·Clinical Research·

An overlooked effect of systemic anticholinergics: alteration on accommodation amplitude

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Abstract

• **AIM: To investigate the effect of oral solifenacin succinate, tolterodine -L -tartarate and oxybutinin hydrochloride (HCl) on accommodation amplitude.**

• **METHODS: Female overactive bladder syndrome (OAB) patients who were planned to use oral anticholinergics, patients that uses solifenacin succinate 5 mg (Group I, *n*=25), tolterodine-L-tartarate 4 mg (Group II, *n*=25), and oxybutinin HCl 5 mg *b.i.d.* (Group III, *n*=25) and age matched healthy female subjects (Group IV, *n*=25) were recruited and complete ophthalmological examination and accommodation amplitude assessment were done at baseline and 4wk after initiation of treatment.**

• **RESULTS: The mean age of 100 consecutive female subjects was 51.6±5.7 (40-60)y and there were no statistically significant difference with regard to the mean age (*P*=0.107) and baseline accommodation amplitude (*P*=0.148) between study groups. All treatment groups showed a significant decrease in accommodation amplitude following a 4-week course of anticholinergic treatment (*P*=0.008 in Group I, *P*=0.002 in Group II, *P*=0.001 in Group III), but there was no statistically significant difference in Group IV (*P*=0.065).**

• **CONCLUSION: A 4-week course of oral anticholinergic treatment have statistically significant effect on accommodation amplitude. Clinicians should avoid both overestimating this result, as this would unnecessarily restrict therapeutic possibilities, and also underestimating it which may lead to drug intolerance.**

• **KEYWORDS:** accommodation; anticholinergics; overactive bladder
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INTRODUCTION

Overactive bladder syndrome (OAB) which has a significant negative impact on health related quality of life can be defined as urgency with or without urge incontinence, generally accompanied by more than eight micturitions in a 24h period and more than one micturition per night [1-4]. As parasympathetic cholinergically mediated innervation is the predominant stimulus for bladder contraction, anticholinergics are the most effective agents currently available to control OAB symptoms [5-8]. However, significant peripheral adverse effects, such as dry mouth, tachycardia, drowsiness, decreased cognitive function, constipation and blurred vision may limit drug tolerability. Blurred vision especially for near objects is thought to occur secondary to blockage of cholinergic stimulation to the ciliary muscle of the crystalline lens[9-12].

Accommodation is an increase in the dioptric power of the crystalline lens that enables the image of near objects to be focused on retina which occurs due to cholinergically mediated contraction of the ciliary muscles [13]. Age related loss of accommodation leads to presbyopia. As patients develop presbyopia, they present clinically with difficulty in near-vision tasks. These problems manifest at about 45y of age when the accommodative reserve starts to become insufficient to focus on near objects[14].

Solifenacin succinate, tolterodine-L-tartarate and oxybutinin hydrochloride (HCl) are different type of anticholinergics that are commonly used to treat OAB. The clinical efficacy of these agents is limited by adverse systemic effects attributed to blockage of muscarinic reseptors throughout the body. In this study, we investigated the effect of these agents on accommodation amplitude (AA) and compared these results with those of healthy control subjects.

SUBJECTS AND METHODS

The study was designed as a prospective study undertaken at a single hospital and was carried out with approval from the Institutional Review Board. Only patients who fulfilled the selection criteria and gave written informed consent in line with the Decleration of Helsinki were included in the study.

Patients were recruited between May 2012 and February 2013 for the study. Female OAB patients who were diagnosed at Department of Urogynecology following detailed gynecologic examination and planned to use solifenacin succinate 5 mg was included in Group I, tolterodine-L-tartarate 4 mg was included in Group II, and oxybutinin HCl 5 mg *b.i.d.* in Group III. The Group IV was composed of consecutive age matched urogynecologically healthy female subjects.

After obtaining detailed medical history, all patients underwent complete ophthalmological examination at first admission and 4wk after initiation of oral treatment, including best corrected Snellen visual acuity testing, slit-lamp examination, Goldmann applanation tonometry, gonioscopic evaluation and dilated fundus examination using a 90-diopter lens in order to exclude the subjects who were contraindiceted to use anticholinergics. The patients at Group IV were also examined at day 0 and day 28. All aforementioned assessments were done by one of the authors (Sekeroglu MA) who was blinded to the group of patients. After detecting best corrected visual acuity of patients at Snellen chart, additional minus spheres were added until the eye was unable to overcome the minus power by accommodation, and was unable to read letters smaller than 20/25 on the chart. This was recorded as AA[15].

All examinations were done by one of the authors (Sekeroglu MA) and were carried out at the same time interval of the day (between 9-10 o'clock a.m.) in order to prevent diurnal variations and also other confounding factors such as fatigue and reading during the day. All assessments were also done in the same room with a standard illumination in order to prevent the effect of environmental factors on AA. In order to eliminate confounding factors that could affect visual acuity and/or accommodation, the patients with ocular diseases such as glaucoma, cataract, ocular surface disorders, retinal diseases, amblyopia, strabismus, a history of ocular surgery or trauma, refraction error ⩾4 D, and those with a history of central nervous system disorders were excluded.

Statistical Analysis SPSS 11.5.0 software for Windows (SPSS, Chicago, IL, USA) was used for statistical analyses. The normality of each variable was tested by using the Shapiro-Wilk test. Kruskal-Wallis one-way ANOVA test was used to determine differences among the four groups for quantitative variables with a normal distribution. Spearman's rho was used to determine the correlation between two quantitative variables. Wilcoxon signed-rank test was used for comparison of two dependent variables for non-normal variables. Descriptive statistics were expressed as frequency and percentage for categorical variables whereas quantitative data were expressed as mean±standard deviation for normally distributed variables and median (minimum-maximum) for non-normally distributed data. P <0.05 was considered statistically significant.

