232

De Laet K[1], De Wachter S[1], Wyndaele J[1]
1. University of Antwerp

ON THE ACTION MECHANISM OF PARENTERAL OXYBUTYNIN: THE EFFECT ON AΔ SENSORY NERVE ACTIVITY OF THE RAT'S URINARY BLADDER.

Hypothesis / aims of study

Oxybutynin is one of the most widely used drugs for treating overactive bladder syndrome and detrusor overactivity. Although oxybutynin has mixed actions, the inhibition of parasympathetically induced detrusor contraction has generally been accepted as the main contributor to its clinical benefit after systemic administration. However, after intravesical instillation a temporary anaesthetic effect was shown on pelvic afferent C fibres in rats without any effect on Aδ fibres (1). Recently, a direct anaesthetic effect on pelvic C fibres was also shown after systemic administration in rats (2). This study evaluates the effect of systemic administration of oxybutynin on Aδ fibres of the pelvic nerve from the rat urinary bladder.

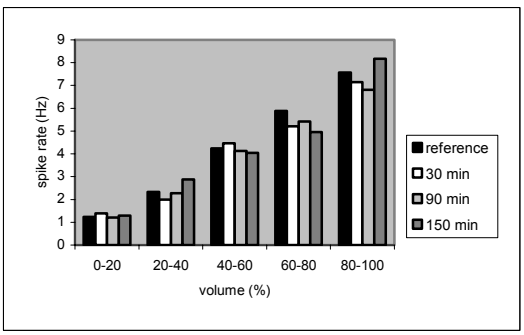
Study design, materials and methods

Nine female rats were used for the experiments. After anaesthesia, the left pelvic nerve was identified and surrounded by an electrode for electrical stimulation. A catheter was inserted into the dome of the bladder for filling and emptying. The spinal cord was exposed by laminectomy and the L6 dorsal roots were both identified and centrally cut. The dorsal skin was tied up to make a pool and the spinal cord was covered with body warm paraffin oil. Fine filaments were split from the dorsal root until a maximum of 3 clearly different unitary action potentials were evoked by electrical stimulation of the pelvic nerve. Afferent units were identified by electrical stimulation. Those with a conduction velocity > 2.5 m/s (i.e. Aδ fibres (3)) were included in this study.

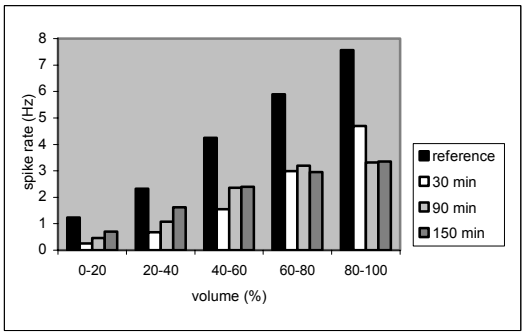
Afferent activity was studied during constant flow cystometry at 80 µl/min. In the control group (n=5) the effect of subcutaneous saline (0.5 ml) was studied, in the study group (n=7) the effect of subcutaneous oxybutynin (1 mg/kg in 0.5 ml) was evaluated. After a baseline bladder filling, saline or oxybutynin was administered and the afferent activity was again assessed during cystometry every 30 minutes up to 150 minutes after administration.

Results

In the control group, no difference was noted in afferent activity between baseline and subsequent fillings (p>0.90). However after subcutaneous administration of oxybutynin a significant decrease in afferent activity was noted after 30 minutes (p=0.005). Although afferent units gradually started to increase afferent activity towards bladder filling at 60 minutes, the basic level of activity was not restored after 150 minutes (p=0.012). The effect of saline in the control group is shown in graph A, the effect of oxybutynin in graph B. The data are presented as mean.



A. Effect of parenteral saline



B. Effect of parenteral oxybutynin

The same results were obtained when comparing the pressure-related nerve activity: in the control group, no difference was noted in afferent activity (p=0.89), whereas a significant decrease was seen in Aδ fibre activity after injection of oxybutynin (p=0.007).
After oxybutynin administration an increase in bladder compliance was noted, which might explain part of the observed effect on afferent activity. However, after normalising afferent activity for the difference in compliance, the reduction in afferent activity was still noted after 30 (p=0.0001), 60 (p=0.0001), 90 (p=0.0001) and 120 (p=0.0007) minutes. After 150 minutes, afferent activity during filling was still reduced compared to baseline, although this was not statistically significant (p=0.07).

Interpretation of results

The common view on the working mechanism of parenteral oxybutynin is that it inhibits parasympathetically induced detrusor contraction through a blocking of muscarine receptors. The findings of this study show that subcutaneous oxybutynin has a direct anaesthetic effect on Aδ fibres, which was shown to exist even after 30 minutes and lasted for at least up to 150 minutes. This effect is similar to the direct anaesthetic effect observed on C fibres (2). Although intravesical oxybutynin at the same dose temporarily decreases afferent activity in pelvic C fibres in the rat, without any effect on Aδ fibres, parenteral administration decreases activity in both C and Aδ fibres.

Concluding message

Parenteral oxybutynin decreases Aδ afferent activity of the rat urinary bladder. Whether the effect is through blocking of muscarinic receptors cannot be deducted from this study, as oxybutynin is an anticholinergic agent with mixed actions.

(1) Intravesical oxybutynin: a local anaesthetic effect on bladder C afferents. J Urol 169: 1892-1895, 2003 / (2) Parenteral oxybutynin: a local anaesthetic effect on bladder C afferents. Eur Urol Suppl 4(3): 69, 2005 / (3) Mechanosensitive properties of pelvic nerve afferent fibres innervating the urinary bladder of the rat. J Neurophysiol, 72**:** 2420-2430, 1994