

DAILY INTRAVESICAL INSTILLATION OF 1 μ M OF NOCICEPTIN/ORPHANIN FQ FOR THE TREATMENT OF NEUROGENIC URINARY INCONTINENCE IN PATIENTS WITH SPINAL CORD INJURY. PRELIMINARY REPORT.**Hypothesis / aims of study**

Nociceptin/Orphanin FQ (N/OFQ), a recently discovered heptadecapeptide, which exerts several physiological actions by activating a specific G-protein coupled receptor named OP₄, is able to elicit a robust acute inhibitory effect on micturition reflex in animals. A preliminary pilot study and a successive randomized, placebo-controlled, double-blind study showed that N/OFQ produced a clear acute inhibitory effect on micturition reflex in patients suffering from neurogenic incontinence.

The aim of this investigation was to evaluate the clinical and urodynamic effects of a daily intravesical instillation of 1 μ M of nociceptin/orphanin FQ (N/OFQ) in spinal cord injured patients suffering from neurogenic urinary incontinence by a non-randomized, non-controlled study.

Study design, materials and methods

The study involved 5 patients who presented neurogenic urinary incontinence due to detrusor overactivity following a spinal cord injury. All the patients used the clean intermittent catheterism (CIC). They received daily intravesical infusion of 10 ml of a saline solution containing 1 μ M N/OFQ at the time of the first catheterization of the morning for 10 days. All the patients completed a voiding diary and reported the daily episodes of urine leakage at baseline conditions, throughout the 10 days-N/OFQ therapy and after 15 days from the end of the treatment. The daily mean voiding-diary bladder capacity (VD-BC) was considered the main clinical parameter. The urodynamic parameters (the bladder capacity: CMG-BC; the volume threshold for the appearance of detrusor overactivity: VT-DO; the maximum bladder pressure: MBP) were also recorded at baseline condition and 2 weeks after the end of the infusion.

Data were expressed as mean \pm SD of determinations.

Results

All the patients completed the study and the baseline urodynamic assessment confirmed the presence of a detrusor overactivity. The baseline mean CMG-BC was 173, 33 \pm 35,11, the mean VT-DO was 134,76 \pm 29,87 and the MBP was 90,66 \pm 17,47. The baseline mean VD-BC was 190 \pm 36,05.

The urodynamic assessments performed 15 days after the end of the intravesical instillation was unchanged with regard to baseline values.

A significant increase of the daily VD-BC was recorded during all the time of therapy. The total mean VD-BC was increased to 317, 66 \pm 82,81. The mean daily episodes of urine leakage during the N/OFQ therapy was 1,1 against the pretreatment baseline value of 2,46.

No significant side effects were recorded.

Interpretation of results

The present study demonstrated that the repeated intravesical instillation of 1mM N/OFQ produces an inhibitory effect on micturition reflex in patients with neurogenic overactive detrusor.

Our study represents a further step in the assessment of potential effects of N/OFQ in the therapy of neurogenic detrusor overactivity and confirm the results of previous findings. A pilot non controlled, non randomized study demonstrated that intravesical instillation of N/OFQ at 1 μ M inhibits the micturition reflex in spinally lesioned patients but not in normal subjects. This observation was reproduced under more controlled conditions by a randomized, double-blind study on 14 patients.

The implications of these findings are very important: they strongly suggest that the action of N/OFQ in the micturition reflex does indeed involve the activation of specific receptors. This

imply that other receptor ligands with more favorable pharmacokinetics features than the natural peptide are worthy of testing as innovative drugs for the control of incontinence in patients with neurogenic bladder.

The possible interpretation for present results is that N/OFQ inhibits the micturition reflex via activation of inhibitory NOP receptors expressed on C fibers of the bladder: some effects of N/OFQ (including the inhibitory effect on micturition reflex in rats) are no longer evident in animal pretreated with high doses of capsaicin that promotes degeneration of C fibers.

Concluding message

In conclusion, this study confirmed and extended previous findings demonstrating that N/OFQ, inhibited the micturition reflex by activating NOP receptors in patients with neurogenic bladder. Further studies are mandatory to confirm the chronic effects of N/OFQ.