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Title: TOLTERODINE ONCE-DAILY IS SELECTIVE FOR THE BLADDER COMPARED TO DITROPAN XL

Aims of Study:

Tolterodine exhibits a favorable selectivity for the urinary bladder over salivary glands *in vivo,* in the anesthetized cat, whereas oxybutynin shows the opposite selectivity profile in this model [1]. In patients with overactive bladder, tolterodine 2 mg bid is equipotent to oxybutynin 5 mg tid with regards to the bladder. However, tolterodine is better tolerated, since it causes significantly less dry mouth than oxybutynin at equipotent dosages [2-4]. Tolterodine has also been shown to be more selective for the bladder than the eye (as measured with visual accommodation) compared to oxybutynin.

Studies have not been conducted to evaluate the selectivity profiles of tolterodine once-daily versus oxybutynin once-daily (Ditropan XL). Therefore, the objective of this study was to evaluate at steady state the tissue selectivity profile of tolterodine once-daily and Ditropan XL by comparing effects on the bladder versus effects on basal salivation in humans.

Methods:

This was a double-blind, randomized, multiple-dose, four-way crossover study comparing tolterodine once-daily (OD) 6 mg versus Ditropan XL 5, 15, and 25 mg in healthy normal subjects. Each study period was six days in duration with patients dosed in the morning of days 2-6. On day 1, baseline measurement of bladder function (following scheduled fluid intake of 300 ml/hour) and basal salivation were recorded. On day 5, basal salivation was measured at 4, 5, 6, and 7 hours after dosing. After salivation measurements on day 5, subjects drank 300 ml/hour until 10 PM. Subjects then began drinking 300 ml/hour starting at 0600 on day 6. They continued this fluid intake until they had 4 normal voids. Safety was measured with adverse events and blood pressure readings.

Results:

A total of 16 subjects enrolled in and completed the study. All subjects were Caucasians and the mean age and weight of subjects was 36 years and 82 Kg, respectively. A linear dose-response effect on basal salivation was found with Ditropan XL with mean decreases in basal salivation of 12%, 27% and 53% for the 5, 15 and 25 mg dosages respectively, while mean decreases in basal salivation with tolterodine 6 mg OD was 23%, comparable to the expected effect of a 10 mg dosage of Ditropan XL. A linear dose-response increase in bladder effect (as measured with mean change in bladder capacity) was also noted for Ditropan XL. Bladder capacity increased by 12%, 17%, and 26% compared to baseline for Ditropan XL 5 mg, 15 mg and 25 mg, respectively. The bladder effect increase with tolterodine 6 mg OD was 22%, comparable to the expected effect of a 20 mg dose of Ditropan XL.

Five, 5, and 7 patients in Ditropan 5, 15, and 25 mg treatment arms and 5 patients in the tolterodine 6 mg OD arm experienced adverse events during the study. A dose response was noted for Ditropan XL with

regards to the total number of adverse events reported. A total of 12, 17, and 29 adverse events were reported by subjects on the 5, 15 and 25 mg dosages, respectively. A total of 15 adverse events were reported by subjects when treated with tolterodine 6 mg OD. The most common adverse events in the Ditropan XL treatment groups were dry mouth and sleepiness. In the tolterodine treatment group, the most common adverse event was fatigue and dry eyes. One case of acute urinary retention occurred on the Ditropan XL 25 mg dosage. No other safety concerns were noted.

Conclusions:

The bladder selectivity of tolterodine IR when compared to oxybutynin IR extends to the once-daily formulation of these products. Tolterodine once-daily has selectivity for the bladder versus salivation while Ditropan XL has an overall greater effect on salivation than on the bladder.

References:

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2) Appell RA, Urology 1997; 50 (6A Suppl.): 90–96
3) Abrams P, et al. Br J Urol 1998; 81: 801–810
4) Drutz H, et al. Int Urogynecol J Pelvic Floor Dysfunct 1999; 10: 283–289

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