humans are notable. By analogy with the model, we have therefore raised the following hypotheses for human subjects:

- *Only when penile cuff pressure exceeds bladder pressure will urine flow be stopped completely;*
- *The knee-point pressure at which flow begins to decrease corresponds to the prostatic opening pressure or opening pressure of the flow-controlling zone [6,7];*
- *Beyond the knee pressure, the flow/pressure relation can be used to estimate the minimum urethral diameter.*

Conclusion

We believe our findings may be of significant benefit in understanding and managing patients with outflow disorders, particularly the role of the putative flow-controlling zone. We now plan to test our hypotheses formally in a large group of both symptomatic and asymptomatic subjects.

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TOLERABILITY AND EFFICACY OF TROSPIUM CHLORIDE IN A LONG-TERM TREATMENT (52 WEEKS) IN PATIENTS WITH URGE-SYNDROME: A DOUBLE-BLIND, CONTROLLED, MULTICENTRE CLINICAL TRIAL

Aims of Study:

Trospium chloride (TCl) is already established as an efficacious anticholinergic in the treatment of urge-syndrome. To confirm also the positive safety results of former studies the primary objective of this study was to investigate the long-term tolerability and safety of trospium chloride over a treatment period of 52 weeks. Secondary objective was to investigate the efficacy of trospium chloride in these patients.

Methods:

As an active control group oxybutynin (Oxy) was chosen because placebo was not justified in this investigation of long-term application due to ethical reasons. Patients were assigned to TCl or Oxy in a randomisation ratio of 3:1. A treatment period of 52 weeks was planned with a follow-up period of 2 up to 4 weeks. Trial medication was 2 x 20 mg TCl daily or 2 x 5 mg Oxy daily, respectively. Main criterion for inclusion was the diagnosis: urge-syndrome or urge-incontinence, solely or associated with stress-incontinence or neurogenic detrusor hyperactivity. For safety evaluation data of adverse events, laboratory tests, physical examination, resting ECG and cardiovascular examinations were obtained. Additionally, the tolerability of the study drugs was assessed by the patient and the investigator. The main efficacy variable was the maximum bladder capacity (CCmax). Further urodynamic variables and data of the patients' diary (frequency of micturitions, incontinences and number of urgencies) were evaluated.

Results:

In this study 358 patients (TCl: 268; Oxy: 90) were enrolled in 20 German, 11 Austrian, 14 Czech, 3 Spanish, 3 Russian and 1 Bulgarian centres. The drop-out rate in both groups was comparably low (TCl: 25.0%; Oxy: 26.7%). Adverse events (AE) were observed in 242 of 357 patients (67.8%) within the study period from May 1996 to May 1999. In the TCl group 64.8% of the patients reported an AE compared to 76.7% in the Oxy group ($p<0.01$). Adverse events judged at least possibly related to the study drug occurred less frequently ($p=0.02$) in the TCl group (47.9%) than in the Oxy group (58.9%). Gastro-intestinal AE with at least possible relationship to study drug were observed in 39% of the patients in the TCl group compared to 51% in the Oxy group ($p=0.02$). Dry mouth - the most expected AE in the treatment with anticholinergics - was reported by only 33% of the patients treated with TCl and by 50% of the patients treated with Oxy ($p<0.01$). All these results are clinically relevant and statistically significant. Three serious AE were at least possibly drug related (TCl: 1; Oxy: 2). The treatments did not influence essentially the laboratory data, vital signs, and the resting ECG. The investigator and patient separately assessed the tolerability. A very good tolerability was reported in 63% of the patients treated with TCl compared to 42 % in the Oxy group ($p=0.004$) according to the investigator's assessment, results of the patient's assessment were similar ($p=0.008$).

After 52 weeks treatment, CCmax was markedly increased both after TCl (+ 115 ml, per protocol (PP): n=132) and Oxy (+ 119 ml, PP: n=43) to a comparable extent. The increase of volume at first unstable contraction appeared much more pronounced in the TCl group (+ 66 ml, PP: n=40) than in the Oxy group (+ 49 ml, PP: n=13). Furthermore, the volume at first desire to void increased: under TCl treatment + 86 ml (PP: n=145) and under Oxy + 75 ml (PP: n=45). These differences did not reach statistically significance between the active treatment groups. TCl reduced the micturition frequency by 31% (n=177), Oxy by 34% (n=58) after a 52 weeks treatment period. The frequency of urgencies was reduced in a comparable number. The mean baseline values were 1.5 incontinences in the TCl group and 2.1 in the Oxy group, respectively. On average, the incontinence frequency per day was reduced by 1 after treatment in both groups.

