Dexmedetomidine-Induced Ocular Hypotension in Rabbits With Normal or Elevated Intraocular Pressures

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This study covered the ocular hypotensive effects of the stereoisomers of the α2-adrenoceptor agonist medetomidine. The dextro-isomer, dexmedetomidine, is known from pharmacologic experiments to be a specific, potent, and selective full agonist at α2-adrenoceptors, whereas the levo-enantiomer seems to be almost inactive. Thus, the levo-isomer (0.5 mg/ml, 25 μl) had no significant effect on intraocular pressure. After unilateral topical administration, dexmedetomidine (0.5 mg/ml, 25 μl) lowered intraocular pressure bilaterally in normal rabbits and in rabbits with intraocular pressure elevated after laser irradiation of the pigmented trabecular band of the anterior chamber angle. In the treated (ipsilateral) eye of normal rabbits, a maximum decrease of 4.6 ± 0.6 mmHg was observed at 2 hr post treatment. In the contralateral eye, the maximum decrease was 4.1 ± 0.5 mmHg at 1 hr after treatment. In rabbits with laser-induced elevation of intraocular pressure, the maximum decrease in treated hypertensive eyes was 13.5 ± 0.3 mmHg 1 hr after dexmedetomidine administration. These results indicate that the selective α2-adrenoceptor agonist, dexmedetomidine, is a potent and effective drug for decreasing intraocular pressure in rabbits. Invest Ophthalmol Vis Sci 33:2019-2023, 1992

Compounds that activate α2-adrenoceptors were shown as early as 1966 to lower intraocular pressure (IOP) in animals and humans. The prototypic α2-adrenoceptor agonist, clonidine, is known to decrease IOP in normal and glaucomatous humans as well as in cats, monkeys, and rabbits. Clonidine is not a very selective α2-agonist. At higher concentrations, it also activates α1-adrenoceptors. More recently, apraclonidine (p-aminoclonidine) has been reported to inhibit the transient rise in IOP in humans and rabbits after laser surgery of the anterior segment. Apraclonidine has significantly less ability than clonidine to penetrate the blood-brain barrier, suggesting a possible peripheral site of action. The clinical success of apraclonidine has renewed interest in α2-agonists as potential antiglaucoma agents.

Medetomidine, 4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole, is a newly developed α2-agonist with high potency, specificity, and selectivity toward the α2-adrenoceptor. Its affinity for α2 receptors is approximately three times higher than that of clonidine, and its α2/α1 selectivity ratio is eight times greater than that of clonidine. It is relatively lipophilic, with an apparent octanol/buffer partition coefficient (log P) of 2.8 at pH 7.4 and a pKₐ value of 7.1. Medetomidine (Domitor; Orion Corp. Farmos, Turku, Finland) is used mainly as an analgesic and sedative drug for dogs and cats. It is a racemic mixture of two optically active isomers. Most, if not all, of the pharmacologic effects seen after medetomidine administration are induced by the dextro-isomer, dexmedetomidine (Fig. 1). Dexmedetomidine is being developed for humans as an adjunctive agent in anesthesia.

Since α1-agonist activity elevates the IOP, we were interested to assess the effects of dexmedetomidine on IOP to get a clearer picture of the potential of α2-adrenoceptor agonists as potential antiglaucoma agents. This paper describes the ocular hypotensive activity of dexmedetomidine (D-MED) in normal rabbits and rabbits with laser-induced elevation of IOP. The compound was compared to the less selective α2-agonist, apraclonidine.

Materials and Methods

Animals

The experimental animals used in this study were mixed breed pigmented rabbits of both sexes (n = 21), weight 3.1 ± 0.6 kg. The rabbits were housed singly in cages under standard laboratory conditions: 10 hr
dark/14 hr light cycle, 20.0 ± 0.5°C, 55–75% relative air humidity. All animals were treated in accordance with the ARVO Resolution on the Use of Animals in Research. The test animals were given food and water ad libitum, except during the tests, when these were withdrawn.

Preparation of Instilled Eye Drops

Dexmedetomidine-HCl (0.05 and 0.5 mg/ml), 1-medetomidine-HCl (0.5 mg/ml), both from Orion Corporation Farmos, and apraclonidine-HCl (0.5 and 5 mg/ml; Sigma, St. Louis, MO) were dissolved in 80 mmol/l sodium phosphate buffer (pH 6.46; \( n = 0.24 \), osmotic pressure 325 mosm). The drug solution (25 \( \mu l \)) or buffer solution (50 \( \mu l \)) was administered unilaterally. The rabbits were allowed 2 hr of equilibration time before drug administration. All drugs were administered randomly with each test day followed by a washout period of 3–4 d. Right and left eyes were tested in turn.

