Alpha-2 Adrenoceptor Agonists: Defining the Role in Clinical Anesthesia

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FEW OF THE more than 20 million general anesthetics delivered to human patients include the use of an alpha-2 adrenergic receptor agonist. This is in significant con-

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to be untenable in the light of the finding of alpha-2 adrenergic receptors postsynaptically and even extrasynaptically that were not linked to neurotransmitter release. As more selective alpha adrenergic receptor antagonists became available, it was possible to definitively separate the alpha adrenergic receptors into two subtypes on a pharmacologic basis. The classification of alpha-2 versus alpha-1 is based on the antagonists yohimbine and prazosin. At alpha-1 receptors, prazosin is more potent than yohimbine, whereas, at the alpha-2 receptors, yohimbine is more potent than prazosin. Currently, the issue is not whether there are two alpha adrenergic receptors, but how many different isoreceptors there are in mammalian tissue.

Pharmacologic Classification of Alpha-2 Adrenoceptors

The current controversy relates to the number and tissue specificity of the different alpha-2 isoreceptors found in mammalian tissue (table 1). Bylund et al. have defined at least three alpha-2 isoreceptors based on affinity for alpha adrenergic receptor ligands. Thus, the prototypic alpha_2A_ receptor has low affinity for prazosin but a high affinity for oxymetazoline and is found in human platelets. Conversely, the alpha_2B_ receptor has a low affinity for oxymetazoline and a relatively high affinity for prazosin and is especially prevalent in neonatal rat lung and renal cortex. The alpha_2C_ isoreceptor is present in opossum kidney cell line and is defined by a rank order of affinity of many alpha-2 antagonists.

Autoradiographic Classification of Alpha-2 Adrenoceptors

Quantitative autoradiographic techniques provide high-resolution anatomic data from single animals and have been applied to the study of the regional distribution of alpha-2 receptors (table 1). When Boyajian et al. used [3H]-idazoxan as the autoradiographic probe, they found that they could label many more receptors than when [3H]-rauwolscine was used. From subtraction analysis, they classified the isoreceptors as being rauwolscine sensitive (R_s) or rauwolscine insensitive (R_i). It is interesting that the R_s and R_i receptors are present in nearly equal proportion in the caudate nucleus, which corresponds to the radiolabeled ligand-binding data provided by Bylund et al. However, the use of idazoxan as a probe for an alpha-2 binding site has been challenged by the demonstration that this ligand binds to nonadrenergic sites, termed imidazoline binding sites.

Molecular Biologic Classification of Alpha-2 Adrenoceptors

Koblika et al. and Regan et al. have succeeded in cloning the genes encoding alpha-2 adrenoceptors from the human platelet and the human kidney (table 1). Cells
of at least three separate components—a receptor protein, a guanine nucleotide binding protein (G protein), and an effector mechanism.

**Molecular Structure of the Receptor Protein**

The alpha-2 adrenoceptor is a member of the G protein-coupled family of membrane receptors. These proteins are similarly sized, ranging from 415 to 480 amino acids in length. Each protein contains seven stretches of predominantly hydrophobic amino acids that are separated by segments of hydrophilic amino acids. The proteins weave backward and forward through the membrane, with the hydrophobic regions, approximately 24 amino acid residues in length, forming alpha helices that are embedded in the membrane. The hydrophilic segments form loops that project either to the cell interior or the exterior. Of the more than 20 proteins that have been cloned from this family of receptors, there is remarkable homology in the membrane-spanning segments, with between 20% and 50% identity of the amino acids in those regions. Proteolytic digestion of the large intracellular and extracellular domains does not alter the binding of ligands to these receptors, suggesting that the ligand-binding sites are associated with the transmembrane segments. Structure–function studies indicate that negatively charged aspartic acid residues within the third transmembrane segments are crucial for agonist binding because they channel the positively charged ligands into the center of the receptor. Thus, it appears that the transmembrane domains fold around to make a pocket in which the ligand binds. The cytoplasmic side of the receptor protein, and especially the domains on the cytoplasmic side of the transmembrane (TM) 5, TM6, and TM7, forms a contact point for G protein, thus providing a means of signal transduction. Chimeric alpha-2, beta-2 adrenoceptors have been constructed, and switching of the transmembrane domains, especially TM7, confers antagonist binding specificity.

**G Proteins**

The ability of alpha-2 adrenoceptors to rapidly stimulate an effector system is transduced by a family of membrane-bound guanine nucleotide binding proteins, or G proteins. The G proteins are heterotrimeric, with subunits designated as alpha, beta, and gamma (in order of decreasing mass). Differences in the alpha subunit provide heterogeneity to the more than ten G proteins and serve to classify the G proteins into major classes (e.g., Gi, Go, Gt, etc.). The beta subunits are usually found in close association with one another and are difficult to separate. The alpha subunit has a molecular weight varying between 39 and 46 kDa and has a very similar secondary structure irrespective of the source. All alpha subunits have a sin-
Single high-affinity binding site for guanine nucleotides, possess an intrinsic guanosine triphosphatase (GTPase) activity, and are substrates for adenosine diphosphate (ADP)-ribosylation by various toxins, including *B. pertussis*, *V. cholera*, and *Clostridium botulinum*. Within each major subclass, there are multiple forms of each subunit. The molecular basis for the microheterogeneity in the alpha subunit results from alternative splicing of a single precursor mRNA. Gs supports receptor-mediated inhibition of adenylate cyclase and is clearly one of the G proteins coupled to the alpha-2 adrenoceptors. Go is a highly prevalent G protein in mammalian brain, accounting for more than 1% of the membrane protein, and is also coupled to alpha-2 adrenoceptors. Although Go is a substrate for ADP-ribosylation by pertussis toxin, it has no obvious role in the regulation of adenylate cyclase; this implies a broader role for G protein-mediated signal transduction in the brain. The functional role played by G proteins in coupling receptors to effectors is described in figure 1.

**Effector Mechanisms**

There are at least five separate effector mechanisms that are directly modulated by the activated alpha-2 adrenoceptor. This diversity does not necessarily indicate that there are that many alpha-2 isoreceptors, because it is probable that any one receptor may promiscuously couple with more than one effector mechanism. Also, the ability of a receptor to couple to any one effector mechanism does not necessarily indicate that that particular effector mechanism represents the pathway for the biologic response.

**Adenylate Cyclase**

A common feature of all alpha-2 adrenergic receptors is the ability, when activated, to inhibit adenylate cyclase. The resulting decrease in the accumulation of cyclic adenosine monophosphate (cAMP) will attenuate the stimulation of cAMP-dependent protein kinase and, hence, phosphorylation of target regulatory proteins. The change in the phosphorylation state of these regulatory proteins may alter the biologic response of the cell. However, in many cases, a decrease in cAMP production is not sufficient to mediate the alpha-2 adrenoceptor effects. For example, the ability of norepinephrine to suppress voltage-dependent calcium conductance in chick dorsal root ganglion cells is not suppressed by artificially maintaining elevated levels of cAMP. Also, alpha-2-mediated platelet secretion and inhibition of insulin release do not result from the accompanying decrease in the cAMP levels. Although alternate or additional signaling mechanisms have been implicated, it is likely that the inhibition of adenylate cyclase plays an important permissive role in transmembrane signaling through alpha-2 adrenoceptors by eliminating the functional antagonism resulting from cAMP-mediated events.

**Acceleration of Na⁺/H⁺ Exchange**

In NG 108-15 cells, alpha-2 adrenoceptor activation results in the alkalinization of the interior of these cultured cells.
cells by accelerating Na⁺/H⁺ exchange.³⁴ This may in turn stimulate phospholipase A₂ to initiate the arachidonic pathway and lead to the elaboration of autacoids such as thromboxane A₂. Thus far, this antipporter mechanism appears to be modulated by the alpha-2 adrenoceptor only in the platelet under physiologic conditions.

**Electrophysiologic Changes**

**Activation of K⁺ Channels**

Opening of outwardly directed K⁺ channels hyperpolarizes membranes and provides an effective means of suppressing neuronal firing³⁵,³⁶ and/or secretion.³⁷ A G protein is involved in receptor-modulated K⁺ channel openings,³⁸ and the alpha subunit of this G protein is thought to be unique.³⁹

**Inhibition of Voltage-Sensitive Ca²⁺ Channels**

Alpha-2 adrenoceptor-mediated inhibition of Ca²⁺ channels⁴⁰ may play a role in suppressing Ca²⁺ entry into the nerve terminals and blocking fusion of transmitter-containing vesicles with the synaptic membrane. This channel is coupled to the alpha-2 receptor through a G protein,⁴¹ and the particular species seems to be similar to Gₐ.⁴² Inhibition of calcium uptake has also been linked to the antinociceptive action of clonidine in rats.⁴³

**Phosphatidylinositol Turnover**

The hydrolysis of phosphatidylinositol bisphosphate into diacylglycerol and inositol triphosphate is mediated by phospholipase C, which may, under certain circumstances, be modulated by the alpha-2 adrenoceptors.