Conclusions:

These results confirm the known safety profile for trospium chloride and oxybutynin. Incidence rates concerning all AE as well as gastro-intestinal AE and especially dry mouth are statistically significant and clinically relevant lower for TCl than for Oxy. Urodynamic data as well as patients' diary data confirm a maintained efficacy of trospium chloride over a period of 52 weeks. The investigators' and patients' assessment of tolerability and efficacy were in favour to trospium chloride.

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EFFICACY AND TOLERABILITY OF TROSPIUM CHLORIDE AND TOLTERODINE IN 234 PATIENTS WITH URGE-SYNDROME: A DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTRE CLINICAL TRIAL

Aims of Study:

Both, trospium chloride (TCl) and tolterodine (Tol) are well accepted anticholinergic

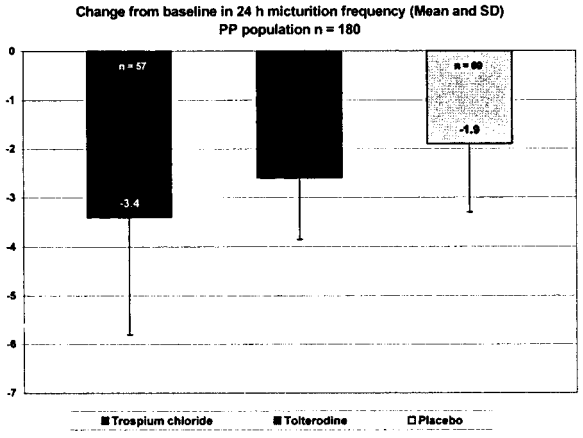
drugs treating patients with urge-syndrome. Former study results of TCl and Tol in separate clinical studies suggest a similar efficacy and safety profile. Thus, the comparison of both drugs versus placebo as regards efficacy and tolerability was the primary aim of this study.

Methods:

Patients with urge-syndrome (motor urge, sensory urge and combined motor urge and stress incontinence) were randomly assigned to TCl (2x20 mg/day), Tol (2x2 mg/day), or placebo and treated for 3 weeks. Patients` medical history (pollakisuria >10/day, nykturia, imperative desire to void) and a urodynamic measurement (minimum one unstable detrusor contraction of 10 cm H_2O or first desire to void at a bladder filling of <150 ml) verified the diagnosis urge-syndrome before the patients received the study medication.
The primary efficacy variable was the change from baseline in the micturition frequency in 24 hours assessed by data of the patients` micturition diaries. The patients filled in the diaries during the wash-out period of 10 days and the entire treatment period. For tolerability and safety evaluation data of adverse events, laboratory tests, and physical examinations were analysed.

Results:

234 patients were enrolled by Bulgarian, Polish and Russian centres and represented the intent-to-treat population. The per-protocol (PP) population consisted of 180 patients: 57 were treated with TCl, 63 with Tol and 60 with placebo.
The change from baseline in micturition frequency/24 hours was -3.4 in the TCl-group, -2.6 in the Tol-group and -1.9 in the placebo-group.



The difference of trospium chloride versus placebo in the PP-population was clinically relevant and statistically significant(p=0.01),whereas the effect of tolterodine versus placebo did not reach statistical significance.
The analysis of the safety population (n=234; TCl:n=76, Tol:n=77, placebo:n=79) showed that 26 patients in the TCl-group, 25 patients in the Tol-group, and 12 patients in the placebo-group reported adverse events.
Gastro-intestinal disorders such as dry mouth of mostly mild intensity were reported most frequently in the active treatment groups (TCl:n=22, Tol:n=21, placebo:n=5). Serious adverse events were not recorded in this study.