Measurements

The rabbits were kept in restraint boxes during the experiments. They could move their heads and eyes freely. IOP was measured using a BioRad (Cambridge, MA) Digilab Modular One Pneumatonometer. Before each measurement, one or two drops of oxybuprocaine (0.06%) were applied to the cornea before tonometry to eliminate discomfort. The upper and lower eyelids were gently retracted and the applanation sensor was brought into contact with the center of the cornea. For each determination, two readings were taken from each eye, alternating between the right and left eye. The measurements were started 2 hr before drug or buffer solution administration and were continued 5 hr after administration. Only the rabbits with IOP of 14 mmHg or more were accepted for the test. The average IOP of the normotensive rabbits was 15.5 ± 0.3 mmHg. Two hours before drug administration it was 3.7 ± 0.4 mmHg higher, but after this initial fall, the ocular pressures remained constant for the remaining 5 hr if the rabbits received only buffer (see control curves in Figs. 3 and 4).

Rabbits With Laser-Induced Ocular Hypertension

The influence of dexmedetomidine on elevated IOP was tested in rabbits with laser-induced ocular hypertension. Before the laser-treatment, the rabbits were sedated with fluanisone 1.4 mg/kg, fentanyl 0.03 mg/kg subcutaneously, and diazepam 0.7 mg/kg s.c. Green argon light was used and the laser beam was focused on the pigmented trabecular band of the anterior chamber angle, avoiding the pectinate ligaments.

Fig. 3. The IOP response to topical, unilateral administration of apraclonidine (125 \( \mu g, 25 \mu l \)) or buffer solution in conscious, normotensive pigmented rabbits. The data are shown as the mean and standard error of mean, \( n = 8 \) per group. * = \( P < 0.01 \).
The laser power was adjusted to produce a visible blanching or a small gas bubble (520-800 mW). A total 360° of the anterior chamber angle was treated, with the number of burns varying between 317 and 618. Total energy delivered varied from 47.5-93.3 J. The IOP elevations remained reasonably constant during 1-4 wk at 30-60 mmHg. Rabbits were allowed to recover after laser treatment for 3-5 d before testing. The laser-treated rabbits in which IOP was elevated less than 10 mmHg over the pretreatment were not considered to have experimentally elevated pressures and were not studied further. The average IOP of the ocular hypertensive rabbits was 38.8 ± 2.5 mmHg. When the rabbits were first brought to the laboratory 2 hr before drug administration, their ocular pressures were 2.4 ± 0.9 mmHg higher than those measured at the start of the experiment. Thereafter, in buffer-treated rabbits, there was little fluctuation in recorded pressures (see control curves in Figs. 5 and 6).

Analysis of the Data

All results are presented as change in IOP (mmHg), means ± standard error of the mean. Statistical significance of the differences were tested with a two-tailed unpaired t-test. Values of \( P < 0.05 \) were considered significant. All comparisons were made between drug-treated and buffer-treated eyes.

Results

IOP Responses in Rabbits With Normal IOP

The intraocular pressure after the two enantiomers of medetomidine (both 12.5 \( \mu \)g/25 \( \mu \)l) were applied to the rabbit eyes are shown in Figure 2. In contrast to dexmedetomidine, levomedetomidine did not induce a decrease in IOP. Apraclonidine caused no significant decrease in IOP in treated or untreated eyes at the studied dosage (Fig. 3). It caused a significant initial increase in IOP that was greater and lasted longer than the corresponding elevation caused by dexmedetomidine (Fig. 3). In rabbits with normal IOP, dexmedetomidine instilled into one eye caused an initial in-
crease in IOP followed by fall in pressure in the treated eye (Fig. 4). The initial increase in IOP was greater, the lower the initial pressure in rabbits (data not shown). In the ipsilateral eye, the onset of hypotension was delayed and occurred between 2–3 hr (Fig. 4). The response in the contralateral eye was immediate and lasted up to 2 or 3 hours post drug administration (Fig. 4). In the treated (ipsilateral) eye, a maximum decrease of 4.6 ± 0.6 mmHg was observed at 2 hr post treatment. In the contralateral eye, the maximum decrease was 4.1 ± 0.5 mmHg at 1 hr after treatment.

