A cross-over study of the cycloplegic effects of a single topical application of cyclopentolate-phenylephrine and routine atropinisation for 3.5 days

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Abstract. Static refraction in children after the topical instillation of atropine twice a day during 3.5 days was compared with the refraction after a single instillation of one drop of 0.85% cyclopentolate + 1.5% phenylephrine in a randomized cross-over study. Atropine eye drops were applied by the parents at home, while the combination drop was applied by personnel at the eye clinic. Refraction was determined by retinoscopy in 40 children (3-6 years) in a single blind manner. No statistically significant difference in cycloplegic effect was found between the 2 methods. The results imply that in clinical practice a single instillation of a combination of 0.85% cyclopentolate and 1.5% phenylephrine can be substituted for conventional -full- atropinisation during 3.5 days.

Key words: cycloplegia - cyclopentolate - phenylephrine - atropinisation - combination drops - retinoscopy.

Local application of the long-acting anticholinergic drug atropine into the eye before retinoscopy is a commonly used method to obtain a full cycloplegic effect in children. This procedure involves the instillation of atropine eye drops twice a day for 3.5 days, a total of 7 times. Usually this treatment is carried out in the home, and it is often difficult for parents who are unfamiliar with the technique of applying eye drops to comply with this regime in a correct manner. Unsatisfactory application technique or the omission of several doses are common mistakes, and it is sometimes impossible for the examiner to decide whether there is complete cycloplegia or not. An additional disadvantage is that atropine cycloplegia may last 2 weeks or longer (Havener 1983). In comparison the cycloplegic effect of the short-acting anticholinergic agent cyclopentolate is usually dissipated within 24 h (Havener 1983). However, cyclopentolate, does not produce complete cycloplegia (Ingram & Barr 1979). Further the cycloplegia is particularly inadequate in eyes with brown iris or in individual with a high degree of hypermetropia (Priestly & Medine 1951; Rosenbaum et al. 1981). Tropicamide, another anticholinergic drug, has an ultrashort duration of action of only one hour and is generally inadequate for cycloplegic refraction (Havener 1983).

Another approach to obtain cycloplegia has been to administer combinations of anticholinergic drugs. The action of cyclopentolate alone has been compared with a combination of cyclopentolate and tropicamide (Miranda 1972). The combination of both drugs gave a more complete cycloplegia in persons with dark iris, but not in persons with light iris. The study, however, is uncontrolled in all aspects and the effect of one drop of cyclopentolate is compared with the effect of one drop each of cyclopentolate and tropicamide.

In man the innervation of the ciliary muscle is mainly cholinergic. However, an adrenergic innervation has been shown by many authors (Cogan 1937; Biggs et al. 1959; Garner et al. 1983; Zetterström 1984). Caputo & Lingua (1980) tested a single instillation of a combination drop consisting of an adrenergic drug (1.6% phenylephrine) and two short-acting anticholinergic agents (0.16% tropicamide and 1.3% cyclopentolate).

The use of two different short-acting anticholi-
nergic drugs would appear unnecessary since these two drugs block the action of acetylcholine by occupying the same receptor sites. Additionally cyclopentolate and particularly tropicamide have been shown to produce an incomplete cycloplegia with a maximum effect after 25-75 min and 20-25 min, respectively, (Havener 1983).

In view of the practical problems associated with atropinisation at home, there is a great need for a more convenient, but still reliable procedure to obtain a full cycloplegic effect in children.

In this study the cycloplegic effect following atropinisation at home by the parents over 3.5 days was compared with a single instillation of a combination drop consisting of 0.85% cyclopentolate and 1.5% phenylephrine. The combination drop was administered at the eye clinic by professional personnel. Since the study was a comparison of "routine" atropinisation at home with a single professional instillation, the parents were unaware of the fact that a trial was going on.

Systemic reactions including hypertension and arrhythmia have been reported after topical application of phenylephrine (Fraunfelder & Scafidi 1978; Kim et al. 1978; Rosales et al. 1981). In order to better evaluate the effect of phenylephrine treatment the blood pressure and heart rate were measured in another group of children before and after topical administration of 1.6% phenylephrine, (a total amount of 1.6 mg phenylephrine).

