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Efficacy and Tolerability of Add-On Trospium Chloride in Patients with Benign Prostate Syndrome and Overactive Bladder: A Non-Interventional Trial Showing Use of Flexible Dosing

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ABSTRACT

OBJECTIVE: This study was performed to elucidate efficacy and tolerability of an oral add-on therapy with trospium chloride in patients with benign prostate syndrome (BPS) without obstruction who showed International Prostate Symptom Score (IPSS) ≥ 8 and distinctive overactive bladder (OAB) symptoms under α-receptor blocker therapy.

RESEARCH DESIGN AND METHODS: This was a multicenter, open, non-interventional, prospective study performed in private urology practices. Only patients with OAB and BPS who were insufficiently treated with α-receptor blockers were eligible to participate. Patients received trospium chloride coated tablets[b] as oral add-on therapy. Dosing and duration of treatment were not predetermined; however, reference was made to the respective details in the product's package leaflet, and a minimal treatment period of 4 weeks was suggested.

MAIN OUTCOME MEASURES: Core symptoms of BPS, IPSS, overactive bladder symptoms, and Quality of Life (QoL) score were assessed at the beginning and end of the observation period. Adverse events and withdrawals, as well as the dosage regimens chosen, were documented at the end of the study. Furthermore, doctors and patients were requested to rate efficacy and tolerability of the treatment. All data were evaluated solely in an exploratory way.

RESULTS: In total, 4104 cases fulfilled the predetermined criteria for the evaluation of efficacy; all 4382 cases were included in the safety analysis. After a mean (SD) treatment period of 40 (17.9) days with trospium chloride as add-on therapy, all core symptoms of BPS had improved: The mean daily micturition frequency was reduced from 11.8 (3.5) to 8.5 (2.5). The percentage of continent patients increased from 66.6% to 83.1%, and the proportion of patients requiring incontinence pads was almost halved from 19.9% to 11.7%. The median IPSS score was reduced from 18 to 12, and the QoL score improved from 4 to 2. Treatment tolerability was assessed as *very good* or *good* by 94.2% of the doctors. There were 121 (2.8%) early treatment withdrawals, and 35 (0.8%) patients experienced adverse events.

CONCLUSION: Patients with moderate to severe lower urinary tract symptoms due to BPS and OAB syndrome who were insufficiently treated with an α-receptor blocker may benefit from add-on therapy with trospium chloride, a compound generally well tolerated by the vast majority of the patients.

KEYWORDS: α-Receptor blocker, Overactive bladder, Benign prostate syndrome, Trospium chloride

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[a] Selected results of this study were presented on a poster at the 48th International Consultation on Incontinence in Paris, 05-08 July 2008.

[b] Trospium chloride coated tablets (Spasmex 30), Dr. R. Pfleger GmbH, D-96045 Bamberg, Germany

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INTRODUCTION

α-Receptor-blockers such as tamsulosin, alfuzosin, doxazosin or terazosin are the current standards in the treatment of lower urinary tract symptoms (LUTS) in men with benign prostate hyperplasia (BPH) [1], while anticholinergics like tolterodine or trospium chloride constitute the first-line pharmacological option in the treatment of an overactive bladder syndrome (OAB) [2].

In recent years, several studies have been published which investigate the combined therapy of α-receptor-blockers with anticholinergics in patients with LUTS due to BPH and concomitant OAB. The authors concordantly reported a therapeutic benefit for the combination therapy (i.e. tamsulosin or doxazosin plus tolterodine or propiverin) compared to mono-therapy with the respective α-receptor-blocker [3,4,5,6].

To the authors' knowledge, no clinical data have been published on combined therapy with trospium chloride and α-receptor-blockers in the aforementioned patient group. The present trial was therefore undertaken to fill this gap, and it focused on the investigation of oral add-on therapy with trospium chloride in patients with BPS without obstruction who showed an IPSS ≥ 8 and moderate to severe OAB symptoms when treated with an α-receptor blocker.

PATIENTS AND METHODS

In total, 4382 patients were entered into this noninterventional prospective trial performed at 692 private urology practices in Germany. The inclusion criterion was the presence of OAB symptoms in patients with BPS without clinically relevant obstruction who had an IPSS ≥ 8 and were under treatment with an α-receptor blocker. Patients' anthropometric data are shown in Table 1.

