

INTRAVESICAL TROSPIUM CHLORIDE ATTENUATES CARBACHOL-INDUCED CONTRACTIONS OF PIG BLADDERS IN A CONCENTRATION- AND INSTILLATION PERIOD-DEPENDING WAY: AN OPTION TO DESIGN A DRUG DELIVERY DEVICE?

Hypothesis / aims of study

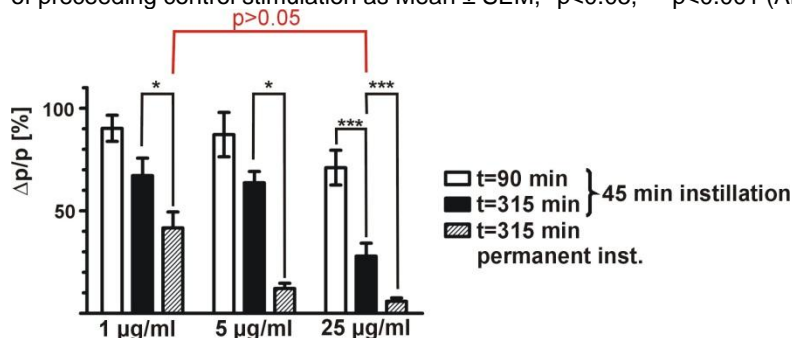
Intravesical anticholinergic therapy, an effective strategy to treat the overactive bladder (OAB), can be optimized by drug-delivery formulations. In order to extrapolate effective concentrations and incubation times prior to in vivo models, we directly monitored the effects of iTrCL on bladder activity in isolated whole pig bladders (PB).

Study design, materials and methods

Bladders from adult female domestic pigs were obtained from the local abattoir and transported in RPMI medium at 22⁰ C. They were suspended and mounted in an organ bath (37⁰C) with CO₂-gassed Krebs solution (KS). Bladder cavity was filled with 100-200 ml artificial urine (AU) via one side of an Y-tube adapter inserted into the urethra. Through the other side of the tube a transurethral pressure transducer was guided intravesically to record pressure readings. PBs were stimulated extravesically (evs) with 8 μ M carbachol in intervals of 45 min replacing KS after recording of each pressure transient (Δp). After 3 control stimulations AU was replaced by 200 ml of respective TrCL in AU (3 PB/dose & incubation time) followed by washout with AU. Carbachol stimulations were continued until the pressure response (PR) decreased no further. Final evs KCL stimulation indicated PB integrity.

Results

In controls the PR to repeated stimulations every 45 min. was stable over 9 cycles (405 min). Intravesical application of TrCL (1,5,25 μ g/ml) resulted in a strongly incubation time and dose-dependent decrease of the last non-treated response (rel. pmax). 25, 5 and 1 μ g/ml iTrCL required a 45, 135 and 225 min. instillation to achieve a 50% decrease of rel. pmax within 135, 180 and 315 min. A sustained attenuation of rel. pmax \geq 90% only arised for 25 and 5 μ g/ml at 90 min. and permanent incubation. Finally permanent instillation of 1 and 5 μ g/ml TrCL was equally effective as 45 min. instillation of 25 μ g/ml. Figure 1 indicates short and longer term effect of 45 min TrCL versus continuous instillation. Bar diagram shows pressure amplitudes as a fraction of preceeding control stimulation as Mean \pm SEM, *p<0.05, ***p<0.001 (ANOVA) with Bonferroni's post hoc test.



Interpretation of results

In this model of whole isolated pig bladder we can differentiate the attenuating effect of different concentrations and different instillation periods of intravesical trospium chloride on cholinergic carbachol-induced contractions.

Concluding message

Our results might indicate a concentration- and instillation-time-depending saturation of receptors / transporters for TrCL. A short term release of a high concentration or the continuous release of low concentration TrCL seem to be feasible approaches for intravesical drug-delivery systems.

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Is this a clinical trial?	No
What were the subjects in the study?	NONE