Role of Alpha-2 Adrenergic Agonist in Anesthesiology.

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Summary: SINCE the early 1970s, alpha-2 – adrenergic receptor agonists have been used successfully to treat patients with hypertension. Alpha-2 agonists produce diverse responses, i.e. Analgesia, anxiolysis, sedation and sympatholysis. This has been reported in the treatment of surgical and chronic pain patients. The Food and Drug Administration registered two alpha-2 – adrenergic agonists i.e. Clonidine and Dexmedetomidine. A role has been found for epidural clonidine in the management of pain. Dexmedetomidine is used as a sedative and analgesic in the intensive care setting. In addition to this, alpha-2 agonists also have been studied in several other perioperative settings.

Keyword: Alpha-2 adrenergic receptor agonist, clonidine, Dexemedetomidine.

Pharmacology: Alpha-2 –Adrenergic agonists produces clinical effect after binding to alpha-2 - adrenergic receptors, of which there are three subtypes (alpha-2 A, alpha-2 B, and alpha-2 C). These receptor subtypes are distributed ubiquitously and each may be uniquely responsible for the same, but not all. Of the actions of alpha-2 agonists; for example the alpha-2 B – adrenoeceptor subtype mediates the short-term hypertensive response to alpha-2 agonists, whereas the alpha-2A adrenoeceptor is responsible for the analgesic and sympatholytic responses.

Alpha-2 agonists can produce either hypotension or hypertension. At lower doses, the dominant action of alpha-2 agonists is sympatholysis, i.e. the ability to block the sympathetic arm of the autonomic nervous system, which is mediated by the alpha-2 A- adrenergic receptor subtype. There are several well-documented mechanisms for the this activity, including inhibition of firing of the locus ceruleus (the pivotal noradrenergic relay nucleus in the brain stem) and inhibition of nor epinephrine release at the neuroeffector junction. Bosnjak et al. have suggested that this receptor subtype may be involved in the pathogenesis of essential hypertension. Pretreatment with a peripherally restricted antagonist before intravenous administration of alpha-2 agonists is a useful drug to facilitate the advantageous sedative-hypnotic and central sympatholytic actions.

The effect on CNS is hypnosis- sedation, analgesia, and anxiolysis. Spatial working memory also may be modulated via the alpha-2A- adrenoceptor subtype. In humans, this would represent the first sedative – hypnotic class of agent that enhances, rather than diminishes cognitive performance. Scheinin et al. have shown the mechanism for the anxiolytic action of alpha-2 agonists. Alpha-2 agonists have been shown to limit the morphologic and functional
effects after ischemic (focal and global) and traumatic injury to the nervous system.

**Clinical studies:** In well -conducted randomized clinical trials, alpha-2-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 hyper dynamic hemodynamic profile, which can be attenuated with alpha-2 agonists. Thus, alpha-2 agonists may prove to be of value in agitated hypertensive patients in the post anesthesia care unit.

**Perioperative usage:** Alpha-2 adrenergic agonist has various actions as adjunct to General Anesthesia as well as regional Analgesia.

1. Analgesia
2. Sedation
3. Hemodynamic stability
4. Post operative shivering
5. Prevention of perioperative cardiac ischemia

**Analgesia:** Epidural clonidine is approved analgesic. However, alpha-2 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 alpha-2 agonist in neuropathic pain, Reuben et al. reported that a Bier block with clonidine (1mg/kg) resolved sympathetically mediated 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 action in patient with sympathetically mediated pain. Interestingly, in a volunteer study of inflammatory pain, a central, rather than a peripheral alpha-2 receptor target has been proposed.

It has been shown that alpha-2 agonists, either alone or in combination with local anesthetics or opiate narcotics, are highly effective in the treatment of short-term pain. Intraoperative (including during cesarean section) analgesic requirements were reduced significantly when clonidine was included in a neuraxially administered combination. Alpha-2 agonists have been used successfully for postoperative pain management in surgical populations as diverse as obstetric and pediatric patients and they have been administered via many different routes, including intercostal block. It is possible that the parturient is uniquely sensitive to the analgesic properties of alpha-2 agonists because clonidine alone has been shown to be effective for pain control after cesarean section. Using alpha-2 agonists in lieu of opioids avoids the problems of respiratory depression, pruritus, urinary retention and abuse liability. Patients sedated with alpha-2 agonists can be aroused easily and demonstrate attentiveness.
Sedation: Alpha-2 agonists have been used to provide preoperative sedation and anxiolysis and to decrease intraoperative anesthetic requirements. Recently, its use for sedation has been explored in a multicenter randomized clinical trial that included several hundred postoperative patients who required mechanical ventilation. Maintenance of attentiveness has been documented by use of the Critical Flicker Fusion test, in which no difference is observed in the frequency at which a flickering light source is first seen as a fused line between Dexmedetomidine-sedated and saline-treated volunteers. Therefore, one may anticipate that patients sedated with alpha-2 agonists may be more cooperative and communicative. The effectiveness of clonidine as a supplemental analgesic in thermal injured patients bodes well for future sedative studies that include wound-dressing changes. However, the usefulness of alpha-2 agonists in diagnostic or therapeutic settings in which a state of “conscious sedation” is desirable has yet to be studied rigorously. The only approved sedative indication is Dexmedetomidine for the intensive care treatment of postoperative surgical patients for up to 24 h. Because of its sympatholytic and vagomimetic actions, Dexmedetomidine is approved with a warning about hypotension, bradycardia and sinus arrest and can be used only in a monitored situation.

Shivering: In patients undergoing elective ear, nose or pharyngeal surgery with general anesthesia (induction with propofol, vecuronium and fentanyl and maintenance with isoflurane in 70% nitrous oxide), the incidence of postoperative shivering (40%) could be eliminated by administering 1.5 mg/kg clonidine before emergence. Similarly, intravenous clonidine (1 mg/kg) reduced the incidence of shivering in patients undergoing knee arthroscopy with epidural anesthesia.

Perioperative Myocardial Ischemia: The main approaches for reducing perioperative myocardial ischemia and thus improving long-term survival include preoperative assessment, modification of anesthetic techniques, and prophylactic therapy. In a placebo-controlled dose-ranging study of 300 patients who experienced perioperative sympatholysis with mivazerol, intraoperative myocardial ischemia and postoperative tachycardia were significantly reduced. Previously, clonidine was shown to ameliorate angina in patients with coronary artery disease.

Comparison of clinically available alpha-2 agonists: Dexmedetomidine has an alpha-2 : alpha-1 – adrenoceptor ratio of 1,600:1, more than 7 times greater than that of clonidine. Its elimination half-life is approximately 2 h, whereas that of clonidine is more than 8 h. The distribution half-life of Dexmedetomidine is approximately 5 min, whereas that of clonidine is more than 10 min.
Conclusions: Because of their registration for analgesic and sedative indications, alpha-2-adrenergic agonists have become part of the anesthesiologists’ therapeutic armamentarium. The use of alpha-2 agonists as adjuncts in pain management is attractive because of the multiplicatively that occurs through their action at the central (spinal and supraspinal) and peripheral sites.


