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URODYNAMIC EFFECTS OF ORAL OXYBUTYNIN IN CONSCIOUS RATS UNDER DIFFERENT CYSTOMETROGRAPHIC CONDITIONS.

Aims of Study

Antimuscarinic agents are the most widely used treatment for overactive bladder. Among them, oxybutynin was the first agent used and its efficacy in man is well documented, producing decrease of urinary frequency and increase of bladder capacity (1). During cystometry in anesthetized and conscious rats, however, the main effect of oxybutynin is a decrease of peak micturition pressure together with scarce or no effect on bladder capacity (2-4). The aim of the present experiments was to study in rats the effect of oxybutynin using different cystometrographic conditions, in order to find the best experimental conditions to reproduce the effects observed in humans, mainly an increase of bladder capacity.

Methods

Cystometrographic studies in conscious rats were generally performed one day after catheter (Portex, ID 0.58 mm, OD 0.96 mm) implantation in the bladder dome. The catheter was exteriorized through a subcutaneous tunnel in the retroscapular area. On the day of the experiment, the free tip of the cannula was connected by a T-shape tube to a pressure transducer and to a peristaltic pump for infusion of warm solutions (37^{o} C) into the urinary bladder at a constant rate. Two urodynamic parameters from the cystometrogram were recorded on a polygraph: bladder volume capacity (BVC) and micturition pressure (MP). Basal values of BVC and MP were calculated as mean values from the cystometrograms recorded in a 30-60 minutes prior to treatment. Then, the animals were treated orally with oxybutynin or vehicle and changes in BVC and MP were evaluated hourly for 5 hr. With this protocol, two rates of saline infusion were tested (0.025 and 0.1 ml/min), as well as bladder infusion of two different concentrations of suramin (3 and 10 M at a constant rate of 0.1 ml/min) instead of saline. Saline infusion at a rate of 0.166 ml/min was also utilized to evaluate the effects of oxybutynin in rats utilized 5 days after catheter implantation.

Results

The changes in cystometrographic parameters induced by administration of oxybutynin were generally constant throughout the period of observation. To summarize the results obtained, therefore, they were expressed as the mean percent change vs the basal values, and shown in Fig. 1.

Oral administration of 1 and 3 mg/kg in rats utilized 1 day after catheter implantation and with saline infusion at constant rate of 0.1 ml/min, gave a dose-dependent decrease of MP (significant after 3 mg/kg), and a trend of increasing BVC that was not significant in comparison with vehicle-treated rats (bars A and B in the figure). When the saline infusion rate into the bladder was decreased at 0.025 ml/min (bar C), the effect of 1 mg/kg of oxybutynin was similar to that previously obtained (bar A).

When administered in rats 5 days after catheter implantation (a situation where the surgical inflammation is reduced) the effect of 1 mg/kg of oxybutynin on MP was higher than that observed in rats 1 day after implantation, but the increase of BVC was yet not significant (bar D). Experiments were performed also in rats with bladder infused with suramin in order to block the non-adrenergic, non-cholinergic component of the contraction. Suramin (10 M) in vehicle treated rats induced a significant increase (in comparison with basal values) of BVC ($p<0.01$). In these conditions, oral administration of 3 mg/kg of oxybutynin reduced significantly MP (as previously observed), but BVC was again not significantly increased (bars E and F).

Conclusions

Despite of the different experimental conditions utilized, the main effect of oxybutynin on cystometrographic parameters in conscious rats is a decrease of MP, whereas BVC is hardly and non-significantly affected. When bladder inflammation due to surgery was less marked (at 5 days after catheter implantation as showed by a mean BVC value of about 1.2 ml in

comparison with a BVC value of about 0.6 ml recorded in rats at 1 day after catheter implantation) the effect of oxybutynin on MP was more pronounced. When the ATP component of bladder contraction was blocked by infusion of suramin, the effect of oxybutynin on MP was similar to that observed in the other experimental conditions.
Summarising, the main effect observed after oral administration of oxybutynin is a reduction of MP and no statistically significant changes of BVC. Therefore, it seems difficult to reproduce in rats the cystometrographic effects observed in humans after administration of this antimuscarinic.

