# The use of dexmedetomidine as premedication In hypotensive anesthesia

Essay

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# Abstract

Dexmedetomidine is sedative agent acts via an unique alpha-2 agonist mechanism; it produces sedation with respiratory stability, sympatholysis and analgesia. It also potentiates anesthetic affect of all intraoperative anesthetics. With its use it may occur hypotension, and bradycardia, but both are readily manageable with fluid administration and atropine.



Key Words :

Average category scale - Cerebrospinal fluid - Heart rate .

# Introduction

Stress Response to Endotracheal intubation and/or surgical stimuli is associated with significant increase in arterial pressure, heart rate, and plasma catecholamine concentrations .[1]$\alpha_2$-Adrenoceptor agonists have been used in the perioperative period for their beneficial effects .[2]
They decrease sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anesthesia and surgery.[3]; reduce anesthetic and opioid requirements.[4]; and cause sedation and analgesia.[6] They allow psychomotoric function to be preserved while letting the patient rest comfortably. Thus, $\alpha_2$-adrenoceptor agonists may offer benefits in the prophylaxis and adjuvant treatment of perioperative myocardial ischemia.

$\alpha_2$-Adrenoceptor agonists include a huge list of drugs such as Methyldopa, Clonidine and Dexmedetomidine.

dexmedetomidine has the following advantages:

1) It attenuates the sympathoadrenal stimulation during tracheal intubation effectively but does not completely abolish the cardiovascular response .[2]
2) It possesses anxiolytic, sedative, analgesic, and sympatholytic properties; it might be a useful adjunct for premedication, especially for patients susceptible to preoperative and perioperative stress. [3]
3) It potentiates the anesthetic effects of all intraoperative anaesthetics, regardless of method of administration (intravenous, volatile, or even regional block).4 Intravenous or intramuscular administration of dexmedetomidine reduced induction requirements of thiopentone by 15 -30% .[5]
4) It has analgesic effect .6and at the same time it reduces the opioid requirements in the perioperative period .[6]
5) It has sympatholytic effect and analgesic effect which is beneficial in the whole perioperative period.[6]

- The aim of the study is to evaluate the role of dexmedetomidine in the perioperative period for patients planned to have hypotensive anaesthesia under G.A.

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# ***Abbreviations***

| | |
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| 8* | 8 times |
| ACS | Average category scale |
| ASA | American society of anesthiologists |
| BSA | Body surface area |
| CAD | Coronary artery disease |
| CDDP | Cardiodynamic data processing system |
| CFF | The critical flicker fusion test |
| CHA | Controlled hypotensive anesthesia |
| CI | Cardiac index |
| CNS | Central nervous system |
| CO2 | Carbon dioxide |
| CSF | Cerebrospinal fluid |
| CVA | Cerebrovascular accident |
| CVP | Central venous pressure |
| CYP2A6 | cytochrome p450 |
| CYP2D6 | Cytochrome P450 2D6 |
| DEX | Dexmedetomidine |
| EEG | Electroencephalography |
| FDA | Food and drug administration |
| GABA | Gamma-aminobutyric acid |
| HR | Heart rate |
| HTN | Hypertension |
| ICP | Intracranial pressure |
| ICU | Intensive care unite |
| LC | Locus ceruleus |
| MAP | Mean arterial pressure |
| MRI | Magnetic resonance imaging |
| N | Number |
| NA | Non available |
| NE | Nor epinephrine |
| NMDA | N-methyl -D- aspratate antagonist |
| NTG | Nitroglycerine |
| OAA/S | Observer's assessment of alertness /sedation |
| PGE1 | Prostaglandin E1 |
| PRN | Pro re nata **=** as needed |
| SI | Stroke index |
| SNP | Sodium nitroprusside |
| SNS | Sympathetic nervous system |
| SVR | Systemic vascular resistance |
| SVRI | Systemic vascular resistance index |
| t½α | The redistribution half life |
| t½β | The elimination half life |
| Tanalg | The first request of postoperative analgesia |
| TEE | Trans- esophageal Echocardiography |
| TIA | Transient ischaemic attacks |
| US | United states |
| USA | United states of America |
| VTE | Venous thromboembolism |

