

The Role of Dexmedetomidine (Precedex®) in the Sedation of Critically Ill Patients

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INTRODUCTION

Critically ill patients requiring mechanical ventilation frequently need sedatives and analgesics to facilitate their care. Inappropriate sedative use in the intensive-care unit (ICU) is associated with adverse outcomes, including patient discomfort, excessive sedation, longer ICU and hospital stays, an increased incidence of ventilator-associated pneumonia, and greater hospital costs.^{1,2} An ideal sedative should provide a rapid onset of effect and a rapid recovery and should have a low propensity to accumulate, leaving no withdrawal effects. It should be easily titratable and should not compromise hemodynamic stability.²

The Society of Critical Care Medicine's current guidelines on sedatives and analgesics for critically ill adults recommend the use of propofol (Diprivan®, AstraZeneca) or midazolam (Versed®, Roche) for short-term sedation and lorazepam (Ativan®, Wyeth/Baxter) for patients requiring long-term sedation. Because pain is often the culprit of agitation, an opioid analgesic is recommended, in addition to the previously mentioned agents, to provide adequate analgesia.³

These recommended agents do not come without associated harm. Propofol lacks analgesic properties, and its usage is often limited by hypotension and respiratory depression. The use of a benzodiazepine is also associated with respiratory depression and the potential for the drug to accumulate, leading to a prolonged recovery period.^{3,4}

Dexmedetomidine (Precedex®, Abbott Laboratories), a short-acting α_2 -agonist, was approved by the U.S. Food and Drug Administration (FDA) as an ICU sedative in 1999. It possesses anxiolytic, anesthetic, hypnotic, and analgesic properties. Patients receiving dexmedetomidine infusions are easily aroused, yet appear calm and comfortable. When they remain unstimulated, patients return to a hypnotic state.⁵ It is the unique characteristics of dexmedetomidine that prompted a number of studies to evaluate its potential clinical role in the management of ICU sedation.

chemically as (+)-4-(S)-[1-(2,3-dimethylphenyl) ethyl]-1H-imidazole monohydrochloride (Figure 1). Its empirical formula is $C_{13}H_{16}N_2 \cdot HCl$, and its molecular weight is 236.7.^{4,6}

The agent's sedative, anxiolytic, and analgesic effects are produced through specific and selective activation of postsynaptic α_2 -adrenoreceptors. It is approximately eight times more selective for the α_2 -adrenergic receptor than clonidine and is 1,620 times more potent as an α_2 -adrenergic receptor agonist than as an α_1 -adrenergic receptor agonist.^{2,4}

PHARMACOKINETICS

Dexmedetomidine has been studied following intravenous (IV), intramuscular (IM), and transdermal administration. IV dexmedetomidine has a volume of distribution (V_d) of approximately 118 liters.⁶ Its mean elimination half-life is 1.5 to 3 hours following IV and IM administration and 5.6 hours following transdermal administration.⁷

When given as an IV infusion, dexmedetomidine demonstrates linear, concentration-dependent kinetics.⁶ After IM administration, the time to maximum concentration (T_{max}) in the blood is 1.6 to 1.7 hours, with an absolute bioavailability of 73%. After transdermal administra-

CHEMISTRY AND PHARMACOLOGY

Dexmedetomidine HCl, an imidazole compound, is the pharmacologically active S-enantiomer of medetomidine, a veterinary anesthetic agent. It is described

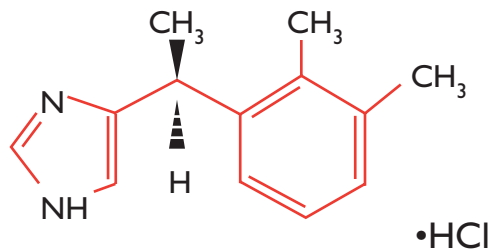


Figure 1 Chemical structure of dexmedetomidine. (Data from Precedex® package insert, Abbott, 2004.⁶)

