Abstract Reproduction Form B-1

Author(s): M. M. Hassouna and R. Lai

Institution University of Toronto
City Toronto, Ontario
Country Canada

Title **INTRAVESICAL CAPSAICIN LOWERS THE DETRUSOR LEAK POINT PRESSURE IN RATS AND HUMANS WITH THE NEUROGENIC BLADDER OF SPINAL CORD INJURY.**

Aims of Study: McGuire et al.,(1) showed that an elevated detrusor leak point pressure (DLPP) above 40 cm of water risks upper urinary tract damage. The lowering of the DLPP is central to the treatment of the neurogenic bladder after spinal cord injury (SCI). Current approaches using anticholinergic medication and clean intermittent catheterization (CIC) are not always successful. Recently, there has been interest in capsaicin(2,3,4,5) and resiniferatoxin (RTX)(6)as intravesical therapies. None of the studies have shown a significant decrease of the DLPP from baseline levels. We hypothesize that high capsaicin doses in combination with anticholinergic medication and CIC will lower the DLPP to safe levels. These conditions were tested first on rats, and then in a clinical trial with spinal cord injury patients with neurogenic bladders refractory to medical therapy. These studies have received approval from the appropriate Research Ethics Boards.

Methods: Animal Studies. Sprague Dawley female rats were given a spinal cord injury at T8 and allowed to recover for at least 3 weeks. Polyethylene tubing (PE-90) was then inserted via the urethra into the bladder as a catheter for the cystometrogram (CMG). The CMG is performed on the awake animal. Saline at room temperature was infused into the bladder at 500 uL/min with simultaneous pressure measurement. When an elevated DLPP was noted, 250 uL of solution of capsaicin from 0.1 to 100 mM, resiniferatoxin 0.1 mM to 1mM, or saline medium as a control were instilled into the bladder. The tube was then clamped for one hour. After draining the bladder, serial CMGs provided dose response and time course information. The primary endpoint was the DLPP as evidenced by leakage around the catheter.

Results: Saline treated control animals showed elevated DLPP above 40 cm of water (range 50 - 100). There was a dose-dependent reduction of the DLPP as capsaicin was given at 10mM to 100 mM, and with resiniferatoxin at 0.1 and 1mM doses. This was significantly below the initial DLPP and also below 40cm of water. DLPP remained depressed for 150 hours with 10mM capsaicin, and for at least 1000 hours with 100mM capsaicin. Light pink hematuria was noted only with the 100mM capsaicin dose. Similar results were obtained with RTX. Thus, we have shown a dose dependent decrease in DLPP, with increasing duration of effect using capsaicin or resiniferatoxin intravesical treatment.

Methods: Human Clinical Trial. A dose-titration model was employed with each patient serving as their own control. Inclusion criteria sought spinal cord injury (SCI) patients with DLPP > 40 cm water even with anticholinergic medication and CIC. The patients remain on anticholinergic medication at the maximum tolerable dose, and CIC throughout the study. Baseline urodynamic testing and a patient reported voiding diary were obtained. Xylocaine 2% x 60ml was instilled into the bladder for analgesia, then drained after 1 hour. Capsaicin in 250ml of solution was instilled into the bladder for one hour. Follow up consists of review of the voiding diary, and CMG. Patients start at the lowest dose and work their way up according to the response of their DLPP. Persistence of DLPP > 40 cm water leads to treatment at a higher capsaicin dose. The capsaicin dosage scale is: 0.5, 1, 2, 5, 10, 20, 30, 40, 50mM.

Abstract Reproduction Form B-2

Author(s): M. M. Hassouna and R. Lai

Results: Five SCI patients, 4 male and 1 female have sufficient data for analysis. The ages range from 19 to 61. All patients are taking oxybutynin 15 to 25mg/day, with CIC at least 4 times per day. At the current time 3 patients have reached the 20mM capsaicin level. The aggregate effects are:

DLPP at start of study (s.d.)	DLPP after capsaicin	p value
79.8 ± 12.3	51.0 ± 11.8	0.012 (significant)

Two patients increased their bladder compliance and volume. They are now continent. One of the remaining patients developed gross bilateral hydroureteronephrosis while he was on the lower doses of capsaicin. His starting DLPP was 98 cm water. After the 10mM capsaicin dose, his hydronephrosis resolved. We are using low ethanol formulations of capsaicin which have minimized the morbidity described in the literature. There is no gross hematuria at 20mM, and only mild increases in urgency and frequency for 48 hours after a treatment.

Conclusion: Vanilloid compounds are capable of producing a dose-dependent decrease in the DLPP of the neuropathic bladder after SCI.

References:

(1) *J. Urol.*, **126**: 205, 1981.
(2) *J. Neurol. Neurosurg. Psychiat.*, **57**: 169, 1994.
(3) *J. Urol.*, **154**: 1825, 1995.
(4) *J. Spinal Cord Med.*, **19**: 190, 1996.
(5) *J. Urol.*, **158**: 2087, 1997.
(6) *J. Urol.*, **158**: 2093, 1997.