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Dapiprazole HCl: A literature review

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Abstract

Dapiprazole HCl ophthalmic eyedrops have been recently introduced to the optometric profession, and more specifically to optometrists practicing in therapeutic states. This diagonostic drug is used in reversing mydriasis induced by adrenergic or parasympatholytic agents. This is a literature review which covers the entire scope of dapiprazole HCl, or better known as Rev-Eyes, with special emphasis on the specific research studies and the subjective reported side effects, both systemic and ocular.

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DAPIPRAZOLE HCL: A LITERATURE REVIEW

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Jacqueline T. Walsh was born and raised in southern Minnesota. She graduated from Austin Pacelli High School in 1984. In 1989, she graduated from the University of Minnesota in Minneapolis, MN with her B.A. in biology. From 1989 to 1993, she attended Pacific University College of Optometry and obtained her O.D. in May, 1993. She plans to practice optometry in Minnesota.

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DAPIPRAZOLE HCL: A LITERATURE REVIEW

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Abstract:

Dapiprazole HCl ophthalmic eyedrops have been recently introduced to the optometric profession, and more specifically to optometrists practicing in therapeutic states. This diagonostic drug is used in reversing mydriasis induced by adrenergic or parasympatholytic agents. This is a literature review which covers the entire scope of dapiprazole HCl, or better known as Rev-Eyes, with special emphasis on the specific research studies and the subjective reported side effects, both systemic and ocular.

Key Words;

alpha-adrenergic blocker, dapiprazole, dapiprazole HCl, eyedrops, miotic, mydriatic, phenylephrine, Rev-Eyes, tropicamide.

Introduction:

The use of dilation as part of the optometric examination began with the passage of the law allowing optometrists to use diagnostic drugs in Rhode Island in 1971. By 1989 every state in the nation had enacted a diagnostic drug law for optometrists. At first, ophthalmologists objected to this, but are now claiming that optometrists should adhere to the same standards as opthalmology when diagnosing ocular disease.[1] Although every institution and practitioner has varying ideas on when or how often to dilate a patient, most would tend to agree that dilation is a becoming the standard of care for optometrists.[1,12] With this being part of the routine ocular examination, there is the question of quick reversal of mydriasis to reduce the risk of accidents for patients who leave the office fully dilated, and to decrease patient complaints of glare and reduced near vision.

There is a new diagnostic ocular pharmaceutical commonly known by its trade name, Rev-Eyes. It is a topical alpha-adrenergic antagonist called dapiprazole HCl. It has been shown to be more effective than another alpha-adrenergic antagonist, thymoxamine, and more safe than pilocarpine, a cholinergic antagonist, to reverse mydriasis.[2,4,7] Extensive research has been done in both rabbit and human eyes to study any ocular or systemic side effects.[2-11]

To reverse mydriasis and cycloplegia is complicated in terms of safety and speed. Certain topical agents have been attempted before the introduction of dapiprazole HCl, including pilocarpine, which is commonly used in the treatment of glaucoma.[2] Unfortunately, pilocarpine produces ocular pain caused by the spasm of accommodation in the ciliary muscle, blurred vision, and it may induce pupillary block due to a shallowing of the anterior chamber and leading to possible angle closure glaucoma.[2,3,8] Dapiprazole does not have any significant activity on the ciliary muscle contraction; therefore, it does not cause significant change in the anterior chamber depth or lens thickness.[8] The manufacturers claim that dapiprazole is safe and effective to reverse the effects of phenylephrine, an adrenergic agonist, and to a lesser degree, tropicamide, a cholinergic antagonist.[6,8] It may partially increase accommodative amplitude which is decreased by tropicamide.[5,7,8]

Instructions for use:

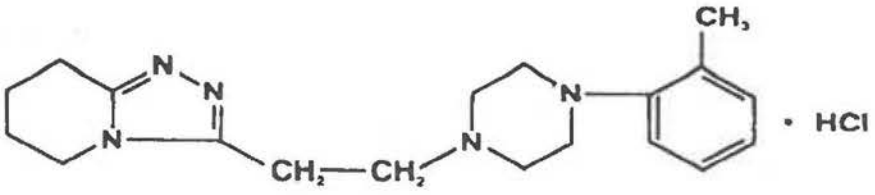
0.5% dapiprazole hydrochloride is a sterile topical solution which is obtained in a form to be mixed by the eye care practitioner. A white, odorless powder is combined with a dilutent and dispensed via an anti-gravity dropper. The reconstituted solution is clear, colorless, and slightly viscous, and lasts twenty-one days at room temperature. It should be discarded after that time or sooner if the solution becomes discolored.

Recommended use is to instill two drops in each eye, then five minutes later instill two more drops[8]; however, published studies differ substantially in the dosage used, so a standard dose has not yet been established. Dapiprazole should not be used in the same patient more frequently than once per week.[10]

Chemical Contents:

Rev-Eyes is marketed by Storz Ophthalmics, Inc. as a kit consisting of one 25 mg vial of dapiprazole HCl, one 5 ml vial of dilutent and a dropper for dispensing.[8]

The contents include the inactive ingredients of mannitol, 2% sodium chloride, hydroxypropyl methylcellulose, 0.4% edetate sodium, 0.01% sodium phosphate dibasic, and sodium phosphate monobasic. The preservative used is 0.01% benzalkonium chloride. It is soluble in sterile saline. Dapiprazole HCl has the emperical formula C19H27N5HCl. It has a molecular weight of 361.93 and a melting point between 193.5 and 196.0 degrees Celsius.[6] The chemical name is 3-[2-[4-(2-methylphenyl)-1-piperazinyl] ethyl]-5,6,7,8,-tetrahydro-1,2,4-triazole[4,3-alpyuridine] HCl[6] and has the following structural formula:



Mechanism of Action:

Dapiprazole HCl is a sympatholytic whose miotic abilities work by blocking the alpha-adrenergic receptors in the smooth dilator muscle of the iris. It does not alter the anterior chamber depth or cause the lens to thicken and move forward because the ciliary muscle is not effected by contractions.[3,8] It has been found that a change in IOP does not occur with either a normal or increased pressure. Minimal systemic absorption has been noted in clinical and laboratory studies.[6] Miosis can be seen within one hour of the last instillation and lasts up to six hours.[3,5]

Cautions and Warnings By the Manufacturer:

Use of dapiprazole is contraindicated in patients with acute iritis or hypersensitivity to the ingredients, especially the preservative, benzalkonium chloride (BAK). There is an increase in the number of liver tumors seen with long term high daily dosages when used in rats (the dose given was 80,000 times the normal human dose administered post-mydriasis). No side effects have been seen in pregnancy; however, no adequate and well controlled studies in pregnant women have been conducted. The manufacturer of dapiprazole, Abbott Laboratories, does advise caution if used in pregnant women. Caution should be exercised when administering this drug to nursing mothers, since many drugs are excreded in human milk; however, this drug has not been found in the secretions of human milk. The safety and efficacy of dapiprazole in children has not been established, and therefore should not be used in pediatric patients. In general, standard toxicologic tests "indicate that dapiprazole is without significant toxicity at dose levels which greatly exceed the human pharmacologic dose."[8]

Adverse Reactions:

Rev-Eyes, a noncholinergic agent, has no effect on pupillary block or blurred vision.[3,8] There are no significant general systemic symptoms involving cardiovascular rate or blood pressure.[6,7] Reported side effects include all of the following: bulbar conjunctival injection, browache, burning, chemosis, corneal edema, dry eye, fluorescein staining of the corneal epithelium, itching, lid edema, lid erythema, palpebral conjunctival injection, ptosis, and tearing.[3,8]

Most of these are due to the dilation of the conjunctival blood vessels from alpha-adrenergic blocking action of dapiprazole.[6,8]

Clinical Studies:

Results of studies performed by the company[8] which manufactures dapiprazole HCl are promising to achieve safe and rapid reversal of mydriasis. With only phenylephrine as the dilating agent, dapiprazole returned 67% of mydriatic pupils to baseline values within thirty minutes and 88% of the pupils by one hour compared to only 7% of the control group. Accommodative amplitude baseline values were calculated at 7.6 diopters. After one-half hour after the last instillation of dapiprazole, treated pupils had 6.8 diopters of accommodation versus the control group which had only 5.7 diopters. Treated groups returned to baseline after two hours, whereas the control group took longer than six hours. There is a lesser effect with the use of tropicamide, since it produces a greater degree of mydriasis and a greater decrease on accommodation. After two hours, 38% of the tropicamide treated subjects were reversed versus only 5% of the controls. They conclude by stating that by using dapiprazole HCl, you will make a significant contribution to your patients' convenience and well being.

Nyman and Keates[6] studied the side effects of dapiprazole on forty subjects. Of those, seven showed treatment emergent adverse reactions either during or after the study. Patient complaints included acne, dizziness, ear popping, fatigue, nausea, stiff neck and ankle, and upper respiratory infection with chest constriction. In these cases, the relation of these events with dapiprazole was remote and the case of acne is completely unproven to be a side effect. No significant difference was found in refraction, visual acuity, diastolic or systolic blood pressure, or pulse rate. Nyman and Keates concluded that treatment with dapiprazole is favored over no treatment when used to reverse the effects of 2.5% or 10% phenylephrine, 0.5% tropicamide, or a combination of 2.5% phenylephrine and 0.5% tropicamide. They theorized that the use of dapiprazole would reduce accidents caused by patients operating vehicles or machinery post-dilation, gives patient comfort and convenience, and would be useful in surgery where miosis is desirable.

In a study done by M.G. Bucci[5], et al, performed on thirty subjects (60 eyes) using only 1% tropicamide as the mydriatic agent, it was found that constriction with Rev-Eyes begins 10 minutes after the last drop and about a 50% reversal occurs in most patients after one hour. The study consisted of ten healthy subjects, ten patients with chronic open angle glaucoma, and ten patients with chronic angle closure glaucoma. Three drops of 1% tropicamide were instilled with five minutes between drops. The baseline pupil mean value was 2.95 mm in both eyes. This evoked a pupil size no less than 6.50 mm in each eye. One eye was used as the control while the other eye received 0.5% dapiprazole HCl. After ten minutes, there was no change in miosis in the control eye and a 9.56% reduction in the treated eye. After three hours, the control pupil decreased to a mean value size of 6.60 mm while the treated pupil decreased to 3.80 mm, a 44.1% reduction. As part of their study, the authors looked at IOP measurements post-mydriasis, ten minutes post-miosis, and three hours post-miosis in those subjects with chronic angle closure glaucoma. Mean IOP for the control eye was 24.67 mm Hg and the mean value for the treated eye was 26.90 mm Hg. Ten minutes post-miosis, the control group read 28.00 mm Hg and in three hours was 27.22 mm Hg. In the treated group, the ten minute post-miosis was 29.40 mm Hg and after three hours read 25.40 mm Hg. They concluded that "dapiprazole HCl is a valid miotic agent that antagonizes the mydriasis that is induced by parasympatholytics" and reduces the risk of dilation in chronic angle closure patients.

In a more relevant study to optometry, Richard W. Allinson[7], et al, demonstrated similar results to the M.G. Bucci study; however, Allison's study dealt with both the systemic and ocular effects using dapiprazole HCl. This was a clinical study using fifty subjects who were not on any medications which could affect pupillary reactions. They dilated patients using 1% tropicamide and 2.5% phenylephrine, the most commonly used dilating solutions for routine fundus examinations among optometrists and ophthalmologists. They found that there were no significant changes in heart rate, blood pressure, visual acuity, or IOP when using Rev-Eyes as a post-dilation miotic.

