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Zellner M[1], Stöhrer M[2], Palmtag H[3], Madersbacher H[4], Bödeker R[5]
1. Urology Dept., Hospital Passauer Wolf, D-Bad Griesbach, 2. Neuro-Urology, lecturer of the University Essen, D-Essen, 3. Urology Dept., Municipal Hospital, D-Sindelfingen, 4. Neuro-Urology Unit, University Hospital, A-Innsbruck, 5. Institute for Medical Informatics, Justus Liebig University, D-Giessen

Hypothesis / aims of study

The aim of the clinical trial was to evaluate efficacy, safety and disease-related quality of life parameters of oral trospium chloride in comparison to oral oxybutynin treatment in patients with urge urinary incontinence (non-inferiority hypothesis).

Study design, materials and methods

Randomised, double-blind, controlled, parallel group multicentre clinical trial in Germany to assess efficacy, safety and quality of life of patients being treated with trospium chloride (TC) in comparison to oxybutynin (OXY, most commonly used worldwide). Patients ≥ 18 years of age suffering from urge urinary incontinence were enrolled who had ≥ 8 micturitions daily and ≥ 5 incontinence episodes/week, both documented in a 7-day bladder diary during the screening phase. Patients also filled in bladder diaries during week 4 and 12 recording each micturition, each incontinence episode, the degree of urgency and (on 2 successive days) the voided volumes. The primary efficacy parameter was the absolute reduction in urge incontinence episodes/week comparing baseline values with those of last treatment week (week 12). Secondary efficacy parameters were the absolute reduction of micturitions/24 hours, changes in the degree of urgency, the mean voided volume, the subjective treatment outcome (visual analogue scale), quality of life parameters (German-language King's Health Questionnaire, KHQ) and the intensity of "dry mouth" (scale: none, mild, moderate, severe). The KHQ was to be scored in accordance to the developers' instructions (1). Given a non-clinical relevant difference of 3.5 or less incontinence episodes/week a two group one-sided t-test (α=0.025, $n_1=n_2$=557) has 90% power to reject the null hypothesis. As the per protocol set is the relevant collective for testing a non-inferiority hypothesis 1640 patients were planned to be randomised. In fact, 1659 eligible patients received either 45 mg trospium chloride (n=829) or 7.5 mg oxybutynin (n= 830) per day for the initial 4 weeks of treatment. At the intermediate visit, the daily dose could be maintained or increased (to twice as much as before). In the adjusted dose group a single dose reduction to the starting dose was allowed. The flexible dose regimen was chosen to achieve the best balance between efficacy and adverse drug reactions for each patient.

Results

The absolute changes in urge incontinence episodes/week from baseline to week 12 in the per protocol (PP, n_{TC}= 615, n_{OXY}= 611) and in the full analysis set (FAS, n_{TC}= 810, n_{OXY}= 798) were comparable in both treatment groups. The median of the observed changes in the FAS was –10.42 (PP: -11.00) for TC and –10.00 (PP: -11.00) for OXY ($p_{non\text{-}inferiority\ hypothesis}$<0.0001 for both analysis sets, Table 1). When considering the secondary parameters, comparable efficacy was shown in both groups from baseline to week 12 in the following variables: the reduction of micturitions/24 hours, reduction in the degree of urgency, increase of mean micturition volume, the subjective treatment outcome, and the improvement of quality of life parameters. The mean change in KHQ domain total score was –18.42 for TC and –18.24 for OXY at the end of treatment (FAS, baseline scores: 47.52 vs. 47.00, respectively). All individual domain scores of the KHQ decreased to a similar extent (all > 5 points) in both groups and can therefore be interpreted as clinically meaningful and important to the patients (2). The greatest improvements (> 20 points) were found in the domains incontinence impact, role limitations, physical limitations and emotions.