IOP Responses in Rabbits With Laser-Induced Elevation of IOP

In rabbits with laser-induced elevation of IOP, dexmedetomidine was topically tested ocularly at two different doses—1.25 and 12.5 μg. The higher dose (12.5 μg) is the same dose that was tested in rabbits with normal IOP. This dose caused a more dramatic fall in IOP in the treated eyes of rabbits with laser-induced elevation of IOP than in normotensive rabbits (Fig. 5). The maximum decrease in IOP of treated glaucomatous eyes was 13.5 ± 0.3 mmHg 1 hr after drug administration. This lasted up to 3 hr. There was no initial increase in IOP. The lower dose of dexmedetomidine (1.25 μg) caused a significant drop in IOP equivalent to that obtained with 125 μg of apraclonidine (P < 0.05 from respective controls), a dose that decreases IOP of glaucomatous eyes in humans.7 Apraclonidine did not affect the IOP in the contralateral eyes of rabbits with laser-induced elevation of IOP in the other eyes (Fig. 6). Dexmedetomidine (12.5 μg) decreased IOP of untreated (contralateral, normal) eyes more than in normal rabbits (Fig. 6).

Discussion

Dexmedetomidine is a recently developed α2-agonist that shows much greater selectivity for the α2- adrenoceptor than other widely used agonists (eg, clonidine).9,11 In contrast to apraclonidine, dexmedetomidine is a selective and specific full agonist on α2-adrenoceptors with high lipid solubility. The compound may have therapeutic potential as an adjunctive agent in anesthesia because it greatly potentiates the action of anesthetic gases and diminishes the need for opiates and anxiolytics.12,13 One of the first subject groups may have those patients with glaucoma who require ophthalmic surgery.14

The mechanisms by which α2-agonists produce their hypotensive effects in the eye are still far from clear. Because levo-isomer is devoid of α2-activity, the efficacy of dexmedetomidine and the inability of levedetomidine to lower IOP in our study support the α2-mediated mechanism of action. Results from other studies have demonstrated that α2-adrenoceptors are located prejunctionally on ocular sympathetic nerve fibers15,16 and postjunctionally in the ciliary body.17,18 It is unclear whether α2-adrenoceptors located in the eye or in the central nervous system are primarily responsible for the reduction in IOP by α2-agonists. The α2-antagonist idazoxan recently has been shown to antagonize the ocular hypotensive effects of racemate medetomidine.19 The results of Ouchi et al20 suggest that the ocular hypotensive effect of clonidine is a result of its α2-adrenoceptor stimulation in the central nervous system and that ocular sympathetic innervation contributes to the IOP lowering effect of clonidine. In contrast, Burke et al21 have demonstrated that UK-14,304-18, another specific α2-agonist, has an ocular hypotensive action after intracameral administration at doses that do not exert central nervous system effects in rabbits.

Controversy exists regarding the specificity of the affinity of imidazole compounds such as dexmedetomidine and imidazolines such as clonidine and apraclonidine, not only to subtypes of the α2-adrenoceptor22 but also to a so-called imidazoline-binding site, the endogenous ligand still to be identified.23 Because many of the newer, specific α2-antagonists such as idazoxan also bind to this site, it is difficult to differentiate between classic α2 responses and those possibly mediated via this binding site. Therefore, we cannot exclude the possibility that the ocular hypotensive effect of dexmedetomidine described here is mediated via this imidazoline binding site.

Because α1-adrenoceptor agonist activity elevates the IOP,4 the initial increase in IOP after dexmedetomidine and apraclonidine administration may be a result of α1-adrenoceptor activation. The apraclonidine-induced increase in IOP was greater and lasted longer than that seen with dexmedetomidine. Although dexmedetomidine is more selective than clonidine and its derivatives, at high concentrations it still may induce α1-mediated effects. It is possible that the local concentrations of dexmedetomidine initially present in the eye may cause transient α1 activation, resulting in a short-term increase in IOP. In eyes with greatly elevated pressure, no such increase is seen, presumably because the α2-mediated hypotension overwhelms any α1-agonistic effects. We are attempting to delineate the various receptor mechanisms involved in the complex effects of dexmedetomidine on ocular pressure.

It is possible that systemic absorption after ocular administration of dexmedetomidine may cause peripheral or central side effects. Although we did not observe sedative nor mydriatic effects in rabbits during this study, the possible systemic side effects of dex-
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Medetomidine must be elucidated fully. However, should these prove to be mild and transient, and provided there is no unexpected ocular toxicity, dexmedetomidine may be a promising drug in the future for the treatment of glaucoma in humans.

Key words: α2-adrenoceptor, dexmedetomidine, intraocular pressure, laser-induced ocular hypertension, rabbits

References