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THE NK1 ANTAGONIST R116301 INDUCES A GREATER INCREASE IN BLADDER CAPACITY COMPARED TO OXYBUTYNIN WITHOUT AFFECTING VOIDING EFFICIENCY

Hypothesis / aims of study

NK_1 receptors are thought to be involved in the micturition reflex, probably via modulation of the sensory limb of the bladder. Our aim was to elucidate the effect of NK_1 receptor blockade on bladder function. To this purpose, the effect of R116301 was assessed on urodynamic parameters in a guinea pig model. R116301 is a selective, orally active and centrally NK_1 antagonist with subnanomolar affinity for the human and guinea pig NK_1 receptor. As an active comparator, oxybutynin was tested in the same model.

Study design, materials and methods

Female guinea pigs (Dunkin Hartley) weighing 300 to 450 g were used. All studies were approved by the local Ethical Committee. Guinea pigs were anaesthetized by injecting 2 g/kg urethane (s.c.). An i.v. catheter was inserted in the jugular vein for drug administration and a tracheal tube was placed to facilitate breathing. The abdominal wall was opened and a flared-tipped PE 50 catheter was inserted through the bladder dome and secured. This transvesicular catheter was connected to a pressure transducer and an infusion pump. The bladder was filled with saline solution (0.3 ml/min). After a stabilisation period of 2 h, the bladder was emptied, the infusion was continued, and one filling cystometrogram was registered as a control value. Then vehicle (20% hydroxypropyl- -cyclodextrin for R116301 or saline for oxybutynin) was administered i.v. Twenty minutes after vehicle, the bladder was emptied again and a single filling cystometrogram was registered. The same procedure was repeated for 3 increasing concentrations of R116301 (1, 3 and 10 mg/kg, n=6), oxybutinin (0.3, 1 and 3 mg/kg, n=6) or vehicle (n=6 per group). Finally, bladder capacity was derived from the time between the start of infusion after bladder emptying until first voiding. Data are normalized to the vehicle control values and expressed as mean ± SD. The data were analyzed by using a non-parametric Wilcoxon Mann – Whitney test. When the data fit in a dose-response model curve, the ED_{50} and the maximal effect with 95% confidence interval were also calculated on the dose-response fit.

Results

In comparison with the control group, R116301 administered at cumulative doses of 1, 3 and 10 mg/kg i.v. increased dose-dependently the bladder capacity in anaesthetized guinea pigs. The maximal effect was of 25% (7% to 42%) and the ED_{50} was 0.64 mg/kg (0.14 mg/kg to 2.81 mg/kg). At a dose of 3 and 10 mg/kg the bladder capacity was significantly increased versus control (P =0.01). R116301 at all doses tested did not affect the maximal pressure during the micturition and the contraction duration.
Oxybutynin tested at cumulative doses of 0.1, 0.3 and 1 mg/kg increased the bladder capacity with a maximal effect of 13±19% at a dose of 3 mg/kg. The maximal pressure was not affected but oxybutynin increased significantly the contraction duration at a dose of 3 mg/kg (P=0.03).

Interpretation of results

NK_1 antagonism modulates the micturition reflex by increasing the bladder capacity without affecting maximal pressure and duration of micturition which may result in a reduced voiding efficiency.

Concluding message

These data show the potential of NK_1 receptor antagonists the treatment of overactive bladder; they might provide similar efficacy as anti-cholinergics without the side-effect profile .