In contrast, a statistically significant difference was observed for the adverse event (AE) "dry mouth". "Dry mouth" was less frequent and less severe in the trospium chloride group. The increase of "dry mouth" intensity at week 4 and 12 was significantly lower (p < 0.0001) in the trospium chloride group (Table 2). The safety results provide additional support for the better tolerance of trospium chloride. There were differences in favour of trospium chloride in the number of AEs (337 vs. 387 AEs), the number of patients with AEs (188 vs. 220 patients), the number of AEs assessed to be related to the study drug (13.9% vs. 18.3%), and the number of patients with AEs resulting in discontinuation of the study drug (48 vs. 68 patients). The number of patients with serious AEs was very low in both groups but slightly higher in the trospium chloride group (13 patients (1.6%) vs. 9 patients (1.1%)). The fact that more patients in the oxybutynin group needed a dose readjustment (19 of 242 vs. 30 of 193 patients of adjusted TC vs. OXY group, respectively; safety population) might also suggest a better tolerance of trospium chloride.

Table 1: Primary efficacy analysis: Absolute change in urge incontinence episodes/week (FAS population)

	Baseline		**Change to week 12**	
	Trospium chloride	Oxybutynin	Trospium chloride	Oxybutynin
N	805	797	788	784
Mean	20.61	18.94	-14.31	-13.60
S. D.	18.103	16.670	15.433	15.402
Min	0.00	0.00	-107.00	-105.00
Median	14.00	14.00	-10.42	-10.00
Max	107.00	120.00	35.00	63.00
HL estimate of difference of changes between both groups: Δ= 0.00 | 95% CI [-1.00; 0.83]				
Testing non-inferiority hypothesis: p <0.0001				

Table 2: Changes in intensity of dry mouth (FAS population)

Baseline	**week 4**	**week 12**

	TC n (%)	OXY n (%)	TC n (%)	OXY n (%)	TC n (%)	OXY n (%)
None (0)	385 (47.5)	366 (45.9)	158 (19.5)	74 (9.3)	141 (17.4)	62 (7.8)
Mild (1)	245 (30.2)	245 (30.7)	290 (35.8)	220 (27.6)	257 (31.7)	217 (27.2)
Moderate (2)	143 (17.7)	161 (20.2)	265 (32.7)	328 (41.1)	263 (32.5)	273 (34.2)
Severe (3)	31 (3.8)	26 (3.3)	74 (9.1)	158 (19.8)	111 (13.7)	204 (25.6)
Unknown	1 (0.1)	0	0	0	1 (0.1)	2 (0.1)
Change from baseline to			**week 4**		**week 12**	
	Improvement		74 (9.1)	52 (6.5)	80 (9.9)	51 (6.4)
	No change		329 (40.6)	217 (27.2)	272 (33.6)	190 (23.8)
	Worsening		380 (46.9)	510 (63.9)	415 (51.2)	514 (64.4)
			p-value <0.0001		p-value <0.0001	

Notes: Percentages are based on the number of patients: Trospium chloride (TC) N=810, Oxybutynin (OXY) N=798. P-value is obtained from the Cochran-Mantel-Haenszel test for general association stratified for centre.

Interpretation of results

In the course of data analysis the results proved to be statistically robust and internally consistent. No differences between the treatment groups could be found, neither for the primary, nor for one of the secondary parameters, except the parameter “dry mouth”. This statistically significant difference together with supportive results of the safety evaluation speak for a better tolerance of trospium chloride. Similar results were shown in a previous smaller study with patients suffering from neurogenic detrusor overactivity (3).

Concluding message

Overall, trospium chloride was shown to be as efficacious as oxybutynin in the treatment of urge urinary incontinence but shows an advantage in tolerance with particular regard to the most common antimuscarinic adverse drug reaction “dry mouth”.

References

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HUMAN SUBJECTS: This study was approved by the Ethics Committee of the Bayerische Landesärztekammer, D-Munich and followed the Declaration of Helsinki Informed consent was obtained from the patients.