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Rapid Communication

The Mydriatic Effect of Tropicamide and its Diagnostic Use in Alzheimer's Disease

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The mydriatic effect of topically administered tropicamide was investigated as a possible diagnostic indicator for Alzheimer's disease. Although an initial series seemed to show a correlation between hypersensitivity to tropicamide and intellectual impairment, subsequent testing showed a greater inter- and intra-individual variation than that between the normal group and the group of patients with intellectual impairment. This procedure seems, therefore, to lack sufficient specificity to be useful for such a diagnostic purpose. Copyright © 1996 Elsevier Science Ltd

Pupil Alzheimer's disease Mydriasis Tropicamide

INTRODUCTION

Sacks and Smith (1989) have found a mydriatic hypersensitivity to 0.01% topically administered tropicamide in patients with Down's syndrome, which was attributed to acetylcholine deficiency. Scinto *et al.* (1994) have reported such a procedure as a simple diagnostic method for the differential diagnosis of Alzheimer's disease from others causing intellectual impairment.

In this paper, the authors have sought to eliminate all other possible causes of variation in pupillary dilation. Firstly, the effects of agitation, distress, unknown systemic pharmaceuticals, and undetected environmental adaptation effects were eliminated by measuring both pupillary diameters, but administering tropicamide to only one eye. All patients were given a Schirmer's test, tear film break up test, Meibomian gland evaluation, endothelial cell count, corneal pachymetry, intra-ocular pressure measurement and iris colour recorded.

The test was repeated after 4 weeks to assess the reproducibility of results over time, and an effect due to corneal permeability was eliminated by comparing the effect of tropicamide after oxybuprocain pretreatment on either eye alternately of three control individuals [see Fig. 6(A, B)].

SUBJECTS AND METHODS

34 intellectually impaired patients (age 69 ± 11) years, 20 male 14 female) were investigated. The onset of impairment varied from 2 to 5 years before the experiment. Full neurological examinations including cognitive tests, magnetic resonance imaging, X-ray computed tomography, electro-encephalography, Doppler ultrasonography and blood chemistry were carried out. Only those patients fulfilling the NINCDS–ADRDA criteria (Tierney *et al.*, 1988) were confirmed as having Alzheimer's disease; these were 23 in number. This left 11 individuals with impairment but not firm diagnosis of Alzheimer's disease.

Thirty-one normal individuals (age 54.6 ± 14.2, 13 male, 18 female) with no intellectual impairment were used as a control group.

Prior to the test each individual underwent a standard ophthalmic workup (visual acuity, biomicroscopic examination including the fundus). The test included tonometry, endothelial microscopy, corneal pachymetry, Meibomian gland evaluation, tear film break-up time and Schirmer's test.

The main part of the test comprised infrared pupillography as described by Schaeffel *et al.* (1993), based on a personal computer receiving data from an infra red sensitive camera (Canon) via an Oculus-OC-300/ 512 × 1024 frame grabber. This recorded the following at a rate of 25 Hz (real time): vertical and horizontal eye movement, accommodation by on-line retinoscopy and pupillary size. Background illuminance was 100 lux, spatial resolution was 0.1 mm.

Data registration is halted during blinking for approximately 1.5 sec to avoid pupil changes. The automated data collection is expressed as the average of 250 measurements calculated off-line. These on-line controls seem to be necessary to obtain reliable results. After baseline pupil measurement, 0.01% tropicamide was administered to one eye chosen at random and pupillary

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TABLE 1. Tear film and corneal parameters of our 34 intellectually impaired patients

	OD	OS	Units
Schirmer	13.3 ± 12.3	14.3 ± 12	mm
Break up t.	7.0 ± 3	7.8 ± 4.2	sec
Meibom	1.2 ± 0.7	1.3 ± 0.7	staging
Endothelial cells	2323 ± 346	2332 ± 330	c/mm^2
Pachymetry	523 ± 37	524 ± 36	μ

All results are within the normal range for elderly individuals. Furthermore, they were not different in the two separate patients groups. $n = 34$.

