Pupillary Response to Tropicamide in Patients with Alzheimer Disease

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Purpose: To determine whether pupillary responses to dilute tropicamide could be used as a diagnostic test for Alzheimer disease (AD). The authors also investigated whether concurrent use of an oral acetylcholinesterase inhibitor (tacrine) alters the pupillary response to dilute tropicamide in patients with AD, and whether pupillary responses to dilute tropicamide differ in young versus older control subjects.

Methods: Pupillary diameter and area of both eyes were measured in light and darkness, at 10-minute intervals for 40 minutes after random instillation of 0.01% tropicamide to one eye. Four groups of subjects were studied: 9 patients with AD, 10 who were treated with tacrine, 11 older control subjects, and 10 young control subjects.

Results: Mean change in anisocoria was not significantly different among groups at any of the measurement time points. Mean percent change in diameter of the treated eyes showed a trend toward faster maximum dilatation in the AD groups, but change in pupillary measurements did not identify individuals with AD.

Conclusion: Pupillary response to dilute tropicamide did not effectively distinguish individual patients with AD from young or older control subjects.
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Alzheimer disease (AD), a neurodegenerative disorder of the central nervous system, is the most common cause of dementia, affecting more than 20 million people worldwide.[1,2] Although the accuracy of clinical diagnosis has improved,[3] definitive diagnosis still requires histopathologic examination of brain tissue. A noninvasive, sensitive, and easily performed diagnostic test for early AD would be received enthusiastically.

Scinto and colleagues[4] proposed that the pupillary response to a cholinergic antagonist, tropicamide, may be such a noninvasive test. They reported a marked hypersensitivity of pupil dilatation to dilute tropicamide in their patients with clinically diagnosed or suspected AD as compared with healthy elderly control subjects, an effect robust enough to distinguish among the individuals in the two groups.

We studied the pupillary responses to dilute tropicamide in four groups of subjects: healthy young control sub-

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jects; healthy elderly control subjects; patients with clinically diagnosed AD not receiving specific therapy; and patients with AD taking tacrine. Because many patients with mild to moderate AD are using tacrine, a cholinesterase inhibitor with modest reported efficacy in this disease,[5,6] we questioned whether the concurrent use of tacrine would alter the pupillary response to the anticholinergic properties of tropicamide.

Materials and Methods

Patients with AD by clinical research criteria[7] were recruited from the Emory University/Wesley Woods Memory Assessment Clinic in Atlanta, Georgia. Nineteen patients with AD completed the study. Of these patients, nine were not taking any psychoactive or cholinergically active medications (NTAD group), and ten were using tacrine (TAD group).

Twenty-one control subjects comprised two groups: 11 patients 57 to 80 years of age (older control [OC] group) and 10 patients 21 to 49 years of age (young control [YC] group). The OC group was recruited from a population of well-characterized control subjects, some of whom participated in previous cognitive studies at our center.[8] Younger controls were a convenience sample of volunteer graduate students and employees of Emory University. No control subject had a history of central nervous system disease, prior head trauma, or used medication that could influence pupillary motor response.

The research protocol was approved by the Human Investigations Committee of Emory University School of Medicine. Informed consent was obtained from all participants and by caregiver proxy for each patient with AD. The Mini-Mental State Examination (MMSE)[9] was administered to each subject at the time of pupillary response testing. Since the MMSE is recognized to be insensitive to subtle cognitive deficits,[10,11] additional neuropsychologic tests were administered to each patient in the OC group. These tests included the Mattis Dementia Rating Scale,[12] modifications of the FAS and Line Orientation Tests, the Boston Naming Test, selected subtests of the Weschler Memory Scale–Revised,[13] and the Symbol Digit and Similarities subtest of the Weschler Adult Intelligence Scale–Revised.

All subjects underwent ophthalmologic evaluation to rule out pre-existing pupillary or corneal abnormalities. The examination included pupil, eyelid, and motility assessment and slit-lamp biomicroscopy. No topical agents were administered, and tonometry was not performed, so that the corneal epithelial integrity would not be disturbed. Exclusion criteria included history or evidence of eye surgery, glaucoma, pupillary abnormalities, third nerve palsy, corneal or iris abnormalities, dry eyes, and use of eye drops, including artificial tear supplements. Thirty-two patients meeting clinical criteria for AD[7] were asked to volunteer for the study. Five refused to participate. Of the 27 remaining volunteers, 2 were excluded because they had glaucoma, 4 were excluded because of previous eye surgery, and 2 were using medications that potentially could influence pupillary response. One control volunteer was excluded because biomicroscopy showed corneal epithelial changes consistent with keratoconjunctivitis sicca.

