ROLE OF DEXMEDETOMIDINE IN ICU

Essay

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Contents

List of tables

List of abbreviations

AWD	Alcohol withdrawal delirium
AWS	Alcohol withdrawal syndrome
ANIST	Acute Neurological ICU Sedation Trial
AVP	Arginine vasopressin
BZDs	Benzodiazepines
CIN	Contrast induced nephropathy
CABG	Coronary artery bypass graft
cAMP	Cyclic adenosine monophosphate
CHF	Congestive heart failure,
CYP	Cytochrome P450
EEG	Electroencephalographic
ESRD	End-stage renal disease
ESWL	Extracorporeal shock-wave lithotripsy
FDA	Food and drug administration
ICU	Intensive care unit
IV	Intravenous administration (IV)
GABA	G-aminobutyric acid
LCF	Liver cell failure
LD	Loading dose
MAC	Monitored anesthesia care
MENDS	Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction study
MD	Maintenance dose

NMDA	N-methyl-D-aspartate
PTSD	Post-traumatic stress disorder
RASS	Richmond Agitation-Sedation Scale
RD	Respiratory depression
SCCM	Society of Critical Care Medicine
SEDCOM	Safety and Efficacy of Dexmedetomidine Compared With Midazolam
t½α	Distribution half life
t½β	Elimination half-life
TMN	Tuberomamillary nucleus
VLPO	Ventrolateral preoptic nucleus
Vss	Steady-state volume of distribution
↓BP	Hypotension,
↓HR	Bradycardia,
↑TGs	Hypertriglyceridemia
α	Alpha
β	Beta

Introduction

Many patients treated in intensive care units (ICUs) require sedation and analgesia to tolerate the tracheal tube, mechanical ventilation, and other intensive care procedures. However, commonly used sedatives like propofol, benzodiazepines, and opioids also have potential adverse effects that may increase morbidity and prolong the patients' clinical course. Consequently, new drugs, with alternate mechanisms of action, have been developed for sedation of ICU patients **(Devlin *et al.*, 2010)**.

More than 50% of critically ill patients are given one or more sedative agents to minimize agitation and anxiety. The 2013 guidelines of the Society of Critical Care Medicine on pain, agitation, and delirium recommend that nonbenzodiazepine sedatives, such as propofol and dexmedetomidine, be used as first-line agents to provide effective sedation for ICU patients who are receiving mechanical ventilation **(Barr *et al.*, 2013)**.

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist with several diverse actions like sedation, anxiolysis, sympatholysis, analgesia, and decreased intraoperative anesthetic requirements (narcotic, inhalational), cardiovascular stability, smooth recovery when used as an adjunct to general anesthesia, preserves respiratory function and results in better cognitive function than

propofol, allowing better patient arousability and interaction and possibly earlier extubation **(Jakob *et al.*, 2012).**

Few studies have focused on the clinical effects of dexmedetomidine in chronic pain conditions. Most of the clinical applications of dexmedetomidine have supported that during perioperative procedure, dexmedetomidine has analgesic effects as an adjunct to anesthesia with different routes. Especially, systemic dexmedetomidine is suitable for controlling postoperative pain on patients with special conditions including lung transplantation, liver transplantation, pregnancy, cardiovascular disease and palliative care. More importantly, in contrast to opioids or propofol, dexmedetomidine can safely be infused through tracheal extubation, because it is especially advantageous to patients with obstructed airways. Furthermore, adding dexmedetomidine to local anesthetics during regional anesthesia and peripheral nerve blockade procedures is a promising new use (**Naguib *et al*., 2013)**.

There is increasing evidence of dexmedetomidine organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection and renoprotection **(Panzer *et al.*, 2011)**.

Aim of the essay

The aim of this essay is to discuss value of dexmedetomidine in different medical fields in ICU.

Pharmacology of Dexmedetomidine

Dexmedetomidine is a potent and highly selective α2-adrenoceptor agonist with a selectivity ratio of 1600:1 (α2:α1). Dexmedetomidine is a highly lipophilic agent that is rapidly distributed to tissues with a distribution half-life (t½α) of approximately 6 minutes. It is extensively distributed and rapidly eliminated, with a mean elimination half-life (t½β) of 2-2.5 hours. This rapid distribution and short elimination kinetics makes dexmedetomidine amenable to frequent titration allowing adjustability of dosage and effects. Generally, dexmedetomidine does not exhibit pharmacokinetic-based interactions; however, dosage modifications of some concomitant medications may be needed to be adjusted due primarily to common pharmacological actions of the two drugs. Dexmedetomidine is eliminated by metabolism to inactive metabolites, primarily glucuronides. Eighty to ninety percent of an administered dose is excreted in the urine and 5%-13% in the faeces **(Panzer *et al.*, 2011).**

Dexmedetomidine is the pharmacologically active dextroenantiomer of medetomidine, the methylated derivative of etomidine, is formulated as dexmedetomidine hydrochloride, a clear, colourless, isotonic solution with a pH of 4.5-7.0. The solution is preservative-free and contains no additives or chemical stabilizers.