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**Applied Pharmacology**

**AGONISTS**

**Clinically Available Alpha-2 Agonists for Humans**

Clonidine is a selective agonist for alpha-2 adrenoceptors, with a ratio of 200:1 (alpha-2/alpha-1) (table 2). In many models of alpha-2 action, clonidine has been identified as a partial agonist.⁴⁴ Clonidine is rapidly and almost completely absorbed after oral administration and, by this route, reaches a peak plasma level within 60–90 min. Clonidine can also be delivered through a time-release transdermal patch, although a minimum of 2 days must elapse before therapeutic levels are achieved.⁴⁵ The elimination half-life of clonidine is between 9 and 12 h, with approximately half of the drug being metabolized in the liver to inactive metabolites, whereas the rest is excreted unchanged in the kidney. Methyldopa is metabolized to methylnorepinephrine, which is a full agonist at the alpha-2 receptor and has a tenfold selectivity for the alpha-2 over the alpha-1 adrenoceptor. Because transformation into the active compound is necessary, effects are slow to develop (4–6 h) and somewhat unpredictable. It is the only parenteral preparation available for clinical use in the United States. Guanabenz is similar to clonidine in its effects; however, it is less potent and shorter acting, with a terminal elimination half-life of 6 h. Guanfacine has the longest half-life (14–18 h) of all the clinically available alpha-2 agonists.

**Novel Alpha-2 Agonists**

Medetomidine — 4(5) - [1 - 2,3 - dimethylphenyl]ethyl]imidazole—is the prototype of the novel superselective...
TABLE 2. Selectivity of Various α₂-adrenergic Agonists

<table>
<thead>
<tr>
<th>α₁ &gt; α₂</th>
<th>α₁ = α₂</th>
<th>α₁ &lt; α₂</th>
<th>α₂ &gt; α₁</th>
<th>α₂ ≫ α₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirazoline</td>
<td>Epinephrine</td>
<td>Clonidine</td>
<td>Azepoxole (B-HT 933)</td>
<td></td>
</tr>
<tr>
<td>Methoxamine</td>
<td>Norepinephrine</td>
<td>Guanabenz</td>
<td>B-HT 920</td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td></td>
<td>Guanfacine</td>
<td>Medetomidine</td>
<td></td>
</tr>
<tr>
<td>Amidephrine</td>
<td></td>
<td>α-methylnorepinephrine</td>
<td>Rimelindine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tizanidine</td>
<td>UK14,304</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Xylazine</td>
<td>Detomidine</td>
<td></td>
</tr>
</tbody>
</table>

The selectivity of these agonists is derived from a compilation of radiolabeled ligand binding and displacement data and are approximate.

> indicates 100 times more selective; ≫ indicates 100 times more selective. (Data taken from Kallo A: Human pharmacology of medetomidine, a selective α₂-adrenoceptor agonist. Thesis submitted to the Departments of Pharmacology and Clinical Pharmacology, University of Turku, Finland, 1989.)

alpha-2 agonists. It is an order of magnitude more selective than clonidine and is a full agonist at this class of receptor.60 Medetomidine is extremely potent and is active at low nanomolar concentrations; it has been widely used in veterinary practice in Europe.

**ANTAGONISTS**

There are no selective α₂-adrenergic antagonists available for clinical human use. Phentolamine, a nonselective α₁-adrenoceptor blocker, is currently available. However, this compound does not easily penetrate the blood–brain barrier and thus will not antagonize the centrally active α₂-adrenergic agonist responses. The following selective α₂-adrenoceptor antagonists are currently being developed for possible clinical use in veterinary practice. Yohimbine—an indole alkaloid—is approximately 60 times more selective for the α₂-adrenoceptor than the α₁-adrenoceptor.47 Idazoxan is a relatively specific antagonist at the α₂-adrenoceptor48 but does exert some partial α₁-adrenoceptor properties.49 Atipamezole is at least 100 times more selective for the α₂-adrenoceptor than idazoxan50 and has no behavioral or neurochemical effects other than to increase the central turnover of norepinephrine.51 The continuing development of these and other novel compounds for the reversal of α₂-adrenoceptor responses will provide an additional useful adjunct in anesthetic practice.

**PHYSIOLOGIC RESPONSES MEDIATED BY ALPHA-2 ADRENOCEPTORS**

**Cardiovascular System**

Postjunctional vascular α₁ and α₂-adrenoceptors coexist in both the arterial and venous vasculature, where they mediate vasoconstriction independent of any action on the nerve supply to the vasculature (table 3).52

There does appear to be a difference in the source of cytosolic calcium that mediates the contractile response produced by the two receptor populations; α₂-adrenoceptor activation results in an influx of extracellular calcium,53 whereas α₁-adrenoceptor activation produces an influx of extracellular calcium and additionally induces the release of intracellular calcium to produce vasoconstriction.54,55 These ligand-gated calcium channels differ from the voltage-operated calcium channels mentioned earlier.

**TABLE 3. Physiologic Responses Mediated by α₂-adrenoceptors**

<table>
<thead>
<tr>
<th>Response</th>
<th>Mechanism</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Postsynaptic smooth muscle</td>
<td>52–54</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>EDRF</td>
<td>58, 59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Central vasomotor</td>
<td>63–69</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Baroreflex sensitivity</td>
<td>71</td>
</tr>
<tr>
<td>Negative dromotropy</td>
<td>Decrease NE release</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>Vagomimetic</td>
<td>73</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease ventilation</td>
<td>&quot;Sleeplike&quot; action</td>
<td>83, 84</td>
</tr>
<tr>
<td>Bronchodilation</td>
<td>Smooth muscle</td>
<td>86</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuresis</td>
<td>Inhibit ADH release</td>
<td>99, 100, 103</td>
</tr>
<tr>
<td></td>
<td>Block ADH action</td>
<td>104, 105</td>
</tr>
<tr>
<td></td>
<td>Increase GFR</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Inhibit renin release</td>
<td>107</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease insulin release</td>
<td>Beta cells</td>
<td>96, 97</td>
</tr>
<tr>
<td>Decrease NE release</td>
<td>Decrease firing rate</td>
<td>87–90</td>
</tr>
<tr>
<td>Decrease cortisol</td>
<td>Inhibit ACTH release</td>
<td>98</td>
</tr>
<tr>
<td>Enhance GH release</td>
<td>Hypophysal cells</td>
<td>91</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease saliva</td>
<td>Inhibit ACh release</td>
<td>109, 110</td>
</tr>
<tr>
<td>Decrease bowel motility</td>
<td>Inhibit ACh release</td>
<td>113, 114</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Na⁺–H⁺ antiporter</td>
<td>116, 33</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Increase stage I and II sleep</td>
<td>117</td>
</tr>
<tr>
<td>Sedation</td>
<td>Decrease NE neurotransmission</td>
<td>46</td>
</tr>
<tr>
<td>Anxiolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td>196, 127</td>
</tr>
<tr>
<td>Analgesia</td>
<td></td>
<td>229–235</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE = norepinephrine; ADH = antidiuretic hormone; GFR = glomerular filtration rate; ACTH = adrenocorticotropic hormone; ACh = acetylcholine.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The effects of alpha-2 adrenergic agonists in the coronary circulation have attracted a fair amount of interest. In a dog model of coronary artery disease, Heusch et al. induced poststenotic myocardial ischemia by stimulation of the sympathetic nerves; this could be blocked with alpha-2 antagonists or the dihydropyridine calcium channel blocker nifedipine. The authors suggested that stimulation of the sympathetic innervation to a poststenotic segment of the coronary vasculature releases norepinephrine, which causes that segment of the coronary artery to contract by activation of the postjunctional alpha-2 adrenoceptors. However, in the same model, administration of clonidine can ameliorate this effect, presumably by producing a centrally mediated reduction in sympathetic outflow with a net decrease in neurotransmitter release. Because it is often difficult to demonstrate the alpha-2 adrenoceptor-mediated vasconstrictive response in vivo, it has been suggested that alpha-2 agonists also mediate the release of endothelial-derived relaxation factor. This has now been substantiated in mammalian coronary arteries. There is remarkable interspecies variation in the presence and distribution of alpha-2 adrenoceptors in the coronary circulation. Changes in regional blood flow in other vascular beds have not been as well studied, although a decrease in cerebral blood flow was reported in both isoflurane and halothane, anesthetized dogs. However, in acutely treated, severely hypertensive patients, cerebral blood flow did not significantly change. The site of action for the centrally active hypotensive agents remains enigmatic. Clonidine exerts its hypotensive action by affecting the lateral reticular nucleus, whereas methylnorepinephrine (the metabolite of alpha methyl dopa and alpha methylnorepinephrine) exerts its hypotensive action by activating alpha-2 adrenoceptors in the nucleus tractus solitarii. Clonidine potently inhibits the firing rate of the locus ceruleus (LC), which ordinarily mediates a pressor response. In fact, this inhibitory effect of clonidine on sympathetic outflow is considered crucial to its hypotensive action because clonidine is ineffective in controlling blood pressure in hypertensive tetraplegic patients in whom central control of sympathetic mechanisms is lacking. Alpha-2 adrenergic agonists will also decrease the sympathetic response to provocative tests; thus, an orthostatic challenge is not accompanied by increases in diastolic pressure in subjects given clonidine. Because the hypotensive action of alpha-2 adrenergic agonists cannot be attenuated by prior depletion of endogenous catecholamines within the central nervous system (CNS), it is suggested that these compounds are acting postsynaptically in the brain to produce this action. Although the bradycardic effect of alpha-2 adrenergic agonists has been known for a long time, the mechanism for this action is in doubt. Alpha-2 adrenergic agonists enhance the baroreflex sensitivity to increases in systolic arterial pressure or the strain associated with the Valsalva maneuver. There is evidence that the bradycardic effect is sustained in tetraplegic patients, which supports the contention that the bradycardic action is caused in part by a presynaptically mediated inhibition of norepinephrine release at the neuroeffector junction or by a vagomimetic effect (see below). As mentioned earlier, alpha-2 agonists stimulate the nucleus tractus solitarii and can thereby produce a vagomimetic action at this site. Somewhat surprisingly, highly selective muscarinic M2 receptor antagonists cannot completely attenuate this response.

