**DEXMEDETOMIDINE**

**THERAPEUTICS**

**Brands**
- Precedex (Dexmedetomidine hydrochloride)

**Generic?**
- No

**Class**
- Centrally acting; alpha-2 agonist

**Commonly Prescribed For**
(FDA approved in bold)
- **Short-term sedation (<24 hours) of initially intubated and mechanically ventilated patients during treatment in an intensive care setting (ICU sedation)**
- Sedation prior to and/or during surgical or other procedures on nonintubated patients (procedural sedation) (e.g. awake fiberoptic intubation)
- Premedication prior to anesthesia induction with thiopental
- Relief of pain and reduction of opioid dose following laparoscopic tubal ligation
- As an adjunct anesthetic in ophthalmic surgery
- Treatment of shivering
- Premedication to attenuate the cardiostimulatory and postanesthetic delirium of ketamine
- Management of alcohol/drug abuse withdrawal

**How the Drug Works**
- Alpha-2-adrenergic agonist
- Selective alpha-2-adrenoceptor agonist with anesthetic and sedative properties thought to be due to activation of G-proteins by alpha-2a-adrenoceptors in the brainstem resulting in inhibition of norepinephrine release; peripheral alpha-2b-adrenoceptors are activated at high doses or with rapid IV administration resulting in vasoconstriction
- Reduces sympathetic nervous system central outflow
- Has an 8-fold increase in specificity for the alpha-2 receptor subunit with an $\alpha_2/\alpha_1$ binding affinity ratio of 1620:1

**How Long until It Works**
- Minutes (roughly 5–30 minutes)

**If It Works**
- Slowly titrate to most effective tolerated dose

**If it Doesn’t Work**
- Increase to highest tolerated dose. If ineffective, gradually reduce dose and consider alternative medications

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- Use other centrally acting muscle relaxants with caution due to potential additive CNS depressant effect

**Tests**
- Blood pressure, heart rate, and consciousness/sensorium should be monitored frequently/closely during treatment

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**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**
- Related to alpha-2-adrenergic agonist effect causing hypotension

**Notable AEs**
- Hypotension, bradycardia
- Respiratory depression
- Atrial fibrillation, hypovolemia
- Hypocalcemia
- Nausea, xerostomia
- Urine output decreased
- Pleural effusion, wheezing

**Life-Threatening or Dangerous AEs**
- Bradycardia, hypotension, and prolongation of QTc interval with higher doses

**Weight Gain**
- Unusual

**Sedation**
- Common

**What to Do about AEs**
- Lower the dose and titrate more slowly
Best Augmenting Agents for AEs
- Most AEs cannot be improved by an augmenting agent

DOSSING AND USE

Usual Dosage Range
- Individualized and titrated to desired clinical effect. Manufacturer recommends duration of infusion should not exceed 24 hours; however, randomized clinical trials have demonstrated efficacy and safety comparable to lorazepam and midazolam with longer-term infusions of up to approximately 5 days
- ICU sedation: IV: initial loading infusion (optional; see "Note" below) of 1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.2–0.7 μg/kg per hour; adjust rate to desired level of sedation; titration no more frequently than every 30 minutes may reduce the incidence of hypotension
- Note: Loading infusion: administration of a loading infusion may increase the risk of hemodynamic compromise. For this indication, the loading dose may be omitted. Maintenance infusion: dosing ranges between 0.2 and 1.4 μg/kg per hour have been reported during randomized controlled clinical trials. Although infusion rates as high as 2.5 μg/kg per hour have been used, it is thought that doses >1.5 μg/kg per hour do not add to clinical efficacy
- Procedural sedation: IV: initial loading infusion of 1 μg/kg (or 0.5 μg/kg for less invasive procedures [e.g. ophthalmic]) over 10 minutes, followed by a maintenance infusion of 0.6 μg/kg per hour, titrate to desired effect; usual range: 0.2–1 μg/kg per hour
- Fiberoptic intubation (awake): IV: initial loading infusion of 1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.7 μg/kg per hour until endotracheal tube is secured

