

Dexmedetomidine

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Dexmedetomidine is the most recently released IV anesthetic. It is a highly selective α_2 -adrenergic agonist that produces sedation, hypnosis, and analgesia.

History

The initiation for the use of α_2 agonists in anesthesia resulted from observations made in patients during anesthesia who were receiving clonidine therapy. Dexmedetomidine was introduced in clinical practice in the United States in 1999. It was approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients.

Dexmedetomidine is now being used off-label outside of the ICU in various settings.

Pharmacological profile

It is a highly selective α_2 -adrenergic agonist. It shows a high ratio of specificity for the α_2 receptor (α_2/α_1 1600:1) compared with clonidine (α_2/α_1 200:1), making it a complete α_2 agonist. Dexmedetomidine belongs to the imidazole subclass of α_2 receptor agonists, similar to clonidine. It is freely soluble in water.

Metabolism and Pharmacokinetics

Dexmedetomidine has rapid redistribution half life - 6 min. Dexmedetomidine is 94% protein bound, and its concentration ratio between whole blood and plasma is 0.66.

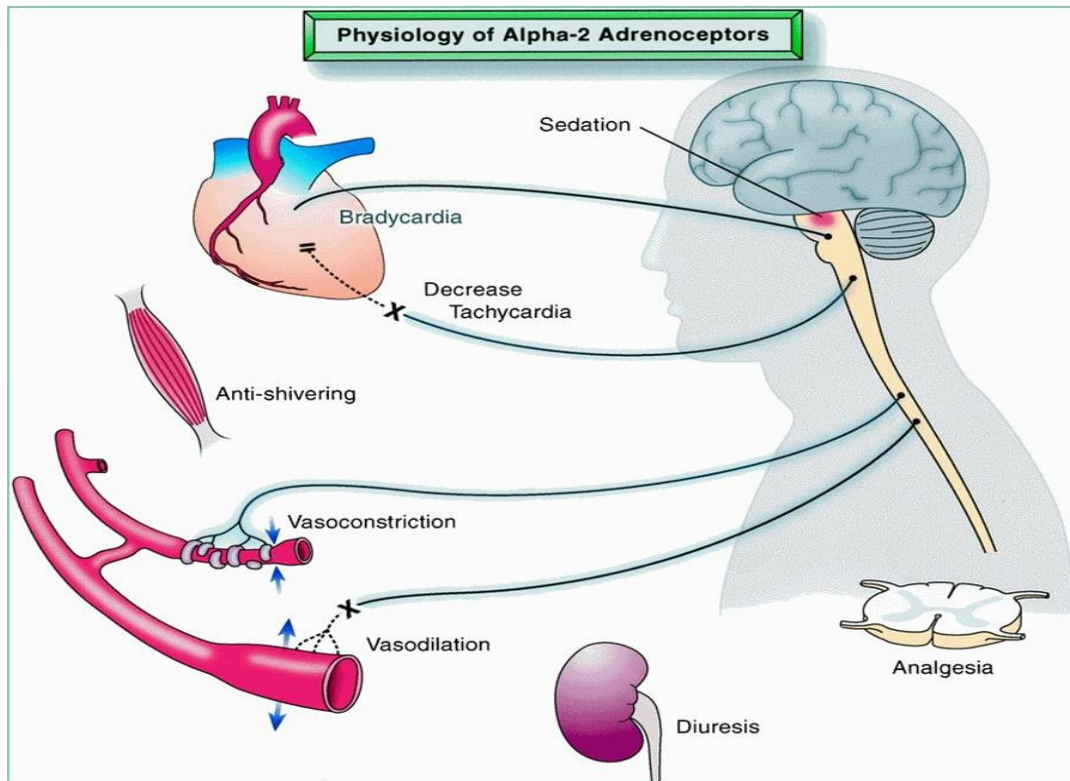
Metabolism: biotransformation by conjugation (41%), n-methylation (21%), or hydroxylation followed by conjugation. in liver. The inactive metabolites excreted in urine and feces .The elimination half-life of Dexmedetomidine is 2 to 3 hours, with a context- sensitive half-time ranging from 4 minutes after a

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10-minute infusion to 250 minutes after an 8-hour infusion. No accumulation after infusions 12-24 h. Pharmacokinetics similar in young adults and elderly.