Contraindications defined in the Summary of Product Characteristics (SPC) of trospium chloride are mechanical stenoses of the gastrointestinal tract, urinary retention, narrow-angle glaucoma, tachycardiac arrhythmia, myasthenia gravis, renal insufficiency requiring dialysis, and hypersensitivity to trospium chloride or any of the inactive ingredients. Before starting treatment with trospium chloride, infravesical obstruction has to be excluded by means of urological routine procedures for residual urine (eg, anamnestic questioning, sonography, or X-ray examination). In addition, hormonal and organic causes of the OAB symptoms have to be excluded in agreement with the SPC.

Table 1. Anthropometric Data of all Patients Included (n=4325)

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	Age (y)	Weight (kg)	Body size (cm)
Mean	68.4	83.4	175.2
SD	8.8	10.9	6.1
Median	69	82	175
Total (n)	3307	4266	4259

The study protocol did not contain any specifications regarding dosing of oral add-on trospium chloride or treatment period. Instead, investigators were asked to follow the recommendations on the package leaflet.

This noninterventional trial was carried out within the indication approved in the marketing authorization and under consideration of the contraindications and precautions defined there.

The individual case report forms required to collect the following data at the first visit included demography, history, OAB symptoms (micturitions per day/night), incontinence episodes per week, use of incontinence pads, as well as the assessment of IPSS (sum of symptom scores, each ranging from 0 = *never* to 5 = *almost always*) and QoL scores (score ranging from 0 = *excellent* to 6 = *very bad*). Additionally, details of baseline α-receptor blocker treatment and its tolerability were to be documented. On the second visit, the following was to be recorded: treatment period and dosing of trospium chloride, OAB symptoms, incontinence episodes, use of incontinence pads, IPSS and QoL scores, investigator's and patient's assessment of treatment efficacy and tolerability, and any adverse drug effects.

Data were entered into the computer and analyzed by SPSS 10 statistical software solely in an exploratory sense. Data are presented as mean (SD) values.

In compliance with § 67 German drug law, the competent authorities were informed of the protocol, the planned start and end of the study, and the participating urologists. All legal preconditions were observed. The official recommendations for the conduct of non-interventional trials were observed [7]. Approval of an ethical committee was not required for such noninterventional post-registration studies in Germany.

RESULTS

Trial Population and Basic Demographic Data

All 4382 case reports obtained were entered into the safety analysis. Fifty-seven patients with retrospective documentation were excluded from further analysis, rendering a baseline population of 4325 patients. The efficacy subset comprised 4104 cases. In accordance with the predefined reasons in the trial protocol, a total of 221 cases did not qualify for the efficacy analysis (IPSS score ≤ 7 at baseline visit or missing IPSS scores, trospium chloride (TC) treatment period less than 10 days, or documentation missing).

The mean age of the patients was 68.4 years (SD = 8.8; median = 69; min = 30; max = 98) and the mean body weight 83.4 kg (SD = 10.9; median = 82; min = 49; max = 183).

History of BPS and OAB Symptoms at Baseline

In the baseline population of 4325 patients, BPS had been present for years in 2672 (61.9%) of the patients and for *months* in 1411 (32.6%) patients. In 205 (4.7%) patients, BPS had been diagnosed for *weeks* and for *some days* in 20 (0.5%) patients. The patients had a mean daily micturition frequency of 11.8 (SD = 3.5; median = 12) with an average of 3.2 (SD = 1.3; median = 3) nightly micturitions. The majority of patients rated the urgency as *strong* (44.2%) or *medium* (48.4%), while in about 7% of the patients urgency was *mild* or *not existent*.

Fourteen hundred (32.4%) patients experienced a mean of 4.9 (SD = 5.3; median = 3) incontinence episodes per week. Eight hundred fifty nine (19.9%) patients used mean of 9.3 (SD = 6.8; median = 7) incontinence pads per week.

Basic α-Receptor Blocker Treatment

The basic α-receptor blocker treatment was tamsulosin in 73.4%, alfuzosin in 14.2%, terazosin in 8.6%, and doxazosin in 3.1% of cases. In 1480 (34.2%) patients, α-receptor blocker treatment had been initiated less than 12 months prior to this study; in 1965 (45.4%) patients treatment duration was longer than 30 days; and in 545 (12.6%) patients longer than 7 days. In most cases, daily doses of α-receptor blocker treatment conformed to the official recommendations (Table 2).