Alpha-2 adrenergic agonists, in high doses, will depress atrioventricular (AV) nodal conduction. There is a slight prolongation in the P-R interval in subjects receiving clonidine, which has prompted some to suggest that the drug be withheld in elderly patients and those with an existing prolongation of the P-R interval or with spontaneous bradycardia. These dromotropic actions of alpha-2 agonists are thought to be mediated through an indirect vagomimetic action. Direct effects of alpha-2 agonists have been found lacking in the mammalian heart. In fact, postjunctional alpha-2 adrenoceptors have never been found in the mammalian heart.

Respiratory System

It is surprising that in the more than 20 yr that clonidine has been used in clinical practice, there exist only anecdotal reports of the respiratory effects in humans and those only in the setting of drug overdoses. In a recent animal study, the respiratory depressant effects of clonidine were reported to be less than those of morphine in mice and rats. Also, preliminary studies in humans confirm the minor respiratory effects of clonidine when compared with those of opiate narcotics. Curiously, there is a hypoxicemic effect of intravenously administered clonidine in hoofed animals, best exemplified by experiments in sheep. This response is blocked by a peripherally acting alpha-2 adrenoceptor antagonist, leading to the suggestion that the response is mediated in part by activation of alpha-2 adrenoceptors on circulating platelets. On the other hand, nebulized clonidine has been shown to reduce bronchoconstriction provoked by histamine in subjects with asthma.

Neuroendocrine System

Alpha-2 adrenergic agonists potently inhibit sympathoadrenal outflow, as evidenced by the decreased levels of circulating norepinephrine and the diminution of catecholamine metabolites in the urine after clonidine administration. This sympathoinhibitory effect of alpha-2 adrenergic agonists was also demonstrated in healthy volunteers and shown to result from a decrease in the release
of neurotransmitter at the neuroeffector junction.\(^{86,87}\) Whether this results from a central action on sympathetic outflow or whether the effect is mainly mediated at the level of the presynaptic autoinhibitory alpha-2-adrenergic receptor at the neuroeffector junction is not known definitively in humans; a central site of action is present in rats,\(^{66}\) and in humans it is known that the metabolites of norepinephrine are reduced in the cerebrospinal fluid (CSF) after administration of alpha-2 adrenergic agonists.\(^{90}\)

Alpha-2 adrenergic agonists enhance the release of growth hormone,\(^{91}\) although the mechanism for this action is not known. It is likely that this action is exerted postsynaptically on the hypophyseal cells that release growth hormone.

Imidazole alpha-2 adrenergic agonists, in common with the antifungal compound ketoconazole, can inhibit steroidogenesis based on the imidazole structure and not its alpha-2 agonist activity \(\text{per se.}^{92}\) Also, after clonidine administration, adrenocorticotropic hormone (ACTH) release is inhibited.\(^{93}\) Furthermore, the increase in cortisol levels, consequent on surgical stimulation, may also be attenuated by clonidine treatment.\(^{94}\) Yet, in another form of stress (exercise), elevations in ACTH levels were unaffected by clonidine in normal male patients.\(^{95}\)

Alpha-2 adrenoceptor agonists inhibit the release of insulin by a direct action on the cells of the islets of Langerhans,\(^{96}\) and thus this effect is also observed in tetraplegic patients.\(^{97}\) Clinically, this effect is quite short lived and does not lead to any problems.\(^{98}\)

\textbf{Renal System}

Alpha-2 adrenergic agonists induce diuresis in all animal models studied, although the mechanism for this diuretic action may vary, depending on the species examined. Clonidine was shown, by both indirect studies\(^{99}\) and direct measurement, to inhibit the release of antidiuretic hormone (ADH) in anesthetized dogs.\(^{100}\) However, there does not appear to be an effect of alpha-2 adrenergic agonists on ADH release in rats when assessed either indirectly\(^{101}\) or by direct measurement of ADH levels.\(^{102}\) Recently, it was demonstrated that vasopressin levels in the CSF do decrease in humans after the administration of clonidine.\(^{103}\) Whatever the effect on ADH release, the renal tubular action of ADH is blocked by alpha-2 agonists.\(^{104,105}\) Alpha-2 adrenergic agonists are also thought to increase the glomerular filtration rate, although the mechanism for this action is not known.\(^{106}\) The highly selective alpha-2 adrenergic agonist, azepoxole, inhibits the release of adenosine-provoked renin from an isolated perfused kidney.\(^{107}\) Thus, the effect must be mediated by receptors located on the juxtaglomerular apparatus. This also may contribute to the diuretic action of this class of drug. Recently, attention has been drawn to the effect of alpha-2 adrenergic agonists on the release of atrial natriuretic factor as a mechanism for the diuretic effect of this class of compound.\(^{108}\)

\textbf{Gastrointestinal System}

Salivary flow is reduced by alpha-2 adrenergic agonists\(^{109}\); a direct component is definitely involved because this effect is also reported in tetraplegic patients.\(^{110}\) Activation of presynaptic alpha-2 adrenergic receptors inhibits the vagally mediated release of gastric acid from parietal cells;\(^{111}\) however, there does not appear to be any change in the pH of the gastric contents in humans.\(^{112}\) Alpha-2 adrenergic agonists also reduce vagally mediated gastric and small bowel motility.\(^{113}\) Intestinal ion and water secretion by the large bowel is inhibited by alpha-2 adrenergic agonists, and clonidine has been used successfully in the management of watery diarrhea.\(^{114}\)

\textbf{Reproductive System}

There are a plethora of alpha-2 adrenoceptors located postsynaptically in the uterine myometrium.\(^{115}\) Although alpha-1 adrenoceptors probably mediate a contractile response and the alpha-2 adrenoceptors mediate a relaxant effect on the myometrium, the functional role of alpha-2 adrenoceptors in the uterine myometrium remains undefined.

\textbf{Hematologic System}

Alpha-2 adrenergic agonists produce aggregation of human platelets.\(^{116}\) However, the functional significance of this action has never been established because the \textit{in vitro} concentrations of epinephrine necessary to produce aggregation are not achieved \textit{in vivo}. A likely explanation is that physiologic control of platelet aggregation involves the action of multiple aggregatory hormones, each present at levels below those necessary for induction of aggregation individually. Nevertheless, the aggregatory activity has been widely used as an indirect assessment of alpha-2 agonist pharmacology.

\textbf{Central Nervous System}

Alpha-2 adrenergic agonists produce sedation;\(^{117}\) EEG studies confirm the increase in stage I and II sleep, with a decrease in rapid eye movement sleep after the administration of alpha-2 agonists.\(^{118}\) Although a presynaptic site of action was initially suggested by the hyperexcitatory response to clonidine in neurotransmitter-depleted rats,\(^{119}\) we found that the sedation-producing action of dexmedetomidine—a more selective alpha-2 adrenergic ago-
nrist—is enhanced in norepinephrine-depleted rats\textsuperscript{129}; thus, the issue concerning the presynaptic versus postsynaptic location of the sedative response is not completely resolved.