Pupillary measurements were made using computerized video pupillometry with the CPM-20 (Escalon-Medical Trek, Mukwanago, WI). This device couples an infrared (IR) light source and IR-sensitive video camera to

Table 1. Patient Characteristics

Characteristics	Group			
	NTAD *(n = 9)*	*TAD* *(n = 10)*	OC *(n = 11)*	YC *(n = 10)*
Age (yrs) (mean ± SD)	75.6 ± 5.2	70.4 ± 10.3	69.5 ± 6.0	36.3 ± 11.4
Sex (% female)	44%	60%	45%	40%
Iris color (% brown)	66%	30%	63%	50%
MMSE (mean ± SD)	19.3 ± 6.2	17.8 ± 7.7	29.4 ± 0.5	29.7 ± 0.5
Baseline pupil diameter (mm) in light, treated eye (mean ± SD)	3.85 ± 0.90	3.84 ± 0.64	4.31 ± 0.79	5.10 ± 1.01
Anisocoria of pupil diameter (mm) in light (mean ± SD)	0.22 ± 0.50	0.13 ± 0.33	0.09 ± 0.38	−0.16 ± 0.51
Baseline pupil area (mm^2) in light, treated eye (mean ± SD)	11.90 ± 5.78	11.18 ± 3.80	14.06 ± 5.37	20.39 ± 8.77
Anisocoria of pupil area (mm^2) in light (mean ± SD)	1.91 ± 3.24	0.19 ± 1.91	−0.10 ± 2.71	−0.91 ± 4.13

NTAD = patients with Alzheimer disease not taking tacrine; TAD = patients with Alzheimer disease taking tacrine; OC = older control subjects; YC = young control subjects; SD = standard deviation; MMSE = Mini-Mental-State Examination scores.

Table 2. Mean Change in Pupillary Measures after Instillation of 0.01% Tropicamide in the Treated Eye

Measure	Time after Instillation (mins)	Group NTAD (n = 9) Mean ± SD	TAD (n = 10) Mean ± SD	OC (n = 11) Mean ± SD	YC (n = 10) Mean ± SD	P*
Diameter (mm), light	10	0.18 ± 0.19	0.24 ± 0.24	0.16 ± 0.29	0.12 ± 0.44	0.95
	20	0.76 ± 0.39	0.95 ± 0.40	0.52 ± 0.50	0.51 ± 0.76	0.11
	30	0.86 ± 0.30	0.84 ± 0.50	0.58 ± 0.54	0.68 ± 0.63	0.50
	40	0.71 ± 0.28	0.89 ± 0.54	0.84 ± 0.54	0.86 ± 0.64	0.86
Diameter (mm), dark	10	0.40 ± 0.31	0.20 ± 0.32	0.27 ± 0.26	0.29 ± 0.42	0.76
	20	0.65 ± 0.35	0.45 ± 0.41	0.47 ± 0.35	0.63 ± 0.48	0.61
	30	0.70 ± 0.30	0.57 ± 0.44	0.61 ± 0.38	0.77 ± 0.59	0.71
	40	0.63 ± 0.46	0.58 ± 0.51	0.64 ± 0.26	0.88 ± 0.61	0.39
Area (mm^2), light	10	1.13 ± 1.62	1.28 ± 1.52	0.89 ± 2.09	0.45 ± 2.82	0.96
	20	5.47 ± 3.01	6.28 ± 2.65	3.84 ± 3.47	3.85 ± 5.56	0.29
	30	6.01 ± 2.98	5.25 ± 3.22	3.98 ± 4.03	5.11 ± 4.28	0.62
	40	4.80 ± 2.22	5.92 ± 3.44	5.75 ± 4.10	6.91 ± 5.02	0.62
Area (mm^2), dark	10	2.82 ± 2.43	2.02 ± 1.99	1.93 ± 1.88	2.25 ± 3.70	0.94
	20	5.77 ± 2.89	4.25 ± 3.46	4.56 ± 2.79	6.29 ± 3.13	0.49
	30	6.83 ± 2.89	6.20 ± 3.52	5.49 ± 3.39	7.63 ± 4.94	0.53
	40	6.01 ± 4.09	6.34 ± 5.19	5.67 ± 2.88	8.41 ± 3.53	0.27

* From a repeated measures analysis of variance comparing the mean value of the four groups.

