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ARE THE EFFECTS OF OXYBUTYNIN ON COGNITION DEPENDENT UPON THE ROUTE OF ADMINISTRATION – TOPICAL OR ORAL? A DOUBLE-BLIND PLACEBO CONTROLLED STUDY EMPLOYING SENSITIVE COGNITIVE AND PSYCHOMOTOR TESTING.

Hypothesis / aims of study

A prospective randomized and double-blinded placebo controlled study was undertaken to compare the effects of topically administered oxybutynin (OTG) and of oral oxybutynin immediate-release (OXY-IR) to placebo on older adults' performance during a battery of cognitive and psychomotor tests (CPTs). Oral oxybutynin has previously been demonstrated to impair cognitive function in older adults in both the immediate- release and extended-release formulations, [1], CPTs have not been previously performed on transdermal preparations of oxybutynin.

Study design, materials and methods

Healthy women and men aged 60-79 years were enrolled at 5 US centers in this phase 1 study (NCT00752141 at clinicaltrials.gov). Patients were randomized in a 1:1:1 ratio to receive either 1g oxybutynin topical gel 10% once daily (Active OTG gel plus placebo OXY-IR capsules), OXY-IR 5mg three times daily (Active OXY-IR capsules plus placebo OTG gel), or Placebo (Placebo OTG gel plus placebo OXY-IR capsules) for one week. The treatment allocation schedule implemented a computer-generated randomized design that sequentially assigned each patient to 1 of 3 treatments according to the randomization number. Double-blind treatment status was maintained throughout the study by use of identical appearing gels, capsules, and packaging. After randomization and baseline testing of cognitive and psychomotor functioning, subjects were instructed to apply the contents of a one gram sachet of gel daily to rotating sites on the abdomen, upper arms/shoulders, or thighs, and to take one oral capsule three times a day. After 1 week, subjects returned to the clinic on an outpatient basis to take study medication in an observed setting and to assess cognitive and psychomotor functioning. Delayed recall of name-face associations, first name-last name associations, and object locations were assessed after a 30-minute interval from initial presentation. Differences in endpoint scores among treatment groups were compared through an analysis of covariance model with terms for baseline score, education, center, treatment, center*treatment. Pairwise comparisons were made between each active treatment group and placebo. Differences were considered significant if $P<.05$. Based on results of prior studies [1], it was estimated that 50 subjects in each treatment group would provide 85% power to detect a significant difference between active and placebo treatments.

Results

152 subjects with a mean age ± SD [min, max] of 68.2 ± 5.76 [60.0, 79.0] years were enrolled; (99 (65.1%) were female, 140 (92.1%) were white). 49 participants received OTG, 52 received OXY-IR, and 51 received placebo. No significant differences were observed between demographic/baseline characteristic categories and treatment group. Performance on the primary endpoint, Name-Face Association delayed recall, showed no significant treatment effect (p=0.273). Comparisons between each treatment group and the placebo group also revealed non-significant group differences (OTG vs. Placebo, p=0.155; OXY-IR vs. Placebo, p=0.177). The Misplaced Objects Test, a measure of the subject's ability to recall the location of common objects 30 minutes after the subject has placed the object in a simulated house, showed a significant treatment effect (p=0.023), with placebo and OTG scores both improving and OXY-IR decreasing (OTG vs. Placebo, p=0.368; OXY-IR vs. Placebo, p=0.069). No significant treatment related group differences were demonstrated on the remaining tests of delayed recall (First-Last Name Association Test, Hopkins Verbal Learning Test [HVLT] -Delayed Recall, Retention, or Delayed Recognition Index), or on tests of immediate recall (Name-Face Association Test, Facial Recognition Test, HVLT-Total Free Recall). However, analysis of Reliable Change scores in the HVLT-Total Free Recall (i.e., a decline ≥ 6 from Baseline) indicates that 10 subjects showed a significant decline on OXY-IR, compared to 6 subjects on Placebo and 5 subjects on OTG. No significant treatment related group differences were demonstrated on measures of psychomotor reaction time (Divided Attention Test, Visual Monitoring Response Time), or for any of the Memory Assessment Clinics Self-Report Questionnaire (MAC-S) variables. Dry mouth was the most common treatment-emergent adverse event overall (Table), and was the reason that 3 subjects in the OXY-IR group discontinued the study prior to completion and did not provide endpoint CPT data at day 8. There were no serious adverse events.

Table. Treatment Emergent (Unsolicited) Adverse Events Reported by ≥2 Participants in any Study Group during Cognitive / Psychomotor Testing Trial

Adverse Events, n (%)	Placebo (n = 51)	OTG (n = 49)	OXY-IR (n = 52)
Dry Mouth	4 (7.8)	3 (6.1)	38 (75)
Headache	2 (3.9)	0 (0)	4 (7.7)
Nausea	0 (0)	0 (0)	4 (7.7)
Constipation	0 (0)	0 (0)	3 (5.8)
Cough	0 (0)	0 (0)	3 (5.8)
Dizziness	0 (0)	0 (0)	3 (5.8)
Nasal Dryness	0 (0)	0 (0)	3 (5.8)
Urinary Hesitation	0 (0)	0 (0)	3 (5.8)
Dry Eye	0 (0)	0 (0)	2 (3.8)
Dry Throat	0 (0)	0 (0)	2 (3.8)
Urine Flow Decreased	0 (0)	0 (0)	2 (3.8)

Interpretation of results

In this multi-center, placebo-controlled, parallel group study of the cognitive effects of OTG and OXY-IR in older, healthy non-demented adult volunteers, there was no significant treatment effect demonstrated for the primary endpoint. However, results of this study demonstrate that OTG was comparable to placebo on sensitive measures of Delayed Recall, as well as on measures of Immediate Recall, Visual Attention, Psychomotor Reaction Time, and Self-Reported Memory Functioning. In contrast, results from this trial demonstrated evidence of impairment for subjects receiving OXY-IR at steady state on specific measures of recent memory. In addition, a decidedly greater number of subjects in the OXY-IR treatment group reported the peripheral anticholinergic side effect of dry mouth than in the OTG treatment group.

Concluding message

Results from this clinical trial demonstrate that in healthy elderly adults OTG is comparable to placebo in its lack of effects on sensitive tests of recent memory and other cognitive functions. It is unknown whether the central nervous system effects seen with oral oxybutynin are dependent upon the peak plasma concentrations of the parent compound and/or the metabolite N-desethyloxybutynin. [2,3] However, these findings suggest the potential for an additional measure of safety and tolerability of OTG versus oral delivery in elderly adults.

References

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