Abstract # 420

Oxybutynin modifies bladder hyperactivity in conscious spinal cord injured rats via a non dependent C-fiber afferent pathway

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PELVIPHARM

OBJECTIVES

- Parasympatholytic drugs such as oxybutynin in association with intermittent catheterization are currently the first-line treatment for spinal cord injury (SCI) induced-neurogenic detrusor overactivity (NDO).
- Parasympatholytic drugs inhibit the binding of acetylcholine on muscarinic receptors expressed on detrusor smooth muscle cells[1].
- Decreased activity of bladder afferent fibers has also been recently reported in normal rats treated with parasympatholytic drugs[2]. Recently it has been shown that in patients with overactive bladder, parasympatholytic drugs affect bladder sensory symptoms such as urgency and voiding frequency presumably by acting on muscarinic receptors located in bladder sensory pathways including primary afferent nerves and urothelium[1,2].

We aimed to evaluate the effects of oxybutynin on urodynamic parameters in conscious SCI rats with NDO related to an increase in bladder afferent nerve activity, in particular C-fibers [3] .

1. Yoshimura N et al, J Urol 2002;168:1897-1913; 2. De Laet K et al, Neurourol Urodyn 2006;25:156-161; 3. Cheng CL et al, Brain Res 1995;678:40-4

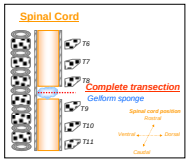
MATERIALS & METHODS

Animals

A total of 12 female adult Sprague-Dawley rats weighing 250-275 g were used in this study.

Complete spinal cord transection

Rats were anesthetized using isoflurane (2.0-2.5 %). A dorsal midline incision was first made to expose dorsally between the 6th and 10th thoracic (T6, T10) vertebrae processes. Tissue and the muscle in front of T7-T8 were then cleared away. To visualize the whole width of the spinal cord, a T7-T8 laminectomy was then performed. Complete spinal cord transection was performed using fine dissecting scissors. A sterile gelform sponge (Gelita® Medical) was next placed between the cut ends of the spinal cord. The overlying muscle and skin were sutured.



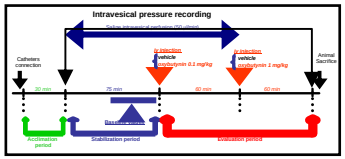
In order to prevent urinary tract infection (UTI), the animals were treated with antibiotics. Postoperatively, the animals were given a single subcutaneous injection of cefovecin (20 mg/kg). From 1 day post-SCI, enrofloxacin (20 mg/kg/day) and sulfamethoxazole/trimethoprim (50 and 10 mg/kg/day respectively) in drinking water were then alternately delivered every week. Urinary bladders were manually expressed by Credé maneuver first 3 times daily then 2 times daily until an abnormal micturition reflex was totally established.

Catheter implantation

At 3 weeks post-SCI, the rats are anesthetized with isoflurane (1.5-2.0%). For intravenous (iv) administration, a polyethylene catheter (PE-10) was placed into the jugular vein. The bladder dome was then exposed via a midline abdominal incision. A polyethylene catheter (PE-50) was then inserted within the bladder through the apex of bladder dome and secured in place. The free ends of the bladder and venous catheters were tunnelled subcutaneously, exteriorized at the back of the neck and sutured between the scapula. Postoperatively, the animals were treated with netilmicin (20 mg/kg, intramuscular injection, a single injection) to prevent UTI.

Cystometric investigation

Cystometry experiment on conscious rats was performed in metabolic cage at 48 hours after catheter implantation. The free tip of the bladder catheter was connected to a pressure transducer (Elcomatic EM 750) for bladder pressure recording and a syringe-pump KDS-200 (Phymep) allowing continuous bladder perfusion (50 µl/min) with room temperature sterile saline. In addition, voided volume was continuously collected and directly measured by means of a weighing device (Sartorius BP2215). Three reproducible micturition cycles were recorded before any drug administration used as baseline values. Then, the effects of two successive doses of oxybutynin (0.1 and 1 mg/kg, intravenous injection, iv, n=6) and vehicle (saline, iv, n=6) were evaluated during a treatment period of 60 minutes for ecah dose.

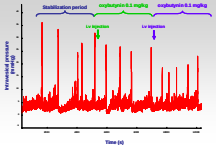


Data Analysis

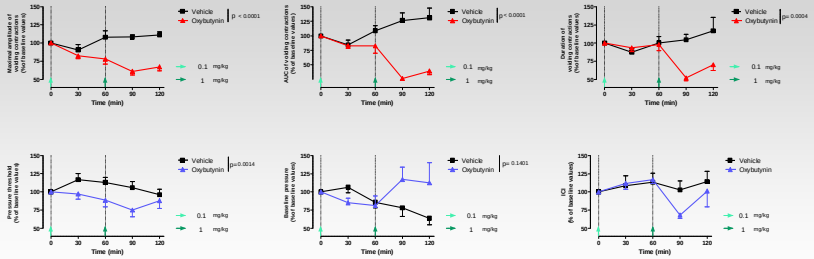
Urodynamic parameters were analysed: micturition pressure (MP); duration and area under the curve (AUC) of micturition contraction; pressure threshold for inducing micturition, PT; basal pressure, BP; voided volume; intercontraction interval, ICI, between two micturitions; amplitude and frequency of non-voiding contractions (NVC) and volume threshold necessary to elicit NVC. Urodynamic parameters were expressed in percentage of baseline values. All the data were expressed as mean±SEM for N experiments corresponding to N animals. Statistical comparisons of urodynamic parameters were performed with a two-way analysis of variance (anova) statistic analysis test followed by Bonferroni post-test with GraphPad Prism®4.03 software. P < 0.05 was considered statistically significant.

RESULTS

Effect of oxybutynin on the micturition reflex in conscious SCI rats

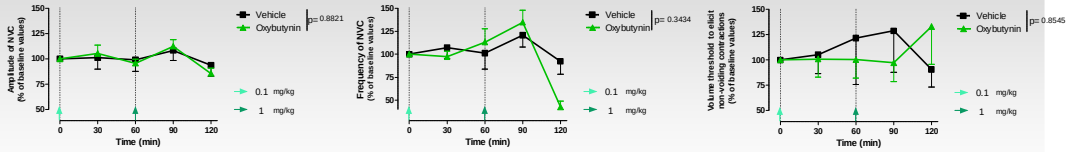


Effect of oxybutynin on urodynamic parameters in conscious SCI rats



➡ **Oxybutynin exerts an inhibitory effect on urodynamic parameters related to voiding function in accordance to its well-known mechanism of action on muscarinic receptors of the detrusor smooth muscle.**

Effect of oxybutynin on urodynamic parameters related to non-voiding contractions in conscious SCI rats



➡ **Oxybutynin did not modify the frequency and the amplitude of non-voiding contractions. It had also no effect on the volume threshold necessary to induce non-voiding contractions.**

CONCLUSIONS

- The absence of effect of oxybutynin on non-voiding contractions suggests that oxybutynin does not modify the activity of C-fiber dependent bladder afferences since these fibers contribute to non-voiding contractions in SCI rats.
- The decrease in PT and ICI could be only a compensatory effect due to the decreased voided volume induced by an inhibition of the detrusor contractility after the treatment with oxybutynin.
- In the pathological model of SCI-induced NDO which is associated with a hyperexcitability of afferent fibers, oxybutynin alters the urodynamic parameters which are most in favour of a mechanism of action on detrusor smooth muscle but less on sensory function/the afferent limb of the micturition reflex.