Alpha-2 adrenergic agonists, especially the superselective variety such as dexmedetomidine, exert anxiolytic effects comparable to those seen with the benzodiazepine compounds.\textsuperscript{46,121} Clonidine exerts a biphasic effect, being anxiolytic at low alpha-2 range concentrations and displaying anxiogenic behavior at the higher doses, through an alpha-1 action.\textsuperscript{122} Other selective alpha-2 adrenergic agonists, including guanabenz and azepoxole, also exert this paradoxic response at higher doses.\textsuperscript{123} In humans, clonidine has been shown to be effective when acutely administered to patients with panic disorder\textsuperscript{124}; however, after chronic administration, this effect is lost. Similarly, the sedative effect of chronically administered alpha-2 adrenergic agonists disappears. Whether this represents an accumulation of drug concentration that exceeds the "narrow alpha-2 range" or whether this represents tolerance to these effects is not known. The alpha-2 adrenergic agonists also exert an effect on memory. Clonidine significantly improves the spatial working memory abilities of aged monkeys performing the delayed-response task.\textsuperscript{125} Recently, the authors from that study have suggested that it is possible to separate the improved cognitive effects from the sedative properties of the alpha-2 agonists because these may be effected by separate alpha-2 isoreceptors.\textsuperscript{126} Centrally active alpha-2 adrenergic agonists exert a powerful analgesic action,\textsuperscript{127} although the site and mechanism for the antinociceptive action of this class of compound remain controversial.

### Clinical Applications of Alpha-2 Adrenergic Agonists

**Cardiovascular Diseases**

Arterial hypertension is still the only Food and Drug Administration (FDA) approved clinical indication for the therapeutic use of alpha-2 adrenergic agonists (table 4). Clonidine has been used as an antihypertensive agent for the last 25 yr\textsuperscript{129} and has become a highly efficacious agent in this regard for a number of reasons. It is useful for hypertension of various causes, including renal and renovascular causes.\textsuperscript{129} Although the response rate is quite high (usually greater than 70%), the incidence of serious side effects is remarkably low. The most troubling side effects include dry mouth and sedation; both of these side effects may diminish with increased use of the drug,\textsuperscript{130} although this has not been a universal finding. Although a modest reduction in heart rate is part of the pharmacologic action of this class of compound, neither symptomatic bradycardia nor orthostatic hypotension is commonly encountered. The most serious side effect associated with the use of alpha-2 adrenergic agonists is the supervision of a specific withdrawal syndrome associated with the sudden discontinuation of therapy after a prolonged period. The clinical profile of this withdrawal syndrome, which includes restlessness, insomnia, headache, and nausea in association with hypertension and tachycardia, results from an increase in sympathetic nervous activity.\textsuperscript{131}

The alpha-2 adrenergic agonists can also be used safely in patients with concurrent disease, including diabetes\textsuperscript{132} and asthma.\textsuperscript{86} Also, in comparison with other common first-line antihypertensive agents (including thiazide di-

<table>
<thead>
<tr>
<th>Disease</th>
<th>Effect</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Hypertension</td>
<td>Decrease blood pressure</td>
<td>128–130</td>
</tr>
<tr>
<td>CHF</td>
<td>Decrease afterload</td>
<td>137, 138</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>Decrease O₂ consumption</td>
<td>139</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>Improve supply/demand ratio</td>
<td>140</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiate addiction</td>
<td>Decrease withdrawal syndrome</td>
<td>145, 146</td>
</tr>
<tr>
<td>Other addiction</td>
<td>Decrease withdrawal syndrome</td>
<td>147–152</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>Anxiolytic</td>
<td>153, 154</td>
</tr>
<tr>
<td>Mania/hyperactivity</td>
<td>Decrease activity</td>
<td>155, 156</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korsakov’s Psychosis</td>
<td>Improve memory</td>
<td>157</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Decrease spasticity</td>
<td>158</td>
</tr>
<tr>
<td>Spastic paraplegia</td>
<td>Decrease micturition reflex</td>
<td>159</td>
</tr>
<tr>
<td>Neuflagia</td>
<td>Improve gait</td>
<td>160</td>
</tr>
<tr>
<td>Migraine</td>
<td>Analgesia</td>
<td>161</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Decrease headache</td>
<td>162</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Antiemetic</td>
<td>164</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure.
uretics and beta-adrenergic blocking agents), the alpha-2 adrenergic agonists have fewer adverse effects on plasma lipids.\textsuperscript{133,134} Of other clinically available alpha-2 adrenergic agonists, both guanabenz\textsuperscript{135} and guanfacine\textsuperscript{136} have pharmacodynamic actions similar to those seen with clonidine in the clinical management of hypertension. Alpha-2 adrenergic agonists also have been used to reduce afterload in the management of patients with congestive heart failure.\textsuperscript{137} However, orally administered clonidine was not as efficacious.\textsuperscript{138} Clonidine has also been used in the treatment of patients with chronic stable angina pectoris\textsuperscript{139} and in those with an acute myocardial infarction complicated by systemic hypertension.\textsuperscript{140}

\section*{Psychiatric Disorders}

\subsection*{Opiate Addiction}

Opiate and alpha-2 agonists act through independent receptors within the LC\textsuperscript{141} but produce similar depressant effects on net LC cell activity\textsuperscript{142} through similar effector mechanisms. In opiate-dependent rats, naloxone will precipitate an increase in the firing rate of the neurons in the LC; although opiates ineffectively inhibit the naloxone-induced increase in firing rate, alpha-2 adrenergic agonists are still highly efficacious.\textsuperscript{143} This provided an insight into the probable mechanism whereby the alpha-2 adrenergic agonists suppressed the abstinence behavioral responses in morphine-dependent rats.\textsuperscript{144} Soon afterward, investigators demonstrated clonidine’s ability to reduce the physiologic and psychologic signs in dependent patients withdrawing from opiates.\textsuperscript{145} Over the ensuing years, the use of alpha-2 agonists has become a mainstay in the management of acute detoxification from opiate addiction.\textsuperscript{146} Subsequent studies in primates revealed that alpha-2 adrenergic agonists will decrease the symptoms and signs that follow electrical stimulation of the LC.

\subsection*{Nonopiate Addiction}

Activation of brain noradrenergic neurons constitutes a common denominator in the pathophysiology of several withdrawal states.\textsuperscript{146} Because clonidine is extremely efficacious in relieving hypernoradrenergic states (including plasma catecholamines, tachycardia, and hypertension), other drug-withdrawal states, including those after chronic benzodiazepine\textsuperscript{147} and alcohol use,\textsuperscript{148} have also been successfully treated with alpha-2 agonists. Clonidine proved to be more effective than chlordiazepoxide in reducing the alcohol-withdrawal scale score and the incidence of nausea and vomiting.\textsuperscript{140,150} It is noteworthy that, although an earlier study reported on the efficacy of clonidine in reducing anxiety, irritability, tension, restlessness, and craving in heavy smokers withdrawing from cigarette smoking,\textsuperscript{151} a subsequent double-blind, placebo-controlled study showed only a significant difference in the number of patients abstaining from cigarette smoking at 1 week but not at longer time intervals.\textsuperscript{152}

\subsection*{Other Psychiatric Disorders}

Alpha-2 adrenergic agonists have also been used to manage anxiety and panic attacks. The noradrenergic hyperactivity hypothesis of clinical forms of human anxiety states that an abnormally high reactivity of brain noradrenergic systems pertains. There is a strong correlation between yohimbine-induced increases in MHPG, a metabolite of brain norepinephrine, which is found circulating in the plasma, and 1) patient-related anxiety; 2) nervousness; and 3) panic attacks.\textsuperscript{153} Lactate-induced panic attacks are effectively blocked by treatment with clonidine.\textsuperscript{154}

Clonidine may also rapidly ameliorate manic symptoms, making it a potential alternative to neuroleptics during lithium initiation and an adjunct or alternative to specific antimanic agents.\textsuperscript{155} Clonidine also appears to be a safe and effective medication for controlling hyperactivity in children.\textsuperscript{156}

\section*{Central Nervous System Disorders}

\subsection*{Memory Disorders}

Age-associated memory impairment and the characteristic memory disorder of Korsakoff’s psychosis are effectively treated with low-doses of alpha-2 adrenergic agonists.\textsuperscript{157}

\subsection*{Spasticity}

In patients with spastic motor disturbances of the lower extremities resulting from multiple sclerosis, the alpha-2 adrenergic agonist, tizanidine, was as effective as baclofen in reducing spasticity.\textsuperscript{158,159} The hyperactive micturition reflexes and motor spasticity that are seen in association with spinal cord injury are also effectively treated with intrathecal clonidine.\textsuperscript{160}

\subsection*{Chronic Pain States}

In patients with intractable postherpetic neuralgia, pain relief after clonidine administration was more effective than either a nonsteroidal antiinflammatory or an opiate narcotic in a double-blind cross-over study.\textsuperscript{161} Recently, transdermal clonidine has been shown to be effective in prophylaxis of headaches in patients with migraines.\textsuperscript{162} Since the first description of the use of epidural clonidine for analgesia, there have been myriads of reports addressing the use of this form of analgesic treatment. This will be discussed in greater detail in the following section.