Conclusions:

The study results confirm that the efficacy of trospium chloride in patients with different types of urge-syndrome is clinically relevant and statistically significant different to placebo. Furthermore, it has been demonstrated that trospium chloride is at least as effective and safe as tolterodine.

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Title (type in CAPITAL LETTERS, leave one blank line before the text):
ORAL AND INTRAVESICAL OXYBUTYNIN IN SPINAL CORD INJURY PATIENTS WITH DETRUSOR HYPERREFLEXIA: CLINICAL, URODYNAMIC AND PHARMACOKINETIC STUDIES.

Aims of Study

Oral oxybutynin, a valuable detrusor spasmolytic, is bedevilled by unpleasant side effects. Several reports indicate that intravesical oxybutynin is efficacious and lacks side effects in adults but no consistent urodynamic and pharmacokinetic patterns are evident. In this report, the urodynamic effects and pharmacokinetics of oxybutynin are described for ten spinal cord injury patients with detrusor hyperreflexia who received oral, intravesical passive diffusion (PD) and intravesical electromotive drug administration (EMDA) single doses of drug. Both sets of measurements are correlated to the methods of administration, therapeutic efficacy and anticholinergic side effects.

Methods

The study plan included six, 8 hour urodynamic sessions at weekly intervals in order to monitor the following situations applied randomly: *(a)* no treatment, *(b)* oral oxybutynin 5 mg, *(c)* intravesical 100 ml NaCl 0.9% x 60 min, *(d)* intravesical oxybutynin 5 mg in 100 ml NaCl 0.45% x 60 min, *(e)* intravesical 100 ml NaCl 0.9% with 5 mA x 30 min, *(f)* intravesical 5 mg oxybutynin in 100 ml NaCl 0.45% with 5 mA x 30 min. Each treatment was associated with periodic blood and bladder content sampling. During the study period patients were free from urinary infection and not receiving any drug that influenced detrusor and striated sphincter behavior. The occurence of local or systemic adverse effects was noted. Differences among group means were analyzed by ANOVA.

Results

The following data were analysed: number, maximum amplitude and duration of uninhibited detrusor contractions and urine volume residual (Table 1). There was subjective but no significant objective improvement over baseline with oral and intravesical PD oxybutynin. Conversely there was significant improvement in all objective urodynamic measurements with intravesical EMDA oxybutynin. Plasma profiles were a single peak and decay following oral oxybutynin and two distinct peaks with both intravesical PD and EMDA oxybutynin. AUC/8 h: intravesical PD 709 ng vs oral 1485 ng ($p < 0.005$) vs intravesical EMDA 2781 ng ($p < 0.001$). Bladder content samples confirmed oxybutynin absorption. Oral oxybutynin caused anticholinergic side effects in 6/10 patients. There were no side effects with intravesical PD or EMDA administrations.

Table 1. Urodynamic outcomes. Data are the means ± SEM of 10 observations per group.

	Uninhibited Detrusor Contractions			Urine Volume Residual	
UDM	Number	Amplitude cm H_2O	Duration sec	4 h ml	8 h ml
(a)	33.6 ± 7.2	64.1 ± 9.0	689.4 ± 406.7	36.2 ± 19.2	48.7 ± 31.2
(b)	25.1 ± 6.2	60.5 ± 10.2	559.3 ± 283.2	41.0 ± 31.4	43.0 ± 21.3
(c)	27.4 ± 6.2	65.4 ± 9.2	671.9 ± 508.4	42.8 ± 23.1	36.2 ± 23.6
(d)	21.9 ± 7.8	58.2 ± 8.8	574.2 ± 345.4	43.5 ± 25.1	47.8 ± 21.9
(e)	35.6 ± 9.0	57.0 ± 7.3	664.7 ± 567.1	44.3 ± 22.8	45.7 ± 12.2
(f)	9.2 ± 3.7	35.7 ± 10.5	265.1 ± 131.0	235.2 ± 110.7	237.5 ± 129.5
P value	0.0006	0.0049	0.0521	0.011	0.015

Conclusions

. Intravesical oxybutynin is a valid route of delivery and, although accelerated intravesical administration (EMDA) leads to significantly higher plasma levels, the side effects seen with oral oxybutynin do not occur.