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The effects of dapiprazole on cyclopentolate

David R. Toland  
Pacific University

Steve A. Larsen  
Pacific University

LaVar W. Kofoed  
Pacific University

Greg L. Chin  
Pacific University

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The effects of dapiprazole on cyclopentolate

Abstract
Pupillary dilation to perform binocular indirect ophthalmoscopy and gain three dimensional evaluation of the disc, cup and macula is a routine part of optometric practice. However, many patients find the resulting photophobia and loss of near vision to be an inconvenience. Therefore, clinical interest in ophthalmic agents that will safely reverse the pharmacologically induced mydriasis and cycloplegia have existed for over fifty years. 0.5% dapiprazole HCL is a relatively new adrenergic agent reported to reverse the effects of pupillary dilation and cycloplegia secondary to tropicamide, phenylephrine hydrochloride and other analogs. To date, there have been no studies published to show the effects of dapiprazole on cyclopentolate, another popular cycloplegic/mydriatic agent. In this study, the clinical usefulness and efficacy of dapiprazole in reversing the effects of cyclopentolate were studied. A placebo in a masked (single blind) study was used. Bilateral cycloplegia was used to eliminate any residual accommodation that might have existed between the two eyes. Twenty seven subjects were tested: nine were used as controls, and eighteen were used as experimentals. The experimental group received two drops of dapiprazole administered five minutes apart in each eye 30 minutes after instillation of the cycloplegic drops. The control group received two drops of ocular lubricant administered five minutes apart. The diagnostic agents used for the experimental group were one drop each of 0.5% proparacaine and 1% cyclopentolate. Pupil diameter, amplitude of accommodation, and intraocular pressure were evaluated on each patient. These measurements were taken: (1) before instillation of the cycloplegic agents; (2) prior to instillation of dapiprazole (1 hour after cycloplegia); and (3) at 30, 60, 120, and 180 minutes after the final instillation of dapiprazole. Results indicated no significant difference on positive relative accommodation or negative relative accommodation, or pupil diameter, but with a statistically significant difference in the other variable: decreased IOP. Suggestive trends to dapiprazole’s effects on cyclopentolate do exist that could be turned into statistical trends with an increase in number of test subjects and thier ages.

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THE EFFECTS OF DAPIIPRAZOLE ON CYCLOPENTOLATE

By

David R. Toland
Steve A. Larsen
Lavar W. Kofoed
Greg L. Chin

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Pacific University
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Advisors:

Robert Rosenow, O.D.
Salisa K. Williams, O.D.
Abstract-

Pupillary dilation to perform binocular indirect ophthalmoscopy and gain three dimensional evaluation of the disc, cup and macula is a routine part of optometric practice. However, many patients find the resulting photophobia and loss of near vision to be an inconvenience. Therefore, clinical interest in ophthalmic agents that will safely reverse the pharmacologically induced mydriasis and cycloplegia have existed for over fifty years.

0.5% dapiprazole HCL is a relatively new adrenergic agent reported to reverse the effects of pupillary dilation and cycloplegia secondary to tropicamide, phenylephrine hydrochloride and other analogs.2 To date, there have been no studies published to show the effects of dapiprazole on cyclopentolate, another popular cycloplegic/mydriatic agent.

In this study, the clinical usefulness and efficacy of dapiprazole in reversing the effects of cyclopentolate were studied. A placebo in a masked (single blind) study was used. Bilateral cycloplegia was used to eliminate any residual accommodation that might have existed between the two eyes.

Twenty seven subjects were tested: nine were used as controls, and eighteen were used as experimentals. The experimental group received two drops of dapiprazole administered five minutes apart in each eye 30 minutes after instillation of the cycloplegic drops. The control group received two drops of ocular lubricant administered five minutes apart. The diagnostic agents used for
the experimental group were one drop each of 0.5% proparacaine and 1% cyclopentolate.

Pupil diameter, amplitude of accommodation, and intraocular pressure were evaluated on each patient. These measurements were taken: (1) before instillation of the cycloplegic agents; (2) prior to instillation of dapiprazole (1 hour after cycloplegia); and (3) at 30, 60, 120, and 180 minutes after the final instillation of dapiprazole.

Results indicated no significant difference on positive relative accommodation or negative relative accommodation, or pupil diameter, but with a statistically significant difference in the other variable: decreased IOP. Suggestive trends to dapiprazole’s effects on cyclopentolate do exist that could be turned into statistical trends with an increase in number of test subjects and thier ages.

