptors located on vascular smooth muscle, with subsequent hypotension and bradycardia due to centrally mediated decrease in sympathetic tone.Dexmedetomidine also has sedative, amnesic,anxiolytic, hypnotic, and analgesic effects with minimal changes in respiratoryvariables. Furthermore, it reduces postoperative nausea, vomiting, and shivering. It also reduces delirium in patients after cardiac surgery **(3, 4).**

Receptors for α2 are found in platelets, the liver, pancreas, kidney, eye and heart. From an anesthesiologist point of view, neuronal hyperpolarization is a key element in the mechanism of action of dexmedetomidine and is achieved by efflux of potassium and suppression of calcium entry. Loss of intracellular potassium and inhibition of calcium entry suppress neuronal firing and can inhibit signal transduction **(5).**

Administration:

- **Injection:**Maybeadministered IMorIV
  - Intramuscular: IM injection (2.5 mcg/kg) of dexmedetomidine has been used for premedication.
  - Intravenous: loading dose of 1 mcg/kg over 10-20 minutes followed by a maintenance infusion in the range of 0.2-0.7mcg/kg/hr. The rate of infusion can be increased or titrated up to 1.5 mcg/kg/hr.
- **Spinal:** 0.1-0.2 mcg/kg.
- **Epidural:** 1-2 mcg/kg.
- **Peripheral nerve block:** 1 mcg/kg.
- **Buccal:** 1-2 mcg/kg.
- **Intranasal:** 1-2mcg/kg **(6).**

SideEffects:

The most frequently reported treatment-emergent adverse events that occurred with ≥2% frequency across the clinical studies were bradycardia, dry mouth, and hypotension.

According to the US manufacturer's prescribing information, clinically significant episodes of bradycardia and sinus arrest have been observed following the administration of dexmedetomidine to healthy volunteers with high vagal tone and following the administration of dexmedetomidine via different routes, including rapid intravenous or bolus administration**(7).**

Contraindications:

There are no absolute contraindications to the use of dexmedetomidine. However, it should be used cautiously in patients with bradycardia and hypotension as the medication may exacerbate these findings. Additionally, it should be used cautiously in patients with known heart failure as there is level B evidence showing dexmedetomidine can potentially exacerbate myocardial dysfunction **(1).**

Monitoring:

The level of sedation, heart rate/rhythm, blood pressure, and pulse oximetry require close monitoring **(1).**

Toxicity:

There have been reports of over dosage of dexmedetomidine, in which higher doses ranging from 10 to 60 times the recommended infusion dose. Hypotension, bradycardia, deep hypnosis, miosis and hypoglycemia can be expected in these patients.

Severity of side-effects of

dexmedetomidine seems more related to the speed of injection and less to the actual dose administered by infusion.

At present, there is no chemical reversal or antidote for dexmedetomidine. Supportive care and close monitoring are the staples of treatment for overdose **(8).**

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