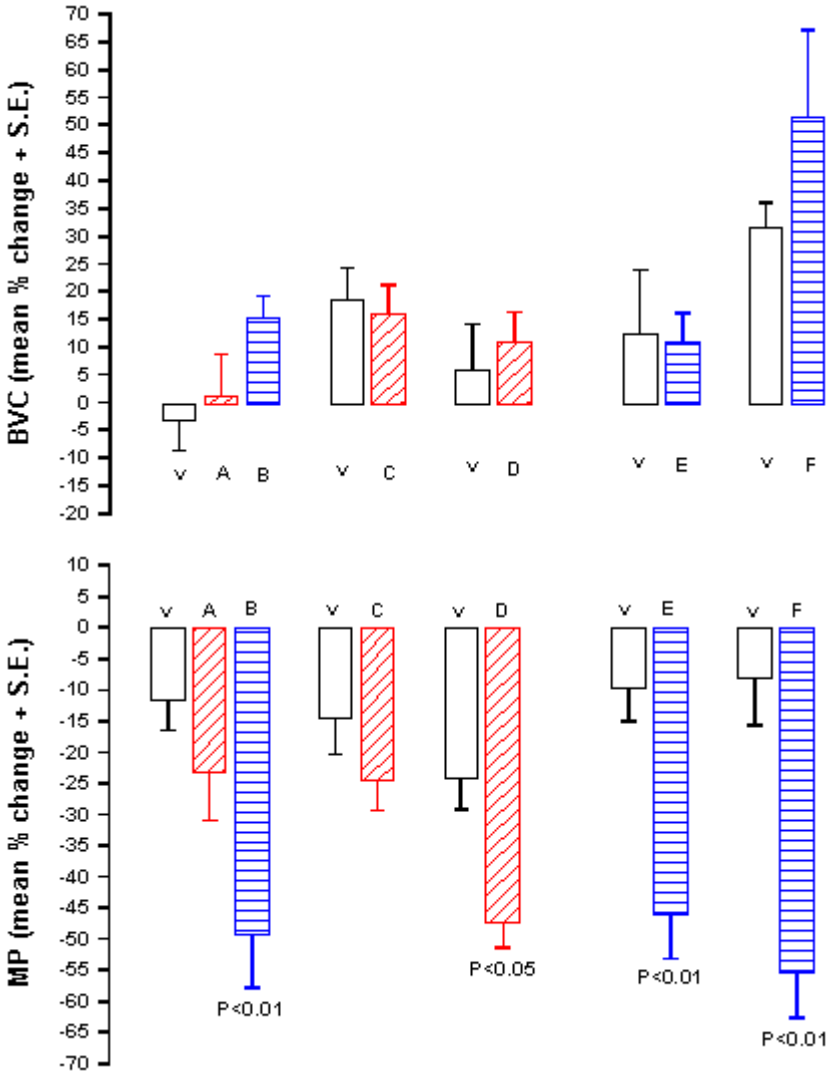

Fig. 1
Effect of oral administration of oxybutynin on BVC (upper panel) and MP (lower panel) in different cistometrographic conditions. V = vehicle; A = 1 mg/kg and B = 3 mg/kg in rats 1 day after catheter implantation and with saline infusion rate = 0.1 ml/min; C = 1 mg/kg and saline infusion rate = 0.025 ml/min; D = 1 mg/kg in rats 5 days after catheter implantation and with saline infusion rate = 0.166 ml/min; E = 3 mg/kg and with suramin (3 M - 0.1 ml/min) infused into the bladder; F = 3 mg/kg and suramin (10 M – 0.1 ml/min) infused into the bladder. Significativity is vs vehicle-treated group.

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