NTAD = patients with Alzheimer disease not taking tacrine; SD = standard deviation; TAD = patients with Alzheimer disease taking tacrine; OC = older control subjects; YC = young control subjects.

a personal computer-based software package. The eye is illuminated using IR so that the pupil size would not be affected. Infrared illumination also allows images to be captured in total darkness. A single image of the eye is transferred to the screen using the video camera and a digital frame grabber. A light pen is used to measure either the distance between pairs of points (pupil diameter), or the area of a traced circumference (pupil area). Subjects were seated with their head in an adjustable chin rest and fixated on a nonaccommodative target. Baseline measurements of horizontal pupil diameter and pupillary area were obtained, both in room light (131 lux, meter candles) and in the dark (below measurable limits), for each eye. One minute of dark adaptation occurred between the light and dark measurements.

One drop of 0.01% tropicamide was placed in the inferior fornix of one eye and balanced saline in the fellow eye. Drops were delivered from coded, single dose containers in a masked, double blinded fashion. Repeat measurements were made every 10 minutes for 40 minutes after instillation. Between measurements room light was maintained and subjects were engaged in relaxed conversation. Drug concentration was verified by assay from an independent laboratory. Iris color was recorded as either brown or non-brown (blue or green).

Statistical Analysis

Data were entered from forms utilizing double entry and verification. Data management and analysis were performed using the Statistical Analysis System (SAS Institute, Cary, NC). The pupil parameters analyzed were change and percent change in diameter and area of the treated eye, and the change in anisocoria of diameter and area. Anisocoria was calculated by subtracting the value of the control eye from the treated eye. All parameters were assessed in light and darkness. The mean changes of these parameters at each postinstillation time point were compared among the four groups using a repeated measures analysis of variance. The effect of eye color was evaluated by comparing mean percent change in diameter between brown and nonbrown eyes using a Student's *t* test, which was done separately for the combined AD groups and the combined control groups. Patient characteristics at baseline were compared among the four groups using a chi-square test for categorical variables and a one-way analysis of variance for continuous variables. *P* less than 0.05 was used to assess statistical significance.

Results

Forty white subjects (19 men and 21 women) of European heritage were studied (Table 1). Sex distribution was similar among groups ($P = 0.82$). Mean ages were comparable among the AD groups and OC group ($P = 0.17$). The MMSE scores for the TAD group and the NTAD group ranged from 4 to 26, consistent with the cognitive impairment expected in patients with AD.[14] All controls scored either 29 or 30 on the MMSE, well within popu-

