Abstract

**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 cells1.
- Decreased activity of bladder afferent fibers has also been recently reported in normal rats treated with parasympatholytic drugs2. 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 urothelium1,2.

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-fibers3.

**RESULTS**

**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.**

**MATERIALS & METHODS**

**Animals**

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

**Complete spinal cord transaction**

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 transaction was performed using a dissecting scissors. A sterile gelform sponge (Sealfilm Medical) was next placed between the cut ends of the spinal cord. The overlying muscle and skin were sutured.

**Catheter implantation**

At 3 weeks post SCI, the rats were anaesthetised with isoflurane (1.5-2.5 %). 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.

**Cystometry 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 (Bicompatic EM 750) for bladder pressure recording and a syringe-pump KDS-201 (Phymec) 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 BP211). These 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, i. v.) and vehicle (saline, i. v.) were evaluated during a treatment period of 60 minutes for each 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. Urinary 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.

**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/afferent limb of the micturition reflex.