113

Kay G[1], Maruff P[2], Scholfield D[3], Malhotra B[3], Whelan L[3], Darekar A[3], Martire D[3]
1. *Cognitive Research Corporation,* ***2.*** *CogState,* ***3.*** *Pfizer*

EVALUATION OF COGNITIVE FUNCTION IN HEALTHY OLDER ADULTS TREATED WITH FESOTERODINE

Hypothesis / aims of study

To evaluate the cognitive effects of fesoterodine (FESO) 4 and 8 mg compared with placebo (PBO) in healthy older adults

Study design, materials and methods

This was a randomized, active-(alprazolam 1 mg) and PBO-controlled, double-blind, double-dummy, 4-way crossover study of healthy volunteers (65–85 y) who scored ≥26 on the Mini–Mental State Exam (MMSE) at baseline. Subjects with cognitive impairment due to any concurrent condition or medication were excluded. The study comprised 4 treatment periods: FESO 4 mg for 6 days with matching alprazolam PBO on day 6; FESO 4 mg for 3 days followed by FESO 8 mg for 3 days with matching alprazolam PBO on day 6; matching FESO PBO for 6 days with matching alprazolam PBO on day 6; and matching FESO PBO for 6 days with alprazolam 1 mg on day 6. Treatment sequence was randomized, and there was a 3–6 day washout period between each treatment period. Subjects completed computer-based cognitive assessments (CogState subtests) and the Rey Auditory Verbal Learning Test (RAVLT) on day 1 (before dosing) and day 6 of each treatment period. The primary endpoint was the effect on psychomotor function; secondary endpoints were the effects on attention, visual memory, paired associate learning, executive function, and verbal memory (see Table). Changes from baseline to day 6 in all endpoints were analyzed using ANCOVA (terms for subject, period, and treatment; within and between subject baselines as covariates). Safety was monitored throughout the study.

Results

Among 20 subjects randomized and treated, 18 were included in the per-protocol analysis set (mean [SD] age, 72.2 [5.2] y; MMSE, 29.1 [1.2]). Changes from baseline to day 6 in the primary endpoint (Table) and in all secondary endpoints in the FESO 4- and 8-mg groups were not statistically significantly different vs PBO (P>0.05); alprazolam produced statistically significant impairment in all endpoints vs PBO (P<0.05). No serious AEs were reported; the most common AEs were dry mouth for FESO and sedation for alprazolam. There was no reported sedation with FESO.

Interpretation of results

At steady state fesoterodine 4 and 8 mg resulted in no cognitive changes in memory or in other cognitive functions in healthy older adults. In contrast, the same adults showed a large, generalized, and statistically significant deterioration in cognition with alprazolam.

Concluding message

Results from this trial support the pre-clinical findings demonstrating the CNS safety of fesoterodine.

Table. Cognitive Effects of FESO 4 and 8 mg Compared With PBO and Alprazolam

Task	PBO (n=18)	FESO 4 mg (n=18)	FESO 8 mg (n=18)	Alprazolam (n=18)
Psychomotor function†				
Detection speed, $\log_{10}$ ms				
Baseline mean	2.58	2.63	2.60	2.61
Adjusted mean change	0.01	–0.02	–0.01	**0.07***
Effect size (Cohen d‡)	–0.34	0.47	0.04	–0.59
Attention†				
Identification speed, $\log_{10}$ ms				
Baseline mean	2.75	2.75	2.77	2.76
Adjusted mean change	0.01	0.01	0.01	**0.08***
Effect size (Cohen d‡)	–0.35	–0.25	0.04	–1.29
Visual memory†				
1-Card visual learning, arcsine sqrt, %				
Baseline mean	0.93	0.96	0.94	0.95
Adjusted mean change	–0.01	–0.01	0.02	**–0.09***
Effect size (Cohen d‡)	0.09	–0.20	0.18	–0.97
Paired associate learning†				
CPAL, total errors				
Baseline mean	107.4	96.3	99.8	89.5
Adjusted mean change	3.1	6.8	–16.8	**58.2***
Effect size (Cohen d‡)	0.07	–0.13	0.31	–0.97
Executive function†				
GMLT, total errors				
Baseline mean	52.3	53.7	58.4	56.8
Adjusted mean change	–4.1	–4.1	–5.8	**24.7***
Effect size (Cohen d‡)	0.06	0.18	0.57	–0.97
Verbal memory†				

RAVLT, words recalled	6.3	6.5	6.7	7.2
Baseline mean	–0.1	0.2	–0.2	**–3.9***
Adjusted mean change	0.07	0.10	–0.04	–1.42
Effect size (Cohen d‡)				

CPAL=continuous paired associate learning; GMLT=Groton Maze Learning Test; LS=least squares; PBO=placebo; RAVLT=Rey Auditory Verbal Learning Test; sqrt=square root.
†CogState subtest.
‡Cohen d calculated as (mean end-of-treatment score – mean baseline score) / pooled SD; negative score indicates performance deterioration and vice versa.
***P*<0.05 vs PBO.**

References

1. Michel MC: Fesoterodine: a novel muscarinic receptor antagonist for the treatment of overactive bladder syndrome. Expert Opin Pharmacother 2008; 9: 1787.
2. Verster JC and Volkerts ER: Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. CNS Drug Rev 2004; 10: 45.
3. Maruff P, Thomas E, Cysique L et al: Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol 2009; 24: 165.

Specify source of funding or grant	**Clinical trial was supported by Pfizer Inc.**
Is this a clinical trial?	**Yes**
Is this study registered in a public clinical trials registry?	**Yes**
Specify Name of Public Registry, Registration Number	**Clinicaltrials.gov NCT01161472**
Is this a Randomised Controlled Trial (RCT)?	**Yes**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**IRB: Aspire Institutional Review Board Suite 105 9320 Fuerte Drive La Mesa, CA 91941 UNITED STATES**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**