Introduction-

"No way, Doc! I have to be able to see in a couple of hours!" This is a common response to dilation and/or cycloplegia in these days of on-the-go living. Fortunately, dapiprazole has emerged and offers to the patient the option of a more rapid recovery from such aforementioned procedures.

To date, numerous studies have been undertaken to illustrate the reversal effects of dapiprazole and associated reactions with tropicamide, phenylephrine, and hydroxyamphetamine. Since cyclopentolate is a cholinergic receptor inhibitor and dapiprazole is an alpha receptor blocking
agent, one would believe that dapiprazole should have no effect on cyclopentolate. No studies could be found to describe the effects of dapiprazole upon reversing the action of cyclopentolate. The purpose of this study is to determine if an interaction does exist.

For this study it was hypothesized that, dapiprazole will have an effect upon cyclopentolate by enhancing the recovery period of cyclopentolate-induced cycloplegia, and that there would be a statistical difference showing definitive differences in accommodative abilities in the experimental and control groups. It was also hypothesized that during the pretest and the immediate 1-hour post-cycloplegic periods no statistical difference in accommodation ability would exist for either the control or the experimental groups.

Methods-

Twenty-seven subjects, ranging in age from six to twenty-eight years, were used for this study. The mean age of the subjects (19 male and 8 females) was ten years. A prudent case history was taken to confirm the absence of systemic or ocular disease. Only subjects meeting the following criteria were included in the study: spherical corrections of +3.00 diopters to -6.00 diopters of correction and less than one diopter of anisometropia between the two eyes. In order to be included in the study, the subjects could not have used any medication other than oral contraceptives in the preceding two week period. Pregnant women were excluded from the study. Each subject signed a waiver of informed consent before beginning the study.
The initial examination included a refinement of auto refraction and an external ocular health examination. Optometric Extension Program norms were used for comparison to confirm that each subject had normal accommodative range for his/her age.

The refinement of the refraction included a reading from an Allergen Humphrey auto refractor as well as a refinement of both the sphere and cylinder at distance.

Also, each subject was matched against OEP norms to verify that the iris appearance, pupil reactivity and visual acuity were within norms for his/her age. Pupil reactivity was checked by using a penlight test for direct and consensual response, including ruling out a Marcus Gunn pupil. Visual acuity was measured by using a 20 foot lane and having the subject read the lowest line possible, first monocular and then binocular.

A biomicroscopic exam was also performed to evaluate the external ocular health of the eye.

Accommodation was evaluated binocularly by measuring both the positive relative accommodation and the negative relative accommodation at near using the 20/20 line. The Donders card was also used as a second measure of positive relative accommodation. The Donders card was held at 40cm and the patient was asked to read the 0.62m print. The card was pushed towards the patient until he/she reached a point where he/she could no longer read it binocularly.
Throughout the study, the pupil diameter was measured via a Burton lamp and a hand held pupillometer. Pupils were measured in the dark to avoid pupillary constriction.

Intraocular pressures were obtained with an AO non-contact tonometer rather than with a Goldman tonometer because the repeated use of the applanation probe could cause an abrasion to the cornea that would affect vision.

An artificial pupil was created by drilling a three millimeter diameter hole in an occluder. The artificial pupil provided a standard so that depth of focus remained constant throughout testing. The use of the three mm diameter artificial pupil was validated by both the study conducted by Nyman and Reich\(^2\) and also the Southall study.\(^2\) Both studies show that a three mm pupil does not affect the depth of field any more than a three and a half mm aperture. Also Nyman and Reich 's study showed that the cornea has better clarity within the central three mm area. Therefore, in this study, a three millimeter aperture was the control for the entrance to the pupil of the eye and when placed in the spectacle plane, provides a constant range of accommodation. According to Nyman and Reich, any larger artificial pupil may affect the accommodation.\(^2\)

Accommodation was measured both under monocular and binocular conditions with the best correction in place in the phoropter. The artificial pupil was placed behind the phoropter to insure that proper distance and measurements remained constant. Illumination used was equal to approximately 30 foot candles. A Donders card was then placed at 40 cm and each subject was asked to the read the 0.62m line. The card was then pushed toward the subject until he/she first noticed an inability to read the line. A 20/20 line was then placed at 40 cm where
a blur out and a recovery were completed on both the negative and positive relative accommodation. This test was then immediately repeated a second time, and the average was recorded.