Table 2: Prescribed Treatment Regimens with α-Receptor Blockers

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Prescribed daily doses with α-receptor blockers		
	Patients	
	n	%
Tamsulosin		
1x0.4mg	2991	94.3
1x 0.8mg	11	0.4
Alfuzosin		
1x10mg	551	90.0
2x5mg	5	0.8
1x5mg	13	2.1
Terazosin		
1x2mg	179	48.0
1x2,5mg	7	1.9
1x5mg	97	26.0
1x10mg	14	3.7
2x2mg	19	5.1
Doxazosin		
1x1mg	2	1.5
1x2mg	32	23.5
1x4mg	71	52.2
1x5mg	6	4.4
2x2mg	8	5.9

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IPSS and QoL Score at Baseline

In the efficacy subset of 4104 patients, the median of the IPSS was 18 (mean = 18.2; SD = 5.1). The IPSS in 2571 patients was 8-19 (moderate LUTS), while 1533 had a score of 20-35 (severe LUTS). The median of the QoL score was 4 (mean = 3.8; SD = 0.9).

Trospium Chloride – Dosing and Treatment Period

The most frequently prescribed daily doses of trospium chloride were 30 mg (45.6%), 45 mg (16.8%), and 60 mg (28.8%). In 1432 (33%) cases, trospium chloride instant-release coated tablets were prescribed as once daily dosage, whereas trospium chloride was prescribed as twice a day dosage regimen in 1907 (44.1%) cases and as 3 times a day regimen in 905 (20.9%) cases (Figure 1). The mean treatment period was 40.5 (17.9) days. Regular administration of the drug was confirmed in 93.8% of the patients.

Figure 1: Dosage Regimens of Trospium Chloride Coated Instant Release Tablets Prescribed (n=4325)

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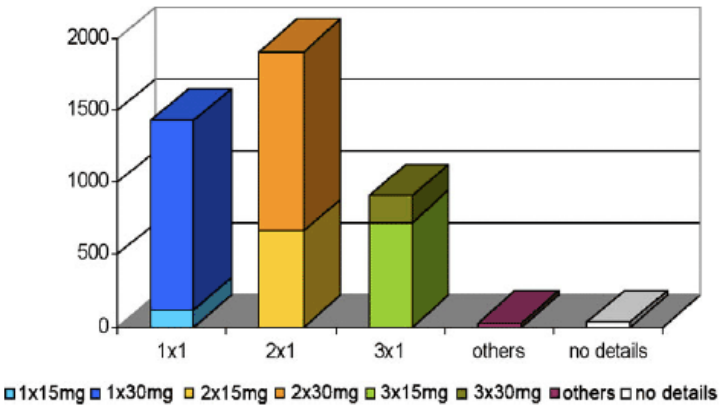

BPS and OAB Symptoms After Add-on Treatment with Trospium Chloride

On the follow-up visit, a significant improvement of all symptoms was evident. The proportion of patients rating the sensation of urgency as *strong* was reduced from 44.2% to 4%. Concomitantly, the percentage of patients with only mild urgency rose from 6.4% to 51.5%, and the fraction of patients without urgency problems rose from 0.5% to 12% (Figure 2). The daily micturition frequency at baseline (11.8) had dropped

Figure 2: Degree of Urgency Before and After Add-on Therapy with Trospium Choride (% patients)

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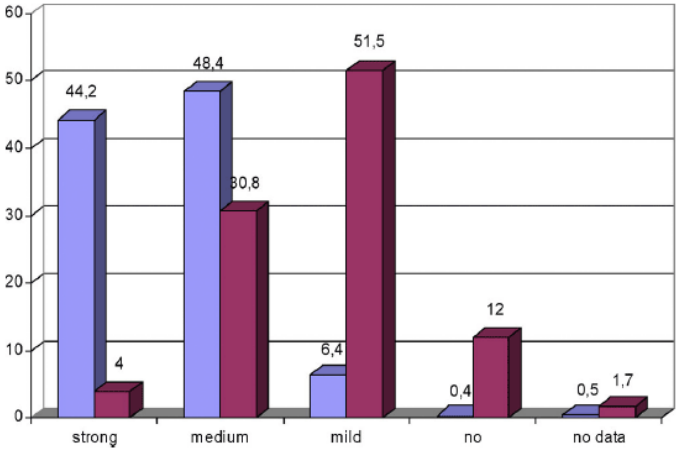

to 8.5 (SD = 2.5; median = 8), and the average of 3.2 nightly micturitions at baseline was almost halved to 1.7 events (SD = 1; median = 2).