Table 1 The initial and final accommodation amplitude of Group I, II, III and IV patients $\bar{x} \pm s$ (min-max)

Groups	Baseline AA (D)	AA at 4wk (D)	*P*
Group I (*n*=25)	2.69±1.40 (0.75-6.50)	2.62±1.38 (0.75-6.25)	0.008
Group II (*n*=25)	2.64±1.28 (1.00-5.50)	2.49±1.29 (0.75-5.50)	0.002
Group III (*n*=25)	2.92±1.53 (0.50-6.50)	2.73±1.55 (0.50-6.50)	0.001
Group IV (*n*=25)	3.21±1.75 (0.75-6.50)	3.18±1.77 (0.75-6.50)	0.065

AA: Accommodation amplitude.

RESULTS

One-hundred consecutive female subjects [(75 OAB patients that uses solifenacin succinate 5 mg (Group I, n =25), tolterodine-L-tartarate 4 mg (Group II, n=25), and oxybutinin HCl 5 mg *b.i.d.* (Group III, n =25) and age-matched healthy control subjects (Group IV, n=25)] with a mean age of 51.6± 5.7 (40-60)y who had completed 4wk of follow-up were recruited for this study.

There were no statistically significant difference with regard to the mean age (52.6±5.3y in Group I, 52.8±4.5y in Group II, 51.9±5.5y in Group III and 49.8±6.7y in Group IV; P= 0.107) and baseline AA (P =0.148) between study groups (Table 1).

All treatment groups showed a significant decrease in AA following a 4-week course of anticholinergic treatment. There was also a decrease in AA of Group IV from baseline to day 28, but this change was not clinically significant (Table 1). AA was found to be decreased in 7 patients in Group I, 11 patients in Group II, 14 patients in Group III and in 5 patients in Group IV at the end of 4wk.

DISCUSSION

Anticholinergic drugs have been the main pharmacotherapy option of OAB for many years [16]. As cholinergically mediated innervation is the predominant stimulus for bladder contraction, anticholinergics can improve frequency, urgency and urge incontinence by blocking receptors of the detrusor muscle. Significant peripheral adverse effects, attributed to blockade of muscarinic receptors throughout the body, may limit drug tolerability. In a study of Garely *et al* [10], of the 2225 OAB patients who were treated with solifenacin, 21.4% reported dry mouth, 13.3% constipation, 3.4% headache, 2.6% blurred vision, 1.8% nausea, 2.5% dyspepsia, and 1.3% dry eye. Dry eye may also cause blurred vision but blurred vision in the aforementioned study was thought to be mostly related to the relaxation of the ciliary muscle and temporary impairment of visual accommodation. This study was conducted to ascertain the change in AA following a 4-week course of oral solifenacin, tolterodine and oxybutinin treatment, and found a clinically significant effect in short term.

Choppin *et al* [17] stated that muscarinic receptors mediating contraction of the rabbit iris sphincter muscle and urinary bladder smooth muscle are similar and equate most closely with the pharmacologically-defined muscarinic M3 receptor. There are many studies regarding the ocular side effects of systemic anticholinergics. But little data present evaluating

the effects on accommodation amplitude which is the possible cause of blurred vision during treatment.

Altan-Yaycioglu *et al* [15] stated that oxybutinin and tolterodine affect the parasympathetic control of the eye and thus reduce accommodation in adults over 22 years old. Chapple and Nilvebrant [18] found that the normal dosage of tolterodine (2 mg twice daily) may have less effect on visual accommodation than the equivalent dosage of oxybutinin (5 mg three times daily) in patients with OAB. Abrams *et al*[19] reported abnormal accommodation in 3% of tolterodine and 7% of oxybutinin treated patients. Wong *et al*[20] reported a 5 years old girl who developed esotropia following oxybutinin treatment for pediatric enuresis. They stated that it was due to a reduction in AA in combination with her uncorrected moderate hyperopia which may have driven the need to generate accommodation using other mechanisms such as convergence accommodation. As far as we know, our study is the first study in the literature investigating the effect of a novel oral anticholinergic, solifenacin succinate on AA.

Elderly patients are both more likely to have OAB and to be very susceptible to the side effects of anticholinergics. Therefore, if an elderly patient is prescribed an anticholinergic drug for OAB, the patient must be followed carefully and must be seen soon after initiation of therapy, to ensure that she does not sustain side effects that are inadvertently attributed to the ageing process. The patients with OAB have usually presbyopia, and the AA change induced by anticholinergics can be easily compensated by changing their presbyopic glasses. Thus, the potential benefit of oral anticholinergics in the treatment of OAB should not be undermined as the AA deficit is fully correctable. But we should be carefull for younger patients who do not use presbyopic glasses.

The present study should be viewed in context of some limitations. First of all, small number of patients and short follow-up duration may influence the power of statistical analysis. Also the effect of these agents on AA can not be generalized to all systemic anticholinergics. Thirdly, the other medications which are used for systemic diseases can be a confounding factor which may also affect AA. Finally, there may be cumulative effect of the drug after prolonged treatment period or these changes in AA may be temporary which can only be detected after a drug free period.

In conclusion, a 4-week course of oral anticholinergic treatment have statistically significant effect on AA. Clinicians should avoid both overestimating this result, as this would unnecessarily restrict therapeutic possibilities, and also underestimating it which may lead to drug intolerance. However further larger and prolonged studies are needed to determine the effect of anticholinergic medication on AA.

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