Once the baseline measurements of pupil size, intraocular pressures and accommodation were taken, one drop of proparacaine 0.5% was instilled in each eye with punctal occlusion. Two minutes later, one drop of cyclopentolate 1.0% was instilled in each eye. One hour later, after the cyclopentolate was instilled, intraocular pressures, pupil size, and accommodation were measured again.

After these measurements were taken, the subjects were randomly divided into two groups. Each subject in Group A received a drop of proparacaine 0.5% followed the placebo consisting of artificial ocular lubricant. This placebo was used to obtain a standard by creating a design that was single masked, i.e. only the examiners were informed about which drugs were used. Five minutes later, another drop of ocular lubricant was instilled.

The subjects in Group B also received another drop of proparacaine 0.5% followed by one drop of dapriprazole 0.5% in each eye. Five minutes later, another drop of dapriprazole 0.5% was instilled.

The subjects in both groups were observed every hour for three hours. Pupil size, intraocular pressures and accommodation were measured at each of these observation times. Throughout the study, examiners noted any adverse side effects from the medications, either objectively or subjectively. Any adverse effects were photographed with the Canon fundus camera (CR-45UAF).
180 minutes after instillation of the first drop of dapiprazole, subjects were instructed to be aware of any side effects that may occur. Each subject received a pair of mydriatic glasses upon completion of the study to minimize glare.

Results-

The initial results support the hypothesis that dapiprazole does aid in enhancing accommodative ability and reversing those effects induced by cyclopentolate.

Comparison of the data in this study utilized the unpaired t-tail statistical analysis to show the difference or indifference between the control (placebo) group of eight subjects and the experimental (dapiprazole) group of seventeen subjects. For the pretest and the one-hour post-cycloplegic periods, two tail analysis was employed. This was done to determine if any deviation in any direction could be seen before dapiprazole was utilized. For this initial period, no difference was observed which was significant to $p>0.05$ (Table 1).

| Table 1 |

<table>
<thead>
<tr>
<th>Unpaired t-Test $X_1$: type (PRA) $Y_1$: Pre-cyclo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF: Unpaired t Value</td>
</tr>
<tr>
<td>23</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Count</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Std. Err.</th>
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<tbody>
<tr>
<td>E</td>
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<td>4.5935</td>
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<tr>
<td>C</td>
<td>8</td>
<td>3.91</td>
<td>1.1085</td>
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<tr>
<th>Unpaired t-Test $X_1$: type (PRA) $Y_2$: 1 hr. cyclo</th>
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</thead>
<tbody>
<tr>
<td>DF: Unpaired t Value</td>
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<th>Group</th>
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<tr>
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<tr>
<td>C</td>
<td>8</td>
<td>-1.04</td>
<td>1.7821</td>
<td>0.6301</td>
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</table>
The data depicted in Table 1 showed that both the control group and the experimental group were statistically indifferent prior to the actual dapiprazole testing period.

Data from the one, two and three hour post dapiprazole testing periods, was analyzed by the one tail "t" test. These results also showed that no statistical difference was observed (p>0.05) between the control and experimental groups in dapiprazole's effect upon positive relative accommodation in the reversal of cyclopentolate (Table 2).

### Table 2

| Unpaired t-Test $X_1$: type (PRA) $Y_3$: 1 hr. Dap |
|---|---|---|---|
| DF: | Unpaired t Value | Prob. (1-tail) |
| 23 | 1.5433 | .0682 |

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<th>Std. Err.:</th>
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<td>E</td>
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<td>-0.7565</td>
<td>2.2064</td>
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<td>8</td>
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<td>1.4121</td>
<td>.4992</td>
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</table>

| Unpaired t-Test $X_1$: type (PRA) $Y_4$: 2 hr. Dap |
|---|---|---|---|
| DF: | Unpaired t Value | Prob. (1-tail) |
| 23 | 1.5459 | .0679 |

<table>
<thead>
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<th>Group</th>
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<th>Mean</th>
<th>Std. Dev.:</th>
<th>Std. Err.:</th>
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<tr>
<td>E</td>
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<td>+0.29</td>
<td>1.9919</td>
<td>.4831</td>
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<td>C</td>
<td>8</td>
<td>-1.72</td>
<td>1.1997</td>
<td>.4242</td>
</tr>
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</table>

| Unpaired t-Test $X_1$: type (PRA) $Y_5$: 3 hr. Dap |
|---|---|---|---|
| DF: | Unpaired t Value | Prob. (1-tail) |
| 23 | 1.4853 | .0755 |

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<th>Group</th>
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<td>E</td>
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<td>1.085</td>
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<td>C</td>
<td>8</td>
<td>-1.38</td>
<td>3.3986</td>
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The difference was close to being significant (p~0.06) and there does appear to be a difference graphically (Graph 1).

