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# SOLIFENACIN IS NOT ASSOCIATED WITH COGNITIVE IMPAIRMENT OR SEDATION IN THE ELDERLY: THE RANDOMISED, DOUBLE-BLIND SCOPE STUDY

Hypothesis / aims of study

Antimuscarinic agents are the mainstay of pharmacological treatment for overactive bladder syndrome (OAB). It is well documented that oxybutynin has the potential to cause cognitive impairment as a result of central anticholinergic activity mediated mainly via $M_1$ receptors in the forebrain. This may be a particular concern in the elderly or in other vulnerable groups with an already high anticholinergic load. Solifenacin is a newer generation antimuscarinic agent which has been shown to be effective and well tolerated in elderly patients. [1] Solifenacin acts preferentially on $M_3$ receptors in the bladder wall, and has a relatively low affinity for $M_1$ receptors.[2] The Solifenacin Cognitive Function Pilot Exploratory Study (SCOPE) was designed to assess the effect of solifenacin on cognitive function in elderly subjects, using a sensitive assessment system with placebo and oxybutynin control arms.

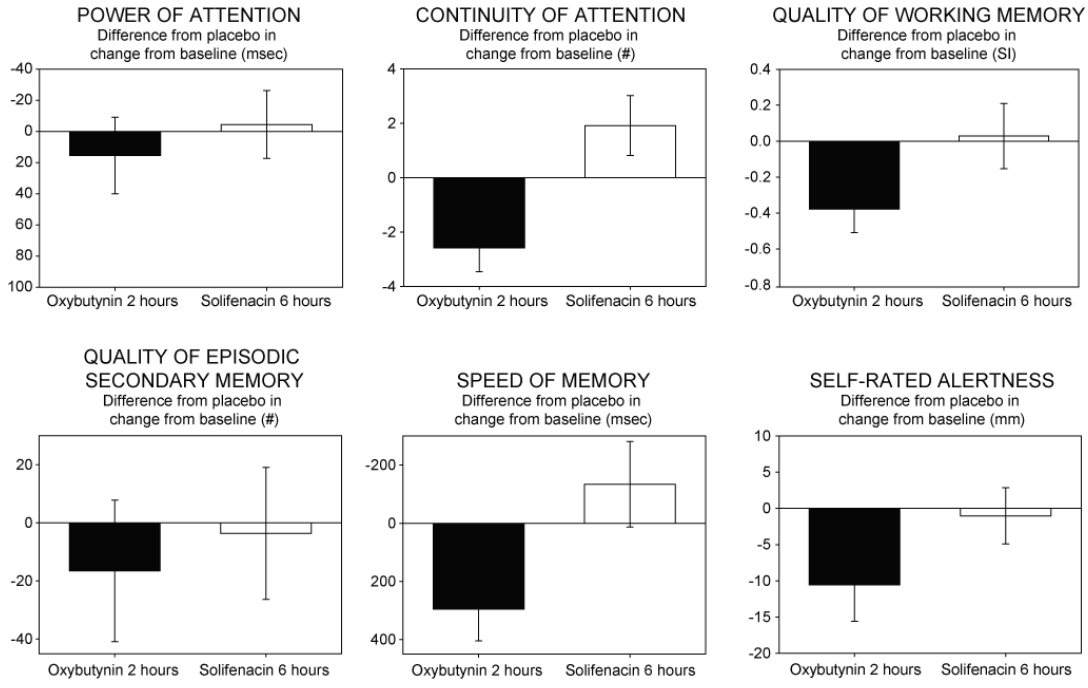
Study design, materials and methods

SCOPE was a randomised, double-blind, placebo- and oxybutynin-controlled, three-period crossover study in 12 elderly (≥65 years) male or female healthy subjects. After screening, subjects received cognitive function assessment training on day -1, and were then enrolled into 6 treatment sequences, each of which included a single dose of solifenacin 10mg in one period, oxybutynin 10mg in another, and placebo in another. The three treatments were separated by 14-day washout periods. Assessment of cognitive function was carried out pre-dose (= baseline) and at 2,4,6,8,10,12 and 24 hours post-dose, using the Cognitive Drug Research (CDR) computerised system to assess aspects of learning, memory, information processing, and self-rated mood (contentment, calmness) and alertness. The CDR system has been shown to be adequately sensitive to detect differential effects of anticholinergic drugs in comparable crossover studies of 12 subjects. Post-hoc analysis of covariance (ANCOVA) was conducted to calculate model adjusted t-tests for mean change from baseline between active treatment and placebo at each time point, together with 90% CI.