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tion, the T_{max} is six hours, with an absolute bioavailability of 88%.⁷

In normal healthy volunteers, the average plasma protein binding is 94% to serum albumin and alpha₁-glycoprotein.⁴ Dexmedetomidine is metabolized extensively in the liver, and it is excreted renally as methyl and glucuronide conjugates.⁴

The agent's pharmacokinetic properties appear to be affected in patients with renal and hepatic insufficiency. Patients with hepatic failure may have an increased V_d and half-life as well as a decreased clearance and decreased protein binding.^{4,8} In patients with renal dysfunction, the elimination half-life appears to be shorter than in healthy volunteers; however, the V_d and the elimination clearance are not affected.⁹

A complete pharmacokinetic comparison of currently recommended agents for the management of ICU sedation is summarized in Table 1.^{3,5,6,10-13}

CLINICAL TRIALS AND EFFICACY STUDIES

Comparison with Placebo

Tritsch et al.¹⁴

In a prospective, randomized, double-blind, placebo-controlled, bicenter phase 2 study, the Philips Bispectral

Index (BIS®) was used to evaluate the safety and efficacy of dexmedetomidine in 30 patients who needed mechanical ventilation after surgery. A score between 60 and 70 was needed to achieve adequate sedation. If the target level was unattainable with the study drug alone, the patient was given additional boluses of propofol, followed by a propofol infusion. The infusion of the study drug was continued for up to 72 hours. Morphine or paracetamol was administered if additional analgesia was required.

The total amount of propofol required by the dexmedetomidine group (0.58 ± 0.14 mg/kg per hour) was less than that needed by the placebo group (0.95 ± 0.20 mg/kg per hour) ($P = .133$). The dexmedetomidine patients also required less morphine (0.28 mg/hour), compared with the placebo patients (0.68 mg/hour) ($P = 4.74$).

There was no significant difference in the time to extubation between the two groups (8.2 vs. 7.5 hours).

After extubation, the heart rate in the dexmedetomidine group was significantly lower than that of the placebo group ($P < .01$), and systolic and diastolic arterial blood pressures were significantly higher in the placebo patients ($P = .05$ and $P < .01$, respectively).

There was no significant difference in

the frequency of adverse drug events (ADEs) between the two treatment groups.

Venn et al.¹⁵

A prospective, observational pilot study was designed to test the efficacy of dexmedetomidine in 12 critically ill medical patients requiring sedation and mechanical ventilation. Patients were allowed to receive up to seven days of sedation with dexmedetomidine. Ramsay Sedation Scale scores were used to assess the level of sedation. Additional sedation and analgesia could be provided with propofol and/or morphine as required.

Seven patients needed the addition of a propofol infusion despite maximum doses of dexmedetomidine, and six patients received additional doses of morphine. Four patients experienced hypotension during the loading dose of dexmedetomidine, and the study drug had to be withdrawn in one patient because of this decrease in blood pressure.

Martin et al.¹⁶

A total of 401 patients were enrolled in a double-blind, randomized, placebo-controlled study to evaluate the safety and efficacy of dexmedetomidine for the

Table 1 Comparison of Selected Sedatives

	Lorazepam (Ativan®, Baxter/Wyeth)	Midazolam (e.g., Versed®, Roche)	Propofol (Diprivan®, AstraZeneca)	Dexmedetomidine (Precedex®, Abbott)	Haloperidol (e.g., Haldol®, Ortho-McNeil)
V_d (liters/kg)	1.3	0.6–6.6	60	1.3	9.5–21.7
Clearance (ml/kg per minute)	1.1	2.5–12.8	23–50	8.3	—
Half-life					
• Alpha (minute)	15–20	6–20	1–8	6	—
• Beta (hours)	9–19	1–12.3	1.5–12.4	2	10–38
Metabolic pathway	Glucuronidation	Oxidation and glucuronidation	Glucuronidation	Glucuronidation and conjugation	Oxidation
Active metabolite	None	Yes	None	None	Yes
Intermittent IV dose	0.02–0.06 mg/kg every 2–6 hours	0.02–0.08 mg/kg every 0.5–2 hours	—	—	0.03–0.15 mg/kg every 0.5–6 hours
Infusion dose range	0.01–0.1 mg/kg per hour	0.04–0.2 mg/kg per hour	5–80 mcg/kg per minute	0.2–0.7 mcg/kg per hour	0.04–0.15 mg/kg per hour

IV = intravenous; V_d = volume of distribution.