Lastly, there are reports of the beneficial effects of clo-
Clonidine has also been used for its antiemetic action in patients with cancer who are being treated with chemotherapy.\textsuperscript{164}

**Alpha-2 Adrenergic Agonists in Veterinary Anesthesia**

**XYLAZINE**

For nearly 2 decades, alpha-2 adrenergic agonists have been widely used by veterinarians to achieve dose-dependent sedation, analgesia, and muscle relaxation in a variety of domesticated and wild species. Although xylazine was first used as an adjunctive agent in the early 1970s,\textsuperscript{165-171} the link to stimulation of central alpha-2 adrenoceptors was not established until 1981.\textsuperscript{172,175}

Xylazine's alpha-2 agonist properties made it an excellent agent to combine with ketamine to smooth out excitatory phenomena and provide muscle-relaxant and analgetic effects. Nevertheless, concern over the moderate cardiodepressant and arrhythmogenic effects of xylazine, whether given alone or in combination with ketamine,\textsuperscript{174-177} has prevented some veterinary anesthesiologists from embracing its use. When injected intravenously as a bolus, xylazine causes bradycardia and a brief period of hypotension, followed by a longer-lasting decrease in blood pressure. In contrast to the hemodynamic effects observed after intravenous (iv) injection, intramuscularly administered xylazine lacks significant pressor response because of lower peak blood concentrations and, hence, less postsynaptic alpha adrenoceptor stimulation. When used in combination, xylazine-induced decreases in heart rate and cardiac output are moderated by ketamine's sympathomimetic action, whereas blood pressure and systemic vascular resistance are sustained at slightly increased levels.\textsuperscript{174,178} Although respiratory rate usually decreases after xylazine administration, tidal volume is increased and thus the arterial \( p \)H, \( P_{A}O_{2} \), and \( P_{A}CO_{2} \) values remain virtually unchanged in dogs\textsuperscript{177,178} and cats\textsuperscript{174} and are only minimally altered in horses.\textsuperscript{165,169,179} However, when xylazine was administered to halothane-anesthetized sheep (0.02–0.05 mg/kg intravenously), airway pressure increased and \( P_{A}O_{2} \) values decreased significantly.\textsuperscript{180} This effect was attributed to alpha-2 adrenoceptors on platelets and subsequent alterations in pulmonary blood flow.\textsuperscript{85}

Other alpha-2 pharmacologic effects that have been reported with xylazine's use include increased urine output and prolonged gastrointestinal transit time.\textsuperscript{181-185} Relaxation of the large intestine coupled with alpha-2-mediated analgesia may result in the alleviation of visceral pain. Accordingly, xylazine has been quite effective in the management of horse colic. Although increased myometrial tone and intrauterine pressure have been observed after xylazine administration in cows,\textsuperscript{184} this compound has been administered during all stages of pregnancy in several domestic species, without obstetric complications.\textsuperscript{184,185}

Xylazine has also been administered epidurally in ponies, in which it induces more profound and longer-lasting analgesia with less motor impairment than does lidocaine at the same dose and volume of injection.\textsuperscript{186} Epidurally administered xylazine is not associated with changes in ECG readings, blood pressure, blood gases, or neurotoxicity in horses.\textsuperscript{187} Cardiopulmonary depressant effects after epidural administration of xylazine (2% solution at 0.05 mg/kg) in cattle,\textsuperscript{188} which included bradycardia, hypotension, respiratory acidosis, hypoxemia, and ruminal hypomotility, were reversed with a 0.5 mg/kg iv dose of tolazoline, whereas sedation and regional analgesia were not influenced.

**Novel Alpha-2 Agonists**

Detomidine has higher potency and greater specificity than xylazine for central alpha-2 adrenoceptor sites.\textsuperscript{169} In horses, detomidine's strong sedative and analgesic effects are more profound and of longer duration than those induced by xylazine.\textsuperscript{190} Detomidine has been used as a preanesthetic in horses and cattle anesthetized with halothane or isoflurane in which the volatile requirements are greatly reduced. Recovery from anesthesia in horses premedicated with detomidine is uneventful and free of excitement phenomena. As is the case with xylazine, increased urine output and hyperglycemia have been observed after detomidine administration.

Medetomidine is the most potent and selective alpha-2 agonist available for use in veterinary medicine.\textsuperscript{191} When compared with 1 MAC (1.38%) isoflurane anesthesia in dogs, a 20 mg/kg iv infusion of medetomidine resulted in less depression of the \( CO_{2} \) ventilatory response than did isoflurane.\textsuperscript{192} As with xylazine, vomiting\textsuperscript{193} and muscle jerking\textsuperscript{194} may occur during the onset of sedation with medetomidine. Medetomidine–ketamine combinations have effectively provided short periods of anesthesia and immobilization in dogs, cats, and many laboratory and zoo animal species.\textsuperscript{193,195,196} As with xylazine and detomidine, the coadministration of an opioid with medetomidine appears quite useful and may enhance sedation and analgesia (neuroleptanalgesia) beyond that achieved with either drug alone.\textsuperscript{197}

**Alpha-2 Adrenergic Agonists in Human Anesthetic Practice**

By now it must be apparent how many different ways the desirable properties of alpha-2 adrenergic agonists
can be used in the anesthetic paradigm. This section will deal with the use of the alpha-2 adrenergic agonist as an anxiolytic, sedative, analgesic, anti-sialagogue, antiemetic, and antihypertensive in humans. If appropriately used, these compounds may produce an ideal pharmacodynamic profile for an adjunctive agent for clinical anesthesia.

**Reducing Anesthetic Requirements**

**Historic Perspective**

The idea for the use of an alpha-2 adrenergic agonist as an adjunctive anesthetic agent started on a cautionary note. Brodsky and Bravo observed an acute hypertensive crisis in a patient in the postoperative period in whom clonidine therapy was abruptly discontinued preoperatively. This prompted Kaukinen et al. to investigate the conditions which obtained during the continuous use of clonidine perioperatively. Not only were they able to prevent the hypertensive crises seen with its acute withdrawal, but its use also “smoothed out” the entire perioperative hemodynamic profile. By then the sedating action of clonidine therapy was well-known, as was the observation made by Taylor and Taylor that clonidine enhanced chiral–hydrate sleep time in rats; therefore, Kaukinen and Pykkö examined the effect of subcutaneously (for 3 days) administered clonidine (50 µg/kg subcutaneously) on halothane MAC in rabbits. They observed a modest (15%) reduction in the dose of halothane required to attenuate a movement response to the application of a vessel clamp on the tip of the rabbit’s ear. Subsequently, Bloor and Flacke defined the dose-response curve of acutely administered clonidine on halothane MAC in dogs and demonstrated that clonidine reduced MAC by a maximum of 50% and that this effect could be reversed with tolazoline, an alpha-2 antagonist. It should not be lost to the purist that Miller et al. used alpha-methyl dopa as a central norepinephrine depletor and demonstrated a decrease in halothane MAC in dogs. Subsequently, alpha-methyl dopa has been characterized as a potent and high-affinity agonist for the alpha-2 adrenoceptor.

**Mechanism of Action**

At first it seemed that clonidine’s actions in decreasing anesthetic requirements related to its attenuating effect on central noradrenergic neurotransmission, especially because there existed a plethora of data in support of the hypothesis that noradrenergic neurotransmission modulates the depth of the anesthetic response. However, the extent of the reduction in MAC (>90%) that was produced when the highly selective alpha-2 adrenergic agonists such as azepoxole or medetomidine were used suggested that additional factors must also be operating because MAC is reduced by only 30–40% when noradrenergic neurotransmission is totally abolished. Subsequent studies with the superselective alpha-2 agonist, dexametomidine, corroborated this suggestion because this alpha-2 agonist could still reduce the MAC for halothane in rats in which the central norepinephrine stores were previously depleted. The profound reduction in anesthetic requirements with dexametomidine raised the possibility that alpha-2 adrenergic agonists may be considered anesthetic agents when administered alone. This sole anesthetic feature was confirmed together with the observation that a central alpha-2 adrenoceptor mediated this action. Subsequently, using molecular biologic techniques, we confirmed that the alpha-2 adrenergic C4 isoreceptor was the probable receptor that mediated the anesthetic response. Finally, we established that the anesthetic action of dexametomidine involved a pertussis toxin–sensitive G protein and a 4-aminopyridine–sensitive potassium channel (fig. 3).