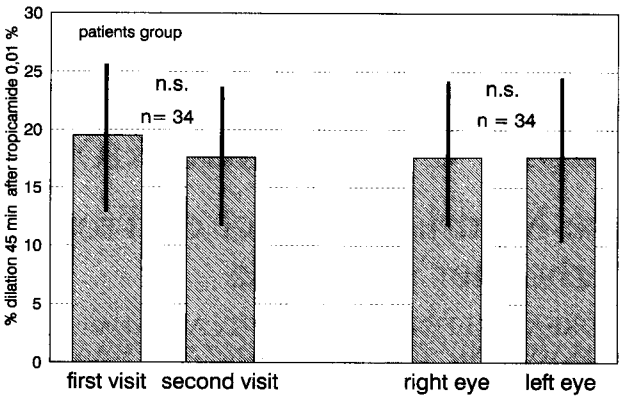

FIGURE 2. Average dilation effect of 0.01% tropicamide after 45 min in intellectually impaired patients. There is little change in the average after 4 weeks (second visit) and no average difference in the fellow eyes.

measurements were taken of both eyes at 15 min intervals for 90 min. After an interval of 4 weeks, the tests were repeated in the same way but with both eyes being treated with tropicamide in order to evaluate intra-individual variation.

Written informed consent was obtained from patients and care-givers, respectively.

STATISTICAL ANALYSIS

Comparing location (mean) and scale (variance) parametrically we used the paired Student's t-test after comparing variances with Fisher's F-test. With the calculation of the Pearson's r product–moment linear correlation coefficient as well as with explorative data analysis we tested the strength of association between tear film parameters, corneal parameters, mind scores, and the dilatory effect of tropicamide. In order to evaluate whether the change in pupil diameter is associated with corneal and tear film variables, the multiple correlation coefficient was calculated.

RESULTS

Tear film and corneal parameters were all within the normal range for elderly individuals (Table 1). Furthermore, they were not different in the two separate groups of patients. Neither single correlation nor multi-variant analysis showed a correlation of pupil dilation with any of the measured ocular anatomy or physiology.

For the intellectually impaired patients, Fig. 1 shows an average % change in pupil diameter 45 min after tropicamide application of 18.6 ± 11.02%. Figure 2 shows that there was little change in the average on the second visit and no average difference in the fellow eyes, however, Fig. 3 shows a striking intra-individual variation. Individual results could show a variation by a factor of 2 between the first and second test in the same eye. Figure 4 compares the results from the two separate groups of those 23 patients confidently diagnosed with AD to those 11 less impaired. On the first occasion a clear difference was seen ($P = 0.05$; not shown in Fig. 4), however, on the second test there was no significant difference.

For the normal controls Fig. 5 shows an extreme variation in the dilation effect. Figures as high as 60%

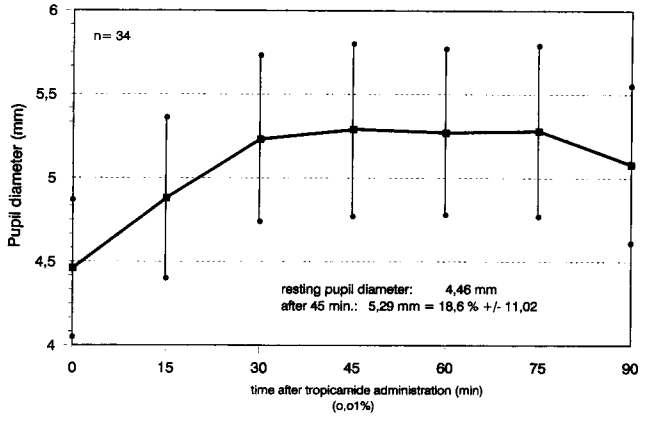

FIGURE 1. Pupil dilation response to topically applied 0.01% tropicamide in 34 intellectually impaired patients. Infrared pupillography measurements were taken in 15 min intervals over the course of 90 min. Maximum effect over baseline is reached after 45 min.

