

EFFECTS OF COMBINED USE OF TROSPIUM CHLORIDE AND MELATONIN ON IN VITRO CONTRACTILITY OF RAT URINARY BLADDER

Hypothesis / aims of study

Pharmacological treatment of overactive bladder (OAB) mainly consists of use of antimuscarinic drugs (1). However, the limiting role of side-effects of antimuscarinic drugs led researchers to develop new drugs or combination of currently used drugs in the treatment of OAB. In the present study, we hypothesised that combining an existing antimuscarinic agent at a very low dose with melatonin, as a smooth muscle relaxator, may inhibit detrusor overactivity efficiently. We therefore examined the effects of combined use of TCI and melatonin on in vitro contractility of normal and partially obstructed rat urinary bladder.

Study design, materials and methods

A total of 30 male Wistar rats were used in these experiments. Partial outlet obstruction (POO) of rat urinary bladder was performed by tying a 2/0 silk ligature loosely around the pre-catheterized urethra in 10 rats. Bladders from all rats with and without POO were removed after 2 weeks of POO and strips were prepared from longitudinally incised bladders and placed in a tissue bath containing physiological saline solution. After equilibration period strip contractions were evoked by 10 μ M ACh. The effects of trospium and melatonin on agonist induced contractions in all strips were assessed. Relaxation responses of trospium and melatonin on ACh-induced responses are expressed as a percentage decrease of the basal contractile response. In the next step, we examined combined use of melatonin and trospium and the level of inhibition in mean amplitude and AUCs for combination effect.

Results

Increasing concentrations of trospium (1 μ M, 3 μ M and 5 μ M), gradually decreased the mean peak amplitudes ($p < 0.05$) of ACh induced contractions. Similarly, the mean peak amplitude of contractions evoked by ACh was significantly inhibited by melatonin in a concentration dependent manner (100 μ M, 200 μ M and 300 μ M) ($p < 0.05$). Normalized data with respect to basal amplitude and percent of inhibition for each drug are shown in Fig 1. We further evaluated the combined use of trospium and melatonin on ACh-induced contractions. The effects at three different combination doses; lowest dose of melatonin and one tenth of trospium (100 μ M melatonin + 100 nM, 300 nM and 500 nM of Trospium, respectively) significantly lowered both the peak amplitude and AUC of contractions ($p < 0.05$) (Fig 2). Considering the effects on AUCs, we showed that after the last trospium dose (500 nM) which was added to the lowest dose of melatonin, (100 μ M), there was significant inhibition compared to individual drug administrations both in normal and partially obstructed bladders (Fig 3).

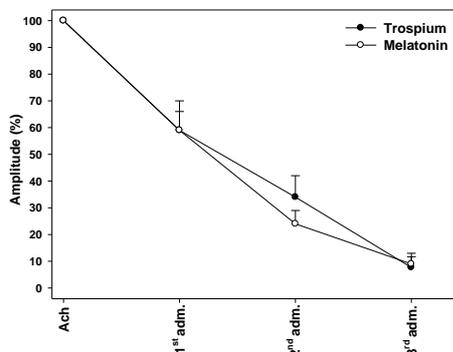


Figure 1. Effects of three subsequently administered (adm.) concentrations of trospium and melatonin on mean amplitude of contractions induced by acetylcholine (ACh)

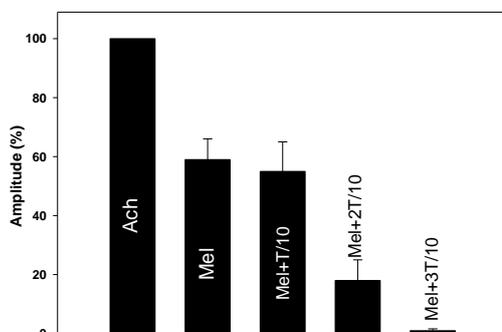


Figure 2. Percent of inhibition by Melatonin (Mel) with combined use of diluted doses of trospium (T) on the mean amplitude of contractions induced by acetylcholine (ACh)

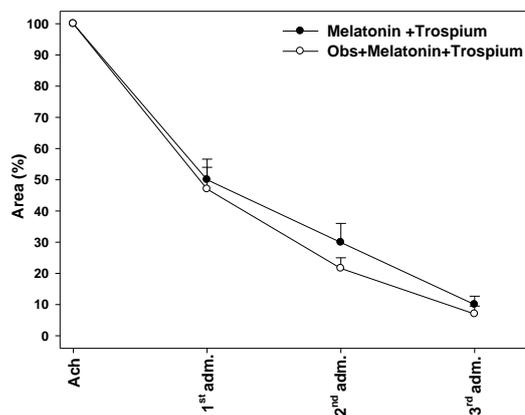


Figure 3. Comparison of responses of bladder strips with normal and partial obstruction (Obs.) to subsequently administered (adm.) trospium and melatonin shown by the area under curve.

Interpretation of results

Using one third of melatonin dose (100 μ M) and combining it with a very low dose of initial trospium dose had the same efficacy compared to the efficacies obtained by each drug separately.

Concluding message

Our study is the first offering an insight for lowering the dose of an antimuscarinic by combining it to an endogenous hormone, melatonin. Confirming these findings in further clinical trials would bring no or slight side effects and may help to decrease the rate of withdrawals of antimuscarinic drugs.

References

1. BJU Int (2007) 100: 987-1006

Specify source of funding or grant	NONE
Is this a clinical trial?	No
What were the subjects in the study?	ANIMAL
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	Yes
Name of ethics committee	Firat University Faculty of Medicine Ethics Committee