They measured a mean baseline pupil diameter in their subjects as 3.70 mm. In the treated eyes, 52% went to baseline after two hours. Of the untreated eyes, none had returned to baseline after the two hour period. The main ocular symptom after using dapiprazole HCl was ocular injection and this was reported in 47 of the 50 subjects; however, it was categorized as mild and short term. They concluded that "dapiprazole may be an important addition to the topical agents available to the ophthalmologist" and the optometrist.

An ultrasonic study on the ocular side effects of topical dapiprazole done by L. Bonomi[3], et al, compared one drop of 2% pilocarpine with one drop of 0.5% dapiprazole. They found that dapiprazole produced miosis and decreased IOP just like its competitor, pilocarpine. However, few side effects were noted with dapiprazole. Pilocarpine induced accommodative spasm, thickening and forward displacement of the lens, narrowing of the anterior chamber depth, and had possibility of producing a pupillary block. Pilocarpine was more effective in giving a rapid decrease in pupil diameter: 36% decrease from mydriasis whereas dapiprazole revealed a 22% decrease. Patient symptoms with pilocarpine were reported as mild ocular pain and blurred vision. In a few cases, patients reported a transient burning sensation when dapiprazole was instilled. Since dapiprazole relaxes the radial iris muscle, it cannot induce a pupillary block. They concluded that "dapiprazole seems a promising candidate for use in those indications where miosis is needed, but cholinergic side effects are contraindicated. It may be considered for use in angle closure glaucomas."

Laboratory Studies:

L. Bonomi[10] , et al, published an article in November, 1989 on the intraocular effects of dapiprazole in the rabbit eye. In their study, intraocular applications of 0.05% and 0.01% dapiprazole reversed mydriasis preoperatively induced by 10% phenylephrine and 0.5% tropicamide. No congestion of the ocular tissues occurred and no increase of the permeability of the blood-aqueous barrier resulted when compared to saline solution. No difference in corneal endothelium was observed in treated or untreated eyes. They concluded that dapiprazole would be useful in anterior segment surgery such as extracapsular cataract extraction (ECCE) and surgery for perforating injuries where miosis is beneficial.

A recent study at the Medical College of Georgia[9] tested rabbit corneal endothelium for toxicity when intracamerally injected with dapiprazole hydrochloride. No toxicity was observed over three hours, until the concentration of dapiprazole exceeded 125 micrograms/ml. At 250 micrograms/ml, an increased swelling rate of the corneal endothelium of 17.8 micrometers/ml was seen and showed a continuous and linear perfusion. The preservative, benzalkonium chloride (BAK) which enhances penetration of the drug through the cornea, induced the endothelial damage when not diluted to the manufacturers recommendations. Only 0.0001% BAK is needed to change the endothelium, whereas the 0.5% dapiprazole HCl ophthalmic solution contains 0.01% BAK. They suggested that topical use of this agent is safe; however its use as a post-surgical intracameral injecting agent should be inhibited.

Conclusion:

Dapiprazole appears to be a safe and efficacious topical ophthalmic drug to reverse the effects of mydriasis. It is not as successful in reducing the effects of tropicamide as it is with reducing the effects of phenylephrine. Systemic side effects are minimal. Ocular complaints are burning upon instillation in approximately 50% of the patients, minimal to severe conjunctival injection, and lid edema. The latter two symptoms can last up to three hours.[6]

Many patients will need to drive home, go back to work, or go out into the sunlight immediately after their exam. Practitioners must seriously consider the risk to these patients when allowing them to leave the eye care institution fully dilated. Some individuals are more sensitive to glare and headaches than others, and may postpone an eye exam to avoid the discomfort of a dilated fundus exam. An agent to reverse mydriasis would be advantageous in these and many other cases.

We feel that the side effects might be reduced by decreasing the manufacturers recommended dosage from two drops to one drop per eye. A study of this nature would be beneficial. We would also recommend a study using proparacaine before the instillation of dapiprazole to reduce patient discomfort. Further research should be done to find a compatible preservative other than BAK, in attempt decrease the possible damage to the corneal endothelium.

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