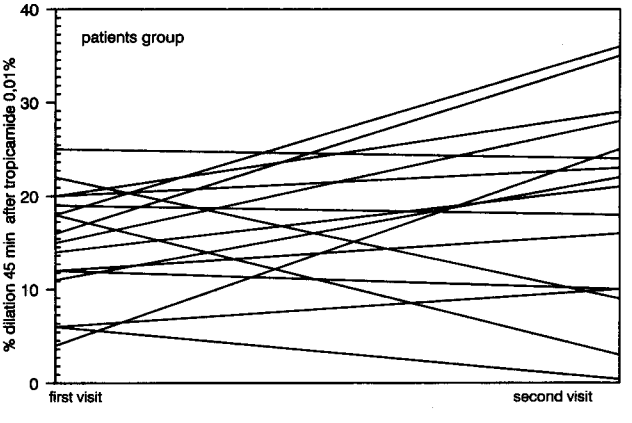

FIGURE 3. Striking intra-individual variation in the response to 0.01% tropicamide in cognitively deprived patients; pupillography measurements were repeated under standardized conditions 4 weeks later (second visit).

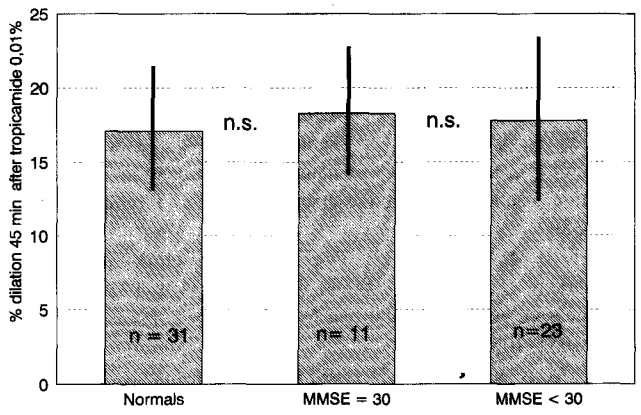

FIGURE 4. The average response to 0.01% tropicamide after 45 min is not significantly different between normals, cognitively deprived patients (MMSE = 30), and Alzheimer patients (MMSE < 30); MMSE = Mini Mental State Examination.

and below 10% were found. Of the control individuals with a dilation of more than 20% on the first test, eight had values below 10% and three individuals between 15 and 20% when tested 4 weeks later.

However, a clear-cut influence of corneal permeability on the response to tropicamide administration could be demonstrated experimentally: prior to tropicamide application healthy controls ($n = 3$, 37 ± 2 yr) received anaesthetic eye drops (oxybuprocain 0.4%) three times in 2 min intervals in one eye. Figure 6(A) shows a 50% pupil dilation over baseline in such pretreated eyes compared to a discrete dilation of less than 10% in the fellow eye. The nonspecific dilating effect due to pretreatment could be verified by repeating the experiments for the other eye [Fig. 6(B)].

DISCUSSION

In the patient collective we found an average mydriatic effect in the tropicamide treated eye of 18.6%—similar to the results obtained by Scinto—and no change in the

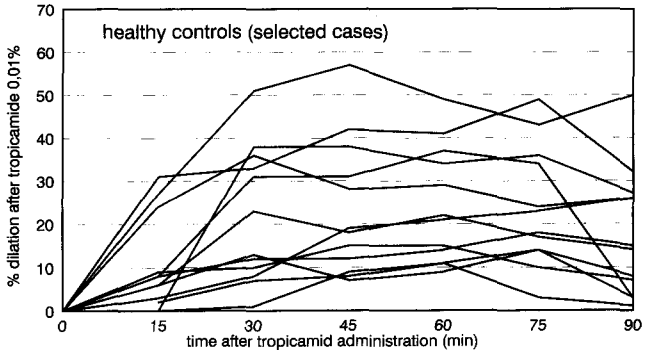

FIGURE 5. Response to 0.01% tropicamide eye drops in healthy controls (mean 12.6% ± 4.5; $n = 31$). After 45 min dilation effects range between 7 and 57%. Selected cases are shown.