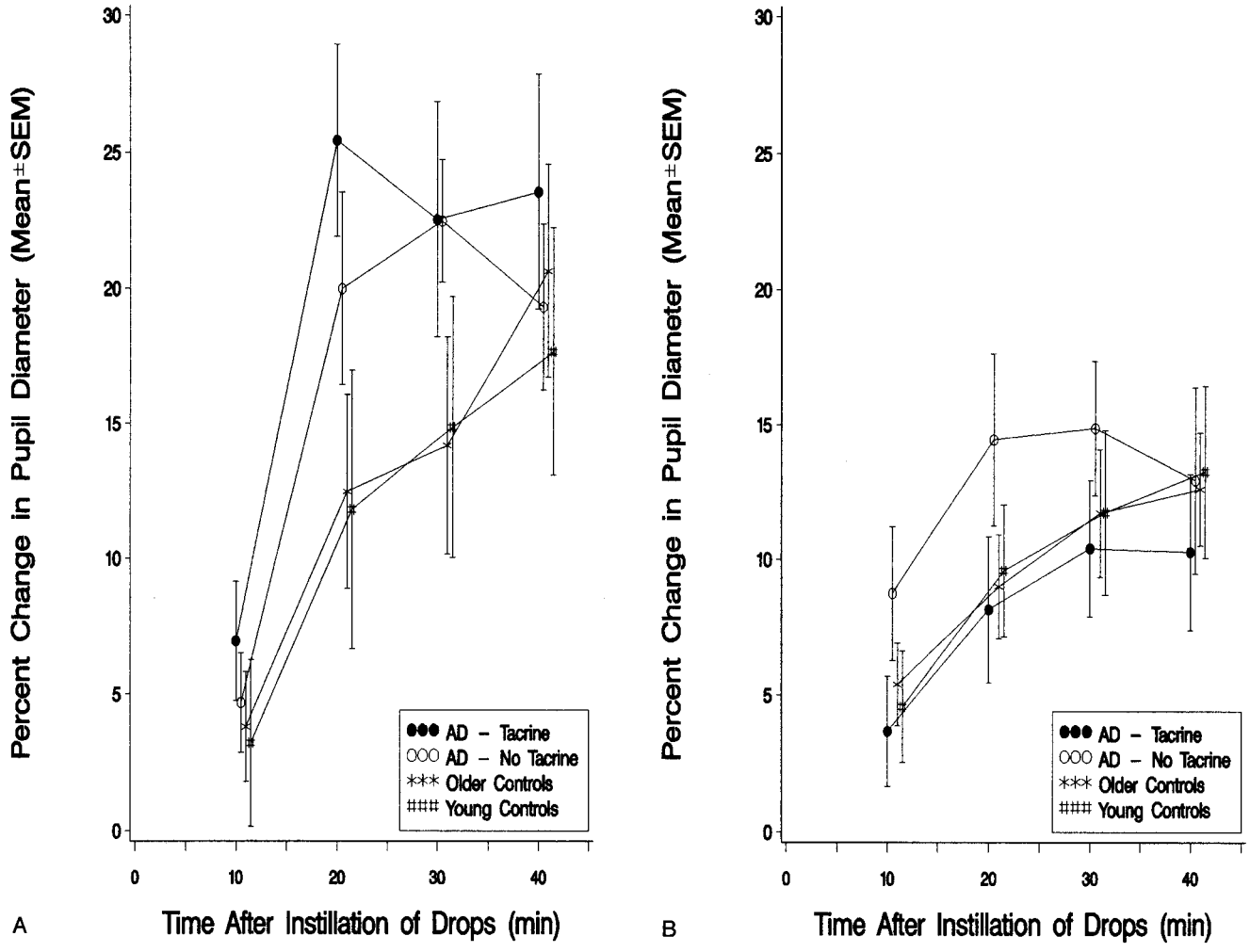

Figure 1. Percent change in pupillary diameter (mean ± standard error of the mean) of the treated eyes in light (A) and darkness (B), versus time after instillation of 0.01% tropicamide.

lation-based norms.[15] The Dimentia Rating Scale scores for the OC group averaged 140.6 ± 1.6 standard deviation, above even conservative criteria for impairment.[16] On the additional neuropsychologic tests administered to the OC group, all scores were within 1 standard deviation of age-appropriate norms, with the exception of a subject who had an aberrantly low score on Visual Reproduction 2, while scoring in the normal or above average range on all other scales.

Iris color was distributed evenly in the YC group. There were more brown eyes in the OC and NTAD groups and more nonbrown eyes in the TAD group (Table 1). Mean baseline pupil diameter of the treated eyes was not significantly different among the OC groups and the two AD groups ($P > 0.05$). Mean baseline pupil diameter of the YC group was statistically different from both AD groups ($P < 0.05$), but not from the OC group ($P > 0.05$). Mean baseline anisocoria was not significantly different among groups ($P = 0.25$) (Table 1).

Among the four groups, there were no significant differences in mean change in pupil diameter or area at any time point, regardless of whether the tests were performed in light or in darkness (Table 2).

Mean percent change measurements of the treated eyes in light demonstrated faster maximum dilatation of the pupils in both AD groups than in the control groups, whereas dark data showed a trend for faster maximum dilatation only in the NTAD group. The greatest difference among groups was at 20 minutes in both light and dark (Fig 1). These results were significant in light ($P = 0.03$) but not in dark ($P = 0.33$). In the light, the TAD group was significantly different from both control groups ($P < 0.05$) but the NTAD group was not significantly different from the TAD group nor either control group. In addition, there was no cut-off point that effectively distinguished individual patients with AD form control subjects (Fig 2). For example, 17 (89.5%) of the 19 patients with AD had more than a 10% change in diameter of the treated eye. Twelve (58%) of the 21 control subjects also measured more than a 10% change in diameter. At 40 minutes, the mean percent change in pupillary dilatation was similar among the four groups (Fig 1).

Mean changes in anisocoria were not significantly different among groups at 20 minutes (in light, $P = 0.21$; in dark, $P = 0.62$), nor at 40 minutes (in light, $P = .69$; in dark, $P = 0.63$) (Fig 3; Table 3). Again, there was no cut-off point that categorized individuals as either having AD or as control subjects (Fig 4). Within each group, there was a greater change in anisocoria when the pupils were measured in the light than when measured in darkness (Fig 3). This difference was statistically significant only in the TAD group ($P = 0.04$).