# Chapter One

# Pharmacology of α2 -Adrenergic agonists

## *In Vitro Studies*

α2 -Adrenergic agonists produce clinical effects after binding to α2 -adrenergic receptors, of which there are three subtypes (α2A, α2B, and α2C). These receptor sub-types are distributed ubiquitously, and each may be uniquely responsible for some, but not all, of the actions of α2 agonists; for example, the α2B -adrenoceptor sub-type mediates the short-term hypertensive response to α2 agonists,[1,2] whereas the α2A adrenoceptor is responsible for the anesthetic and sympatholytic responses. [3]

All the subtypes produce cellular action by signaling through a G-protein; a functional assay of G-protein activation has been implemented to screen for subtype specificity and effectiveness of the various α2 agonists. From these and other related studies, it is apparent that there are no subtype-selective agonists; therefore, the goal of producing a single discrete desirable α2 action *(e.g*., analgesia) without producing another unwanted effect *(e.g*., hypotension) is elusive. G-proteins couple to effector mechanisms, which appear to differ depending on the receptor subtype (and possibly the location of the receptor). For example, the α2A -adrenoceptor subtype seems to couple in an inhibitory fashion to the L-type calcium channel in the locus ceruleus, whereas, in the vasculature, the α2B-adrenoceptor subtype couples in an excitatory manner to the same effector mechanism.

Because all of the clinically available α2 agonists have an imidazole ring in their structure, these compounds interact with the imidazoline receptor. It is unlikely that these receptors transduce the

cardiovascular responses to α2 agonists because studies of genetically engineered mice have indicated that each of the cardiovascular properties of the α2 agonists seem to be mediated by α2 adrenoceptors (with the possible exception of enhanced vagal tone).

## *In Vivo Studies*

### Cardiovascular System.

α2 Agonists can produce either hypotension or hypertension. At lower doses, the dominant action of α2 agonists is sympatholysis, *i.e*., the ability to block the sympathetic arm of the autonomic nervous system, which is mediated by the α2A -adrenergic receptor subtype.[3] There are several well-documented mechanisms for this activity, including inhibition of firing of the locus ceruleus (the pivotal noradrenergic relay nucleus in the brain stem) and inhibition of norepinephrine release at the neuroeffector junction. Bosnjak *et al.*[4] have suggested that the central and peripheral sympatholytic effects of α2 adrenoceptor stimulation may be augmented further by inhibition of ganglionic transmission (fig. 1).

At higher doses of α2 agonists, the hypertensive action dominates *via* the activation of α2B adrenoceptors, located on smooth muscle cells in the resistance vessels. There is even some suggestion that this receptor subtype may be involved in the pathogenesis of essential hypertension.[5] Pretreatment with a peripherally restricted antagonist before intravenous administration of α2 agonists may become a useful pharmacologic strategy to facilitate the advantageous sedative– hypnotic and central sympatholytic

actions while avoiding The possible detrimental hemodynamic effects of vaso-constriction, which are mediated in the periphery. Thus far, no peripherally restricted antagonist is clinically available.

