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DIFFERENTIAL EFFECTS OF THE ANTIMUSCARINIC AGENTS TOLTERODINE TARTRATE ER AND OXYBUTYNIN CHLORIDE ER ON RECENT MEMORY IN OLDER SUBJECTS

Hypothesis / aims of study

Chronic use of anticholinergic drugs by older adults can result in a non-progressive mild cognitive impairment [1]. The extent to which memory and other cognitive functions are disrupted by antimuscarinic drugs used to treat OAB depends upon the ability of the drug to cross the blood-brain-barrier and bind to critical CNS muscarinic receptors. This study compared the cognitive effects of tolterodine tartrate extended release (Detrol LA®) and oxybutynin chloride extended release (Ditropan-XL®) on recent memory as measured by accuracy on a test of delayed recall of name-face associations in healthy older subjects at steady state dosing.

Study design, materials and methods

In this 2-way crossover design, subjects were randomized to 3 weeks' double-blind treatment with tolterodine tartrate extended release (Detrol LA® 4 mg QD which was sham titrated after Week 1 and Week 2) and 3 weeks' treatment with oxybutynin chloride extended release (Ditropan-XL® titrated at weekly intervals from 10 mg to 15 mg to 20 mg). Following each period of treatment (4-7 days of dosing) subjects were administered computerized cognitive function tests (Psychologix® and CogScreen® tests). The Psychologix® Name-Face Association Test was previously shown to be sensitive to oxybutynin ER at doses ≥ 15 mg [2]. At the end of the first 3-week treatment period there was a 7-day minimum washout before beginning the second 3-week treatment period.

Results

A total of 22 subjects were enrolled in the study, of which 17 completed the full protocol and were included in the analyses. This was a highly educated sample of healthy, older adults (mean age 63.4, mean education 16.2 years). Subjects were taking no other anticholinergic or CNS active medications and had baseline MMSE scores ≥ 28.

Tolterodine ER (4 mg) had no effect on the primary outcome measure (delayed recall on the Name-Face Association Test) or on other measures in the cognitive function test battery at any time point. There was no decline, relative to baseline, in cognitive test performance when subjects were taking tolterodine ER. In contrast, there was a significant decline in delayed recall on the Name-Face Association Test for oxybutynin ER 20 mg. Performance declined from 7.9 names correctly recalled (at baseline) to 4.8 names recalled (at Week 3). Delayed recall performance at Week 3 demonstrates significantly worse memory performance ($p=.026$; one-tailed; observed power = .499, alpha = .05) for oxybutynin ER (4.8 names recalled) compared to tolterodine ER (7.2 names recalled). No significant differences were found between tolterodine ER and oxybutynin ER on cognitive functioning following Week 1 and Week 2 (i.e., oxybutynin ER at doses of 10 mg and 15 mg). On a validated memory questionnaire subjects reported no awareness of changes in their memory functioning at any time point.

Interpretation of results

Tolterodine ER did not affect recent memory performance in older subjects. In contrast, in this healthy, highly-educated sample of older adults, oxybutynin ER (20 mg), had the effect of diminishing memory performance to the same extent as 20 years of additional aging [3]. At baseline this group of subjects was functioning at a 50-59 year age level (compared to published norms [3]). In contrast, they were functioning at the level of 70 year old individuals after one week of oxybutynin ER 20 mg.

Concluding message

The present results are the first test findings demonstrating the cognitive safety of tolterodine ER. Prior studies investigating the CNS safety of tolterodine have found the drug to be comparable to placebo on measures of quantitative EEG, self-reported sleepiness, and sleep architecture. However, none of these studies investigated memory changes. A previous study demonstrated impairment of recent memory following doses of oxybutynin ER ≥ 15 mg [2]. The failure of the present study to show an effect of oxybutynin ER 15 mg may be explained by the high level of baseline functioning of this sample; an indication of heightened "brain reserve". The subjects' lack of awareness of changes in their memory, even when their performance decline was comparable to 20 years of additional aging, helps explain the lack of complaints by patients regarding changes in their memory when taking this medication.

References

1. *British Med J.* 2006; 24 Feb 06 on-line
2. *Developmental neuropsychology*, 1993;9:103-113.
3. *Eur Urol.* 2006 in press

FUNDING: Pfizer; independent research grant

DISCLOSURES: G Kay; consultant, investigator & speaker for Pfizer & Novartis & publisher of CogScreen; T Crook consultant to Pfizer & Novartis & publisher of Psychologix

CLINICAL TRIAL REGISTRATION: This clinical trial has not yet been registered in a public clinical trials registry.

HUMAN SUBJECTS: This study was approved by the Chesapeake Research Review, Inc and followed the Declaration of Helsinki Informed consent was obtained from the patients.