Iris color did not significantly influence pupil dilatation in any of the groups, when measured in the dark at 20 minutes (AD, $P = 0.8$; controls, $P = 0.4$). In light, however, the mean percent change in diameter of the treated eyes was significantly greater for nonbrown eyes than for brown eyes in the patients with AD, but not significantly different in the control subjects. For the 19 patients with AD the mean change was 29% for nonbrown eyes (n = 10) and 16% for brown eyes (n = 9) ($P = 0.006$). Among the 21 control subjects, the mean change was 13% for nonbrown eyes (n = 9) and 12% for brown eyes (n = 12) ($P = 0.9$).

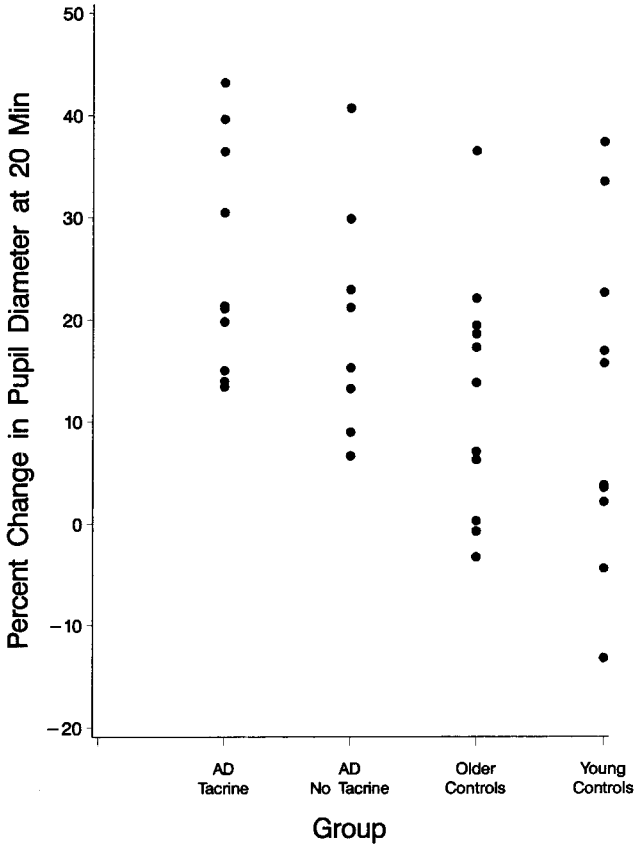

Figure 2. Percent change in pupillary diameter of the individual treated eyes, measured in light at 20 minutes after instillation of 0.01% tropicamide.

Discussion

The uncertainty and expense of diagnosing AD in living patients has led researchers to seek biologic markers that could be used as early diagnostic tests.[17,18] Neuropathologic and neurochemical similarities between Down syndrome (DS) and AD led to speculation that abnormalities seen in DS could be used as the basis of a diagnostic marker for AD.[19,20] Both cardiac and pupillary supersensitivity to anticholinergics have been reported in individuals with DS.[20–22] These studies led Scinto and colleagues[4] to propose that patients with AD, as with those with DS, might have a hypersensitivity to the acetylcholine receptor antagonist, tropicamide. In one previous study, cognitive and behavioral hypersensitivity to the cholinergic antagonist scopolamine was demonstrated in patients with AD, but pupil measurements were not performed.[23] Scinto and colleagues[4] measured the change in pupillary diameter after the instillation of 0.01% tropicamide in 58 elderly subjects. At 29 minutes after administering the eye drops, a mean percent change in diameter of 23.4% was demonstrated in the probable AD group compared with a mean change of 5% in the control subjects. Furthermore, when designating a 13% change in diameter at 29 minutes as a cut-off point, there was a clear separation between the probable AD, suspect AD, and patients who were "cognitively abnormal" (95% ≥ 13% change) and patients with non-Alzheimer-type dementias and control subjects (94% ≤ 13% change). They concluded that dilute tropicamide might be useful as an early diagnostic test for AD. Two subsequent tropicamide investigations did not support the results of Scinto et al.[4] In the study conducted by Marx and colleagues,[24] 13 young healthy subjects dilated as much to dilute tropicamide as the patients with AD in Scinto et al's[4] study. Treloar et al[25] were unable to distinguish patients with probable AD from those with multi-infarct dementia by their pupillary response. In neither study were their subjects compared with healthy control subjects in the Alzheimer age group.

Other investigators have used the paradigm of hypersensitivity of pupillary function to test patients with AD, using the cholinergic agonist, pilocarpine (Hannannel M, Ofry VF, Kushnir M, Korczyn AD. Parasympathetic function of the eye in dementia of the Alzheimer type. Neurology 1995;45 (Suppl 4):A356).[26–28] These authors reported a pupillary response in patients with AD similar to the denervation supersensitivity seen in Adie pupil. In all four studies, pupillary constriction to dilute (0.0625%–0.125%) pilocarpine was greater in patients with AD than in control subjects.

