Selectivity of site of action and systemic effects of topical alpha agonists

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Clonidine hydrochloride, apraclonidine hydrochloride, and brimonidine tartrate constitute the three topical α agonists that are used in the treatment of elevated intraocular pressure. All the α agonists have prejunctional (α_2) as well as postjunctional (α_1) effects. Within the past year, questions have arisen about their local and systemic effects, and their effects upon the optic nerve. We will, therefore, attempt to clarify these points, to provide a greater understanding of the role of α agonists in glaucoma therapy.

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Abbreviation

IOP intraocular pressure

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Mechanism of action

The ocular hypotensive effects of clonidine hydrochloride, apraclonidine hydrochloride, and brimonidine tartrate are mediated via α_2 receptors in a number of ways. There are at least three different types of α_2 receptors. There is a difference in species specificity of these receptors: that is, one compound may be more selective for a particular α_2 receptor in one animal model, while less selective in a second animal model.

When α_2 adrenoreceptors in the ciliary body are acted upon, intracellular cyclic AMP levels diminish and subsequently, aqueous production decreases [1]. Outflow facility as well as episcleral venous pressure may be affected by all three compounds [2–4]. In one report, brimonidine was found to increase uveoscleral flow [4]. Central nervous system penetration, while contributing to adverse effects, may play a role in the reduction of intraocular pressure (IOP) by both clonidine and brimonidine [5]. IOP is a well-known risk factor for the progression of glaucomatous damage. To date, it has been the only risk factor that we have attacked in the therapy of most forms of open-angle glaucoma. An ideal therapeutic modality would protect axons from both primary and secondary nonapoptotic axoplasmic death in addition to lowering IOP. It has been suggested, but in no way proven, that α agonists may also provide neuroprotection [6].

Neuroprotection

The definition of glaucoma has gradually changed over the past few decades to include a set of diseases sharing a particular pattern of optic nerve damage. Most, but not all, have elevated IOP as a major risk factor. Many glaucoma medications, notwithstanding α agonists, have proven efficacious in reducing IOP. What would be perhaps more desirable, however, is a medication aimed at protecting the optic nerve in addition to decreasing a risk factor.

Burke and Schwartz [6] have suggested that brimonidine might be able to accomplish this goal. Verbal communication with Schwartz has confirmed that they have seen this neuroprotective capability with clonidine, although it has not yet been evaluated for apraclonidine.

Burke and Schwartz used a rat model in which the rat optic nerve was crushed and intraperitoneal brimonidine was then administered. After 2 weeks, axonal excitability was

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fourfold. Whether or not this acute crush model is analogous to what happens in humans with chronic glaucoma is uncertain. Many problems such as drug formulation and delivery, species specificity, and toxicity must be addressed before any claims or realistic suggestions can be made. Additionally, even without regard to species differences, it is important to determine whether this model is at all applicable to human glaucoma. It is likely that crush damage which is produced acutely is not related to the chronic slow damage seen in humans. It could be that apoptosis is much more critical than this type of cell death. Brimonidine may not get to axons in adequate concentrations when given locally to the eye, and not by intraperitoneal injection. Also, adverse reactions such as sedation and systemic hypotension might override any local optic nerve benefits if an adequate amount of the drug was administered.

Burke and Schwartz found similar results with clonidine, but not timolol maleate (personal communication). Prior studies with dexmedetomidine (another α_2 agonist) used in 14 rabbits found that it also protected against ischemic brain damage [7]. It is possible that many α agonists have some type of neuroprotective ability, but it is far too early to suggest that this class of medications has any clinical applicability for humans with glaucoma.

Efficacy and dosing

Apraclonidine shows a peak hypotensive effect of 30% to 40% 3 to 5 hours after administration and a trough level reduction of 20% to 30% [8]. Brimonidine has a maximum effect at 2 hours with a 20% to 30% pressure lowering [9]. It has been claimed that tachyphylaxis occurs with chronic use of apraclonidine, but this has not been shown with brimonidine [10]. However, there is no well-documented evidence that tachyphylaxis truly occurs with apraclonidine. Reports of tachyphylaxis have been from uncontrolled studies of eyes with glaucoma on maximal–tolerated medical therapy. It could be that if these studies had either active or placebo controls, there would not be any clinically significant tachyphylaxis. The absence of a control group makes it difficult to truly monitor response to a medication. Additionally, eyes requiring surgery may respond differently to medications than those eyes that are well controlled on either one or two eye-pressure-lowering medications.

