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ASSESSMENT OF TIME TO ONSET: THE EFFECT OF SINGLE ORAL DOSE OF TOLTERODINE ON NEUROGENIC DETRUSOR OVERACTIVITY IN SPINAL CORD INJURY PATIENTS

Hypothesis / Aims of Study

Based on daily micturition charts in patients with detrusor hyperreflexia, efficacy of 2 mg BID tolterodine immediate release (IR) is seen within 1 week of treatment [1]. Tolterodine is known to be rapidly absorbed with peak concentrations occurring at 1 hour after oral administration its IR formulation. Consistent with the pharmacokinetic (PK) profile, an early onset of the pharmacologic effect of tolterodine would be expected.

Physiologic alterations that accompany spinal cord injury (SCI) can lead to significant neurogenic detrusor overactivity (NDO) [2]. Force-fill cystometry (FrFC) has been previously demonstrated to provoke uninhibited detrusor contractions in SCI patients with NDO. This response can be attenuated by treatment with neuromodulation and with antimuscarinic drugs [2, 3]. This exploratory study assessed the time course of the effects of a single 2 mg oral dose of tolterodine vs. placebo on the reduction of uninhibited detrusor contractions induced by provocative testing.

Study design, materials and methods

This was a double-blind, randomized, 2-way cross-over, single-dose study of tolterodine vs. placebo. Eight (8) patients, who had urodynamic evidence of NDO secondary to SCI or other pathology, were enrolled and completed the study. Prior to Period 1, subjects had to demonstrate phasic uninhibited and provoked detrusor contraction following FrFC and fast-fill cystometry (FsFC), respectively. In both periods, before catheterization, a single 500 mg oral dose of ciprofloxacin was given as a prophylactic antibiotic.

FsFC: Prior to dosing, FsFC was performed to establish the volume at first uninhibited contraction. Two 8F plastic catheters were introduced through the urethra. Bladder filling was performed at a rate of 50 mL/min through one of the catheters whilst continuous intravesical pressure recording during filling and voiding was obtained through the other catheter.

FrFC: At 0 (pre-dose), 0.5, 1, and 2 hours after dosing, blood samples for PK analysis were taken. Immediately after PK sampling, FrFC was performed in triplicate, at 2-5 min intervals. The bladder was filled to a volume of 100 mL less than the previously established volume at first uninhibited contraction. A 100-mL volume of saline was then rapidly infused (rate 10-20 mL/sec) to produce an uninhibited contraction.

The time to onset was determined for the effect of tolterodine on uninhibited detrusor contractions induced by force-fill cystometry. The primary endpoint was the area under the pressure curve (AUC) of the provoked detrusor contraction calculated pre-dose and at 0.5 hr, 1 hr and 2 hr post-dose. The secondary endpoints included the maximum pressure (P_{max}) of provoked detrusor contraction at each time point.