**Fig. 3.** Proposed molecular mechanism for anesthetic action of alpha-adrenergic agonists. After the alpha-adrenergic agonist binds to the receptor, the bound GDP is displaced from the a subunit of the pertussis toxin-sensitive G protein to be replaced by GTP. The activated subunit can either change the gating of a 4-aminopyridine-sensitive ion conductance channel by a membrane-delimited process (right) or alter the activity of an effector enzyme. The effector enzyme changes the rate of generation of a second messenger and turnover rates in the biochemical cascade downstream. Ultimately, the intracellular pathway can also modulate this 4-aminopyridine-sensitive membrane protein (arrow).
ALPHA-2 ADRENOCEPTOR AGONISTS

TABLE 5. Applications of α2-adrenergic Agonists in Anesthesia

<table>
<thead>
<tr>
<th>Clonidine Dose</th>
<th>Effect</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthetic requirements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–4 μg/kg × 2</td>
<td>Decrease sufentanil by 40%</td>
<td>222</td>
</tr>
<tr>
<td>5 μg/kg</td>
<td>Decrease fentanyl by 45%</td>
<td>223</td>
</tr>
<tr>
<td>5 μg/kg</td>
<td>Decrease isoflurane by 40%</td>
<td>224</td>
</tr>
<tr>
<td>5 μg/kg</td>
<td>Decrease IOP, fentanyl, forane</td>
<td>225</td>
</tr>
<tr>
<td>5 μg/kg</td>
<td>Decrease droperidol</td>
<td>226</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Decrease isoflurane, morphine</td>
<td>227</td>
</tr>
<tr>
<td>3 μg/kg</td>
<td>Decrease isoflurane, sufentanil</td>
<td>228</td>
</tr>
<tr>
<td>Analgesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrathecal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 μg</td>
<td>18 h of pain relief</td>
<td>260</td>
</tr>
<tr>
<td>400 μg/day</td>
<td>Continuous pain relief</td>
<td>261</td>
</tr>
<tr>
<td>Variable</td>
<td>To &quot;rescue&quot; morphine tolerance</td>
<td>262</td>
</tr>
<tr>
<td>Variable</td>
<td>To &quot;rescue&quot; morphine tolerance</td>
<td>263</td>
</tr>
<tr>
<td>150 μg</td>
<td>To supplement spinal analgesia</td>
<td>264, 265</td>
</tr>
<tr>
<td>Epidural</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–150 μg</td>
<td>Neurogenic pain relief</td>
<td>268</td>
</tr>
<tr>
<td>100–500 μg</td>
<td>Postoperative surgical pain relief</td>
<td>269</td>
</tr>
<tr>
<td>100–900 μg</td>
<td>Cancer pain relief</td>
<td>270</td>
</tr>
<tr>
<td>150 μg</td>
<td>Supplement epidural analgesia</td>
<td>274</td>
</tr>
<tr>
<td>Parenteral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 μg/kg + 0.3 μg·kg⁻¹·h⁻¹</td>
<td>Decrease postoperative morphine</td>
<td>277</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 μg po</td>
<td>Decrease isoflurane for induced hypotension</td>
<td>280</td>
</tr>
<tr>
<td>150 μg iv</td>
<td>Less postoperative shivering</td>
<td>276</td>
</tr>
<tr>
<td>7 μg/kg × 2 hiv</td>
<td>Postoperative hemodynamic stability</td>
<td>278</td>
</tr>
<tr>
<td>Experimental Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>Decrease opioid-induced muscle rigidity</td>
<td>280</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Prevent opioid-induced muscle rigidity</td>
<td>279</td>
</tr>
</tbody>
</table>

IOP = intraocular pressure.

Clinical Studies

The following is a nonexhaustive compilation of the types of surgery, doses, and routes of administration in which alpha-2 agonists have been used in clinical practice (table 5). Aortocoronary bypass surgical patients were studied to determine the hemodynamic and anesthetic effects of preoperative and intraoperative administration of clonidine.216 Patients were given placebo or clonidine (200 or 300 μg orally, based on patient weight) 90 min before arrival in the operating room, and a second clonidine dose was administered through a nasogastric tube while the patient was on cardiopulmonary bypass (n = 10 in each group). The clonidine-treated patients were more sedated on arrival in the operating room and required less sufentanil, as assessed by strict hemodynamic criteria, at all time periods studied. Thus, the total amount of sufentanil administered was reduced by 40%. Despite the lower dose of opiate narcotic used, the heart rate and blood pressure were significantly lower in the clonidine-treated group preinduction, postinduction, postintubation, and postincision. The cardiac output was consistently higher and systemic vascular resistance was lower in the clonidine-

TABLE 6. Considerations for Use of α2-adrenergic Agonists in Anesthesia

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Potential Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Hypertension (parenteral bolus administration)</td>
<td>Preservation of renal function in presence of insult</td>
</tr>
<tr>
<td>Preservation of hemodynamic stability</td>
<td>Hypertension (parenteral bolus administration)</td>
<td>Limitation of increase in ICP/ IOP</td>
</tr>
<tr>
<td>(prevent wild swings in HR and BP)</td>
<td>Hypertension (parenteral bolus administration)</td>
<td>Decrease of narcotic-induced muscle rigidity</td>
</tr>
<tr>
<td>Anxiolysis/sedation/analgesia without</td>
<td>Hypertension (parenteral bolus administration)</td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>respiratory depression</td>
<td>Hypertension (parenteral bolus administration)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>Hypertension (parenteral bolus administration)</td>
<td></td>
</tr>
<tr>
<td>Limitation of the use of potentially</td>
<td>Hypertension (parenteral bolus administration)</td>
<td></td>
</tr>
<tr>
<td>toxic anesthetic/adjunctive agents</td>
<td>Hypertension (parenteral bolus administration)</td>
<td></td>
</tr>
<tr>
<td>Induced hypotension</td>
<td>Hypertension (parenteral bolus administration)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Rebound&quot; (only after prolonged use)</td>
<td></td>
</tr>
</tbody>
</table>
treated group after cardiopulmonary bypass. Plasma catecholamine levels remained lower at all times studied. Time to meet the extubation criteria was significantly shorter in the clonidine-treated group. It is important to remember that this study was not blinded; however, it may be quite difficult to perform a blinded study on patients in whom bradycardia and xerostomia are consistent consequences of the drug’s administration.

Ghignone et al. have conducted three studies examining the anesthetic issues from a somewhat different perspective. In each of the studies, the treatment group received 5.0 μg/kg clonidine orally 90 min before arrival in the operating room, whereas the control group received a placebo.217 With the use of an EEG measurement of anesthetic depth, namely supervision of delta wave activity (i.e., shift to 0.5–3 Hz frequency range), they demonstrated a 45% reduction in fentanyl requirements. Even with this lower dose of fentanyl, the hemodynamic response to endotracheal intubation was as effectively attenuated as in the group of patients who received the larger dose of fentanyl. Next, the authors examined the hemodynamic response to endotracheal intubation in mildly hypertensive patients receiving either clonidine alone or a combination of diazepam (0.15 mg/kg po preoperatively) and lidocaine (1 mg/kg intravenously) plus fentanyl (2 μg/kg) immediately before a standard induction with thiopental (3 mg/kg) plus vecuronium (0.1 mg/kg).218 Preoperative blood pressure was more effectively controlled in the clonidine-treated group, and there was no tachycardic response to intubation. Once again, they used the EEG as an index of anesthetic depth and demonstrated that the volatile anesthetic requirements were reduced by 40% and the fentanyl dose by 74% while a greater hemodynamic stability was maintained. In a third study conducted in an elderly ophthalmic surgical population, Ghignone et al. examined the clinical effect of oral premedication with clonidine versus diazepam (0.1 mg/kg po).219 There were 40 patients in each treatment group who were further stratified to receive either a local or general anesthetic for their elective surgery. Eighty-five percent of the clonidine-treated patients had a satisfactory level of sedation on arrival to the operating room compared with 50% in the diazepam-treated group. The intraocular pressure (IOP) was significantly reduced in the patients receiving clonidine. The increase in IOP that was seen with endotracheal intubation in the diazepam-treated patients was also attenuated in the clonidine-treated patients. Whether patients underwent general or local anesthesia for their procedures, the clonidine-treated patients had significantly less variation in heart rate and blood pressure throughout the surgical procedure. The isoflurane and fentanyl requirements to control episodes of hypertension and tachycardia were significantly lower in the patients who received clonidine.

Engelman et al. studied the effect of clonidine (5 μg/kg po 90 min before arrival in the operating room) versus a placebo on the anesthetic drug requirements in patients having aortic surgery (n = 10 in each group).220 Using hemodynamic end points as criteria of anesthetic depth, they examined the need to supplement the anesthetic with additional doses of alfentanil and droperidol. Clonidine-treated patients required significantly less droperidol and had fewer episodes of tachycardia and hypertension than the placebo-treated group.