Dosage Forms
- Injection, solution (preservative free): Precedex®: 100 μg/mL (2 mL)

How to Dose
- Add 2 mL (200 μg) of dexmedetomidine to 48 mL of 0.9% sodium chloride for a total volume of 50 mL (4 μg/mL)
- Shake gently to mix. Administer using a controlled infusion device. Must be diluted in 0.9% sodium chloride solution to achieve the required concentration (4 μg/mL) prior to administration. Advisable to use administration components made with synthetic or coated natural rubber gaskets. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If loading dose used, administer over 10 minutes; may extend to 20 minutes to further reduce vasoconstrictive effects. Titration no more frequently than every 30 minutes may reduce the incidence of hypotension when used for ICU sedation

Dosing Tips
- The sedative, bradycardic, and hypotensive effects of dexmedetomidine are likely additive (esp. when administered with other sedatives, analgesics, vasodilators, or other negative chronotropic medications)
- Slowly and carefully titrate infusion to target effect
- Ensure patients are euvoletic
- High doses (esp. as possible loading infusions) may lead to a hypertensive response by activating peripheral alpha-2b-receptors (which could cause vasoconstriction)
- Dexmedetomidine has a dose-dependent bradycardic effect, mediated by a decrease in sympathetic tone and enhanced vagal activity

Overdose
- In order to avoid overdose; dosing is in micrograms/kg per hour
- If significant overdose occurs; immediately discontinue infusion
- Signs/symptoms which may occur with overdose include excessive sedation, hypertension/hypotension, bradycardia/ cardiac arrest, respiratory depression/respiratory arrest

Habit Forming
- No

How to Stop
- Taper slowly to avoid rebound tachycardia and hypertension (although much less problematic than clonidine)

Pharmacokinetics
- Onset of action: IV bolus: 5–10 minutes
- Peak effect: 15–30 minutes
- Duration (dose dependent): 60–120 minutes
- Rapid distribution
- Protein binding: −94%
**Metabolism:** hepatic via \(N\)-glucuronidation, \(N\)-methylation, and CYP2A6

**Half-life elimination:** \(~6\) minutes; terminal: \(~2\) hours

**Excretion:** urine (95%); feces (4%)

**Metabolism/transport effects**
- Substrate of CYP2A6 (major); inhibits CYP1A2 (weak), CYP2C9 (weak), CYP2D6 (strong), CYP3A4 (weak)

**Drug Interactions**
- Beta-blockers: may enhance the rebound hypertensive effect of alpha-2 agonists. This effect can occur when the alpha-2 agonist is abruptly withdrawn
- CYP2A6 inhibitors (moderate): may decrease the metabolism of CYP2A6 substrates
- CYP2A6 inhibitors (strong): may decrease the metabolism of CYP2A6 substrates
- Hypotensive agents: may enhance the adverse/toxic effect of other hypotensive agents
- Iobenguane I 123: Alpha-2 agonists may diminish the therapeutic effect of Iobenguane I 123 (avoid combination)
- MAO inhibitors: may enhance the orthostatic hypotensive effect of orthostatic hypotension producing agents
- Serotonin/norepinephrine reuptake inhibitors: may diminish the antihypertensive effect of alpha-2 agonists
- TCAs: may diminish the antihypertensive effect of alpha-2 agonists

**Other Warnings/Precautions**
- Episodes of bradycardia, hypotension, and sinus arrest have been associated with rapid IV administration (e.g. bolus administration) or when given to patients with high vagal tone. When used for ICU sedation, use of a loading dose is optional; for the maintenance infusion, titration no more frequently than every 30 minutes may reduce the incidence of hypotension. If medical intervention is required, treatment may include stopping or decreasing the infusion, increasing the rate of IV fluid administration, use of pressor agents, and elevation of the lower extremities
- Transient hypertension: has been primarily observed during loading dose administration and is associated with the initial peripheral vasoconstrictive effects of dexmedetomidine. Treatment of this is generally unnecessary; however, reduction of infusion rate may be required

