Mervyn MAZE  
Imperial College London, Faculty of Medicine  
Chelsea and Westminster Hospital, Magill Department of Anaesthetics  
London, United Kingdom  

Saturday May 31, 2003  
Euroanaesthesia 2003 - Glasgow  

Disclaimer: Dr Maze consults for Abbott Laboratories which markets the alpha-2 agonist dexmedetomidine

INTRODUCTION

Since the early 1970s, alpha-2 adrenergic receptor agonists have been successfully used for the treatment of patients with hypertension and in those withdrawing from chronic abuse of drugs and/or alcohol. The alpha-2 agonists produce diverse responses including analgesia, anxiolysis, sedation and sympatholysis each of which has been reported in the management of surgical and chronic pain patients. The Food and Drug Administration has registered two novel alpha2 adrenergic agonists for anaesthetic-related purposes. Epidural clonidine (Duraclon™) has found a role in the management of pain in a variety of clinical settings; since this has been extensively covered in a recent review [1], studies up to that time will not be exhaustively discussed here. Dexmedetomidine (Precedex™) has been registered for use as a sedative/analgesic in the Intensive Care setting. Apart from these approved settings, alpha-2 agonists have also been studied in several other peri-operative settings which will be discussed. Allusion to these “off-label” uses does not necessarily indicate that these applications are advocated by the author.

PHARMACOLOGY

IN VITRO STUDIES

The alpha-2 adrenergic agonists produce their clinical effects after binding to alpha-2 adrenergic receptors of which there are three subtypes (alpha 2A, alpha 2B and alpha 2C). These receptor subtypes are ubiquitously distributed and each may be uniquely responsible for some but not all of the actions of alpha 2 agonists; for example the alpha2B adrenoceptor subtype mediates the acute hypertensive response to alpha-2 agonists [2] while the alpha 2A adrenoceptor is responsible for the anesthetic and sympatholytic responses [3].

All the subtypes produce their cellular action by signaling through a G protein; a functional assay of G protein activation has been implemented to screen for both subtype specificity as well as efficacy of the various alpha2 agonists. From these and other related studies it has become apparent that there are no subtype selective agonists; therefore, the goal of producing a single discrete desirable alpha 2 action (e.g. analgesia) without producing another unwanted effect (e.g. hypotension) remains elusive. G proteins couple to an effector mechanism which appear to differ depending on the receptor subtype (and possibly the location of the receptor too). For example the alpha 2A adrenoceptor subtypes appears to couple in an inhibitory fashion to the L-type calcium channel in the locus coeruleus whereas in the vasculature, the alpha 2B adrenoceptor subtype couples in an excitatory manner to the same effector mechanism.

Since each of the clinically available alpha-2 agonists have an imidazole ring in their structure, these compounds do interact with the imidazoline receptor. It is unlikely these receptors transduce the cardiovascular responses to alpha-2 agonists since studies on genetically-engineered mice have indicated that each of the cardiovascular properties of the alpha-2 agonists appear to be mediated by alpha-2 adrenoceptors (with the possible exception of enhanced vagal tone).

IN VIVO STUDIES (SEE FIGURE 1)

Cardiovascular System

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 alpha 2A adrenergic receptor subtype[3]. There are several well-documented sites for this activity including inhibition of firing of the locus coeruleus (the pivotal noradrenergic relay nucleus in the brainstem) and inhibition of norepinephrine release at the neuro-effector junction. Bosnjak’s group have now suggested that the central and peripheral sympatholytic effects of alpha2-adrenoceptor stimulation may be further augmented by inhibition of ganglionic transmission [4].
The site for the sedative action is in the locus ceruleus of the brainstem while the principal site for the analgesic action is probably in the spinal cord although there is clear evidence for both a peripheral and supraspinal site of action too. In the heart, the dominant action of alpha-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 is both a vasodilatory action via sympatholysis and vasoconstriction mediated through the receptors in the smooth muscle cells. The mechanism for both the anti-shivering and diuretic actions have yet to be firmly established.

At higher doses of alpha 2 agonists the hypertensive action dominates via the activation of alpha-2B 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\cite{5}. Pretreatment with a peripherally-restricted antagonist, before intravenous administration of alpha 2 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 vasoconstriction which are mediated in the periphery. Thus far, no peripherally-restricted antagonist is clinically available.

**CNS**

Apart from the well-documented hypnotic-sedative, analgesic, and anxiolytic actions of alpha-2 agonists, spatial working-memory may also be modulated via the alpha2A adrenoceptor subtype\cite{6}. If confirmed in humans, this represents the first sedative/hypnotic class of agent that *enhances*, rather than *diminishes* cognitive performance. Using experimental strategies which either “knocked out” or overexpressed the gene encoding alpha2C-adrenoceptors, Scheinin’s group have shed light on the mechanism for the anxiolytic action of alpha-2 agonists. Mice with targeted inactivation of the gene encoding alpha2C-adrenoceptors had enhanced startle responses, and shortened attack latency in the isolation-aggression test; conversely if the mice were engineered to overexpress alpha2C-adrenoceptors the opposite behavioral effects were noted\cite{7}. Thus, drugs acting via alpha2C-adrenoceptors may have therapeutic value in disorders associated with enhanced startle responses and sensorimotor gating deficits such as schizophrenia, attention deficit hyperactivity disorder, post-traumatic stress disorder, and drug withdrawal states.