In our study, pupil response to dilute tropicamide did not distinguish between young and elderly control subjects, between patients with AD who received tacrine and those who did not, or between individuals with AD and control subjects. There was a difference between the averaged pupillary responses of our tacrine-treated AD group and the NTAD group, when measured in light at 20 minutes after instillation of dilute tropicamide. The mean percent change in diameter of the TAD group was significantly greater than the control groups, whereas the

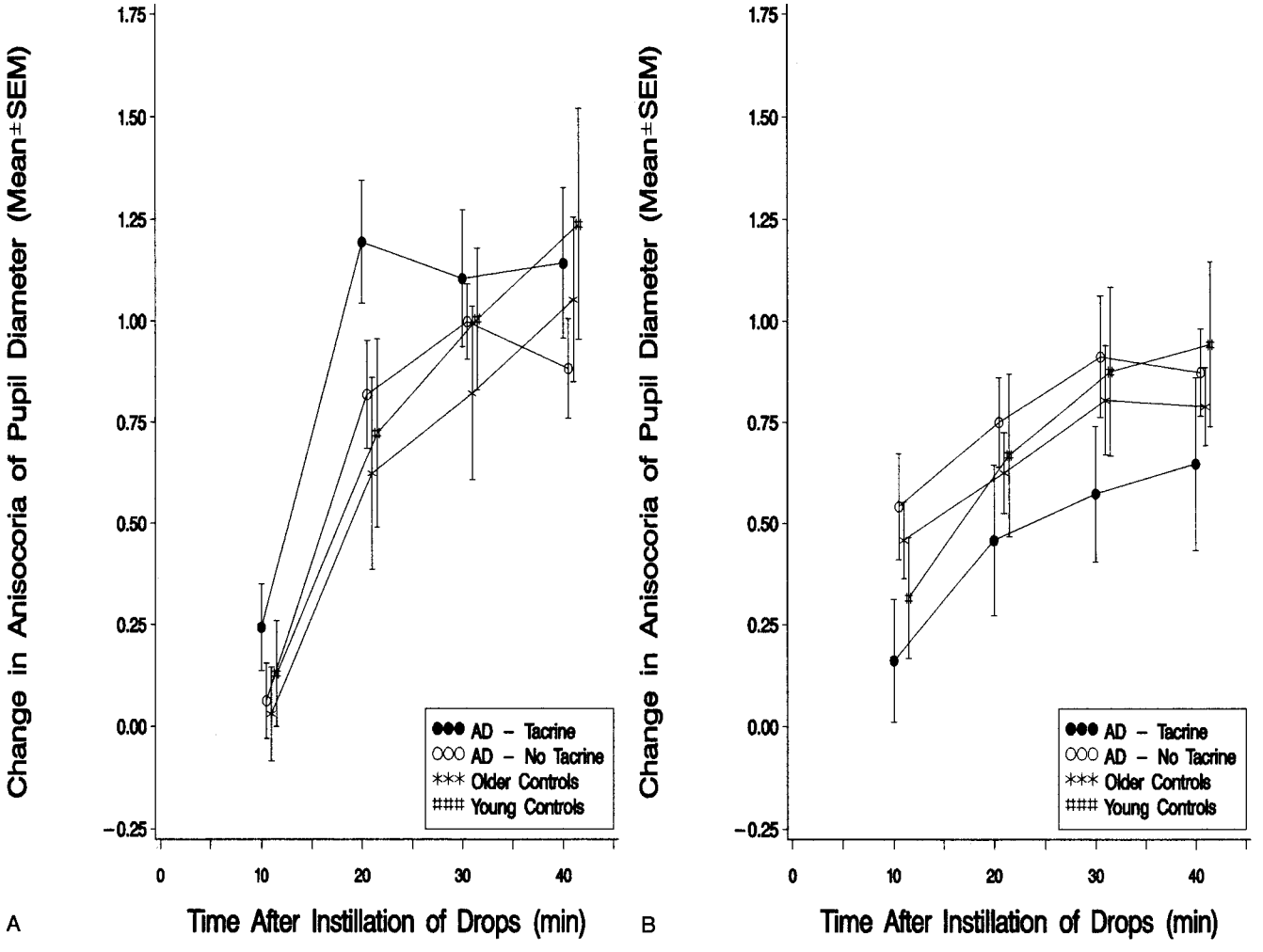

Figure 3. Change in anisocoria of pupillary diameter (mean ± standard error of the mean) in light (A) and darkness (B), versus time after instillation of 0.01% tropicamide in the treated eye.

