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Review Article

Use of Dexmedetomidine in Cardiothoracic and Vascular Anesthesia

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Dexmedetomidine is a highly selective α_2-adrenergic agonist with analgesic and sedative properties. In the United States, the Food and Drug Administration approved the use of the drug for short-lasting sedation (24 h) in intensive care units (ICUs) in patients undergoing mechanical ventilation and endotracheal intubation. In October 2008, the Food and Drug Administration extended use of the drug for the sedation of nonintubated patients before and during surgical and nonsurgical procedures.

In the European Union, the European Medicine Agency approved the use of dexmedetomidine in September 2011 with a single recognized indication: ICU adult patients requiring mild sedation and awakening in response to verbal stimulus.

At present, the use of dexmedetomidine for sedation outside the ICU remains an off-label indication. The benefits of dexmedetomidine in critically ill patients and in cardiac, electrophysiology-related, vascular, and thoracic procedures are discussed.

Key Words: Dexmedetomidine sedation; cardiothoracic and vascular anesthesia; delirium; cardiac catheterization laboratory and electrophysiology (EP)-related procedures sedation

DEXMEDTOMIDINE IS A highly selective α_2-adrenergic agonist with analgesic and sedative properties. It reduces opioid requirements and hemodynamic variations, despite side effects such as initial hypertension (caused by bolus dosing secondary to peripheral $\alpha_{2\beta}$-adrenergic receptor effects), hypotension, and bradycardia.

In the United States, the Food and Drug Administration approved the use of the drug for short-lasting sedation (24 h) in intensive care units (ICUs) in patients undergoing mechanical ventilation and endotracheal intubation. In October 2008, the Food and Drug Administration extended use of the drug to the sedation of nonintubated patients before and during surgical and nonsurgical procedures.[1,2] In the European Union, the European Medicine Agency[3] approved the drug a few months later (September 2011). At present, the use of dexmedetomidine for sedation outside the ICU remains an off-label indication.

The present review offers an update on the different applications of dexmedetomidine in the cardiothoracic anesthetic setting that may be relevant for patients with significant comorbidity.

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Pharmacokinetics, Pharmacodynamics, Adverse Effects, and Precautions With the Use of Dexmedetomidine

Dexmedetomidine is an imidazole, which is closely related to medetomidine, which is the racemic form of this compound. Its action manifests after about 15 to 30 minutes when the drug is administered as a continuous intravenous infusion (IVI), and the peak concentration is reached approximately 1 hour after infusion start. Dexmedetomidine is highly lipophilic and rapidly distributes within the tissues, with a mean half-life of 6 minutes and clearance of about 2 to 3 hours. It is strongly bound to proteins, with a free fraction of 6%, and a relatively large volume of distribution (1.33-2.1 L/kg). Dexmedetomidine is metabolized in the liver through biotransformation mediated by the P450 cytochrome system (fundamentally isoenzyme CYP2A6), followed by glucuronide conjugation. The inactive metabolites mainly are eliminated in urine, whereas the remaining 5% to 13% are eliminated in stool.[4] The recommended initial infusion rate of 0.7 μg/kg/h can be adjusted gradually over a range of 0.2 to 1.4 μg/kg/h to achieve the desired sedation level. No significant differences in the pharmacokinetic drug profile have been observed according to age and sex, not even in elderly patients. The pharmacokinetic profile of the active dexmedetomidine molecule does not seem to differ in patients with renal failure. A summary of pharmacokinetic and pharmacodynamic properties and adverse effects of dexmedetomidine are shown in Table 1.

Dexmedetomidine is a selective and specific presynaptic and postsynaptic α_2-adrenergic receptor agonist with an α_2:α_1 receptor affinity of 1620:1, compared with 220:1 in the case of clonidine.[5] Dexmedetomidine possibly mediates both sympatholytic and vasoconstrictive hemodynamic effects. It exerts sedating and anxiolytic action through presynaptic α_2-adrenergic receptor stimulation of the locus coeruleus in the brainstem. The locus coeruleus also is the origin of the descending adrenergic component of the spinal cord, known to be the key pathway intervening in the regulation of nociceptive neurotransmission responsible for the analgesic effect of dexmedetomidine, although interaction between the drug and the opioid receptors also has been implicated in this effect.[6]

The administration of a 1 μg/kg bolus dose initially induces a transient increase in blood pressure and a reflex decrease in heart rate, particularly in young and healthy individuals.[7] This initial effect can be explained by peripheral stimulation of the $\alpha_{2\beta}$-adrenergic receptors of the vascular smooth muscle and can be attenuated by a slow infusion over 10 or more minutes. This effect justifies using the drug without the prior bolus dose. However, even at slower infusion rates, mean blood pressure decreases can be observed during the first 10 minutes in 7% of cases, with a decrease in heart rate of 16% to 18%.[8] The initial response lasts 5 to 10 minutes and is followed by a drop in blood pressure to approximately 10% to 20% below the baseline pressure value and stabilization of the heart rate, likewise below the baseline value. These 2 effects likely are a consequence of inhibition of the central sympathetic conduction prevailing over the effects of direct stimulation.[9] Another possible explanation for the heart rate decrease is presynaptic stimulation of the α_2-adrenergic receptors, resulting in a decrease in noradrenaline release.[10]

The adverse effects of dexmedetomidine are summarized in Table 1. These can be reduced by omitting or lowering the loading dose. It is advisable to avoid dexmedetomidine or to administer it carefully in patients who are receiving digoxin, β-blockers, calcium antagonists, or other drugs that predispose the patient to bradycardia or hypotension.[3]

At the pulmonary level, dexmedetomidine induces minimal respiratory depression with preservation of ventilatory response to carbon dioxide and increases ventilatory frequency.[7,11] This is accompanied by a transient increment in pulmonary pressure and in pulmonary vascular resistance in both animal models[12] and healthy adult volunteers (when administered as an infusion reaching a concentration of 1.9 ng/mL).[7,13] However, after cardiac surgery, these effects have not been observed as long as adequate dose titration is performed.[14]

Dexmedetomidine is not recommended in hemodynamically unstable patients or in individuals with first- or second-degree atrioventricular block, bradycardia (heart rate < 50 bpm), serious cerebrovascular disease, hypersensitivity to the drug, or heart disease with an ejection fraction $< 30\%$.

Table 1
Summary of Pharmacokinetic and Pharmacodynamic Properties and Adverse Effects of Dexmedetomidine

Pharmacokinetics	Pharmacodynamics	Adverse Effects
Infusion: 0.2-1.4 μg/kg/h	Sedation and hypnotic effects (PC: 0.2-0.3 ng/mL)	Hypotension
Half-life distribution: 6 m	Deep sedation: (PC: 1.9 ng/mL)	Arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest
(t1/2): 2-3 h	Analgesic effects	Dry mouth
Free F: 6%	Cardiovascular effects (hypotension/hypertension: biphasic hemodynamic response)	Anemia
Bound to proteins: 94%		Hepatic function abnormal, hyperbilirubinemia
Vss: 118 L (1.33-2.11 L/kg)		
Metabolism: liver (P450)	Bradycardia	
Excretion: 95% urine, 4% feces, $< 1\%$ unchanged	Respiratory effects	

Abbreviations: Free F, free fraction; PC, plasma concentration; t1/2, elimination half-life; Vss, steady-state volume of distribution.

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