

EFFICACY AND TOLERABILITY OF DARIFENACIN, A MUSCARINIC M₃ SELECTIVE RECEPTOR ANTAGONIST, COMPARED WITH OXYBUTYNYN IN THE TREATMENT OF PATIENTS WITH OVERACTIVE BLADDER

Hypothesis / aims of study

This study compared the efficacy and tolerability of darifenacin, a new muscarinic M₃ selective receptor antagonist (M₃ SRA), with oxybutynin in the treatment of patients with overactive bladder (OAB); safety was also assessed. Because the muscarinic M₃ receptor subtype is known to mediate detrusor muscle contraction, the selectivity (and M₁ and M₂ sparing properties) of darifenacin may provide effective relief of OAB symptoms without the wide diversity of adverse events seen with less selective antimuscarinic agents.

Study design, materials and methods

This was a multicenter, randomized, double-blind, placebo-controlled, crossover study of: oral darifenacin CR 15 mg (controlled release) once daily (qd); oxybutynin 5 mg three times daily (tid), and matching placebo. Enrolled adult patients had urodynamically verified OAB, with ≥ 4 significant urge incontinence episodes per week (requiring a change in pads or clothing) and frequency ≥ 8 voids/day, on average. After a 2-week run-in period, patients received each of the following treatments for 2 weeks, according to a randomized sequence: darifenacin CR 15 mg qd; oxybutynin 5 mg tid; and matching placebo. Efficacy was evaluated using daily paper diaries recording incontinence episodes, frequency of micturition, urgency and severity of urgency episodes throughout the run-in and treatment periods. Both efficacy and tolerability were assessed primarily by the statistical analysis of 'complete cases'. For efficacy, the subject was regarded as a 'complete case' if an efficacy variable value for week 2 was recorded for all treatment periods. For tolerability, a 'complete case' was defined as one in which the subject was exposed to all double-blind treatments for at least 7 days (or less if antimuscarinic adverse events causing withdrawal occurred earlier).

Results

Seventy-six patients (93% female) entered the study. Based on the criteria for 'complete cases', 58 patients were included in the efficacy analysis and 61 patients in the tolerability analysis. Darifenacin and oxybutynin were associated with significantly fewer incontinence episodes/week and fewer and less severe urgency episodes at week 2 than placebo (all $p < 0.05$); effects of darifenacin and oxybutynin on OAB symptoms were comparable (Table).

Outcome variables (daily/weekly averages for week 2)	Efficacy evaluable patients (n=58)		
	Darifenacin 15 mg qd	Oxybutynin 5 mg tid	Placebo
Incontinence episodes/week	10.93*	9.45*	14.64
Urgency episodes/day	7.95*	8.12*	8.71
Severity of urgency episodes†	1.93*	1.89*	2.03
Number of micturitions/day	9.33	9.24	9.62

All values means adjusted for sequence and period from the crossover analysis of variance.

* $p < 0.05$ versus placebo.

†Severity of urgency episodes recorded as: 1=mild; 2=moderate; 3=severe.

Among patients evaluable for tolerability (n=61), oxybutynin was associated with a higher rate of dry mouth (36%) when compared with either darifenacin (13%, $p < 0.05$) or placebo (5%, $p < 0.05$). Blurred vision and dizziness were only reported during oxybutynin therapy (3% and 2%, respectively). Rates of constipation were comparable between darifenacin (10%) and oxybutynin (8%), although both tended to be ($p > 0.05$) higher than placebo (3%). The majority of adverse events were mild to moderate in severity with each treatment. Four patients receiving oxybutynin discontinued from the study due to dry mouth. The low incidence of

laboratory abnormalities was similar with all treatments and there were no clinically relevant, treatment-related changes in blood pressure, pulse rate or ECG.

Interpretation of results

Both darifenacin and oxybutynin produced significant improvement in number of incontinence episodes/week, number of urgency episodes/day and severity of urgency episodes compared with placebo. However, oxybutynin was associated with a significantly higher rate of dry mouth compared with either darifenacin or placebo. In addition, patients only reported blurred vision and dizziness when receiving oxybutynin. The high selectivity of darifenacin for M₃ receptors along with M₁ and M₂ sparing characteristics therefore provide clinical efficacy with a reduced propensity for adverse events related to the blockade of non-M₃ receptors.

Concluding message

Oral darifenacin CR 15 mg qd was shown to provide comparable clinical efficacy with improved tolerability (less dry mouth, no blurred vision or dizziness) versus oxybutynin 5 mg tid in the treatment of patients with OAB.

References

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