Introduction

Dexmedetomidine is a sedative agent that acts via a unique alpha-2 agonist mechanism. It produces sedation while frequently preserving the ability of the patient to interact with other individuals such as caregivers or family. Other properties of Dexmedetomidine including respiratory stability, sympatholysis, and analgesia make it an important new drug for patients requiring sedation in the critical care setting. Although only minimally explored at this time, additional areas of potential use may include amelioration of opioid, alcohol, and sedative withdrawal syndromes, use for sedation in settings outside the critical care unit, and use in pediatric intensive care ***(Chen et al., 2000).***

The primary known risks of Dexmedetomidine are extensions of its alpha-2 agonist mechanism: hypotension and bradycardia. Both are readily manageable with fluid administration and atropine. At higher plasma concentrations that may occur during loading of the drug, hypertension may be briefly seen. Sympatholytic effect of Dex may be particularly useful for hypertensive or tachycardic patients who require sedation. In hemodynamically marginal or unstable patients, however, the potential for significant hypotension should be considered. A careful consideration of volume status and

potential conduction abnormalities is necessary before starting the drug in any patient ***(Riker et al., 2001).***

Sedation in the ICU is often administered for days to weeks. Presently, the safety of Dex has only been documented for infusions up to 24 hours due to a lack of controlled studies extending beyond this time frame. As a result, the agent is approved only for <24 hour use. No adverse effects from long-term infusions, however, have been observed in small studies ***(Talke et al., 2000).***

Unanswered questions include the potential for tolerance and withdrawal, accumulation of parent drug and/or metabolites, and potential changes in the pharmacokinetic profile of long term infusions of Dex. Although Dex already represents a significant addition to the arsenal of ICU sedatives, further work is necessary to identify patient groups most likely to benefit ***(Talke et al., 2000).***

The benefits of a sedative that minimally affects the control of breathing are clear. The lack of respiratory depression with Dex use provides practitioners with a sedative and anxiolytic tool that can be used before, during, and after completion of the extubation process. In the ICU, such a tool may allow control of sympathetic stimulation associated with awake intubation, airway manipulation, and extubation, as well

as the anxiety associated with weaning. Dex may also allow control of agitation immediately after extubation, or with the use of mask ventilation where a calm, cooperative patient is essential to successful management. In recognition of this property, Dex is the only ICU sedative approved by the FDA for continuous infusion in patients following their extubation ***(Venn et al., 2000; Hsu et al., 2001).***

Aim of the Work

The aim of this work is to demonstrate the current role and new advances of Dexmedetomidine perioperatively and in ICU.

Chapter (1)
Pharmacology Of Dexmedetomidine

Dexmedetomidine

Since the advent of clonidine as an antihypertensive four decades ago, alpha-2 agonists have seen extensive use. Although anesthesiologists have attempted to use clonidine perioperatively to reduce anesthetic requirements, control shivering, and protect against nausea and vomiting, difficulties in drug dosing have prevented widespread acceptance. Dexmedetomidine differs from clonidine in two important respects: significantly greater (8x) affinity for the alpha-2 receptor, and increased titratability. The chemical platform for dexmedetomidine is the racemic drug medetomidine, which has been used as a sedative in veterinary anesthesia in Europe since 1987, and in the US since 1996.Dexmedetomidine is constituted from the dextro-rotatory isomer only of medetomidine, which appears to result in superior sedative and fewer cardiovascular side effects than the levorotatory isomer ***(Ostermann et al., 2000 and Kuusela et al., 2001).***

Because of its sympatholytic properties, dexmedetomidine was initially developed as a surgical premedicant and anesthetic adjunct, with the goal of attenuating the sympathetic response to perioperative stresses such as laryngoscopy and intubation.

