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Title: DARIFENACIN DEMONSTRATED NO ADVERSE EFFECT ON COGNITIVE AND CARDIAC FUNCTION: RESULTS FROM A DOUBLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED STUDY

Aims of Study:

To compare the effects of darifenacin, a selective muscarinic M_3 receptor antagonist, with dicyclomine, an M_1 receptor antagonist, and with placebo on cognitive function, heart rate (bpm) and heart rate variability (%).

Methods:

Randomised, double-blind, double-dummy, placebo-controlled, four-way crossover study in 27 healthy male subjects (age 19 to 44 years). Subjects received single daily doses of darifenacin (7.5 or 15 mg), or a standard dose of dicyclomine 20 mg qds or placebo for 7 days in each period. Study periods were separated by 7 days' washout. Subjects underwent computerised testing designed by Cognitive Drug Research (CDR) Ltd to measure cognitive processes such as ability to access short-term memory, ability to concentrate, and ability to respond rapidly. In addition, a computerised questionnaire (Bond-Lader Visual Analogue Scales) was used to measure self-rated alertness, and calmness and contentment. 'Body sway' was also assessed using a CDR meter modelled on the Wright Ataxiameter. During each of the four treatment periods cognitive function tests were performed pre-dose on the first and last days (Days 1 and 7). Cognitive function was also assessed at intervals up to 12 hours post-dose on Day 7. A 15-minute, continuous ECG recording was also made on Day 7. Heart rate and variations in heart rate were calculated for the middle 5 minutes of this time period using a validated system developed for the Mortara Cardio 'Prodigy' analyzer. Cognitive function and cardiac parameters were analysed by ANOVA.

Results:

Darifenacin (7.5 mg and 15 mg) produced no detectable effects on cognitive function processes relative to placebo. In contrast, dicyclomine produced statistically significant impairment to simple reaction time ($p<0.01$), speed of numeric working memory ($p<0.05$), speed of spatial working memory ($p<0.05$), sensitivity of picture recognition ($p<0.05$) and speed of picture recognition ($p<0.05$), versus placebo. Darifenacin had no significant effect on heart rate or heart rate variability whereas dicyclomine significantly reduced heart rate (-4.79bpm; $p=0.003$) and was also associated with significantly greater heart rate variability (12%; $p=0.005$), compared with placebo. Darifenacin was generally well tolerated at both dose levels and the majority of adverse events were mild or moderate in severity. More subjects reported treatment-related adverse events in the dicyclomine group than in either the darifenacin 7.5 mg or 15 mg groups. No changes in vital signs or ECG were attributed to darifenacin.

Conclusions:

Darifenacin (7.5 mg and 15 mg od) did not produce any detectable effect on cognitive or cardiac function. In contrast, dicyclomine (20 mg qds) produced cognitive impairment that was considered to be similar to drinking 2 to 3 units of alcohol.

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