Alpha-2 Agonists

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KEYWORDS

• Clonidine • Dexmedetomidine • Alpha-2 adrenoreceptors • Pons • Locus coeruleus • Medullospinal tracts • Dorsal horn • Premedication

KEY POINTS

- Clonidine and dexmedetomidine are alpha-1 and alpha-2 receptor agonists. Dexmedetomidine is a highly selective alpha-2 receptor agonist with an affinity 8 times greater than clonidine for the alpha-2 receptor.
- Their sedative effect is modulated by affecting the pontine locus coeruleus, which is the center for the sympathetic outflow to the forebrain.
- They affect the vasomotor centers of the rostral ventrolateral medulla, which leads to vasodilatation and bradycardia. This action can be associated with an increase in the activity in the parasympathetic neurons.
- Their application is increasing in clinical anesthesia practice. They are used for premedication, sedation, analgesia, and as adjuvants to general and regional anesthesia.
- They have a good safety profile with few side effects, which include hypotension, bradycardia, and sometimes airway obstruction associated with dexmedetomidine.

The 2 major drugs in this category of alpha-2 agonists that are commonly used in anesthesia practice are clonidine and dexmedetomidine, and these are discussed in this article.

CLONIDINE

Introduction

Clonidine, an alpha-2 agonist, is most widely known and used as an antihypertensive agent. Although most of the focus on clonidine is on its ability to reduce blood pressure, it also has sedative and analgesic effects that are of particular interest in anesthesiology.[1–3] Because of its sedative effects, clonidine has long been used as an adjuvant to other anesthetic agents. It also has been used as a premedication to

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sedate children before surgery as well as a sedative agent in the pediatric intensive care unit (ICU).[4] Its analgesic effects have also been appreciated as adjuvant to regional and general anesthesia in both the pediatric and adult populations. Because of the effects of clonidine on the cardiovascular system it can be beneficially used in operative cases in which controlled hypotension is desired.[2] Although there are benefits of clonidine usage in anesthesia, care and vigilance must be maintained during the operative process and throughout the perioperative period because adverse effects do occur. Abrupt withdrawal of clonidine can lead to extreme rebound hypertension resulting in hypertensive crisis perioperatively. Clonidine has been shown to decrease the minimum alveolar concentration (MAC) of sevoflurane, so adjustments must be made accordingly.[1,5]

Mechanism of Action

Clonidine produces its effects by stimulating alpha-2 adrenergic receptors in the brainstem. This stimulation in turn activates inhibitory neurons, resulting in decreased central nervous system sympathetic outflow. Decreased outflow manifests in decreased peripheral vascular resistance, decreased renal vascular resistance, and decreases in heart rate and blood pressure. Stimulation of different subtypes of the alpha-2-adrenoreceptor produces particular effects.[1,6]

There are 3 subtypes of adrenergic receptors: alpha-2a, alpha-2b, and alpha-2c.[1]

- Sedation, analgesia, and sympatholysis are produced by stimulating alpha-2a receptors.
- Stimulation of the alpha-2b receptor subtype results in vasoconstriction and trigger antishivering mechanisms.
- Activation of alpha-2c receptors produces the startle response, which in humans results in withdrawal from stimuli, contraction of the extremity muscles, blinking, and variation in blood pressure and breathing patterns.
- Clonidine acts on centrally located alpha-2 receptors, with varying stimulation on all alpha-2 subtypes creating different manifestations.

Pontine locus coeruleus is one of the centrally located areas of alpha-2 receptors that clonidine affects. This area is chiefly responsible for sympathetic nervous system innervations of the forebrain, which is responsible for vigilance. Sedative effects of clonidine result from stimulation of alpha-2 receptors in this area.[1]

Clonidine also activates receptors in the medullary motor center. Clonidine's action in this centrally located area results in a multitude of effects:

- Decreased sympathetic nervous system outflow from the medulla to peripheral nerves, which results in peripheral vasodilatation and a decrease in blood pressure, heart rate, and cardiac output.
- Modification of the potassium channels by clonidine in the neurons in the central nervous system, which causes hyperpolarization of their cell membranes. It has been postulated that this is the mechanism for the recognized decrease in anesthetic requirements attributed to clonidine.

In addition, there are alpha-2 adrenoreceptors located both peripherally and centrally in the neuraxium. Application of clonidine in these areas leads to the inhibition of the release of spinal substance P and nociceptive neuron transmission after stimulation by noxious stimuli. Clonidine's analgesic effects are caused by decreasing pain by stimulating the alpha-2 adrenoreceptors in this area; specifically, at the presynaptic and postsynaptic receptors in the spinal cord, thereby preventing pain signal transmission to the brain.[7–9]

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