However, an emerging need for effective sedative strategies in the ICU combined with the agent's remarkable ability to produce anxiolysis and analgesia with respiratory stability, ultimately shifted its developmental focus to critical care sedation ***(Scheinin et al., 1993).***

Dex received approval from the US Food and Drug Administration (FDA) in 1999 for the sedation of initially intubated patients in a critical carelike setting for no greater than 24 hours. In addition to the USA, Dex is approved in more than 27 countries worldwide, including Australia, Brazil, and Israel. It has seen an estimated 85,000 patient uses at the time of this publication ***(Ferguson et al., 1999).***

Available for intravenous use only, Dex is a colorless, water-soluble agent at physiologic pH. The redistribution half-life (t½α) of Dex is 6 minutes, and its elimination half-life (t½β) is approximately 2 hours **(Table 1-1)**. The pharmacokinetic profile is unchanged in elderly patients. Metabolism is primarily hepatic, with approximately 15% overall dependence on the cytochrome P450 system (CYP 2A6). Because of the dependence on the liver to clear the drug, subacute dosage reductions (following loading and stabilization with an efficacious dose) should be considered for patients with hepatic impairment. The metabolites of Dex have not been recognized to date as having any pharmacological activity or toxicity ***(Khan et al., 1999).***

Table (1): Dexmedetomidine: Basic Pharmacokinetic Profile

- Loading dose Up to 1 µg/kg over at least 10 min
- Maintenance dose 0.2-0.7 µg/kg/hr
- t_{V2} α 6 min
- $t_{l/2}$ β 2h
- Volume of distribution 118 liters
- Clearance 39 I/h
- Protein bound 94%
- Excreted unchanged 0% (Virtually all drug is in urine metabolized; 95% of metabolites excreted in urine.)

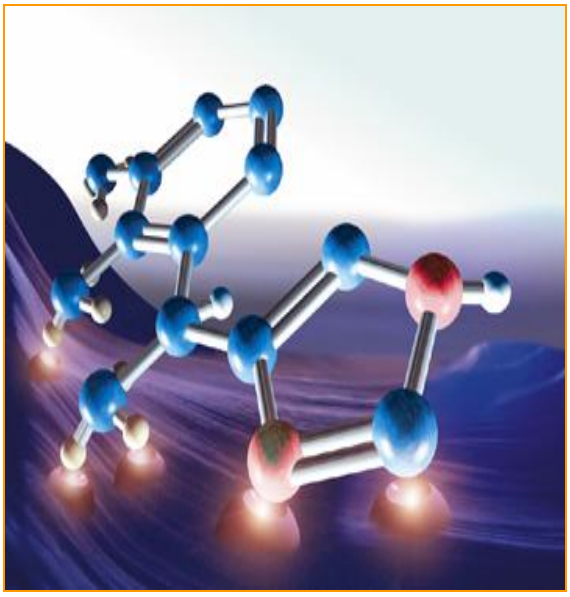

Figure (1): The structure of dexmedetomidine Dyck, Shafer. Anapest Pharm Review.1993;1

Mechanism of action: Physiology and clinical ramifications

Alpha-2 receptors are a subgroup of noradrenergic receptors (receptors utilizing norepinephrine as their agonist) that mediate the function of the sympathetic nervous system. Widely distributed both within and outside the central nervous system (CNS), these receptors modulate the function of a variety of organ systems, including cardiovascular, endocrine, and hematologic. Some alpha-2 effects may actually be antagonistic to each other; an example would be central sympatholysis occurring concurrently with peripheral vasoconstriction. Several subsets of alpha-2 receptors exist in the human, including:

- Alpha-2a
- Alpha-2b
- Alpha-2c

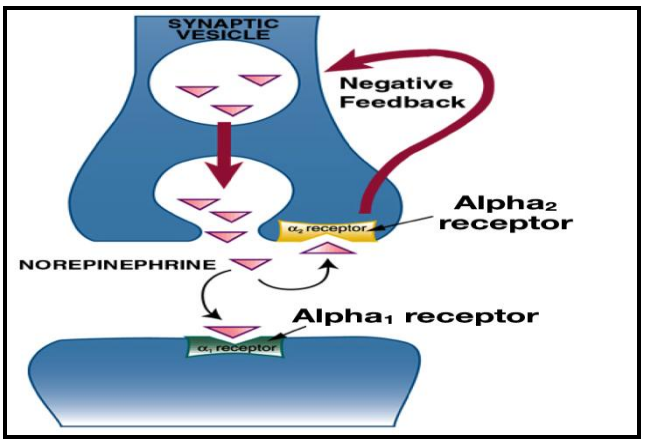

Figure (2): Receptor signaling ***(Khan et al., 1999)***

Dexmedetomidine is equally active at all three subtypes, but sedative effects of dexmedetomidine occur primarily by actions on alpha 2a receptors, which participate in control of arousal in the brain and analgesia in the spinal cord. Alpha-2b receptors appear post-ganglionically on blood vessels outside the CNS and produce vasoconstriction. Alpha-2c receptors are diffusely distributed through-out the brain, particularly in the basal ganglia, but their function is unclear ***(Kuusela et al., 2001).***