At one-hour post-cycloplegia and one-hour after dapiprazole instillation, a significant difference (p=0.0015) was noted between the control and experimental groups in negative relative accommodation. Another interesting finding is the largely significant difference (p=0.0282->p=0.0031) found in intraocular pressure in the two and three-hour post dapiprazole findings with no significant difference between groups before the instillation of dapiprazole (graph 2).¹⁰,¹²
Graph 2

IOP (Intra-ocular pressure)

Pupil diameter was measured throughout the testing and showed no significant difference (graph 3).

Graph 3

Pupil Size

There were no adverse side effects noted in this study.
Discussion-

Dapiprazole is specifically marketed as an agent to reverse mydriasis. Many recent studies of dapiprazole have concentrated on its effect on the mydriasis produced by several common dilating agents, including phenylephrine, tropicamide, other analogs and their combinations. These studies suggest that dapiprazole hastens pupillary recovery. Full recovery of pre-dilation pupil size occurs in approximately three hours when dapiprazole is used after instillation of these dilating agents, whereas without dapiprazole, recovery occurs in nearly six hours. The manufacturer's literature suggests that mydriasis is the primary discomfort in routine dilation, but other studies show that the lack of accommodation is often even more annoying. At any rate, dapiprazole is shown to have effects upon both mydriasis and accommodation recoveries when using either parasympatholytic (i.e. tropicamide) or sympathomimetic (i.e. phenylephrine) drugs, even though literature indicates that dapiprazole should have no accommodative effects on the ciliary body. There are, however, alpha receptors on the ciliary muscle tissue and the accommodative recovery effects have been shown.

Though tropicamide and phenylephrine tend to be the most popular drugs for routine dilation, often times there is a need for a drug that induces more cycloplegia for the purpose of a cycloplegic refraction in combination with dilation. Cyclopentolate is a commonly used drug for this purpose. This study explored dapiprazole’s effect on the reversal of cyclopentolate. Because of the presence of alpha receptors on the ciliary muscle tissue it was postulated that dapiprazole might, indeed, have an effect.
Despite the fact that no statistical evidence could be shown to reveal that dapiprazole reverses cycloplegic effects, it is worth noting that a very interesting and suggestive trend does exist to show that dapiprazole does appear to have some effect in cycloplegic reversal. Examination of the data illustrates that accommodation recovery is quicker in the experimental group than that of the control group. A significant difference is not obtained possibly due to insufficient numbers. The age of the test subjects could also have had a negative effect on the results. Another study showed that dapiprazole has limited effectiveness in the very young population\(^6\). Increasing the number of test subjects would aid in increasing the data validity obviously, but more importantly, could turn this suggestive trend into a statistical trend. Further studies using non-presbyopic middle aged subjects would also give expanded useful information. The end result could then lead to an affirmation of the initial proposed hypothesis that dapiprazole does significantly speed the time of recovery of accommodation after cycloplegia via cyclopentolate.

There is no statistical significance to the change in mydriasis shown by the measurements of the pupil diameter, but again, increasing the number of test subjects and their mean age could also turn this suggestive trend into a statistical trend. Iris color was not controlled for in this study, but previous studies show that there is no statistical difference in the regain of accommodation or of mydriasis between darker verses lighter iris color\(^8\). Much like this study there was a trend that showed a faster regain of accommodation and increased miosis with the lighter iris.

Though not a focus of the study, a statistically significant trend was seen with regards to IOP measured. Other literature suggest that dapiprazole has
effects on IOP only after months of use\textsuperscript{10}. But through the use of the two tailed "t" analysis, a 21.36\% difference was seen between control and experimental groups after the third post dapiprazole instillation period in this study. The results showing that the experimental group percent change decrease was, indeed, higher than that of the control group. This is an interesting point and sideline to the drug as this was not what its main purpose was for. Further evidence to this occurrence can be seen in another study\textsuperscript{1}, where a 24\% statistical decrease between experimental and control groups was seen after a short term duration period when utilizing the use of Rev-Eyes and tropicamide. Likewise, in the previously mentioned glaucoma study\textsuperscript{10}, a 2-3 mmHg statistical difference in IOP measure was noted between the test groups over a longer test period of 6 months.

Bibliography-