Material and Methods

A total of 40 children (3-6 years) were examined, and all were referred to the Department of Ophthalmology from the Children's Health Care Centres. The first group of 20 children was consecutive new cases. The second group was also consecutive new cases, but only those who were at least +2.5 D hypermetropic were selected. They all had equal and normally reacting pupils, clear fundus and media. The static refraction was measured in each child twice in both eyes. At the first examination all children were randomly allocated for treatment with either 0.5% atropine or a combination of 0.85% cyclopentolate and 1.5% phenylephrine. The refraction measurement was then repeated with the other cycloplegic agent following a wash-out period of at least 2 weeks. Atropine eye drops (0.5%) were administered topically by the parents at home for 3.5 days. One drop was applied to each eye twice a day for 3 days and in the morning of the 4th day before retinoscopy. The alternative treatment involved the application of a single drop consisting of 0.85% cyclopentolate and 1.5% phenylephrine which was topically administered to each eye 45 min before the examination. The children were given the combination drop by professional personnel at the hospital. The single drop was instilled in the lower conjunctival sac. Eyelid closure or nasolacrimal obstruction was not employed. The cyclopentolate-phenylephrine solution was prepared and manufactured at the hospital pharmacy. The drops from the bottle were about 40-50 μl. The determination of the cycloplegic refraction was made with a Heine Streak Retinoscope, and 2 dioptres were subtracted from the point of neutrality to compensate for the working distance of 0.5 metre. No attempt was made to determine whether the cycloplegic effect after atropinisation at home was complete or not.

All the determinations were made by the same examiner. The study was performed in a single blind manner, with the examiner having no knowledge of the method used to obtain cycloplegia. The study was approved by the ethical committee of the University of Uppsala.

Blood pressure and heart rate were determined in 100 children 2-10 years (5.8±0.17 (mean ± SEM)). The children were consecutively selected from new and old cases. One drop of 1.6% phenylephrine was instilled in each eye (a total amount of 1.6 mg phenylephrine). Blood pressure and heart rate were measured immediately before the instillation and 15, 30 and 45 min after the instillation. In most cases the measurements were repeated 60 min, and in some 75 min, following drug administration.

Results

The data showing the cycloplegic effect of the two examinations are plotted in Fig. 1. The measurements from the most hypermetropic eye of each child were chosen. In those cases where both eyes had similar refraction at the first examination, the right eye was chosen. Just the spherical refraction from each child is recorded. Eighteen out of 40 children showed an increase in hypermetropia after atropinisation. One out of the 18 had a difference of +1.0 dioptre, while all the remaining 17
Fig. 1.
The static refraction measurements in dioptres in children after 3.5 days treatment with 0.5% atropine eyedrops (A) (abscissa) compared with a single instillation of 1.5% phenylephrine and 0.85% cyclopentolate (C) (ordinate). Each point represents paired measurements obtained from a single child. There was no significant difference between the two treatments (Student's t-test for paired samples). Correlation coefficient $r = 0.987$.

Table 1.
Blood pressure and heart rate measurements before and at 15 min intervals after, topical instillation of 1.6 mg phenylephrine.

<table>
<thead>
<tr>
<th>Time after topical administration of 1.6 mg phenylephrine</th>
<th>Before (N = 100)</th>
<th>15 min (N = 98)</th>
<th>30 min (N = 99)</th>
<th>45 min (N = 75)</th>
<th>60 min (N = 58)</th>
<th>75 min (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>115.4 ± 0.9/</td>
<td>115 ± 0.9/</td>
<td>114.3 ± 0.8/</td>
<td>114.9 ± 0.9/</td>
<td>114.3 ± 1.0/</td>
<td>116.1 ± 1.2/</td>
</tr>
<tr>
<td></td>
<td>77.7 ± 0.9</td>
<td>77.4 ± 0.8</td>
<td>77.1 ± 0.7</td>
<td>77.3 ± 0.9</td>
<td>75.2 ± 1.5</td>
<td>75.9 ± 1.3</td>
</tr>
<tr>
<td>Range</td>
<td>100–150/</td>
<td>100–140/</td>
<td>100–150/</td>
<td>100–130/</td>
<td>100–135/</td>
<td>110–135/</td>
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<tr>
<td></td>
<td>60–120</td>
<td>60–110</td>
<td>60–105</td>
<td>70–100</td>
<td>60–95</td>
<td>65–105</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>86.0 ± 0.9</td>
<td>86.1 ± 0.9</td>
<td>85.7 ± 0.8</td>
<td>85.9 ± 1.0</td>
<td>86.6 ± 0.9</td>
<td>86.3 ± 1.4</td>
</tr>
</tbody>
</table>
showed a difference of +0.5 dioptre. Three children showed a slight increase (+0.5 D) in hypermetropia after the combination drop. There was no statistical difference between the two methods \((P>0.3, t\text{-test for paired samples})\). Furthermore the calculation of Pearsons correlation coefficient showed \(r = 0.987\).