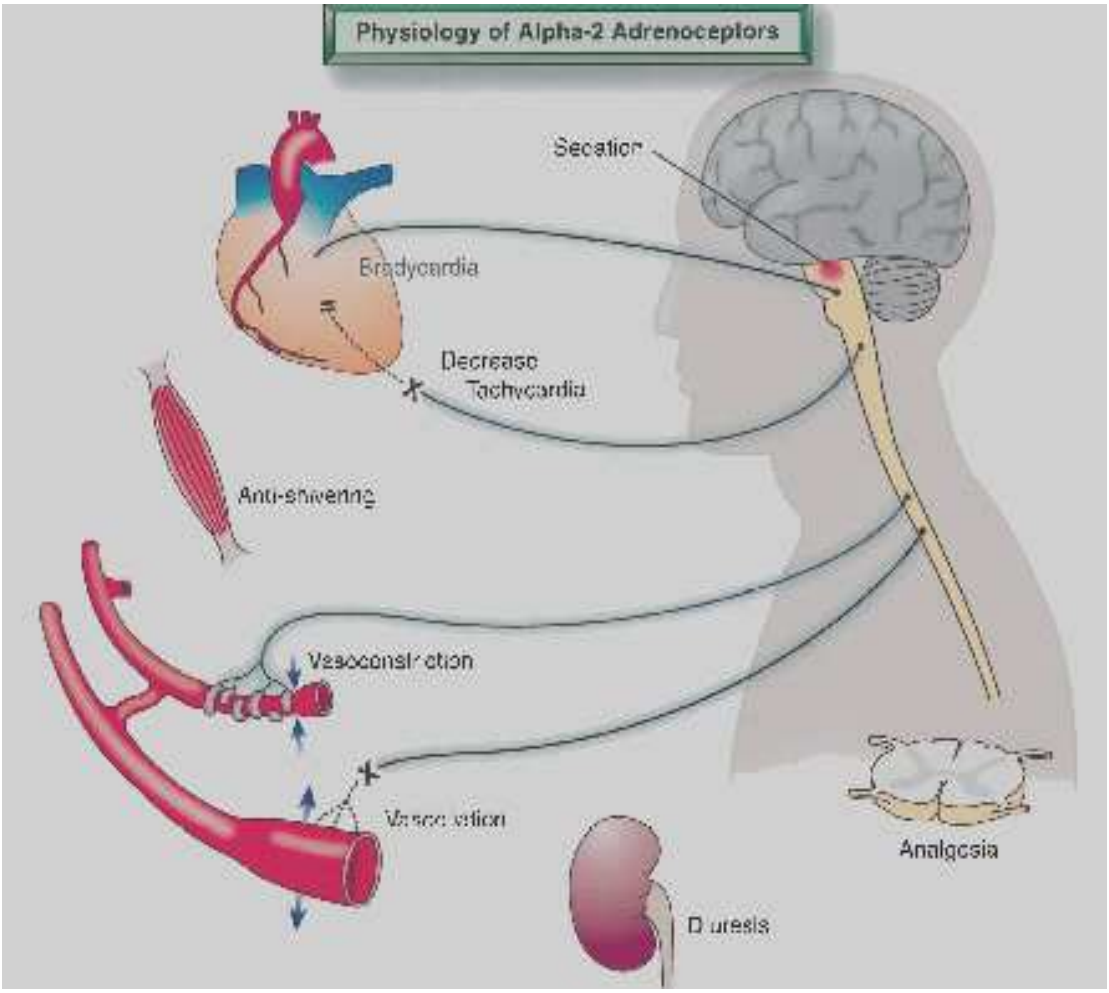


**Fig. 1. Responses that can be mediated by** a **2 -adrenergic receptors. The site for the sedative action is in the locus ceruleus of the brain stem, whereas the principal site for the analgesic action is probably in the spinal cord; however, there is clear evidence for both a peripheral and a supraspinal site of action. In the heart, the dominant action of** a **2 agonists is a decrease in tachycardia (through block of the cardio accelerator nerve) and bradycardia (through a vagomimetic action). In the peripheral vasculature, there are both a vasodilatory action *via* sympatholysis and vasoconstriction mediated through the receptors in the smooth muscle cells. The mechanism for the antishivering and diuretic actions have yet to be established firmly.**

## Central Nervous System.

In addition to the well-documented hypnotic– sedative, analgesic, and anxiolytic actions of α2 agonists, spatial working