A concentration of 0.5% proved most efficacious for apraclonidine [11]. For brimonidine, a dose-response effect was observed during the first week of treatment, with a greater response with the use of 0.5% brimonidine. By the second week, a similar effect was achieved with 0.2% solution [9].

Apraclonidine probably requires three times a day dosing monidine administered twice daily are based on the fact that the morning IOP levels, approximately 2 hours after administration, were the same whether the drug was administered twice or three times a day [12]. The afternoon trough level, however, showed a difference of 3.5 mm Hg between the two groups, rendering twice a day administration far inferior to three times a day dosing. Similarly, in a comparison of brimonidine twice daily to timolol during a 12-month period, mean peak IOP decreases were comparable to timolol, whereas mean decrease from baseline was significantly less for trough values of brimonidine than for timolol [13]. Brimonidine, like apraclonidine, should be administered thrice daily for a constant, around the clock hypotensive effect.

Side effects related to localized α_2 effects

There are several points to keep in mind when discussing the side-effect potential of α_2 agonists such as clonidine, brimonidine, and apraclonidine. The degree to which a centrally mediated side effect occurs depends upon the concentration of the drug within central nervous system tissues, which in turn is related to its ability to cross the blood-brain barrier. Drug penetration into the brain is dependent upon the lipophilicity of the drug. Both brimonidine and clonidine are more highly lipophilic than apraclonidine [14]. This increased lipophilicity suggests that they can be absorbed much more easily into both the blood stream and the central nervous system through the blood-brain barrier.

The degree to which a peripherally mediated side effect occurs depends upon the concentration of the drug within the systemic circulation in relation to the drug's potency. Apraclonidine is less likely than brimonidine to be absorbed systemically from topical ocular administration because it is less lipophilic (*ie*, it is more hydrophilic and charged at physiologic pH).

All three medications are relatively selective α_2 agonists. The degree of selectivity is only important if tissue concentrations are within the range required for α_1 activity. If tissue or circulating levels of drug are insufficient to produce α_2 effects, then α_1 effects are highly improbable.

The degree of selectivity reported depends on whether it is based upon receptor affinity or functional potency, as well as the experimental conditions of the assay. Functional potency seems more appropriate for agonists, whereas receptor affinity is more relevant to antagonists. Binding affinity data has been used to characterize the selectivity of all three medications [15–17]. The functional data has been ignored and it shows apraclonidine's selectivity to be higher [18]. Moreover, other published binding affinity data, using cells with cloned human receptors that showed the α_2 to α_1 selectivity of apracloni-

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is largely ignored [19]. α_2 Selectivity is sufficient for both drugs to consider their primary ocular effect to be related to α_2 activation.

It is questionable whether α_1 activation, either locally or systemically, occurs at usual ophthalmic doses. For example, Allergan's (Irvine, CA) published data shows the EC_{50} of apraclonidine to be 216 nmol/L for causing *in vitro* contraction of the rabbit iris dilator muscle (mydriasis), with this response considered to be mediated by α_1 receptors [18]. Moreover, they reported an EC_{50} of 1.9 nmol/L for apraclonidine in activating α_2 receptors. Additional data show that iris concentrations of brimonidine are about 10 times higher than those of apraclonidine, which tends to nullify the difference between the drugs with regard to functional potency and affinity.

Side effects of selective α_2 agonists

Central nervous system effects

Sedation is mediated by postsynaptic receptors located in the locus coeruleus, which lies behind the blood-brain barrier. This pharmacologic effect is potentiated by benzodiazepines and can be used advantageously to reduce anesthetic requirements. Clonidine is used in certain circumstances as a sedative to reduce the amount of anesthesia required for humans. Xylazine, another α_2 agonist, is used by veterinarians in large nonhuman animals to induce sedation. A limitation of xylazine is the variability of the sedation.