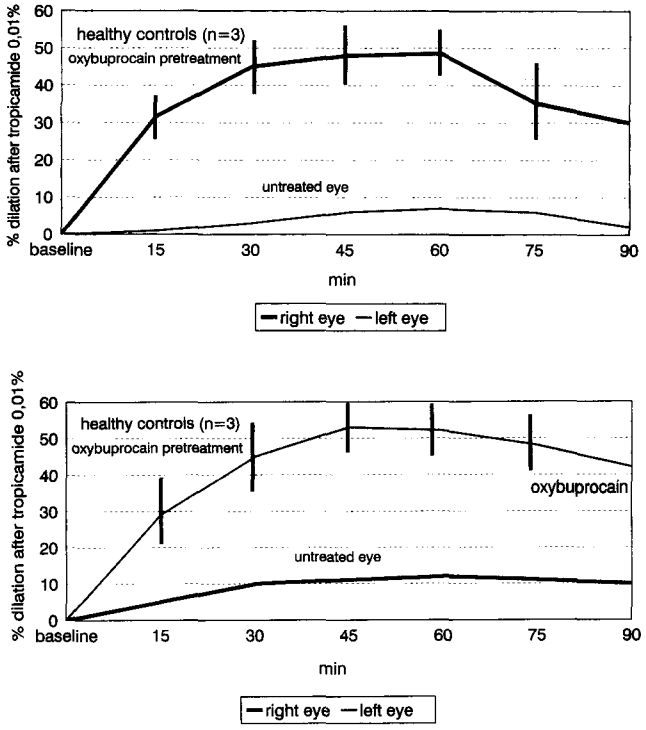

FIGURE 6. The influence of corneal permeability on the response to 0.01% tropicamide eye drops is shown. Prior to tropicamide application to both eyes three healthy controls received oxybuprocain eye drops in one eye. Subsequently, infra-red pupillography was performed as described. In such pretreated eyes up to 50% dilation over baseline was observed (A). The nonspecific dilating effect due to pretreatment was verified by repeating the experiments for the other eye (B).

average diameter of the untreated eye. The same results—as regards the average mydriatic effect—were obtained in a second test series performed 4 weeks later. No difference was seen between the right and the left eye. Those patients complaining about memory impairment although passing the MMSE showed less dilating response in the first test series. However, on retesting, this finding could not be reproduced; indicating that at this point pupillary response to pharmacological agents is not able to distinguish diagnosed AD patients from patients complaining about memory impairment but lacking clinically notable cognitive defects.

Despite the fact that pupillography was performed under standardized conditions, intra-individual variation in all subgroups of patients as well as in control subjects was extremely high, indicating that this test is not specific enough. Taking 13% of pupil dilation as a cut-off value we would have missed 39% of diagnosed AD patients, while 67% of normal controls would have reacted false positive.

Although the influence on corneal permeability of oxybuprocain [see Fig. 6(A, B)] altered the effect of tropicamide, no ocular pathologies were found in the subjects tested to account for the large variability in results found between individuals or occasions. Never-

theless, the influence of epithelial barrier function and endothelial pump function needs further attention.

All measurements of tear film condition are still imprecise, however, Down's syndrome patients appear (Shapiro & France, 1985) to have anatomical anomalies in the anterior segment (e.g. iris stromal atrophy, keratoconus, blepharitis, nasolacrimal duct obstruction etc.) which may cause a difference in the effect of tropicamide.

The expected differentiation of intellectually impaired from normal individuals due to a cholinergic deficit was not found using this testing method. Further experimentation with alternative pharmaceutical agents or a testing regime carried out over different time intervals will have to be conducted before the utility of this simple test of pupillary reaction in the diagnosis of Alzheimer's desease can be determined.

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