

Authors: R Dmochowski, T Boone, B Greene, K Jacoby, M Kennelly
Institution: Urology Associates of North Texas, Baylor College of Medicine, Sheperd Center, Urology Northwest, McKay Urology
Title: PHARMACOKINETIC EVALUATION AND PRELIMINARY EFFICACY RESULTS OF INTRAVESICAL OXYBUTYNIN AS A TREATMENT FOR URGE INCONTINENCE

Aims of Study:

Intravesical delivery of oxybutynin (I-OXY) is a promising approach to the treatment of urge incontinence. However, the systemic pharmacokinetics of this therapy have not been fully characterized. As part of the development of an oxybutynin solution formulated expressly for intravesical use, a pharmacokinetic study (A) and a dose titration efficacy study (B) were evaluated.

Methods:

Women with urodynamic proven urge incontinence enrolled in a pharmacokinetic study (A) and patients with neurogenic reflex incontinence on clean intermittent catheterization (CIC) enrolled in a dose titration efficacy study (B). In study A, single intravesical bolus doses of 5 mg, 10 mg and 20 mg of I-OXY were delivered by catheter. Patients had blood samples for I-OXY levels, ECGs, and adverse effects evaluated at baseline, 30 minutes, 1, 2, 4, 8, 12, and 24 hours. In study B, patients self-administered intravesical doses of up to 15 mg/day of I-OXY in QD, BID or TID dosing regimens. Serial evaluations following dosing over 1-3 weeks included blood samples for I-OXY levels, ECGs, adverse effects, anticholinergic effects, and voiding diaries. Success was considered a 75% reduction in incontinence episodes as documented on voiding diaries.

Results:

Study A

Twelve women with a mean age of 45 years (range 27-70 years) enrolled in study A. They have had incontinence for a mean of 23 years (range 1-39 years).

Oxybutynin (mg)	Number of Subjects	C _{max} (ng/mL)	T _{max} (hrs)	t _{1/2} init (hr) (initial)	t _{1/2} term (hr) (terminal)	AUC ₀₋₂₄ (ng•hr/mL)
5	6	11.2 ± 8.4	0.9 ± 0.2	3.1 ± 1.5	12.5 ± 7.5	61.5 ± 44.4
10	6	32.9 ± 11.6	0.8 ± 0.6	2.6 ± 0.6	11.8 ± 1.7	119.1 ± 47.8
20	12	50.6 ± 35.1	0.9 ± 0.6	4.0 ± 1.8	11.6 ± 5.3	256.2 ± 156.9

At 72 hours, trough plasma concentrations of oxybutynin were approximately 1 ng/mL after the 20 mg dose. For the metabolite (desethyloxybutynin), mean maximum plasma concentrations occurred approximately four hours post-dosing. Mean AUC₀₋₂₄ values were almost twice as high as those of the

parent although C_{max} levels were comparable. The mean plasma terminal half-life for the metabolite ranged from nine to sixteen hours. Trough plasma concentrations of the metabolite at 72 hours were approximately 1-2 ng/mL. Some transient QTc prolongation not deemed clinically significant was noted at the highest dose. The majority of anticholinergic effects were mild, transient and did not require any intervention. There were no serious adverse events.

Study B

Sixteen patients, 10 females and 6 males, with a mean age of 44 years (range 21-73 years) enrolled and were dosed in study B. Etiology of neurologic reflex incontinence was multiple sclerosis (6), and spinal cord injury (9).

A total of twelve patients completed dose escalation with intravesical I-OXY. 5/12 patients (42%) were successfully managed with QD dosing; an additional 4/12 patients (33%) were successfully managed with BID dosing; and the remaining 3/12 patients (25%) were successfully managed with TID dosing. I-OXY plasma levels mirrored the rapid uptake and low concentrations reported in study A, and are consistent with the clinical literature about this treatment modality. Variable and transient QTc prolongation was noted in 1 patient. 7/12 patients (58%) reported no anticholinergic effects and the remaining 5/12 patients (42%) reported mild to moderate effects. There were no serious adverse events.

Conclusions:

No remarkable changes in the pharmacokinetic parameters were observed as bolus doses were escalated from 5 mg to 20 mg, suggesting no change in the metabolic profile for I-OXY, and no evidence for saturation of any clearance mechanism for I-OXY from the plasma. At doses up to 20 mg, these values are not different from those in the published literature after oral doses of oxybutynin. Preliminary data from a dose escalation study in patients who perform CIC indicate greater than 75% reduction in incontinence in these subjects. Further studies are in progress.

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