As with receptors for opioids, adenosine, histamine, and dopamine, all alpha-2 receptors are G-protein coupled receptors. Activation of the alpha-2 receptor produces a conformational change in the transmembrane G-protein, which in turn leads to a series of cellular responses that include inhibition of adenylyl cyclase activity and reduction in intracellular concentrations of cAMP ***(MacDonald et al., 1997).***

The apparent purpose of the alpha-2 system is to attenuate inappropriate increases in sympathetic nervous system (SNS) activity. Centrally-induced upsurges in sympathetic tone, such as those produced in the "fight or flight" response, are accomplished through initiation of a neural signal in the hypothalamus, transmission of that signal through the brainstem and the spinal cord to the sympathetic chain, and finally activation of effector organs such as the adrenal medulla. Within the brain stem, norepinephrine (NE) appears to

act as the primary neurotransmitter communicating SNS activation; release of NE into the synaptic cleft and its subsequent binding to post-synaptic alpha-1 receptors leads to propagation of the SNS-activating signal to the periphery ***(MacDonald et al., 1997).***

Binding of alpha-2 agonists to their receptors impedes transmission of these SNS-triggering signals. Alpha-2 receptors in the brain are concentrated primarily in the pons and medulla, areas involved in communicating SNS activation from higher brain centers to the periphery. Activation of alpha-2 receptors reduces conduction down noradrenergic neurons via presynaptic and postsynaptic mechanisms. Presynaptically, alpha-2 receptor activation reduces NE release, and activation of postsynaptic alpha-2 receptors hyperpolarizes neural membranes. Activation of these receptors by NE thus acts as an inhibitory feedback loop, reducing further release of NE. The alpha-2 system thus allows the body to increase sympathetic activity dramatically to manage major threats while at the same time preventing excessive responses that may be physiologically detrimental ***(Ferguson et al., 1999).***

Because Dex is an imidazole derivative, it interacts with imidazoline receptors as well as alpha-2 receptors. Although not as well understood as the alpha-2 system, imidazoline receptors mediate many critical functions

including regulation of blood pressure and insulin secretion.The imidazoline system probably has little impact on Dex's ability to sedate or augment general anesthesia, but effects of Dex on imidazoline receptors may play a role in its sympatholytic effect ***(Ferguson et al., 1999).***

Clonidine

Clonidine, the first to be developed, is a direct-acting alpha-adrenergic agonist with a strong preference for the alpha-2 receptor with a ratio of 200:1 (α_2/α_1).

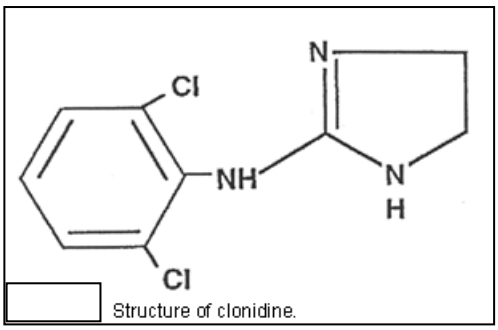

Figure (3): Structure of clonidine

Clonidine hydrochloride is an imidazoline derivative. It was synthesized in Boehringer Laboratories by Dr. Stahle, a German Chemist in 1962. It began its career as a nasal decongestant but failed because it lowered blood pressure, reduced heart rate, and produced sedation. Its hypotensive property was discovered by Dr. Martin Wolf, who used it on himself as a nasal drops for cold.