No changes in blood pressure or heart rate were noted in a group of 100 children after topical application of 1.6\% phenylephrine (0.8 mg phenylephrine per drop in each eye, totally 1.6 mg) (Table 1).

**Discussion**

It is generally considered necessary to use long-acting atropine at home for 3.5 days in order to obtain complete cycloplegia. However, the parents often have difficulties in applying the drops in a correct manner and doubts often arise whether a full cycloplegic effect has been achieved. Moreover, a prolonged cycloplegia during a sensitive period might, in some cases, potentiate stimulus deprivation and contribute to amblyopia (Ikeda & Tremaine 1978). In the present cross-over study a comparison has been made between the routine instillation of atropine at home by the parents with a single instillation of a combination drop of cyclopentolate and phenylephrine administered at the hospital. The two treatments in this cross-over study appear remarkably similar. The data show that the dual effect of cyclopentolate, a short-acting anticholinergic drug and phenylephrine, an adrenergic agent, did not differ from "full" atropinisation at home. Cyclopentolate alone does not produce a complete cycloplegia (Ingram & Barr 1979), particularly not in the eyes with brown iris (Priestly & Medine 1951) or in children with a high degree of hypermetropia (Rosenbaum et al. 1981). Rosenbaum et al. (1981) found that 22\% of the children in their study had an additional hyperopia of +1.0 dioptre or more which was uncovered by atropine. Almost all children in this subgroup had an initial cyclopentolate retinoscopy of +2.0 dioptres or more.

With this in mind half of the children in our study were consecutively selected from new cases who were at least +2.5 dioptres hypermetropic. However, even in children with a high degree of hypermetropia we found a good correlation between the two treatments. Hartgraves & Kronfeld (1931) studied whether the addition of epinephrine, an adrenergic drug, after complete atropinisation would change the refraction towards hypermetropia. They could not find any synergistic interaction between the drug used and atropine. However, most of their test subjects were adults (17-44 years) with a low degree of hypermetropia. In our previous investigation on children (Zetterström 1984) the addition of phenylephrine after complete atropinisation caused an increase in hypermetropia, although possible because of the small sample size \((N=20)\) the difference was not statistically significant compared to atropinisation alone. In clinical practice Caputo & Lingua (1980) also tested a single instillation of phenylephrine but in combination with cyclopentolate and tropicamide. However, their results remain unproven since this was an open rather than blind study.

Caputo & Lingua (1978) could not find any change in blood pressure or heart rate in 23 newborns after topical instillation of 2.5\% phenylephrine (2.5-7.5 mg). However, this latter study also showed in 13 babies that 10\% phenylephrine (total amount of 30 mg phenylephrine) produced a considerable rise in blood pressure and blanching around the eyes. Further, systemic reactions after topically administered 10\% phenylephrine have been reported elsewhere. Fraunfelder & Scafidi (1978) reported 53 cases of adverse side effects probably related to topical application of 10\% phenylephrine. They concluded that pre-disposing factors included overdosing of the drug, cardiac disease, advanced age and drug interactions. Also Kim et al. (1978) found that patients with sympathetic denervation showed a significant increase in blood pressure after topical application of one or two drops of 10\% phenylephrine (5-7.5 mg per drop) up to 3 or 4 doses administered every 15 min. Additionally, a significant hypertensive reaction was noted in 10 low weight infants after instillation of 7.5 mg phenylephrine, with 3 of these children having systolic blood pressure increasing 50\% or more (Rosales et al. 1981).

In the present study there was no change in either heart rate or blood pressure in 100 children (2-10 years) after the instillation of 1.6 mg phenylephrine. This might thus be regarded as a safe dose to use for future refraction measurements in children. Similarly in a double-blind study Borromeo-Mc Grail et al. (1973) found that blood pressure remained stable in infants receiving 2.5\% phenylephrine (2.5 mg).
The results of the present study have clinical importance. There are many disadvantages with atropinisation at home. Compliance is often unsatisfactory, the drug effects are long-acting, and it is often difficult to decide whether a complete cycloplegic effect has been achieved. We have to accept that in addition to practical difficulties of atropinisation there is no guarantee of a full cycloplegic effect. A single instillation of a short-acting combination drop by trained personnel at the time of examination offers many advantages. The present results suggest that it should be possible to replace atropinisation at home with a single instillation of a combination drop of cyclopentolate and phenylephrine.

Acknowledgments

I wish to thank the Carmen and Bertil Regnér Foundation for grants and the staff at Skeholvsranken, Sabbatsbergs sjukhus, Stockholm who made this trial possible.

References


Received on March 1st, 1985.

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