The proportion of patients without incontinence episodes rose from 66.6% to 83.1%, and the mean total of incontinence episodes fell from 4.9 (5.3) to 3.6 (3.9) events per week. As shown in Figure 3, the percentage of patients requiring incontinence pads was almost halved to 11.7% (baseline 19.9%), and the mean number of incontinence pads used per week was reduced from 9.3 (6.8) to 7.1 (4.8).

IPSS and QoL Score After Add-on Treatment with Trospium Chloride

In the efficacy subset of 4104 patients, the median of the IPSS was reduced by one third to 12 (baseline = 18), and the median of the QoL score had improved by 50% to 2 (baseline = 4).

Rating of Add-on Treatment Efficacy

The general assessment of add-on treatment efficacy by investigators and patients is shown in Table 3. In 82.6% of cases,

the investigators rated the therapy outcome as *very good* or *good* and as *poor* in only 5%. The patients' ratings were comparable.

Figure 3. LUTS and Use of incontinence Pads Before and After Add-on Treatment with Trospium Chloride (n=4325); Means of: Total Daily Micturitions, Nightly Micturitions, Incontinence Episodes/Week, and Incontinence Pads Used/Week.
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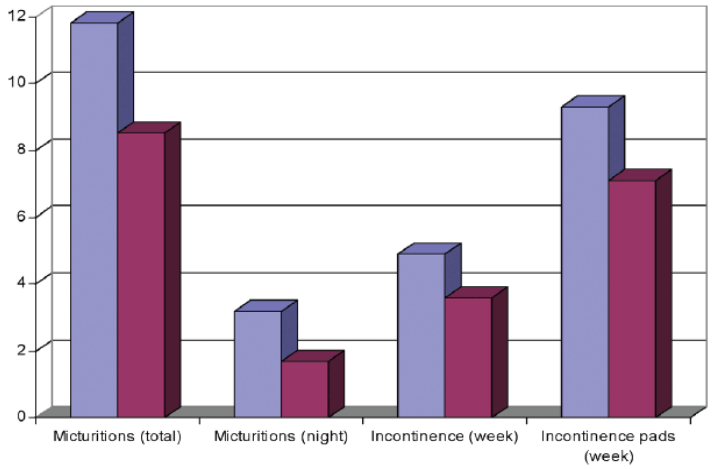

Table 3: Assessment of Add-on Treatment Efficacy (n=4104)
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Assessment of Add-On Treatment Efficacy					
Investigator			Patient		
	n	%		n	%
Very good	1475	35.9		1424	34.7
Good	1915	46.7		1788	43.6
Fair	496	12.1		614	15.0
Bad	183	4.5		217	5.3
Very bad	20	0.5		43	1.0
No data	15	0.3		18	0.4
Total	4104	100		4104	100

Rating of Add-on Treatment Tolerability

General tolerability of oral add-on treatment with trospium chloride was rated as *very good* or *good* by 94.2% of the investigators and 89.2% of the patients (Table 4).

Table 4: Assessment of Add-on Treatment Tolerability (n=4325)
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Assessment of Add-on Treatment Tolerability				
	Investigator		Patient	
	n	%	n	%
Very good	1831	41.8	1686	38.5
Good	2298	52.4	2221	50.7
Fair	208	4.7	386	8.8
Bad	24	0.5	58	1.3
Very bad	7	0.2	12	0.3
No data	14	0.3	19	0.4
Total	4382	100	4382	100

Therapy Withdrawals and Side Effects

Add-on treatment with trospium chloride was prematurely terminated in 121 of 4382 (2.8%) patients: 56 (1.3%) cases due to lacking efficacy, 49 (11%) due to lacking acceptance by the patient, and 17 (0.4%) due to adverse effects. In total, 42 indications of adverse effects in 35 (0.8%) patients were found in the case report forms, including typical side effects such as dry mouth and constipation and 9 (0.2%) cases of urinary retention.

DISCUSSION

The benefits of combined administration of α-receptor blockers and anticholinergic agents in the treatment of BPH associated LUTS and OAB syndrome has been investigated in a variety of combinations. The appraisal of pertinent clinical results can be summarized by saying that this is a promising treatment option which needs to be confirmed by larger controlled trials [8,9].