mean pupil response of the NTAD group was not. In addition, unlike the NTAD group, the TAD group measured a significantly greater mean change in anisocoria in light than in darkness. It is presumed that tacrine, a centrally acting cholinesterase inhibitor, enhances acetylcholine bioavailability, thereby producing the functional improvement seen in some patients with AD treated with the drug.[6] The tacrine effect on iris receptors, blink rate, or corneal permeability is unknown. It is unclear why, on average, the patients treated with tacrine tended to respond more rapidly to dilute concentration of the acetylcholine antagonist tropicamide.

Our study was designed to minimize the pitfalls inherent in pupillary drug studies.[29] Drug concentration was verified by subsequent assay. Because increased corneal permeability can enhance topically applied drug effects,[30] careful slit-lamp examination excluded subjects with obvious signs of dry eyes or other corneal abnormalities. Pupil area, as well as diameter, were measured to account for irregularities in pupil shape which might cause misleading measurements of change in pupil size. Measurements were performed not only in dark, but also in light, the latter to accentuate the relative weakness of the medicated iris sphincter.

Iris color was noted and analyzed because some studies have shown differences in pupillary drug response between light- and dark-eyed people,[31,32] whereas other studies have not.[33,34] Although the averaged data in our study suggested that nonbrown eyes dilated more than brown eyes in the AD groups, the control groups showed no difference in dilatation based on iris color. Although it is possible that AD influenced this trend, it could also be a manifestation of other, perhaps genetically determined, factors that are responsible for differences in drug sensitivity among individuals with similar eye color.[35]

Changes in anisocoria were measured to account for bilateral pupil size fluctuations that occur during the course of testing with changes in the subjects' physiologic and psychologic state.[29] It is known, for example, that pupils constrict with fatigue.[36] Therefore, under the same testing conditions, subjects who are more alert or agitated will have larger pupils than those more sedate. If change

Table 3. Change in Anisocoria of Pupillary Measures after Instillation of 0.01% Tropicamide in the Treated Eye

Measure	Time after Instillation (mins)	Group: NTAD (*n* = 9)	TAD (*n* = 10)	OC (*n* = 11)	YC (*n* = 10)	P*
		Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	
Diameter (mm), light	10	0.06 ± 0.28	0.24 ± 0.34	0.03 ± 0.38	0.13 ± 0.41	0.84
	20	0.82 ± 0.40	1.19 ± 0.48	0.62 ± 0.79	0.72 ± 0.74	0.12
	30	1.00 ± 0.27	1.11 ± 0.53	0.82 ± 0.71	1.00 ± 0.55	0.71
	40	0.88 ± 0.37	1.14 ± 0.58	1.05 ± 0.67	1.24 ± 0.90	0.57
Diameter (mm), dark	10	0.54 ± 0.39	0.16 ± 0.48	0.46 ± 0.31	0.32 ± 0.47	0.34
	20	0.75 ± 0.33	0.46 ± 0.59	0.62 ± 0.33	0.67 ± 0.64	0.61
	30	0.91 ± 0.45	0.57 ± 0.53	0.80 ± 0.45	0.88 ± 0.63	0.45
	40	0.87 ± 0.32	0.65 ± 0.68	0.79 ± 0.32	0.94 ± 0.64	0.57
Area (mm^2), light	10	0.16 ± 1.93	1.48 ± 1.95	0.62 ± 1.92	0.94 ± 2.31	0.92
	20	5.73 ± 3.10	7.97 ± 4.02	4.70 ± 4.76	5.82 ± 5.87	0.35
	30	6.54 ± 2.81	7.04 ± 3.81	5.93 ± 4.41	7.77 ± 4.49	0.78
	40	5.53 ± 2.82	8.01 ± 5.10	7.55 ± 4.80	10.40 ± 7.55	0.09
Area (mm^2), dark	10	3.45 ± 3.29	1.44 ± 3.82	3.50 ± 1.88	1.42 ± 5.04	0.51
	20	6.54 ± 2.95	4.41 ± 4.50	5.65 ± 2.68	6.18 ± 4.40	0.70
	30	8.02 ± 3.68	5.83 ± 4.67	6.60 ± 4.32	7.43 ± 5.64	0.69
	40	7.49 ± 2.87	6.44 ± 6.26	6.13 ± 3.12	7.91 ± 5.66	0.75

* From a repeated measures analysis of variance comparing the mean value of the four groups.

