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OXYBUTYNIN MODIFIES BLADDER HYPERACTIVITY IN CONSCIOUS SPINAL CORD INJURED RATS VIA A NON DEPENDENT C-FIBER AFFERENT PATHWA

Hypothesis / aims of study: 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] .

Study design, materials and methods: Complete T7-T8 spinal cord transection was performed in female adult Sprague-Dawley rats (250-275g). At day 21 post-spinalization, cystometry was performed to determine the effects of oxybutynin with two successive doses (0.1 and 1.0 mg/kg i.v.) and its respective vehicle (saline, n=6 in each group) on the following urodynamic parameters (micturition pressure, MP; duration and area under the curve, AUC of micturition contraction; pressure threshold for inducing micturition, PT; basal pressure, BP; intercontraction interval, ICI, between two micturitions; amplitude and frequency of non-voiding contractions) in conscious SCI animals. The results were expressed as percentage of the control period i.e before oxybutynin administration.

Results: Administration of oxybutynin significantly decreased MP ($P<0.0001$), duration of micturition ($P<0.0001$) and AUC ($P<0.0001$). MP, duration of micturition and AUC reached 61±5%, 52±4%, 27±3% of the baseline respectively versus 108±3%, 104±8%, 127±13% of baseline for vehicle, 30 minutes after oxybutynin administration at 1.0 mg/kg. PT was also significantly decreased, reaching 75±9% of baseline versus 105±9% of baseline for vehicle, 30 minutes after oxybutynin 1.0 mg/kg ($p<0.001$). No significant effect was observed on BP ($P=0.15$). There was a trend for oxybutynin to decrease ICI and voided volume. At 1.0 mg/kg, these parameters reached 68±5 % and 59±9 % of baseline versus 102±13 % and 104±7 % of baseline for vehicle respectively. Neither oxybutynin 0.1 mg/kg nor 1 mg/kg had a significant effect on frequency and amplitude of non-voiding contractions.

Interpretation of results: These results indicate that acute treatment with oxybutynin exerts an inhibitory effect on urodynamic parameters related to voiding function in conscious SCI rats. This is in accordance with oxybutynin's well-known mechanism of action on muscarinic receptors of the detrusor smooth muscle. Oxybutynin could also exert this effect by inhibiting Aδ-fiber afferents which trigger voiding contraction in SCI rats[3]. Surprisingly, the absence of effect of oxybutynin on non-voiding contractions suggests that oxybutynin would not modify the activity of C-fiber bladder afferents since these fibers contribute to non-voiding contractions in SCI rats[3]. 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.

Concluding message: **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.**

References

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Specify source of funding or grant	**none**
Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**authorization from competent French authorities obtained (Ministry of Agriculture - Agreement No. 91-86, 7/20/2001)**