The pooled results obtained in this non-interventional trial of 4382 patients with BPH associated LUTS and OAB provide clear evidence of a beneficial clinical effect of oral trospium chloride when administered in addition to the baseline treatment with tamsulosin, alfuzosin, terazosin, or doxazosin. In the efficacy subset

of 4104 patients with moderate to severe LUTS, the improvement of all OAB symptoms was pronounced, and the improvement of the IPSS and QoL score were comparable to the results described for the combination of tolterodine and tamsulosin[10].

The combination of trospium chloride and an α-receptor blocker was generally well tolerated. The rate of adverse effects was low (0.8%), and there was no indication for an additional risk of acute urinary retention (AUR). Of the 4382 patients, the 9 (0.2%) cases of AUR were on a comparably low level, as is also reported for other combinations of anticholinergics and an α-receptor blockers [10] or during sole treatment with an α-receptor blocker [11]. Considering that tolterodine and tamsulosin are metabolized by the cytochrome P450-Isoenzymes [12,13], combined treatment with tamsulosin and trospium, which is not degradated by these enzymes, may be favorable.

Either the trospium chloride dose levels reported in the present study (ranging from 15 mg to 90 mg), or the application intervals prescribed by the doctors (once a day to 3 times a day) suggest that urologists are used to adjusting dosage of trospium chloride individually in order to reach the optimal balance between efficacy and side effects, as is also common practice for several other anticholinergic drugs [14,15]. Moreover, from the rate of adverse events reported, it becomes obvious that TC doses up to 90 mg/day are well tolerated and without increased risk for the patient.

CONCLUSIONS

The results of this trial suggest that add-on treatment with trospium chloride provides benefit to patients with moderate to severe LUTS including OAB symptoms who are insufficiently treated with an α-receptor blocker.

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REFERENCES

1 Chapple CR. Pharmacological therapy of benign prostatic hyperplasia/lower urinary tract symptoms: an overview for the practicing clinician. *BJU Int*. 2004;94(5):738-744.

2. Andersson, K-E. Treatment of the overactive bladder syndrome and detrusor overactivity with antimuscarinic drugs. *Continence*. 2005;1:1-8.

3. Saito H, Yamada T, Oshima H et al. A comparative study of the efficacy and safety of tamsulosin hydrochloride alone and in combination of propiverine hydrochloride in the benign prostatic hypertrophy with pollakisuria and/or urinary incontinence. *Jpn J Urol Surg*. 1999;8:525-536.

4. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Fisfis J, Perimenis P, Barbalias G. Combination treatment with an α-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol*. 2003;169(6):2253-2256.

5. Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB. Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. *BJU Int*. 2004;94(6):817-820.

6. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol.* 2006;175(3):999-1004.

7. BfArM. Empfehlung zur Planung und Durchführung von Anwendungs-beobachtungen. *Banz*. 1998;229:16884-5.

8. Athanasopoulos A, Perimenis P. Efficacy of the combination of an α1-blocker with an anticholinergic agent in the treatment of lower urinary tract symptoms associated with bladder outlet obstruction. *Expert Opin Pharmacother*. 2005;6(14):2429-2433.

9. Novara G, Galfano A, Ficarra V, Artibani W. Anticholinergic drugs in patients with bladder outlet obstruction and lower urinary ract symptoms: a systematic review. *Europ Urol.* 2006;50(4):675-683.

10. Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan, Z. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder. *JAMA*. 2006;296:2319-28.

11. Oelke M, Höfner K, Berges RR, Jonas U. Drug therapy of benign prostatic hyperplasia syndrome with alpha 1-receptor blockers. Basic principles and clinical results. *Urologe A*. 2002;41(5):425-441.

12. Rovner ES. Tolterodine for the treatment of overactive bladder: a review. *Expert Opin Pharmacother.* 2005;6(4): 653-666.

13. Kamimura H, Oishi S, Matsushima H, et al. Identification of cytochrome P450 Isoenzymes involved in metabolism of the alpha1-adrenoceptor blocker tamsulosin in human liver microsomes. *Xenobiotica*. 1998:28(10):909-922.

14. MacDiarmid SA. Maximizing anticholinergic therapy for overactive bladder. Has the ceiling been reached? *Brit J Urol Int*. 2007:99(3):8-12.

15 Staskin DR, MacDiarmid SA. Using anticholinergics to treat overactive bladder. The issue of treatment tolerability. *Am J Med*. 2006:119(3A):9S-15S.

CONFLICT OF INTEREST
Wiedemann A - Consultant to Sponsor
Neumeister C - Employee of Sponsor
Kusche W - Study Investigator Funded by Sponsor
Schwantes U - Employee of Sponsor

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