Results

There was no evidence to suggest that solifenacin impaired cognition or self-ratings of mood and alertness. Evaluation of the data at 6 hours post-dose, closest to the Tmax of solifenacin in this population, did not show any indication of possible impairment. The results of the ANCOVA showed no statistically significant deterioration in any of the five cognitive function tests or subjects' self-ratings of alertness and mood compared with placebo. By contrast, oxybutynin was consistently associated with impairment of attention, working and episodic memory, speed of memory, and self-rated alertness, primarily at 2 hours post-dose ($p<0.05$ at 2 hours post-dose for all variables except for quality of episodic memory, speed of memory and self-rated mood).
Results at the Tmax for solifenacin (6 hours) and oxybutynin (2 hours) are summarised in Figure 1.

Figure 1: Mean (+/- SEM) placebo-adjusted changes from baseline with single doses of solifenacin 10mg and oxybutynin 10mg with respect to cognitive measures and self-rated alertness at the Tmax of each drug in an elderly population. Bars going downwards indicate deterioration in cognitive function.




Interpretation of results

The test battery assessed all those domains of cognition which might have been expected to have been impaired by compounds with this mode of action. The dose of oxybutynin in this study was used as a positive control to demonstrate the success of the

study design and to validate the assessment procedures. The impaired cognitive function and alertness found with oxybutynin validates the study procedures and is consistent with previous findings with this drug. Adverse cognitive effects with oxybutynin tended to peak at 2 hours post-dose, corresponding with its Tmax.
There was no clear indication of cognitive impairment with solifenacin at its Tmax of 6 hours or at any other time point. From these results it appears unlikely that cognitive impairment will be seen with solifenacin in routine practice, not least because the 10mg dose of solifenacin used in this study is the highest licensed dose. The recommended starting dose of solifenacin is 5mg, and this would only be increased to 10mg if the patient required extra control of symptoms. A European post-marketing surveillance study of solifenacin in 4,450 OAB patients found that the 10mg dose was only needed by approximately 21% of patients under real-life practice conditions.[3]
Solifenacin has enhanced bladder and $M_3$-receptor selectivity compared with oxybutynin, which may in part explain the lack of cognitive impairment with solifenacin. In animal studies, solifenacin had a low ability to cross the blood-brain barrier, and it is possible that this characteristic may also contribute to the lack of cognitive impairment seen in the SCOPE study.

Concluding message
The randomised, double-blind, placebo-controlled SCOPE study found no evidence to suggest that solifenacin impairs cognitive function in elderly subjects. These findings suggest that solifenacin may be valuable for use in elderly patients with OAB where management of total anticholinergic load is a concern.

References: 1. Am. J Geriatr Pharmacother 2006;4:14-24., 2. Naunyn-Schmiederberg's Arch Pharmacol 2002;366:97-103., 3. Drug Safety 2008 (accepted for publication)

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| ***Specify source of funding or grant*** | **This study was undertakan with a research grant from Astellas Pharma Europe Ltd.** |
| ***Is this a clinical trial?*** | **Yes** |
| ***Is this study registered in a public clinical trials registry?*** | **No** |
| ***What were the subjects in the study?*** | **HUMAN** |
| ***Was this study approved by an ethics committee?*** | **Yes** |
| ***Specify Name of Ethics Committee*** | **Independent Ethics Committee (IEC) operating according to ICH GCP guidelines** |
| ***Was the Declaration of Helsinki followed?*** | **Yes** |
| ***Was informed consent obtained from the patients?*** | **Yes** |