Alpha 2 agonists have been shown to limit the morphologic as well as the functional effects following ischemic (both focal and global) and traumatic injury to the nervous system. The efficacy of alpha 2 agonists as neuroprotectant agents in humans has not yet been investigated.
A particularly difficult problem to treat is the intractable pain which follows neuropathic injury. The combination of sub-effective doses of MK 801 (the NMDA antagonist) and clonidine resulted in a significant antihyperalgesic action in an animal model of neuropathic pain; interestingly, the neurotoxic effects of NMDA antagonists could also be blocked by relatively small doses of clonidine[8]. In another paradigm of neuropathic pain, the antihyperalgesic action of dexmedetomidine could be blocked by a peripherally-restricted alpha-2 antagonist suggesting that an alpha 2 agonist which did not cross the blood-brain barrier (and therefore would not produce sedation) may be useful in the management of neuropathic pain.

CLINICAL STUDIES

In well-conducted randomized clinical trials, alpha-2 agonists have been shown to be efficacious for its analgesics, sedative-hypnotic, and sympatholytic properties. As such this class of agent has been shown to effectively decrease the intra- and post-operative stress response. Following emergence from general anesthesia with a potent volatile anesthetic agent, patients may exhibit a hyperdynamic hemodynamic profile which can be attenuated with alpha-2 agonists. Thus, alpha 2 agonists may prove to be of value in the agitated, hypertensive patient in the post-anesthesia care unit—Despite their relatively long history of clinical use (clonidine was introduced in the 1970’s), no idiosyncratic adverse effects have been discovered other that an extension of its pharmacologic profile (i.e., hypotension, bradycardia, xerostomia and hypertension). In fact this class of drug appears to have a remarkably wide safety margin. All but one of a cohort of 10 volunteers could tolerate plasma concentration of dexmedetomidine which are 4-fold greater than the projected therapeutic concentration of dexmedetomidine without the need for cardiovascular or ventilatory support; adverse effects, which are an extension of its pharmacologic actions (increases in systemic and pulmonary vascular resistance; hypertension, bradycardia, and a decreased cardiac output), are evident at concentrations two-fold the therapeutic level [9].

INTRA-OPERATIVE APPLICATIONS

From the mid 1980’s many publications have reported on the significant volatile anesthetic MAC reduction produced by alpha-2 agonists; in fact in animal studies, no apparent “ceiling effect” was noted for halothane MAC reduction when the highly-selective alpha 2 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’s group, profound sedation (“no arousal with very vigorous shaking”) was noted in two healthy volunteers who tolerated the highest dose of dexmedetomidine which achieved a plasma concentration of ~ 13 ng/ml (for comparison, the sedative concentration for ICU patients is ~ 0.7 ng/ml) [9].

ANALGESIA

Epidural clonidine for cancer pain is the only approved analgesic application of this class of compound and a warning against its use in non-approved clinical settings because of side-effects (hypotension and bradycardia) is provided in its package insert. However, alpha 2 agonists have been administered by a variety of routes for both chronic as well as acute peri-operative pain control. In keeping with the animal studies indicating a potential peripheral target for alpha 2 agonists in neuropathic pain, Reuben et al reported that a Bier block with clonidine (1 mcg/kg) resolved sympathetically maintained pain [10]. Because the plasma concentrations of clonidine 30 min after deflation of the tourniquet (0.12 ng/ml) were significantly lower than that required for a central sympatholytic effect (1.5-2.0 ng/ml), the authors concluded that clonidine exerted a peripheral analgesic action in patients with sympathetically maintained pain. Interestingly, in a volunteer study of inflammatory pain, a central, rather than a peripheral, alpha 2 receptor target has been proposed [11].

A plethora of studies have shown that alpha-2 agonists, either alone or in combination with local anesthetics and/or opiate narcotics, are highly efficacious in the treatment of acute pain. Intra-operative (including during cesarean section) analgesic requirements are significantly reduced when clonidine was included in a neuraxially-administered combination. In parturients, extremely small doses of intrathecal clonidine (~30 mcg) provided analgesia comparable to that of 2.5 mcg of intrathecal sufentanil, for approximately 60 minutes [12]. Alpha-2 agonists have been successfully used for postoperative pain management in surgical populations as diverse as obstetric and pediatric, and by many different routes including intercostal block [13]. It is possible that the parturient is uniquely sensitive to the analgesic properties of alpha-2 agonists given the fact that clonidine alone has been shown to be quite effective for pain control after cesarean section. Using alpha-2 agonists in lieu of opiate narcotics will avoid the side-effects of respiratory depression, pruritus, urinary retention and abuse liability. However, of potential concern is the overlapping dose-response profiles for alpha-2 induced sedation and analgesia when the compound is administered neuraxially; since subjects sedated with alpha-2 agonists can be easily aroused and demonstrate attentiveness [14], this property
may not be deleterious and may in fact facilitate care in settings where the ratio of patients to nursing staff is high. If and when subtype-selective alpha-2 agonists become available, it may be possible that the sedative action can be mitigated while still ameliorating some types of pain states which could be modulated by a different receptor subtype than that which transduces the sedative response [15].