NTAD = patients with Alzheimer disease not taking tacrine; SD = standard deviation; TAD = patients with Alzheimer disease taking tacrine; OC = older control subjects; YC = young control subjects.

from the baseline size of the treated pupil is measured, it may reflect a subject's physiologic or psychologic state at two points in time rather than a true response to the drug. Measuring the change in anisocoria should compensate for such pupillary fluctuations and provide a better measure of drug effect.

In the Scinto et al[4] study, the patients with AD had a faster and more robust pupillary response to dilute tropicamide than the controls, which persisted throughout the 60 minutes of testing. Our AD patients had a 22.5% mean change in pupillary diameter at 30 minutes, which is similar to the 23.4% change shown by the patients with AD in the previous study. Our control subjects were slower to respond, but by 40 minutes they had dilated as much as the patients with AD. The pupillary responses of our OC group and the Scinto et al[4] control group may differ for various reasons. First, the preferred measurement of change in anisocoria was not provided in the Scinto et al[4] study. If their control subjects were more fatigued or bored than the patients with AD, the percent change in diameter measurements may have been a reflection of variations in the subjects' autonomic equilibrium, and not a true measure of drug effect.[29]

Other possible variables that might account for the difference between the current study and the previous study control groups include undetected early dementia in our OC group or differences in corneal permeability between the two groups. It is unlikely that our OC group included individuals with early undiagnosed dementia, given the normal cognitive function demonstrated on the neuropsychologic testing battery. Corneal permeability differences in our OC group compared with the Boston group could result from differences in the prevalence of dry eyes. The cornea is very sensitive to the outside environment,[37] and regional climatic differences between Atlanta and Boston may influence the prevalence of dry eyes, especially in the more frequently affected older population. We attempted to minimize the likelihood of including subjects with dry eyes or other causes of abnormal corneal permeability by excluding subjects who used eye drops or had biomicroscopic evidence of corneal changes. However, results of routine clinical examination does not definitively rule out abnormalities which might influence corneal permeability.

Our findings raise issues that cannot be answered in this study, given the small number of subjects. Factors not controlled among our four groups, such as corneal permeability or unspecified genetic factors, may influence the pupillary effects of dilute tropicamide. However, regardless of study shortcomings and of trends using averaged group data, the test did not distinguish individuals with AD from individual control subjects. Unless a much more robust sensitivity and specificity can be demonstrated in representative populations, pupillary response to dilute tropicamide should not be used in individuals as a test for the early diagnosis of AD.

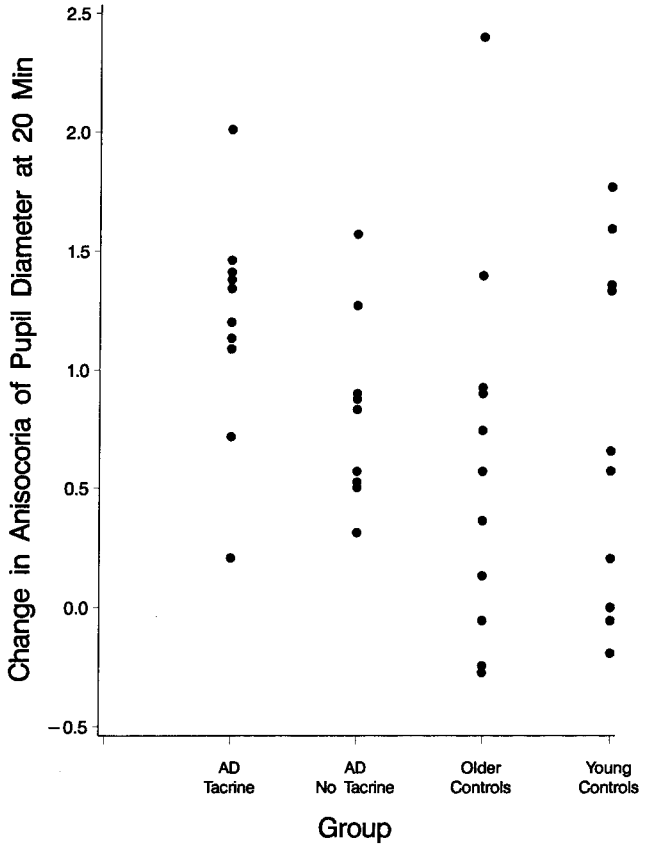

Figure 4. Change in anisocoria of individuals' pupillary diameters, measured in light at 20 minutes after instillation of 0.01% tropicamide in the treated eye.

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