Data from *Am J Health Syst Pharm* 2002;59:150–178;³ Young CC, Prielipp RC, 2002;⁵ Precedex® package insert, 2004;⁶ Diprivan® package insert, 2004;¹⁰ American Hospital Formulary Service Drug Information, 2002;¹¹ lorazepam package insert, 2003;¹² and Micromedex, 2005.¹³

short-term sedation of postsurgical, ventilated patients. The primary outcome of this study was the total dose of propofol required to maintain sedation at a Ramsay Sedation Scale score greater than 3. Secondary endpoints included the dose of morphine needed for adequate analgesia, weaning duration, the time to extubation, and nurses' assessments of patient management.

Patients in the dexmedetomidine group required significantly less propofol than the placebo patients (71.6 ± 17.51 mg vs. 513.2 ± 55.6 mg; $P < .001$) and less morphine ($1.31 + 0.19$ mg vs. 4.14 ± 0.45 mg; $P < .001$).

There was no significant difference in the time to extubation between the dexmedetomidine patients and controls. When surveyed regarding their experience in the ICU, fewer patients in the dexmedetomidine group remembered their pain (23% vs. 34%) and discomfort from the endotracheal tube (33% vs. 37%).

More dexmedetomidine patients than placebo patients experienced hypotension (30% vs. 10%), bradycardia (9% vs. 2%), atelectasis (fewer than 1% vs. 5%), and rigors (fewer than 1% vs. 4%).

Comparison with Other Sedative Agents

Venn and Grounds¹⁷

A randomized trial was conducted to compare the efficacy and safety profiles of dexmedetomidine with propofol in 20 adults. Each patient was randomly assigned to receive a loading dose of dexmedetomidine 2.5 mcg/kg, followed by a continuous infusion of 0.2 to 2.5 mcg/kg per hour, or a loading dose of propofol 1 mg/kg, followed by a maintenance rate of 1 to 3 mg/kg per hour. Ramsay Sedation Scale scores and BIS® scores were used to evaluate the degree of sedation.

Alfentanil (Alfenta®, Janssen), a short-acting opioid, was provided to all patients for analgesia if required. The infusion rates for the two groups were adjusted to meet a goal Ramsay Sedation Scale score above 2. There was no difference in the percentage of time spent at the target level of sedation between the propofol and the dexmedetomidine groups (49.1% vs. 46.3%). Patients receiving propofol needed a significantly higher amount of alfentanil (2.5 mg/hour) than patients receiving dexmedetomidine (0.8 mg/

hour) ($P = .004$).

A statistically significant reduction in heart rate was observed in patients receiving dexmedetomidine compared with those receiving propofol ($P = .034$). There was no difference in the extubation time between the two groups (28 minutes vs. 29 minutes).

Herr et al.¹⁸

Herr and colleagues conducted an open-label, randomized, multicenter study consisting of 308 patients in order to compare the sedative efficacy of dexmedetomidine with that of propofol. Patients were randomly selected to receive dexmedetomidine or propofol continuous infusion. Morphine or non-steroidal anti-inflammatory drugs (NSAIDs) were allowed for additional pain relief.

Sedation was adjusted to maintain a Ramsay Sedation Scale score of 3 or higher before extubation and a score of 2 or higher after extubation.

Of the dexmedetomidine-treated patients, 11% required propofol at some point during mechanical ventilation. For the duration of intubation and for six hours after extubation, fewer dexmede-

tomidine patients needed morphine compared with the propofol patients ($P < .001$). There was no difference between the two groups in the time to weaning or extubation.