Segal et al. examined the effect of transdermally administered clonidine, at two doses, versus placebo on the anesthetic conditions of patients undergoing lower abdominal surgery.221 They measured the effect on preoperative sedation, intraoperative anesthetic requirements and hemodynamic stability, and postoperative analgesia as adjudged by the use of morphine administered by a patient-controlled analgesia (PCA) pump in patients undergoing lower abdominal surgery. The clonidine-treated patients (n = 14 in each group) received clonidine orally before operation and had a 7-cm or 10-cm patch applied to the anterior chest wall to achieve a plasma level of 1.0 or 1.5 ng/ml perioperatively. The control group (n = 15) received placebo tablets and a patch. Both clonidine-treated groups were more sedated at the time of arrival in the operating room, had lower volatile anesthetic requirements to achieve hemodynamic end points, had greater intraoperative hemodynamic stability, and emerged from anesthesia more rapidly. Patients in the high-dose clonidine-treated group also required significantly less morphine by PCA. An interesting sidelight of the study, which requires corroboration and additional workup, is the higher alfentanil plasma levels reported in patients who were in the clonidine-treated groups. It is possible that the pharmacokinetics of “fixed” anesthetic agents could be affected by coincident alpha-2 adrenergic agonist treatment.

In a recently reported double-blinded randomized study, investigators reported a decrease in sufentanil and isoflurane requirements in aortocoronary artery bypass graft patients after the administration of 3 μg/kg clonidine po 90 min preoperatively.222 What was especially interesting was the finding that the usual deterioration in renal function, as evidenced by an increase in serum creatinine levels, did not occur in the clonidine-treated patients.

Thus far, there are two studies reported in which no clear-cut advantage of clonidine was apparent. In the first, cimetidine appeared to be superior to clonidine (4.5 μg/kg po, 70–160 min before arrival in the operating room) in modifying gastric acidity.223 Secondly, clonidine did little to allay the anxiety of women undergoing breast biopsy.224
Woodcock et al. examined the use of clonidine (0.6 mg po, 2 h before surgery) in an anesthetic regimen designed to induce hypotensive conditions in patients undergoing middle ear or nasal surgery (n = 10 in each group). In the clonidine-treated patients, the dose of isoflurane required to achieve a hypotensive end point was reduced by 33%, as was the need to supplement the technique with labetalol (one patient in the clonidine-treated group vs. five patients in the control group).

ALGALVES EFFECTS OF ALPHA-2 ADRENERGIC AGONISTS

Historic Perspective

At the turn of the century, Weber demonstrated the analgesic properties of adrenergic agonists when he was able to attenuate the thermally-evoked withdrawal response in a cat by applying epinephrine to the spinal cord. Some 70 yr later, Paalzow showed that clonidine could increase the threshold for vocalization in rodents provoked with a noxious stimulus. Thereafter, Schmitt et al. demonstrated the profound analgesic activity of intracerebroventricularly administered alpha-sympathomimetic compounds and set the stage for the use of alpha-2 adrenergic agonists in the epidural and subarachnoid spaces. The use of centrally administered alpha-2 adrenergic agonists has recently been buoyed by the search for an effective alternative and/or adjunct to central opiate therapy in the management of moderate to severe pain because of the side effects (including respiratory depression, pruritus, urinary retention) associated with that form of therapy.

Mechanism of Action

Because the mechanisms and pathways of spinal opiate analgesia had been earlier investigated and characterized, there was a strong sentiment that the alpha-2 adrenergic agonists modulated this well-established analgesic mechanism. The data in support of this contention include the ability of an opiate antagonist (naloxone) to antagonize alpha-2-mediated analgesia, the existence of cross-tolerance between alpha-2 and opiate antinociceptive effects and the release of endogenous opiate compounds by alpha-2 stimulation. However, there is contradictory evidence rejecting the role of opioidergic mechanisms because cross-tolerance is not universally present. Also, alpha-2 agonist-mediated analgesia is not reversed with naloxone in other settings. The most plausible nonopioidergic mechanism for the analgesic action of alpha-2 agonists relates to the role of the descending medullospinal noradrenergic pathway modulating spinal nociceptive processing. There is clear evidence that alpha-2 adrenergic receptors are strategically located on the dorsal horn neurons of the spinal cord, where they can either inhibit the release of nociceptive neurotransmitters such as substance P or calcitonin gene-related peptide. Recently, we demonstrated that nociceptive pathways are exquisitely sensitive to dexmedetomidine, a highly selective alpha-2 adrenergic agonist, in a neonatal spinal cord preparation that is insensitive to blockade by naloxone. Still others have implicated either adenosinergic or serotoninergic mechanisms in the mediation of alpha-2 agonist–induced analgesia.

Whether or not opioidergic mechanisms are directly involved, there are data in support of a synergistic interaction between alpha-2 adrenergic agonists and opiates in the spinal cord. In a study in cats, Omote et al. demonstrated a synergistic interaction between opiates acting through the delta opiate receptor and clonidine on the wide dynamic range neuron. Ossipov et al. delivered a subanalgous combination of intrathecal morphine and clonidine and demonstrated a heightened analgesic response in rodents. In a rat analgesia model, Drasner and Fields demonstrated enhancement of the analgesic response when subanalgous doses of intrathecal clonidine and systemic morphine were administered concomitantly.

Concerning the molecular components involved, there appears to be clear-cut dependence on a pertussis toxin-sensitive G protein for the analgesic response to an alpha-2 adrenergic agonist. There is indirect evidence to implicate a voltage-operated calcium channel for the effects of alpha-2 adrenergic agonists at the level of the dorsal root neuron. First, noerpinephrine inhibits the inward calcium current that is generated by a depolarizing impulse in embryonic chick dorsal root ganglion neurons. Next, the same authors demonstrated in whole cell patch clamp studies that noerpinephrine works through a pertussis toxin-sensitive G protein to inhibit voltage-dependent calcium channels. Furthermore, electrically evoked release of substance P is sensitive to the action of dihydropyridine antagonists working at these channels. Lastly, although it has not been demonstrated for alpha-2 adrenergic agonists, it was recently shown that the antinociceptive effects of morphine are enhanced by dihydropyridine antagonists.

Clinical Studies

Because there are no FDA-approved alpha-2 adrenergic compounds available for central administration, there are few clinical studies addressing this issue. Those that have appeared in the literature mostly include anecdotal reports.

INTRATEHAL USE

Coombs et al. were the first to report on the use of intrathecal alpha-2 adrenergic agonists. Intrathecal clo-
clidine (300 μg) provided more than 18 h of pain relief in a patient with terminal cancer who had become tolerant to intrathecal morphine. Associated with this intervention, there was a hypotensive episode (to a systolic pressure of 70 mmHg) that was controlled with metaraminol. Sedation lasted 3–4 h. This form of therapy was tested in a dose-response manner and compared with placebo in a double-blind fashion. The lower doses provided intermediate quality and duration of relief, whereas the placebo was ineffective. Subsequently, this group reported on a second patient with terminal cancer in whom a combination of hydromorphone and clonidine (0.4 mg/day) provided good pain relief.255

Laugner et al. reported on the use of clonidine in 18 patients treated by continuous intrathecal morphine who had become tolerant.256 Similarly, a report from Belgium indicated that the addition of clonidine to an intrathecal regimen that consisted of only morphine rendered a previously tolerant patient pain-free in the final 3 months of life. At autopsy, no neurotoxic effects of clonidine were observed in the spinal cord.257

Recently, a case was reported in which intrathecal clonidine produced pain. This patient was also taking tricyclics, which may have produced a functional antagonism of the alpha-2 agonist property by increasing neurotransmitter in the synaptic cleft which can activate alpha-1 adrenergic receptors.258

French investigators reported on the use of intrathecal clonidine to supplement spinal analgesia obtained with bupivacaine. Patients undergoing hip surgery under spinal anesthesia were randomly allocated to receive bupivacaine 0.5% with clonidine (150 μg), epinephrine (200 μg), or saline (n = 20 in each group). In the clonidine-treated patients, the mean time for two-segment regression was considerably longer than for the saline- or epinephrine-supplemented anesthetics.259 In a subsequent study by these authors, they found that the prolongation seen with clonidine could be matched when 400 μg epinephrine was included in the intrathecal space in a hyperbaric bupivacaine technique.260 Lastly, it has been demonstrated recently that tourniquet pain can be attenuated by including clonidine in the tetracaine solution.261

**Epidural Use**

Tamsen and Gordh were the first to report on the epidural use of clonidine in two patients with intractable neurogenic pain.262 The first patient had a contusion injury to the lumbar plexus that produced numbness in the leg and exacerbating pain in the foot. Epidural clonidine (150 μg) was as effective as 5 mg morphine. When the two drugs were coadministered, the patient had double the duration of pain relief that could have been expected if the two durations of pain relief were simply additive. In a second patient with paresthetic neuralgia, epidural clonidine 75 μg was as effective as epidural pethidine 25 mg; the combination of the two drugs enhanced neither the quality nor the duration of the pain relief. There was a mild hypotensive effect of clonidine in the first patient, but sedation was not a prominent feature in either case.