**Use with caution in patients with heart block, bradycardia, severe ventricular dysfunction, hypovolemia, or chronic hypertension**

**Diabetes:** use with caution in patients with diabetes mellitus; cardiovascular adverse events (e.g. bradycardia, hypotension) may be more pronounced

**Vasodilators:** use with caution in patients receiving vasodilators or drugs which decrease heart rate

**Arousability:** patients may be arousable and alert when stimulated. This alone should not be considered as lack of efficacy in the absence of other clinical signs/symptoms

**Experienced personnel:** should be administered only by persons skilled in management of patients in intensive care setting or operating room. Patients should be continuously monitored

**Withdrawal:** when withdrawn abruptly in patients who have received >24 hours, withdrawal symptoms similar to clonidine withdrawal may result (e.g. hypertension, nervousness, agitation, headaches). Use for >24 hours is not recommended by the manufacturer

**Do Not Use**
- Known hypersensitivity

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**SPECIAL POPULATIONS**

**Renal Impairment**
- Clearance is reduced in patients with creatinine clearance less than 25 mL/minute. Reduce dose
- Dosage reduction may need to be considered. No specific guidelines available

**Hepatic Impairment**
- Use with caution in any patient with significant hepatic disease. If using in patients with significant hepatic disease reduce dose
- Dosage reduction may need to be considered. No specific guidelines available

**Elderly**
- Drug metabolism is slower in elderly patients. Use with caution
- Dose reduction may be necessary. Cardiovascular events (e.g. bradycardia, hypotension) may be more pronounced
- ICU sedation: IV: refer to adult dosing. Dosage reduction may need to be considered. No specific guidelines available. Dose selections should be cautious, at the low end of dosage range; titration should be slower, allowing adequate time to evaluate response
Procedural sedation: IV: refer to adult dosing. Initial loading infusion of 0.5 μg/kg over 10 minutes. Maintenance infusion: dosage reduction should be considered

Children and Adolescents
- Not studied in children

Pregnancy
- Category C: use only if there is a clear need

Breast-Feeding
- Unknown if excreted in breast milk but likely due to lipid solubility. Do not use

Potential Advantages
- Effective for achieving sedation and appears to have reasonable analgesic properties with relatively benign AE profile

Potential Disadvantages
- Hypotension can be problematic. Sedation often limits use
- Needs to be administered as a continuous intravenous infusion

Primary Target Symptoms
- Sedation, pain

Pearls
- Dexmedetomidine generally causes minimal respiratory depression, inhibits salivation, and is analgesic-sparing

Assess the patient for pain during infusion; the sedation produced by this agent is not equivalent to analgesia
- Adequate pain management should be addressed. Dexmedetomidine does not provide adequate and reliable amnesia; therefore, use of additional agents with amnestic properties may be necessary
- Dexmedetomidine is associated with hypotension and bradycardia due to inhibition of norepinephrine release from presynaptic neurons. Hypertension due to stimulation of peripheral vascular alpha-2b-adrenoceptors may also occur with rapid IV administration or high-dose infusion rates
- In addition, rapid IV administration may also induce bradycardia
- The loading infusion may be administered over a longer period of time (e.g. 20–30 minutes) or may be omitted
- Initiation of a maintenance infusion without administration of the loading infusion achieves similar levels of sedation without the undesirable hemodynamic effects
- When used for ICU sedation, a dosing protocol using a slower titration (≥ every 30 minutes) may reduce the incidence of hypotension associated with dexmedetomidine
- Potential off-label uses (other than sedation) may include treatment of pain, shivering delirium, and/or alcohol/drug withdrawal
- Use is likely safe beyond 24 hours
- Intuitively, theoretically may be useful in conjunction with opioids since it may lead to a decrease in toll-like receptor 4 (TLR4)
- Anecdotal preclinical reports suggest that dexmedetomidine may exhibit potential renoprotection, cardioprotection, and/or neuroprotection
- In the future an intranasal formulation may be available
- Appears to be less apt to contribute to delirium in older adults than benzodiazepines
Suggested Reading