Pain management following thermal injury may be quite troublesome given the rapidly escalating opioid dose requirements and the high addiction potential. The attendant tachycardia and hypertension may pose problems in their own right in susceptible patients. Recently, clonidine was shown to decrease fentanyl requirements by more than 50% and also attenuated the hyperdynamic hemodynamic state [16].

SEDATION

For more than a decade alpha-2 agonists have been employed to provide preoperative sedation and axiolyis and to decrease intra-operative anesthetic requirements. Recently, its use for sedation [17] has been explored in a multi-center randomized clinical trial involving several hundred postoperative patients requiring mechanical ventilation. Patients receiving dexmedetomidine required significantly less propofol than placebo-treated patients for the same level of clinical sedation; qualitatively, a unique type of sedation was produced in which patients could be readily aroused and then returned to their sleep-like state when left alone [14]. Maintenance of attentiveness has been documented by 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. Thus, one may anticipate that patients sedated with alpha-2 agonists may be more co-operative and communicative than patients sedated with current strategies in the intensive care setting. The efficacy clonidine as a supplemental analgesic in thermal-injured patients bodes well for future sedative studies involving wound-dressing changes [16]. However, the utility of alpha-2 agonists in diagnostic and/or therapeutic settings in which a state of “conscious-sedation” is desirable, has yet to be rigorously studied and their only approved sedative indication is dexmedetomidine for the intensive care management of postoperative surgical patients for up to 24 hours. Because of its sympatholytic and vagomimetic actions, dexmedetomidine is approved with a warning about hypotension, bradycardia and sinus arrest and can only be used in a monitored setting (which invariably occurs in the intensive care setting).

Given that the target for the sedative action of alpha-2 agonists is precisely known, it raised the possibility that strategies to terminate this action could be readily employed. In a landmark manuscript, Scheinin et al have reported on the ability of atipamezole, a novel (unregistered) selective alpha-2 adrenoceptor antagonist, to reverse the sedative properties of dexmedetomidine in volunteers [18]. Both the sedative and sympatholytic effects of intramuscular dexmedetomidine were dose-dependently antagonized by intravenous atipamezole although the sensitivity for reversal of these two responses may be different. Since the agonist and the antagonist have similar elimination half-lives, the likelihood of recurrence of dexmedetomidine’s clinical effects, after reversal by atipamezole, is small. Thus, the alpha-2 agonists provide a titratable form of hypnotic-sedation which can be readily reversed. This holds out the promise that we may yet be able to achieve the same type of control at the anesthetic site of action as we currently enjoy for the production and reversal of muscle relaxation.

SHIVERING

In patients undergoing elective ear, nose or pharyngeal surgery under 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 clonidine 1.5 mcg/kg before emergence [19]. Similarly, intravenous clonidine (1 mcg/kg) reduced the incidence of shivering in patients undergoing knee arthroscopy under epidural anesthesia.

PERIOPERATIVE MYOCARDIAL ISCHEMIA

The main approaches for reducing perioperative myocardial ischemia and hence improving long-term survival include preoperative assessment, modification of anesthetic techniques, and prophylactic therapy. In a placebo-controlled dose-ranging study of 300 patients experiencing perioperative sympatholysis with mivazerol, intraoperative myocardial ischemia and postoperative tachycardia was significantly reduced [20]. Earlier, clonidine was shown to ameliorate angina in patients with coronary artery disease. Whether or not these transient actions change outcome is not yet known. Such outcome data are needed since there are theoretical reasons why alpha-2 agonists may be pro-ischemic through their hypotensive and vasoconstrictive properties.
COMPARISON OF CLINICALLY-AVAILABLE ALPHA-2 AGONISTS

Dexmedetomidine has an alpha-2:alpha-1 adrenoceptor ratio of 1600:1, more than seven times greater than clonidine. Its elimination half-life is around 2 hours whereas that of clonidine is in excess of 8 hours. The distribution half-life of dexmedetomidine is approximately 5 minutes while that of clonidine is in excess of 10 minutes.

CONCLUSION

By virtue of their registration for analgesic and sedative indications, the alpha-2 adrenergic agonists have now become part of the anesthesiologists therapeutic armamentarium. The use of alpha-2 agonists as adjuncts in pain management is attractive because of the multiplicativity that occurs through their action at both central (spinal as well as supraspinal) and peripheral sites. Clinicians should be mindful that many of the perioperative applications of alpha-2 agonists remain “off-label.”

REFERENCES

15. Maze M, Fujinaga M: Alpha2 adrenoceptors in pain modulation: which subtype should be targeted to produce analgesia? Anesthesiology 2000; 92:934-6