Results

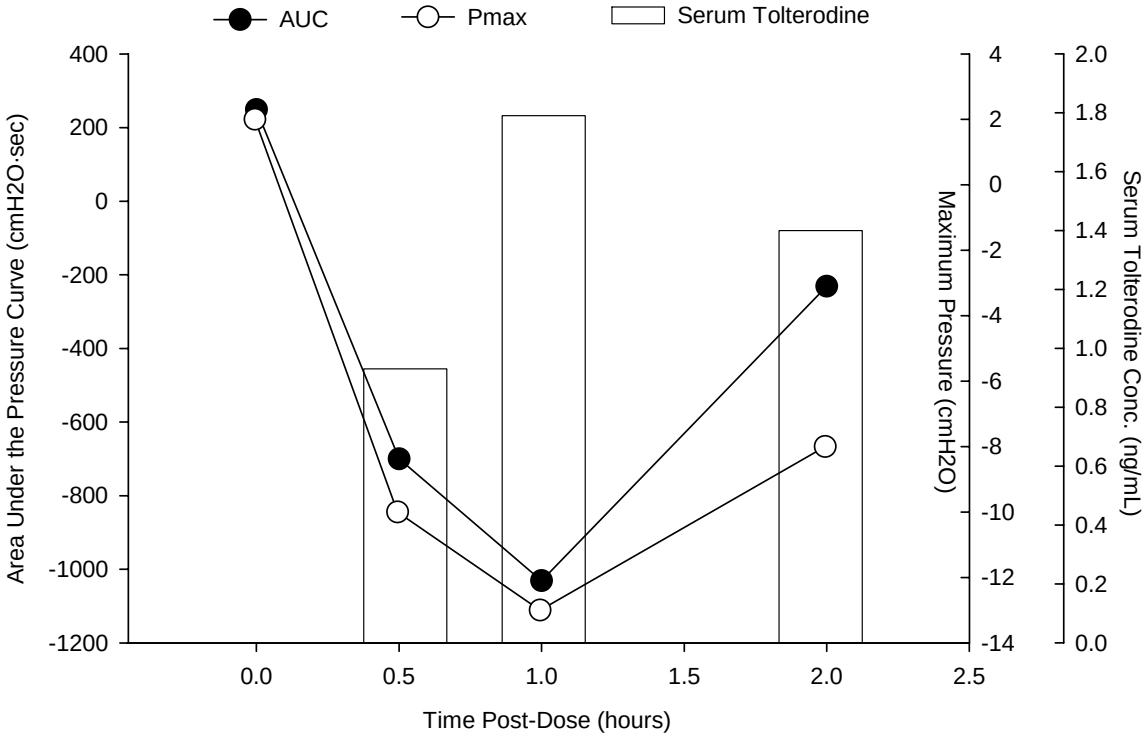
The mean (SD) values for detrusor pressure AUC and P_{max} are shown in Table 1 (N=8).

Table 1. Mean (SD) AUC and P_{max} Following Tolterodine and Placebo Treatments

Endpoint	Treatment	Pre-Dose	0.5 hr	1 hr	2 hr
AUC (cmH_20.sec)	Tolterodine	3713 (1702)	1513 (996)	1036 (383)	1133 (718)
	Placebo	3464 (1342)	2213 (1134)	2067 (2144)	1363 (899)
P_{max} (cmH_20)	Tolterodine	49.4 (22.3)	24.8 (22.2)	13.5 (4.9)	12.9 (6.8)
	Placebo	47.8 (30.4)	34.8 (26.8)	26.3 (25.5)	20.8 (23.8)

The time profiles of the serum concentrations of tolterodine and the tolterodine-placebo treatment differences are shown in Figure 1. The tolterodine-placebo treatment differences observed at 0.5 hours post-dose approached statistical significance for the mean AUC of the provoked detrusor contraction and reached statistical significance for the mean P_{max}. While the largest difference between treatments was seen at 1 hour, variability after placebo treatment was large for both endpoints.

Figure 1. Time-Course of Mean Serum Concentrations and Placebo-Subtracted Effect of Tolterodine on Provoked Uninhibited Detrusor Contractions



Interpretation of Results

The placebo-subtracted AUC and P_{max} values were reduced up to the last observation time of 2 h after a single dose of 2 mg tolterodine. While a similar trend was also noted with the placebo treatment, the mean AUC and P_{max} of the provoked detrusor contractions following FrFC decreased more rapidly following dosing with tolterodine than with placebo. The repeated FrFC procedures in this study appeared to have an effect on the detrusor contraction in most patients, as apparent from the placebo response as well the response across the successive triplicates at each measurement time. The physiological explanation for these repeat-measurement effects needs further investigation. Overall, the time course of the placebo-subtracted pharmacologic effects of tolterodine on provoked detrusor contractions was consistent with that of its systemic exposure.

Concluding Message

In this exploratory study in 8 SCI patients with NDO, a single dose of 2 mg tolterodine appeared to have an effect on detrusor overactivity as early as 0.5 hours post-dose.

References

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CLINICAL TRIAL REGISTRATION: This clinical trial has not yet been registered in a public clinical trials registry.
HUMAN SUBJECTS: This study was approved by the Bioethics Committee, Reykjavik, Iceland and followed the Declaration of Helsinki Informed consent was obtained from the patients.