Mode of Action

It acts centrally to produce inhibition of sympathetic vasomotor centers by inhibiting release of norepinephrine in the medulla. Sympathetic tone is reduced, thus decreasing systemic blood pressure ***(Inomata et al., 2002).***

Pharmacological effects of Dexmedetomidine

1- SEDATION AND ANALGESIA

Dex has been demonstrated to be an effective sedative in critical care settings. Early studies comparing premedication between Dex and midazolam noted no difference in the quality of anxiolysis.**(Ramsay et al., 2000)**

There is a dose-response relationship that correlates increasing Dex plasma levels with the greater degrees of sedation. Dex has been documented as being used clinically in doses up to 2.5 µg/kg/hr; since the package insert indicates an upper limit of infusion of 0.7 µg/kg/hr, the aforementioned data suggest that Dex can be readily titrated in its clinically relevant range (**Ebert et al., 2000)**

Although the mechanism by which dexmedetomidine attenuates arousal to produce sedation is not precisely known, one recognized site of action is the locus coeruleus (LC), a dorsolateral pontine nucleus of approximately 30,000 neurons. this LC is the origin of practically all noradrenergic

neurons within the CNS. As a result, the LC plays a critical role in communicating sympathetic nervous system activity from the CNS to the periphery. Additional roles for this tiny nucleus include modulation of anxiety and attentiveness levels, control of arousal and sleep, and mediation of sedative drug withdrawal and rebound syndromes (**Rabin et al., 1992)**

Through its action on pre and post-synaptic alpha-2 receptors, Dex reduces transmission across the synapse. Since noradrenergic output from the LC plays a vital role in arousal, reduced NE output resulting from Dex infusion results in anxiolysis and sedation. This ability of Dex to modulate LC activity is more than a neuroanatomic curiosity: it may explain how it can produce sedation without obscuring cognitive function ***(Gold et al., 1993).***

In clinical use, patients sedated with Dex usually become alert, and are frequently capable of cooperating with diagnostic or therapeutic procedures while sedated **(Maze et al., 2001)**

Dex lacks two key characteristics of traditional ICU sedatives. First, although Dex has significant anesthetic-sparing properties and can reduce the need for potent inhaled agents by 17-90%, it can not act alone as a general anesthetic. Second, Dex is not a powerful amnestic. Healthy subjects receiving Dex experienced only a modest, dose-

dependent impairment of short-term memory Moreover, patients receiving Dex may be amnestic when left undisturbed, but not when stimulated ***(Mattila et al., 1991)*** & ***(Venn et al., 2001).***

In addition to sedative effects, Dex has significant analgesic qualities and has been labeled as "analgesia-sparing" by the FDA. Analgesia with Dex is mediated primarily through interaction at alpha-2a within the spinal cord, where drug activity attenuates nociceptive signal transduction. The actual mechanism of action appears to involve an interaction with opioid receptors, and although Dex alone has been documented to reduce pain, the effect when given jointly with opioids may be additive or synergistic ***(Fairbanks et al., 2000).***

Evidence is also present for an analgesic site of action for Dex in the LC, which in some animals is heavily invested with *mu* opioid receptors. Dex may also mimic midazolam's ability to prevent ketamine-induced delirium ***(Kalso et al., 1999).***

Regarding the effectiveness of Dex with different origins or types of pain. However, evidence in rats indicates that the analgesic potency of Dex increases following experimentally-induced nerve injury, suggesting potential efficacy in controlling neuropathic pain ***(Venn et al., 1999).***

Clinically, Dex's analgesic properties may result in several potential benefits for patients. Use of Dex may permit a reduction in the total amount of narcotic a patient requires, with a commensurate reduction in opioid-associated side effects such as constipation or nausea. Because Dex has virtualIy no depressant effects on ventilation at clinically relevant doses (discussed below), the analgesic effects of Dex may offer a significant advantage for patients at risk for respiratory decompensation. Furthermore, Dex is not a controlled substance and has not been reported to have abuse potential. These characteristics may make Dex an important component of the clinical approach to patients at increased risk for opioid dependence. Dexmedetomidine has not been described to cause the hypersympathetic withdrawal syndrome characteristic of clonidine, although published data on prolonged use (>24 hours) is minimal. Dex's intense specificity for alpha-2 receptors, including those in the spinal cord, suggest that Dex may produce superior analgesia to clonidine when used neuraxially ***(Puke et al., 1993; Riker et al., 2001).***