Mechanism of actions

A selective α_2 -adrenoceptor agonist. Its action is unique and different. Three subtypes of α_2 adrenoceptors have been described in humans: α_{2A} , α_{2B} , and α_{2C} (Fig). The α_{2A}



α_{2A} adrenoceptors are primarily distributed in the periphery, whereas α_{2B} and α_{2C} are in the brain and spinal cord.

- Presynaptic activation of alpha2-adrenoceptors inhibits the release of nor epinephrine.
- Postsynaptic activation of alpha2-adrenoceptors in the central nervous system inhibits sympathetic activity and can decrease blood pressure and heart rate, so sedation and anxiolysis can result from this activity.
- Analgesia is provided through binding of Dexmedetomidine to alpha2-adrenoceptors in the spinal cord.

The overall response to α_2 adrenoceptors agonists is related to the stimulation of α_2 adrenoceptors located in the CNS and spinal cord. The α_2 agonists produce their sedative-hypnotic effect by an action on α_2 receptors in the locus caeruleus and an analgesic action at α_2 receptors within the locus caeruleus and within the spinal cord.

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Actions

Effects on the Central Nervous System

Sedation

The α_2 agonists act through the endogenous sleep-promoting pathways to exert their sedative effect.

It produces unique sedative quality - **someone be clinically sedated yet arousable.**

- Patients sedated, remaining so when unstimulated. But, when stimulated, they are arousable, alert, and able to respond without becoming uncomfortable.
- It 's also observed that they would quickly return to their sleep-like state.
- This characteristic allows for “daily wake up” tests to be done in a safe fashion.
- Despite sound levels of sedation with dexmedetomidine, there is limited respiratory depression, providing wide safety margins.

Analgesia

The analgesic effects of dexmedetomidine are complex. Alpha₂ agonists do have an analgesic effect when injected via the intrathecal or epidural route. The primary site of analgesic action is thought to be the spinal cord. Systemic use of dexmedetomidine shows narcotic sparing. In the postoperative ICU setting, narcotic requirements were reduced by 50% when patients were receiving a dexmedetomidine

In human pain studies, the results of systemically administered dexmedetomidine are inconsistent. Modest reductions in pain were observed. In the clinical setting, when pain is likely to occur, if dexmedetomidine is to be used, the addition of a narcotic seems warranted.

Other Central Nervous System Effects

Dexmedetomidine in animal models of incomplete cerebral ischemia and reperfusion reduces cerebral necrosis and improves neurologic outcome by reducing the intracerebral catecholamine outflow and the reduction of the excitatory neurotransmitter glutamate during injury.

Dexmedetomidine also is able to reduce muscle rigidity after high-dose opioid administration.

Effects on the Respiratory System

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Dexmedetomidine at concentrations producing significant sedation reduces minute ventilation, but retains hypercapnic ventilatory response. The changes in ventilation appeared similar to those observed during natural sleep. Dexmedetomidine has been implicated in blocking histamine-induced bronchoconstriction in dogs.

Effects on the Cardiovascular System

The basic effects of α_2 agonists on the cardiovascular system are decreased heart rate; decreased systemic vascular resistance; and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure.

The hemodynamic effects of a bolus of Dexmedetomidine in humans have shown a biphasic response- an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at 5 minutes after injection(probably due to the vasoconstrictive effects of dexmedetomidine when stimulating peripheral α_2 receptors)followed by Heart rate return to baseline by 15 minutes, and blood pressure decrease 15% below baseline by 1 hour.