The most common ADE in both groups of patients was hypotension (24% of patients receiving dexmedetomidine vs. 16% of patients receiving propofol) ($P = .111$). Hypertension occurred more frequently in the dexmedetomidine group ($P = .018$). Seven propofol patients and none of the dexmedetomidine patients experienced ventricular tachycardia.

Tobias and Berkenbosch¹⁹

A prospective, randomized trial was performed in mechanically ventilated infants and children in the pediatric intensive care unit (PICU). The trial compared the efficacy of sedation between continuous infusions of midazolam (0.1 mg/kg per hour), low-dose dexmedetomidine (0.25 mcg/kg per hour), and high-dose dexmedetomidine (0.5 mcg/kg per hour).

Three sedation scales (Ramsay scores, PICU sedation scores, and tracheal suctioning scores) were used to review

Table 2 Commonly Reported Adverse Drug Reactions in Patients Taking Dexmedetomidine and Placebo

Adverse Event	Dexmedetomidine	Placebo
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

Data from Precedex® package insert, Abbott, 2004.⁶

sedation levels every two hours. Each group consisted of 10 patients. The midazolam patients needed more morphine (36 boluses) than patients receiving low-dose dexmedetomidine (29 boluses) or high-dose dexmedetomidine (20 boluses).

The total amount of morphine used was significantly higher in the midazolam group of patients (0.74 ± 0.5 mg/kg per day) than in the high-dose dexmedetomidine patients (0.28 ± 0.12 mg/kg per day) ($P = .01$).

Heart rates were significantly lower in the two dexmedetomidine groups than in the midazolam group. There was no significant difference in blood pressure between the three treatment arms.

ADVERSE DRUG EVENTS

The most common ADEs experienced with dexmedetomidine therapy in clinical trials are hypotension and bradycardia.^{6,14-16,18,19} Hypertension is common with the administration of the loading dose.^{6,18} Other side effects reported in patients who have received this drug include dystonic movements, hypertension, atelectasis, nausea and vomiting, hypoxia, dry mouth, tachycardia, atrial fibrillation, hemorrhage, acidosis, confusion, agitation, and rigors.^{6,16}

Table 2 summarizes the incidence of adverse reactions reported in clinical trials.

DRUG INTERACTIONS

Dexmedetomidine has been shown to inhibit CYP2D6 *in vitro*, but the clinical significance of this inhibition is not well established. Dexmedetomidine appears to have little potential for interactions with drugs metabolized by the cytochrome P450 system.⁴

Coadministration of dexmedetomidine with sevoflurane, isoflurane, propofol, alfentanil, and midazolam may result in enhancement of sedative, hypnotic, or anesthetic effects.⁶

PRECAUTIONS

Dexmedetomidine should be used with caution in patients who are hypovolemic, hypotensive, or elderly and in those with advanced heart block, severe ventricular dysfunction, diabetes mellitus, or chronic hypertension.^{2,6} Caution should also be used when dexmed-

etomidine is administered to patients with renal or hepatic impairment.^{8,9}

DOSAGE AND ADMINISTRATION

The recommended dexmedetomidine dose is an IV infusion bolus of 1 mcg/kg over a 10-minute period, followed by a continuous IV infusion of 0.2 to 0.7 mcg/kg per hour. The maintenance dose should be titrated until the sedation goal is reached.⁶

It is not necessary to discontinue dexmedetomidine before, during, or after extubation. Doses up to 2.5 mcg/kg per hour for up to seven days, with no rebound effect on withdrawal and no compromise in hemodynamic stability, have been used in clinical trials.^{15,20}

CONCLUSION

Dexmedetomidine is as effective as propofol and midazolam for producing and maintaining adequate short-term sedation of critically ill, mechanically ventilated patients. The benefits of dexmedetomidine over currently available sedative agents include its lack of respiratory depression and its ability to decrease the need for opioid analgesics.

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