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CONTINENCE DRY RATE OF TROSPIUM CHLORIDE-TREATED PATIENTS: AN INVESTIGATION OF EQUIVALENT COHORTS IN THE ANTIMUSCARINIC CLASS

Hypothesis / aims of study

Currently there are several antimuscarinic agents available for the treatment of overactive bladder but few head to head studies to guide the physician in choosing one over another. Comparison of data from different studies is largely invalid given the vagaries in study population and design. The aim of this paper is to propose ways in which continence data could be viewed to allow a more “apples to apples” comparison. Three specific areas of cross-study comparison have been addressed: baseline severity of disease, duration of diary collection periods, and differences in the underlying placebo effect.

Study design, materials and methods

Data from trospium chloride 20 mg twice daily were collected from a large randomized Phase III double-blind, placebo-controlled clinical study on OAB patients (Rudy et al, 2004).
The “dry rate” was defined as no incontinence episodes (urge or stress) during the period of on-treatment diary collection and was used as the end point. The week 12 or last observation carried forward values were used. Data on solifenacin dry rates were obtained from a publication (Cardozo et al, 2004) of two pooled studies with a similar design but with 2 active arms (5mg and 10mg once daily) and a placebo arm. The essential differences between the solifenacin studies and the trospium study were: 1) Patients in the trospium study had more severe disease at baseline, and; 2) Diary collection periods were 7-day diaries for trospium as opposed to 3-day diaries for solifenacin. Possibly reflecting these two differences in the study designs was the large observed difference in the placebo response between the two studies at Week 12: a placebo rate of 38% was observed in the solifenacin studies versus 15% in the trospium study.

In order to account for the severity of disease at baseline, an iterative method was applied to the trospium data to exclude patients with the most severe incontinence until the residual baseline mean of the trospium data was comparable with the solifenacin baseline mean. The cut-point arrived at was 6 incontinent episodes per day per patient (42 episodes per week). This residual dataset reflected 75% of the patients randomized in the trospium study. This residual dataset was then used in the analysis.

In order to account for the difference in the duration of the diary collection periods, the 7 day diary data from the trospium chloride study were grouped into five overlapping 3-day consecutive blocks: Days 1, 2, and 3 comprised the first block, Days 2, 3, and 4 comprised the second block, and so forth through the fifth block (Days 5, 6, and 7). In the statistical analyses, all five 3-day trospium chloride blocks were derived and in addition, an average across the 5 trospium chloride blocks was calculated to provide an overall estimate of the dry rate given only 3 days of diary collection. These dry rates were calculated for the active and placebo groups in each of the five 3-day diary blocks (table 1).

In order to account for the difference in the underlying placebo rates, two methods were used to compare the solifenacin and trospium data: 1) subtraction, i.e., active minus placebo dry rate, and 2) benefit ratio, i.e., active divided by placebo dry rate.

Results

The baseline number of incontinence episodes were: for the solifenacin dataset, an average of 2.8 episodes per 24 hours (Cardozo et al, 2004); for the full trospium dataset, 4.32 episodes per 24 hours; and for the residual trospium dataset, 2.75 episodes per 24 hours. Table 1 demonstrates the solifenacin dry rate for the 3-day diary was 38% for placebo and

51% for active, yielding a treatment difference of 13% and a treatment benefit ratio of 1.35. The trospium 7-day dry rates were 12% for placebo and 26% for active giving a treatment difference of 14% and a benefit ratio of 2.17 while the trospium 7-day dry rates for the residual dataset were 12% for placebo and 30% for active giving a treatment difference of 18% and a benefit ratio of 2.50. The trospium 3-day average dry rate (averaged over the five 3-day blocks) was 42% compared to 18% for the placebo group, yielding a treatment difference of an average of 24% and an average benefit ratio of 2.29.

Table 1: Urinary continence rates at Week 12: Three-Day Diary Collection Period Comparisons

	Placebo (%)	Active (%)	Offset from Placebo (Difference, Active-Placebo) (%)	Treatment Benefit Ratio (Active/Placebo)
Solifenacin 3-Day Diary (All Patients)[1]	38	51	13	1.35
Trospium 7-Day Diary (All Patients)[2]	12	26	14	2.17
Trospium 7-Day Diary (Patients With ≤6 Leaks/day at baseline)[3]	12	30	18	2.50
Trospium 3-Day Diary (Patients With ≤6 Leaks/day at baseline)				
Days 1-3	20	41	21	2.05
Days 2-4	18	43	25	2.39
Days 3-5	18	45	27	2.50
Days 4-6	17	41	24	2.41
Days 5-7	19	40	21	2.11
Block Average	18	42	24	2.29

(1) N=943 patients in the Solifenacin studies with at least one incontinence episode at baseline, approximately 2/3 of whom were actively treated with either 5mg or 10mg/day and 1/3 placebo treated.
(2) N=648 in the trospium chloride study: 326 Placebo and 322 Trospium Chloride
(3) Residual N=490 in the trospium chloride study: 246 Placebo and 244 Trospium Chloride

Interpretation of results

The residual trospium dataset was well matched with the solifenacin study with respect to the baseline number of incontinence episodes per day (2.75 versus 2.8, respectively). As might be expected, 3-day diaries yielded a higher dry rate than the 7-day diary, however, when correcting for the effect offset due to placebo, the magnitude of effect of trospium was greater than that of solifenacin. By assessing the treatment benefit ratio within each study, one can compare more accurately the *relative* efficacy of the active products.

Conclusions

In the absence of a head to head, well-controlled clinical study, some valid comparison of continence rates is possible if logical adjustment is made for baseline severity, duration of diary data collection and the differing placebo effects. From this analysis, it would appear that the dry therapeutic rate for trospium is greater than for solifenacin.

References

Cardozo L. et al. Solifenacin Statistically Significantly Increased Continence Rates In Subjects With Symptoms Of The Overactive Bladder Syndrome. ICS.2004
Rudy D. et al. A Multicenter Phase III Trial Studying Trospium Chloride in Patients with Overactive Bladder. *Urology*. In Press. 2005.

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