The incidence of hypotension and bradycardia may be related to the administration of a loading dose. Omitting the loading dose or not giving more than 0.4 $\mu\text{g}/\text{kg}$ reduces the incidence of hypotension. Giving the loading dose over 20 minutes also minimizes the transient hypertension.

Dosage and administration

- Dexmedetomidine is supplied in a 2-mL ampoule, 100 mcg/ml .
- Dexmedetomidine must be diluted in 0.9% sodium chloride to achieve the required concentrations prior to administration. To prepare the infusion, withdraw 2 ml of dexmedetomidine and add to 48 ml of 0.9% sodium chloride injection to a total of 50 ml.
- The target concentration is 4 mcg/ml. So 2 ml of dexmedetomidine needs to be diluted to 50 ml in 0.9% sodium chloride.
- Loading dose -0.5 μg -1 $\mu\text{g}/\text{kg}$ [6-12ml] over 10 min (36-72 ml /hr)
- Maintenance -0.3 μg -0.7 $\mu\text{g}/\text{kg}/\text{hr}$ [4-9ml/hr]
- Titration \pm 0.1 $\mu\text{g}/\text{kg}/\text{hr}$ -1.25ml/hr

Uses

Dexmedetomidine has been approved as a short-term sedative for adult intubated patients in the ICU. Given its well-documented beneficial effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression, it also has been used in various other clinical scenarios.

1.Intensive Care Unit

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Dexmedetomidine has following advantages for sedation in mechanically ventilated postoperative patients.

- Decreased requirement for opioids (>50%) when dexmedetomidine is used for sedation compared with propofol or benzodiazepines.
- The PaO₂/F_IO₂ ratio was significantly higher in the dexmedetomidine group.
- Providing adequate sedation with minimal respiratory depression—can be used when weaning patients from the ventilator.

α₂-adrenoreceptor agonists have been used in the treatment of alcohol and drug withdrawal of narcotics, benzodiazepines, alcohol, and recreational drugs

2. Anesthesia

a) Dexmedetomidine, at IV doses of 0.33 to 0.67 μg/kg given 15 minutes before surgery attenuates the hemodynamic response to endotracheal intubation.

b) As a premedicant IM injection (2.5 μg/kg).

c) Dexmedetomidine is used as a premedication 10 minutes before general surgery for cataract removal, intraocular pressure is decreased (33%), catecholamine secretion is reduced, perioperative analgesic requirements are less, and recovery is more rapid.

d) Dexmedetomidine used for securing the airway with a fiberoptic intubation

e) Dexmedetomidine has been used for sedation for monitored anesthesia care in gynaecological, urological, burns patients, trauma patients, paediatric patients, and in obese, OSA patients.

f) Sedation during regional anesthesia.

g) Dexmedetomidine also useful as anesthetic adjuvant in Bariatric surgery, Sleep apnea patients, Craniotomy aneurysm, AVM [hypothermia], Cervical spine surgery, Off-pump CABG, Vascular surgery, Thoracic surgery, Conventional CABG, Spine surgery, evoked potential study, Head injury, Burns, Trauma, Alcohol withdrawal.

Contraindications

- Infusion over 24 hours.
- In obstetric procedures, cesarean section deliveries, as the safety has not been studied.
- Patients with pre-existent severe bradycardia and related bradydysrhythmias (e.g., advanced heart block).
- Patients with impaired ventricular functions (ejection fraction <30%).
- Patients who are hypovolemic or hypotensive.
- Patient with raised intracranial tension.
- Used with Caution

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When other vasodilators or negative chronotropic agents are administered, and with renal or hepatic impairment, dose reductions needed as may accumulate with long-term infusions.

Conclusion

Our search for safe drugs will always continue and new products will keep on appearing. The new alpha2 agonist Dexmedetomidine has shown its usage in perioperative period and in ICU . The use of dexmedetomidine has dramatically increased .To conclude careful evaluation and selection of patients has to be made to use this drug or any new drugs.