Because of its α2-adrenoceptor agonist properties, dexmedetomidine has a broad range of pharmacological properties, including sedation associated with arousability and orientation without respiratory depression. Additional properties include analgesia, anxiolysis, haemodynamic stability, anti-shivering effects, reduced nausea and vomiting, and anesthetic-sparing effects **(Panzer *et al.*, 2011).**

Physiology of alpha-2 receptor

Alpha-2 adrenergic receptors (or adrenoceptors) are transmembrane receptors composed of excitable G-proteins, which cross the cell membrane and link selectively with extracellular ligands: endogenous mediators or exogenous molecules, such as drugs. The α-2 adrenergic receptor consists of three α-2 isoreceptors α-2a, α-2b and α-2c. Sub-receptor specific agonists or antagonists that enhance advantageous effects while limiting deleterious effects may be forthcoming **(Coursin and Maccioli 2001).**

Alpha-2 adrenoceptors have been implicated in a variety of physiological functions. The pharmacology of α-2 adrenoceptors is complex, but pharmacological studies, helped by the development of genetic mouse models, have elucidated the physiological effects

mediated by the different α-2 adrenoceptor subtypes **(Paris and Tonner 2005)**.

Specific α-2 receptor subtypes mediate the varied pharmacodynamic effects of dexmedetomidine. For example, agonism at the α-2a receptor appears to promote sedation, hypnosis, analgesia, sympatholysis, neuroprotection and inhibition of insulin secretion. Agonism at the α-2b receptor suppresses shivering centrally, promotes analgesia at spinal cord sites, and induces vasoconstriction in peripheral arteries. The α-2c receptor is associated with modulation of cognition sensory processing, mood and stimulant-induced locomotor activity, and regulation of epinephrine outflow from the adrenal medulla. Inhibition of norepinephrine release appears to be equally affected by all three α-2 receptor subtypes **(Panzer *et al.*, 2011)**.

These receptors appear to possess presynaptic, postsynaptic and extrasynaptic sites of action. In fact, α-2 adrenergic receptors have been found in platelets and in a variety of organs, including the liver, pancreas, kidney and eye and in the central and peripheral nervous system, at autonomic ganglia and presynaptic and postsynaptic sites. The presynaptic sites of action are clinically significant because they modulate the release of norepinephrine and adenosine triphosphate through a negative feed-back mechanism. The physiological responses regulated by α-2 receptors vary depending on their location. The

stimulation of α-2 receptors in the brain and spinal cord inhibit neuronal firing, which leads to hypotension, bradycardia, sedation and analgesia. The responses from other organs containing α-2 receptors include decreased salivation, secretion, and gastric motility; inhibited renin release; increased glomerular filtration rate; increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin secretion from the pancreas. The stimulation of α-2 receptors decreases calcium entry into nerve terminals, which may contribute to its inhibitory effect on neurotransmitter release **(Haselman 2008).**

Mechanism of action

The hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons in the locus ceruleus of the brain stem (a small bilateral nucleus that contains many adrenergic receptors), which is the primary site in modulating wakefulness. When the α-2 adrenergic receptor is activated, it inhibits adenylyl cyclase. This latter enzyme catalyzes the formation of cyclic AMP (cAMP), a crucial second messenger molecule that acts in many catabolic cell processes. By reducing the amount of cAMP in the cell, dexmedetomidine favors anabolic over catabolic pathways. Simultaneously, there is an efflux of potassium through calcium-activated potassium channels and an

inhibition of calcium entry into calcium channels in nerve terminals. The change in membrane ion conductance leads to a hyperpolarization of the membrane, which suppresses neuronal firing in the locus ceruleus as well as activity in the ascending noradrenergic pathway **(Kamibayashi and Maze 2000).**

The locus ceruleus is also the site of origin for the descending medullospinal adrenergic pathway, which is known to be a key mechanism in regulating nociceptive neurotransmission. The similar mechanisms of α-2 receptors and opioid receptors in this area of the brain have contributed to the thought that there must also be extra-spinal sites of action. When these sites are stimulated, they decrease the firing of nociceptor neurons stimulated by peripheral A and C fibers and also inhibit the release of their neurotransmitters. The analgesic effects are believed to be in the dorsal horn of the spinal cord. When a hypnotic dose of dexmedetomidine was administered to laboratory animals, norepinephrine release from the locus ceruleus was inhibited. The absence of inhibitory control over the ventrolateral preoptic nucleus (VLPO) resulted in the release of G-aminobutyric acid (GABA) and galanin, which further inhibited the locus ceruleus and tuberomamillary nucleus (TMN). This inhibitory response also causes a decrease in the release of histamine, which results in a hypnotic response. This response is similar to that found in normal sleep in that the reduction of

norepinephrine release by the locus ceruleus triggers the release of GABA and galanin by the VLPO. These neurotransmitters further inhibit norepinephrine release by the locus ceruleus and suppress histamine secretion by the TMN. The reduced occupancy of the histamine receptors on the cells of the subcortical areas induces a hypnotic state **(Nelson *et al*., 2001).**

Pharmacokinetics

Dexmedetomidine pharmacokinetics have been estimated following diverse intra-venous administration regimens, resulting in a variety of concentration versus time exposure profiles. Dexmedetomidine clearance is approximately constant within the expected therapeutic range, resulting in dose proportionality. However, in a maximum tolerated dose study, including concentrations 13 times the upper limit of the anticipated therapeutic range, a diminished clearance was noted of about 20% at dexmedetomidine concentrations well above the desired therapeutic range **(Dutta *et al*., 2000).**

Dexmedetomidine follows linear or zero-order kinetics, meaning that a constant amount of the drug is eliminated per hour rather than a constant fraction of the drug eliminated per hour, which is characteristic of first order kinetics. After intravenous administration (IV) in healthy