memory also may be modulated *via* the α2A -adrenoceptor subtype.[6] If confirmed in humans, this would represent the first sedative–hypnotic class of agent that enhances, rather than diminishes, cognitive performance. Using experimental strategies that either "knocked out" or overexpressed the gene that encodes α 2C adrenoceptors, Scheinin *et al.*[7] have shed light on the mechanism for the anxiolytic action of α2 agonists. Mice with targeted inactivation of the gene that encodes α2C adrenoceptors had enhanced startle responses and shortened attack latency in the isolation–aggression test; conversely, if the mice were engineered to overexpress α2C adrenoceptors, the opposite behavioral effects were noted. Therefore, drugs acting *via* α2C adrenoceptors may have therapeutic value in disorders associated with enhanced startle responses and sensorimotor gating deficits, such as schizophrenia, attention deficit hyperactivity disorder, posttraumatic stress disorder, and drug-withdrawal states. α2 Agonists have been shown to limit the morphologic and functional effects after ischemic (focal and global) and traumatic injury to the nervous system. The efficacy of α2 agonists as neuroprotectant agents in humans has not been investigated.

Intractable pain after neuropathic injury is a particularly difficult problem to treat. The combination of subeffective doses of MK 801 (the N-methyl-D-aspartate[NMDA] antagonist) and clonidine resulted in significant antihyperalgesic action in an animal model of neuropathic pain; interestingly, the neurotoxic effects of NMDA antagonists also could be blocked by relatively small doses of clonidine.[8] In another paradigm of neuropathic pain, the antihyperalgesic action of dexmedetomidine was blocked by a peripherally restricted α2 -antagonist, indicating that an α2 agonist

that does not cross the blood brain barrier (and, therefore, does not produce sedation) may be useful in the management of neuropathic pain.

## Clinical Studies

In well-conducted randomized clinical trials, α2 agonists have been shown to be effective for their analgesic, sedative– hypnotic, and sympatholytic properties. As such, this class of agent has been shown to decrease intraoperative and postoperative stress response effectively. After emergence from general anesthesia with use of a potent volatile anesthetic agent, patients may show a hyperdynamic hemodynamic profile, which can be attenuated with α2 agonists. Thus, α2 agonists may prove to be of value in agitated hypertensive patients in the post anesthesia care unit. Despite their relatively long history of clinical use (clonidine was introduced in the1970s), no idiosyncratic adverse effects have been discovered, other than an extension of its pharmacologic profile *(i.e*., hypotension, bradycardia, xerostomia, and hypertension). This class of drug seems to have a remarkably wide safety margin. Without the need for cardiovascular or ventilatory support, all but 2 of a cohort of 10 volunteers could tolerate a plasma concentration of dexmedetomidine that was fourfold greater than the projected therapeutic concentration of dexmedetomidine; adverse effects, which are an extension of the pharmacologic actions of this class of drugs (increases in systemic and pulmonary vascular resistance; hypertension, bradycardia, and a decreased cardiac output), are evident at concentrations twofold greater than the therapeutic level.[9]

***Intraoperative Applications:***

Since the mid 1980s, many publications have reported the significant volatile anesthetic minimum alveolar concentration reduction produced by α2 agonists; in animal studies, no apparent ceiling effect was noted for halothane minimum alveolar concentration reduction when the highly selective α2 agonist dexmedetomidine was used. This has led to the suggestion that this drug may be a “complete” anesthetic agent. In a tolerability study performed by Ebert *et al*.,[9] profound sedation (“no arousal with very vigorous shaking”) was noted in two healthy volunteers who tolerated the highest dose of dexmedetomidine that achieved a plasma concentration of approximately 13 ng/ml (for comparison, the sedative concentration for intensive care unit patients is approximately 0.7 ng/ml).

***Analgesia:***

Epidural clonidine for cancer pain is the only approved analgesic application of this class of compound, and a warning against its use in nonapproved clinical settings because of side effects (hypotension and bradycardia) is provided in its package insert. However, α2 agonists have been administered *via* a variety of routes for long-term and short-term perioperative pain control. In keeping with the animal studies that indicate a potential peripheral target for α2 agonists in neuropathic pain, Reuben *et al.*[10] reported that a Bier block with clonidine (1 μg/kg) resolved sympathetically maintained pain. Because the plasma concentration of clonidine 30 min after deflation of the tourniquet (0.12 ng/ml) was significantly less than that necessary for a central sympatholytic effect (1.5–2.0 ng/ml), the authors concluded that clonidine exerted a peripheral analgesic