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CAN MEDICATION PROLONG WARNING TIME?

Aims of Study

Symptoms of an overactive bladder (OAB) syndrome are very common and can have a serious negative impact on quality of life. For individuals with OAB, urgency and the associated 'warning time' (the time from the first sensation of urgency to micturition) are important. The longer the warning time, the greater the chance of avoiding the social embarrassment of urinary incontinence. Furthermore, recognition of the concept of warning time is important if patients wish to achieve continence (1). However, the application of warning time as an outcome measure in clinical trials evaluating antimuscarinics for the treatment of OAB is not routine and is only rarely mentioned in the literature (2). The objectives of this proof-of-concept study were to assess the potential of anti-muscarinic medication (darifenacin) to prolong warning time and to evaluate the potential utility of warning time as a novel method of assessing urgency.

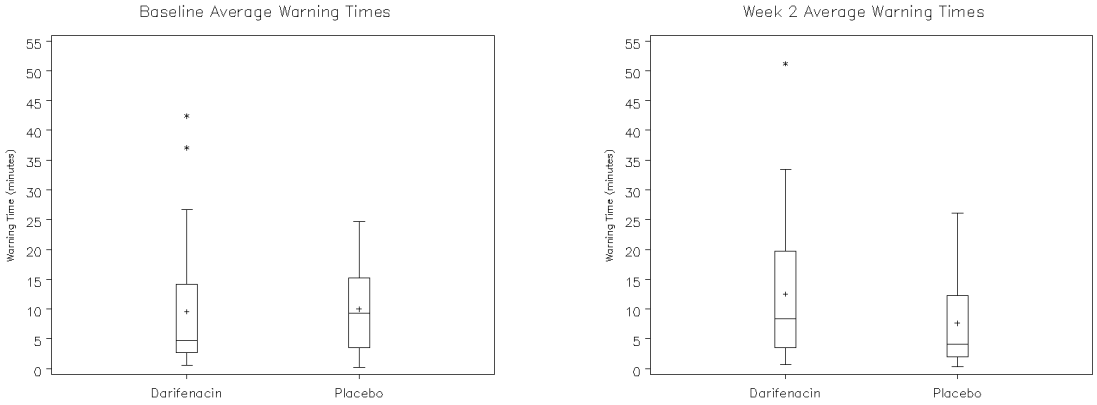
Methods

This was a randomised, double-blind, placebo-controlled, parallel-group study with a 2-week, medication-free run-in period. Individuals who had the symptom of urgency for at least 6 months prior to the study, and the same symptom occurring a minimum of 4 times/day during the run-in period, were randomised to 2 weeks' treatment with darifenacin 30 mg once daily or placebo. Warning time was defined as the time from first sensation of urgency to voiding. Average warning time (the mean of at most 3 warning times recorded at each clinic visit) was used as the primary endpoint. Warning time and the levels of sensation were recorded in ambulatory individuals with the aid of small portable electronic event recorders. The primary analysis was based on the change from baseline to end of treatment (Week 2) in average warning time. The Wilcoxon rank-sum test was used to test for differences between the two treatment groups (3). A secondary endpoint (response defined by 30% improvement in average warning time) was analysed using a logistic regression model (adjusting for baseline warning time, age and gender).

Results

Seventy-two individuals (mean age 54 years) entered the study and 67 of them (those with both baseline and post-baseline warning times) were included in the primary efficacy analysis, 32 having received darifenacin, and 35 a matching placebo. Change in average warning time from baseline to Week 2 was 4.3 min longer in the darifenacin group than in the placebo group, and the difference was statistically significant (95% CI 1.2, 7.4; p=0.003). The number of individuals who showed at least a 30% improvement in average warning time was significantly higher in the darifenacin group compared with the placebo group (47% compared to 20%, p=0.009). The odds of an individual in the darifenacin group responding with an increase of at least 30% in warning time were calculated to be 5.6 times (95% CI 1.5, 20.1) higher than in the placebo group.

Figure 1: Box-whisker plots of average warning times at baseline and Week 2



Warning time was assessed using the mean of at most three warning times. Some individuals exhibited a large variation in warning times, indicative of the inherent difficulty in measuring this parameter, and suggesting that other summary measures may be more appropriate. Possible alternate measures could be the median warning time, which would lessen the influence of extreme values, or the minimum warning time which, it could be argued, is the measure of most relevance to an individual. Reanalysis of this study using these alternate endpoints was consistent with the initial analysis in demonstrating that darifenacin produced a statistically significant change in warning time compared with placebo. Using the minimum warning time, the difference in the change from baseline to Week 2 between the darifenacin and placebo groups was 1.9 min (95% CI 0.2, 4.2; p=0.017).

Conclusions

In this study, average warning time proved to be an effective and novel endpoint for the assessment of urgency. This study is the first to provide an objective demonstration of a significant, positive effect of an antimuscarinic on warning time indicating that warning time could be employed to assess the efficacy of treatments for urgency or OAB.

References

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