Eisenach et al. reported on two series of patients receiving epidural clonidine for either postoperative surgical pain263 or intractable cancer pain.264 After total knee arthroplasty or abdominal surgery (n = 22), surgical patients were tested at doses of epidural clonidine ranging from 100 to 900 μg in an open-dose escalation study. Analgesia was determined by verbal pain score and the need for supplemental narcotics. At the highest dose, analgesia was produced for more than 5 h with no sensory or motor blockade. There was a small decrease in blood pressure with the intermediate dose, but this was “corrected” at the highest dose administered. The presumptive reason for this biphasic response relates to the systemic vasoconstrictive effect of the drug at higher concentrations, which reverses the centrally mediated hypotensive action of this compound. Transient sedation, with between 50% and 75% of patients sleeping at the early time periods, was also a feature at the higher doses, probably because of the high systemic levels that were reached (up to 3.5 ng/ml). In contrast, the level achieved from a 7-cm clonidine patch is 1.0 ng/ml. Chemistry and, specifically, arterial blood gases were hardly affected; however, there was a slight decrease in circulating cortisol levels, which is not likely to be of great biologic significance.

This last study did not investigate any provocative test of respiratory function; when this was recently examined in patients undergoing orthopedic surgery, there was a decrease in the slope of minute ventilation to the change in end-tidal CO₂.265 In another less well-controlled study, a similar depression in ventilation was reported in postthoracotomy patients who received epidural clonidine either alone or in combination with morphine.266

In the study of patients with pain resulting from cancer,264 Eisenach et al. tested nine patients who received escalating doses (ranging from 100 to 900 μg epidurally) on successive days. There was a clear-cut dose-dependent reduction of the average pain score by clonidine during the 6-h study period. Remarkably, morphine supplementation was not decreased. Onset time was 20 min and lasted 6 h. Sedation was significant and long lasting after the highest dose range. Seven of the nine patients in the study were subsequently discharged to their homes on a continuous epidural infusion containing clonidine and morphine.

In a study investigating epidural clonidine action on postoperative pain, Gordh treated postthoracotomy patients with either clonidine (3 mg/kg) or saline (n = 10 in each group).267 There was no clear-cut decrease in the use of meperidine by pca pump in the clonidine-treated group.
Vercauteren et al. have demonstrated that the addition of clonidine (1 mg/kg) to an epidural solution containing sufentanil significantly increases the duration of block. In a recent study comparing the effects of epidurally and intramuscularly administered clonidine (2 mg/kg) in patients recovering from orthopedic or perineal surgery, equal pain relief was reported in the two groups. It was notable that similar plasma clonidine levels were achieved, and the incidences of hypotension, bradycardia, and sedation were quite similar.

**Parenteral Use**

Clonidine has also been administered parenterally in the postoperative period for various indications. Clonidine, 150 mg intravenously, was found to effectively diminish shivering when compared with droperidol or a saline control. Surgical patients recovering from spinal fusion were given clonidine by continuous infusion (5 mg/kg loading dose over 1 h, followed by 0.3 mg·kg⁻¹·h⁻¹ for an additional 12 h) or saline. Clonidine-treated patients required significantly less supplementation with morphine and had little hemodynamic disturbance if the preload was maintained. In patients recovering from aortic surgery, the perioperative administration of clonidine (7 μg·kg⁻¹·h⁻¹ by iv infusion) resulted in fewer postoperative hypertensive episodes and maintained circulating norepinephrine, epinephrine, and noradrenaline levels at much lower values.

**Alpha-2 Adrenergic Agonists and Muscle Rigidity**

One of the more difficult problems that is encountered in the operating room is the muscle rigidity that occurs after the rapid administration of large doses of narcotics. Recently, we and others have demonstrated that alpha-2 adrenergic agonists can block the onset of this complication of opiate therapy. If these data can be extrapolated to the clinical paradigm, then this provides yet another reason for combining alpha-2 adrenergic agonists with opioid.

**Side Effects**

**Cardiovascular Effects**

There are certain pharmacologic effects on the cardiovascular system that may prove to be undesirable in the clinical setting. These include acute hypertension and bradycardia after bolus iv administration and persistent bradycardia and hypotension. These may be mitigated to some extent by carefully selecting the route and speed of administration and carefully titrating dose to effect. Upon clinical availability of the appropriate alpha-2 antagonist, side effects may be completely resolved (see below).

**Withdrawal Syndrome after Alpha-2 Adrenergic Agonist Therapy**

Dangerous hypertensive episodes have been reported after withdrawal of chronic clonidine treatment, but there is no evidence that sympathetic hyperactivity results after single-dose administration. It probably takes up to 6 days of continuous therapy to produce the adaptive changes necessary for the prevention of the clonidine withdrawal syndrome. Thus, the perioperative use should be of short enough duration (less than 6 days) to avoid the possibility of hypertensive rebound. Recently, the successful treatment of this syndrome with iv labetalol was reported.

**Reversal of Alpha-2 Agonists**

One of the more exciting advances in veterinary anesthesiology during the last decade has been the development of specific antagonists for the reversal of injectable anesthetic regimens. Yohimbine has been the most studied and has recently been approved by the FDA for use by veterinarians in reversing the sedative effects induced by xylazine in dogs. Yohimbine quickly and effectively antagonizes xylazine and clonidine sedation and analgesia in laboratory animals, dogs, and cats. Beginning in 1982, Hatch et al. published a series of reports establishing the efficacy of the combination of yohimbine and 4-aminopyridine for anesthetic reversal in many domestic and wild species. In several species, yohimbine alone has been effective in antagonizing the sedative-immobilizing actions of xylazine when used in combination with other anesthetic agents. Tolazoline has also been used safely in a number of species to reverse xylazine sedation or partially reverse the depressant effects achieved with anesthetic regimens incorporating xylazine. As might be expected, alpha-2 antagonists are not effective in reversing CNS depression from other classes of anesthetic agents.

Administration of alpha-2 antagonists for the reversal of sedation is not completely without risk. Hypotension and tachycardia occur after rapid iv injection. These undesirable effects can be prevented by the slow administration of an appropriately calculated dose. Overall, the incidence of unfavorable reactions to tolazoline and yohimbine administration for reversal of CNS depression is extremely rare.

More potent, selective, and specific alpha-2 antagonists, such as idazoxan and atipamezole (MPV-1248), have recently been developed for use as reversal agents in veterinary practice. In a recent study, Virtanen et al. documented that the alpha-2/alpha-1 selectivity ratio of atipamezole was 200–300 times higher than that of either idazoxan or yohimbine.
Future Implications

The development of more specific and selective alpha-2 agonists and antagonists together with improved delivery techniques will continue to enhance the safety and reliability of this novel class of compounds. The unique spectrum of anesthetic properties induced by alpha-2 agonists has assured them of an increasingly prominent role in the development of new and sophisticated ways of achieving anesthesia.

Although opioid narcotics and benzodiazepines do not produce reliable analgesia and sedation in all species or people, alpha-2 agonists universally induce reliable dose-dependent sedative–analgesic actions that are readily reversible. In recent studies, the effects of low doses of alpha-2 agonists, opioid agonists, and benzodiazepines have focused attention on the coadministration of drugs that activate separate CNS receptor populations (i.e., alpha-2, opiate, benzodiazepine), resulting in a synergistic response.247,248 In addition, in view of the fact that each of these classes of drugs can be selectively reversed with antagonists (e.g., atipamezole, naloxone, flumazenil), we may now be entering a new era in which various states of analgesia and anesthesia are achieved by the activation of two or more populations of CNS receptors that in turn can be modified or completely reversed with one or more selective receptor antagonists.

Conclusions

The full clinical promise of the alpha-2 adrenergic agonists has not yet been realized. Whether its introduction represents an advance as fundamentally significant as the use of opiate narcotics in anesthetic practice will depend, to a large extent, on the continued development of more selective and potent compounds than those that are currently available. We should continue to study the utility of a drug that has the potential to be 1) as analgesic as potent opiate narcotics, 2) as anxiolytic and sedating as potent benzodiazepines, 3) as sympathetic as modern volatile anesthetic agents, and 4) as reversible as the nondepolarizing muscle relaxants. “When the dust settles, we shall see whether we are riding a horse or an ass.”

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