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PROOF OF PRINCIPLE: DOES ORAL ANTIMUSCARINIC TREATMENT AFFECT RESTING HEART RATE VARIABILITY? A PLACEBO CONTROLLED INVESTIGATION WITH 4 & 8MG TOLTERODINE ER.

Hypothesis / aims of study

The incidence of overactive bladder (OAB) increases with age [1] and so does the incidence of cardio-vascular diseases. Antimuscarinics are still the first line drug therapy for OAB. However, antimuscarinic drugs can have significant adverse effects on cardiac function [2]. Most studies reporting about antimuscarinic cardiac side effects usually investigated the effect of the drugs on the QT-time. Some studies also evaluated the effect on the heart rate but no study investigated changes in heart rate variability (HRV).

However, HRV is an important indicator of cardiac autonomic function and a reduced HRV has been shown as a possible predictor for mortality due to cardiac diseases but also of all-cause mortality [3]. It was therefore the aim of this study to investigate the influence of the widely-used antimuscarinic drug tolterodine extended release (ER) on the human HRV.

Study design, materials and methods

In a healthy female volunteer sample we measured a 10 minutes baseline electrocardiogram (ECG) while subjects were in a relaxed supine position. Afterwards the subjects were randomly assigned to either placebo, tolterodine ER 4mg or 8mg. 4 hours post dose, when tolterodine ER plasma levels reach its maximum, a second 10 minutes ECG in supine position was performed. From both measurements, the middle 5 minutes section was cut out and evaluated, using both, frequency domain and time domain analysis.

Results

Table 1: Summary of all HRV parameters analysed from the ECG recordings in all three groups

Groups	**Placebo**		**Tol 4mg**		**Tol 8mg**	
Condition	**Pre**	**Post**	**Pre**	**Post**	**Pre**	**Post**
HR	68.0 ±9.8	72.7 ±12.9	58.6 ±11.1	67.2 ±14.4	62.5 ±12.5	74.7 ±14.0
Sig.	none		p = 0.047		p = 0.005	
VLF	46.5 ±15.5	42.1 ±15.7	66.6 ±30.9	52.2 ±23.9	60.4 ±35.0	40.5 ±17.0
Sig.	none		p = 0.047		p = 0.005	
LF	1.2 ±1.2	0.8 ±0.5	2.4 ±2.0	3.2 ±5.8	1.5 ±2.1	0.9 ±0.6
Sig.	none		none		none	
HF	1.4 ±1.4	1.1 ±1.2	3.4 ±2.9	2.0 ±1.8	4.7 ±7.8	0.4 ±0.5
Sig.	none		none		p = 0.028	
LF/HF	1.1 ±0.5	1.5 ±1.4	1.1 ±1.2	2.8 ±4.5	1.1 ±1.1	4.3 ±4.1
Sig.	none		none		p = 0.007	
RMSSD	57.1 ±35.1	51.4 ±34.5	99.1 ±51.1	70.7 ±48.7	90.6 ±67.4	31.3 ±17.5
Sig.	none		none		p = 0.009	
SDNN	61.4 ±25.9	52.3 ±22.9	89.4 ±33.8	72.7 ±39.9	83.3 ±46.0	43.1 ±16.5
Sig.	none		none		p = 0.005	

30 subjects (mean age: 23.7 ±2.3, mean BMI: 20.5 ±1.7) were included. All subjects tolerated the measurements and the drug treatment very well. There were single reports regarding tiredness (4), headache (6), nausea (2) and dry mouth (2) from all groups.

No significant changes for HRV parameters could be observed in the placebo group. In the tolterodine 4 mg group a significantly increased heart rate and a significantly decreased very low frequency (VLF) could be found. In the 8mg group significant decreases were found for high frequency (HF), VLF, root mean square of differences of successive NN intervals (RMSSD) and standard deviation of the NN intervals (SDNN). Significant increases could be observed for the heart rate and the LF/HF ratio. Nevertheless, a difference between groups post dosing could be only detected for the LF/HF ratio (table 1).

Interpretation of results

Both treatment groups showed significant changes in HRV parameters, whereas 4 mg caused less and minor changes than 8 mg. However, some changes observed in the treatment groups were still in the range of the placebo group values.

Nevertheless, in the 8 mg group a highly significant decrease in the RMSSD could be observed and the post treatment mean RMSSD value in the 8 mg group was well below the mean RMSSD value of the placebo group. The RMSSD is an indicator for the variability itself, and a decrease means a reduction in HRV. For the LF/HF ratio, which is an indicator for the sympatho-vagal influence on the heart, a significant increase could be observed in the 8 mg group, meaning an increase in sympathetic cardiac input.

Those results are not surprising according to the mechanism of action of antimuscarinics and it seems that the approved and recommended dose of 4 mg is not causing statistically and clinically relevant changes in HRV in contrast to 8 mg. However, it might not be clinically relevant in young healthy females taking a single dose, but elderly patients and those with pre-existing cardiac problems, who are on a once daily treatment for their OAB symptoms, might be negatively affected. This applies also to patients who are not adequately treated with the recommended standard dose but require more and are treated off label with higher doses (e.g. spinal cord injured patients).

The conclusions from the results of this small proof of principle study are of course limited. However, we think that HRV evaluation should be included in clinical trials investigating antimuscarinic drugs to provide more safety data and to become aware of the influence of antimuscarinics on HRV.

Concluding message

Although most post treatment HRV parameters were still in the range of the placebo group data, tolterodine ER does affect the resting HRV in the supine position (8mg >> 4mg). This might be particular relevant for elderly patients or patients with preexisting cardiac conditions and should be further evaluated and considered in future clinical trials using antimuscarinic drugs.

References

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