Procedural sedation and analgesia in day-case gastrointestinal endoscopies
A comparative study between dexmedetomidine, propofol and midazolam

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List of Abbreviations

ACTH Adrenocorticotropic hormone
ANOVA Analysis of variance
ASA American Society for Anesthesiologists
BIS Bispectral index
BVMV Bag-valve-mask ventilation
cAMP Cyclic adenosine monophosphate
CBF Cerebral blood flow
$CMRO_2$ Cerebral oxygen consumption
CNS Central nervous system
DSST Digit symbol substitution test
ECG Electrocardiography
ED Effective dose
EEG Electroencephalogram
ERCP Endoscopic Retrograde Cholangio-pancreatography
FDA Food and Drug Administration
GABA γ-aminobutyric acid
GI Gastrointestinal
HR Heart rate
ICP Intracranial pressure
ICU Intensive care unit
MAC Monitored anesthesia care
MAP Mean arterial blood pressure
NIBP Non-invasive blood pressure
NMDA *N*-methyl-D-aspartate
NMLA N-methyl-L-arginine
NO Nitric oxide
PACU Postanesthesia care unit
PCS Patient-controlled sedation
PSAA Procedural sedation and analgesia
RR Respiratory rate
RSS Ramsay's sedation score
SBP Systolic blood pressure
SpO_2 Peripheral arterial oxygen saturation

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Introduction

Over the past 30 years, gastrointestinal (GI) endoscopy has become one of the most commonly performed procedures in clinical practice. Gastroscopy and colonoscopy have become established as the definitive diagnostic procedures for the upper gastrointestinal tract and colon, respectively. GI endoscopy is usually performed on an outpatient or day-case basis. During most of these examinations, the case is sedated to ensure patient comfort and enable the procedure to be completed without interference from patient restlessness **(Clarke et al., 2002)**.

Although once largely diagnostic, GI endoscopy has evolved such that therapeutic procedures are often performed at the same time. This may prevent the need for major surgery. Safe and effective sedation has been a major factor in the development of therapeutic endoscopy **(Andrew, 2006)**.

Sedation for endoscopy reduces patient anxiety and pain. It increases the acceptability of procedures to patients, results in greater willingness to undergo repeat procedures, and improves endoscopists' satisfaction **(Zubarik et al., 2002)**.

As GI endoscopy is performed so frequently, it is vital that it is undertaken as safely as possible **(Quine et al., 1995)**. However, all drugs used to sedate endoscopy patients can result in airway obstruction, hypotension or respiratory depression. In particular, even small doses of benzodiazepines may occasionally induce prolonged apnea. Therefore, it is essential that endoscopy is performed only in a setting where complications can be promptly recognized and corrected; whatever drugs are used **(Bell and Charlton, 2000)**.

Procedural sedation and analgesia (PSAA) produces a suppressed level of consciousness that is adequate to allow the administration of painful or unpleasant diagnostic or therapeutic maneuvers in a way that minimizes patient awareness, discomfort, and memory, while attempting to preserve spontaneous respiration and airway-protective reflexes. PSAA should be viewed as a continuum ranging from light to deep sedation, with the depth of sedation easily titrated by selective administration of sedatives and analgesics **(Brown et al., 2005)**.

Aim of the Work

The aim of this study is to compare the use of dexmedetomidine (the new selective α_2-adrenoceptor agonist) with propofol, and with midazolam, which are the most two commonly used agents in procedural sedation and analgesia during day-case GI endoscopy, and to evaluate their sedative, haemodynamic and respiratory effects, in order to adapt a safe and reliable regimen for sedation in those procedures.

Pharmacology of Dexmedetomidine

The first α_2-adrenoceptor agonist (Clonidine) was synthesized in the early 1960s to be used as a nasal decongestant. It showed unexpected side effects, with sedation for 24 hours and symptoms of severe cardiovascular depression. Subsequent testing led to the introduction of clonidine as an antihypertensive drug in 1966. Over the years, clonidine gained acceptance as a powerful therapy not only for high blood pressure but also for the management of alcohol and drug withdrawal, for adjunctive medication in myocardial ischemia, and for pain and intrathecal anesthesia **(Tamsen and Gordh, 1984)**.

Veterinarians employed xylazine and detomidine for a long time to induce analgesia and sedation in animals, and much of our knowledge was gained from this application **(Khan et al., 1999)**.

Complete anesthesia is possible by employing new, more potent α_2 agonists, such as medetomidine and its stereoisomer, dexmedetomidine. Dexmedetomidine was approved by the Food and Drug Administration (FDA) at the end of 1999 for use in humans as a short-term

medication (<24 hours) for analgesia and sedation in the intensive care unit (ICU). Its unique properties render it suitable for sedation and analgesia during the whole perioperative period. Its applications as a premedication, as an anesthetic adjunct for general and regional anesthesia and as a postoperative sedative and analgesic are similar to those of the benzodiazepines **(Gertler et al., 2001)**.

Physiology of the α_2 receptors (Fig. 1)

Adrenergic receptors were originally differentiated into α and β receptors. Later, a subclass of α adrenoceptors (α_2 receptor) located at the presynaptic site and regulates the release of neurotransmitters, was discovered. $\alpha_2$receptors have also been found at postsynaptic and extrasynaptic sites. Presynaptic α_2 receptors may be of the greatest clinical import, because they regulate the release of norepinephrine and adenosine triphosphate through a negative feedback mechanism **(Drew and Whiting, 1979)**.