This could result in a possible overdose situation if brimonidine is used in a patient who has received either clonidine for anesthesia or is on benzodiazepines. It might be unusual for an anesthesiologist who is about to use clonidine for induction to ask a patient requiring surgery, especially urgent surgery, whether he or she is on brimonidine eye drops. Likewise, many physicians prescribing benzodiazepines would probably not know a patient is taking brimonidine.

Sedation related to brimonidine could interfere with a patient's ability to operate machinery, drive a car, or remain alert and awake, particularly after alcohol consumption. It is unlikely that a patient would associate this complication with brimonidine. Additionally, a patient might not associate fatigue with the use of an eye drop. Apraclonidine is far less likely to produce sedation, because it does not enter the central nervous system to the degree that brimonidine does, nor is it absorbed into the system circulation as effectively.

Cardiovascular system

Hypotension and bradycardia

The cardiovascular actions of α_2 agonists are classified as peripheral or central and include systemic hypotension in patients with little counteracting sympathetic stimulation (*ie,* those at rest) and is related to both central and peripheral actions of these agents. Recently, it has been postulated that the hypotensive effect of imidazoline-like compounds is mediated by imidazoline-preferring receptors located in the rostal ventrolateral medulla that mediate peripheral sympathoinhibition [20]. The central nervous system side effects are believed to be mediated via α_2 receptors.

Clonidine can produce systemic hypotension and bradycardia via a site in the central nervous system. The mechanisms may involve inhibition of sympathetic outflow and enhancement of parasympathetic nervous activity.

It is reasonable to assume that α_2 agonists that reach higher concentrations within the central nervous system are more likely to produce systemic hypotension and sedation. The production of hypotension and sedation by α_2 agonists has been shown to correlate well with their partition coefficient (their ability to penetrate the central nervous system) [21].

α_2 Agonists inhibit norepinephrine release from peripheral prejunctional nerve endings. This action contributes to their bradycardic effect. Presumably, the greater the lipophilicity of the compound, the more likely it is to reach the systemic circulation and, depending on the dose, produce this effect.

Hypertension and vasoconstriction

α_2 Agonists produce vasoconstriction by their activation of vascular extrajunctional α_2 receptors. If the concentration of a relatively selective α_2 agonist is sufficiently high to enable stimulation of vascular α_1 receptors, this too will result in vasoconstriction. Nevertheless, even without α_1 activation, α_2 receptor activation can produce vasoconstriction. Locally in the eye, both brimonidine and apraclonidine produce anterior segment (*ie,* conjunctiva, iris, ciliary body) vasoconstriction [22].

Under certain clinical situations, this added stimulation of vasoconstrictive receptors can produce systemic hypertension. This is particularly true if there is excessive sympathetic tone present (*ie,* if the patient is under stress or is taking a monoamine oxidase inhibitor or a tricyclic antidepressant [norepinephrine reuptake blocker]). Because this is a peripheral action, it too depends upon the circulating drug level and potency of the particular agent whether or not vasoconstriction occurs.

Respiratory system

Clonidine itself does not produce any marked effects upon respiration. Brimonidine and apraclonidine, in normal human volunteers, have not been found to produce

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Endocrine system

α_2 Agonists can potentiate the secretion of growth hormone and inhibit the release of insulin by a direct action on pancreatic β cells [24]. Neither of these is considered important in normal clinical situations.

Hematologic system

α_2 Agonists induce platelet aggregation. A concurrent reduction in circulating catecholamines may clinically offset this effect.

Gastrointestinal system

α Agonists inhibit salivation and produce dry mouth via activation of peripheral postsynaptic α_2 receptors. This peripherally mediated inhibition of salivary secretion can be augmented by the centrally mediated sympathetic inhibition. Activation of peripheral postsynaptic α_1 receptors has been shown to enhance parasympathetic-mediated salivation [24]. Thus, any α_1 activity occurring would produce less dry mouth compared with the absence of α_1.

Conclusions

The α agonists have proven to be a powerful addition to the armamentarium of pressure-reducing agents. A solid understanding of their actual and potential strengths and limitations is crucial so that they may be used in a safe and efficacious manner.

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