At least 3 different α_2 isoreceptors have been defined both by pharmacologic studies (affinity for different α_2 antagonists) and by biological probes. Receptors for α_2 are found in the peripheral and central nervous systems, platelets, and a variety of organs, including the liver,

pancreas, kidney, and eye. Physiologic responses mediated by α_2 adrenoreceptors vary with location **(Gertler et al., 2001)**.

The α_2-adrenergic receptor mediates its effects by activating guanine-nucleotide regulatory binding proteins (G proteins). Activated G proteins modulate cellular activity by signaling a second messenger system or by modulating ion channel activity **(Gertler et al., 2001)**.

The second messenger system, when activated, leads to the inhibition of adenylate cyclase, which, in turn, results in decreased formation of 3,5-cyclic adenosine monophosphate (cAMP). Specific cAMP-dependent kinases modify the activity of target proteins by controlling their phosphorylation status **(Cotecchia et al., 1990)**.

Modulation of ion channel activity leads to hyperpolarization of the cell membrane. Efflux of potassium through an activated channel hyperpolarizes the excitable membrane and provides an effective means of suppressing neuronal firing. Stimulation of the α_2 adrenoceptor also suppresses calcium entry into the nerve terminal, which may be responsible for its inhibitory effect on secretion of neurotransmitters. From an anesthesiologic

viewpoint, neuronal hyperpolarization is a key element in the mechanism of action of α_2-adrenoceptor agonists **(Birnbaumer et al., 1990)**.

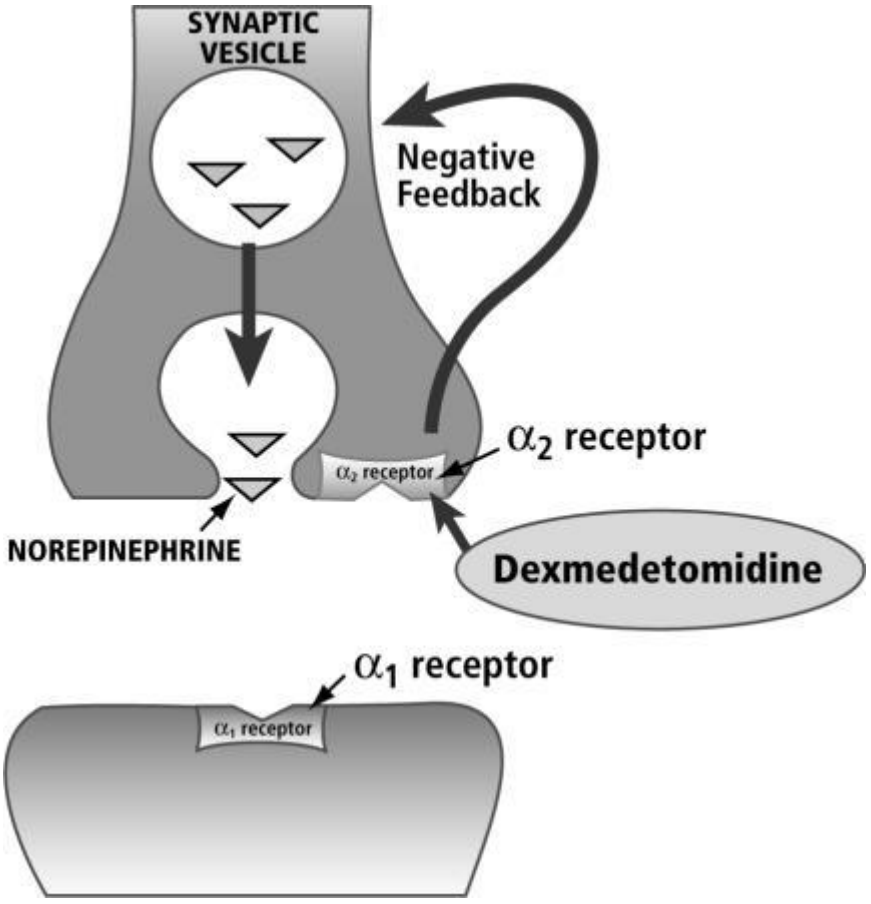

Figure (1): Physiology of the α_2-adrenoceptor agonists **(Gertler et al., 2001)**

Mechanism of action of Dexmedetomidine

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α_2-adrenoceptor agonism. The mechanism of action is unique and differs from those of currently used sedative agents, including clonidine. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the GI tract; contraction of vascular and other smooth muscles; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas **(Metz et al., 1978)**.

In general, presynaptic activation of the $\alpha_2$adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can

produce analgesia, sedation, and anxiolysis. Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multiagent therapies **(Gertler et al., 2001)**.

The mechanisms of the analgesic actions of α_2 agonists have not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the CNS. Even peripheral α_2 adrenoceptors may mediate antinociception **(Nakamura and Ferreira, 1988)**.

The activation of inwardly rectifying G_1-protein-gated potassium channels results in membrane hyperpolarization, decreasing the firing rate of excitable cells in the CNS. This is considered a significant mechanism of the inhibitory neuronal actions of α_2-adrenoceptor agonists. Another prominent physiologic action ascribed to α_2 adrenoceptors is their reduction of calcium conductance into cells, thus inhibiting neurotransmitter release. This effect involves direct regulation of calcium entry through N-type voltage-gated calcium channels and is independent of cAMP and protein phosphorylation. It is mediated by G_0 proteins. These 2 mechanisms represent 2 very different ways of effecting