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EFFICACY AND SAFETY OF MIRABEGRON IN THE TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY – PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY

Hypothesis / aims of study
Deterioration of the neural control at any level usually leads to the development of neurogenic dysfunction of the lower urinary tract. Neurogenic detrusor overactivity (NDO) is defined as a urodynamic observation characterised by involuntary contraction of the detrusor during the filling phase, where there is a evidence of a neurological disorder.[1] NDO is a typical urodynamic observation in patients suffering from suprasacral spinal cord injury (SCI). NDO is most frequently reported urodynamic observation in patients with multiple sclerosis (MS).
Anticholinergics are considered standard way to treat NDO, however especially side effects represent a significant limitation for long term treatment.[2,3] Mirabegron is approved for treatment of idiopathic overactive bladder, however the data about use of mirabegron in neuropathic patients are missing. The aim of the study was to assess efficacy and safety of mirabegron in the treatment of NDO in patients with SCI or multiple sclerosis MS.

Study design, materials and methods
In total, 78 patients were enrolled into this prospective, multi-centre, randomised, double blind, placebo controlled study conducted in three tertiary centers. The study protocol was approved by the Institutional Review Board. Three visits were scheduled during the study. After signing of informed consent, patients were advised to stop their anticholinergic medication and were administered with placebo for single blind run-in period (2 weeks). Subjects with proven NDO during filling cystometry at the end of the wash-out period were considered suitable for randomisation. Eligible subjects were randomised in 1:1 ratio using a central computerised randomisation scheme to active treatment arm (mirabegron 50 mg) (Group A) or placebo arm (Group B) for 4 weeks of double blind treatment period.
Urodynamic parameters, 24hours pad weight test (24PWT) and patient – reported outcome variables were assessed at randomisation (baseline) and the end of study visit (Week 4). Safety assessments included the monitoring of the incidence and severity of adverse events (AE). Changes in time and differences between groups were assessed using non-parametric Kruskal-Wallis one-way ANOVA test. p values ≤ 0.05 were considered statistically significant.

Results
Total of 66 patients were eligible to be included into final analysis. Baseline demographic and clinical characteristics were similar among placebo and mirabegron group. There was a significant increase of volume at first detrusor contraction (p=0.00047) and improvement of bladder compliance (p=0.0041) in mirabegron group compared to placebo, while the effect on increase of cystometric capacity was of borderline statistical significance (p= 0.061). There was clear trend to reduce urine leakage (p=0.056) as measured by 24PWT in Group A. There were significant changes in all patient – reported outcome variables in favour to mirabegron group – PPBC scale (p=0.0013), I – QoL questionnaire (p=0.006), Treatment satisfaction – visual analog scale (p=0.00045).
Total seven AEs in seven patients were observed during the study (8.97%). The incidence of AEs in placebo arm during double blind treatment period was 2.94%. The incidence of AEs in mirabegron arm was 6.25%, however incidence of study drug related AEs was 3.13% (1 of 32 patients). In addition, there were no statistically significant changes from baseline to end of treatment found neither in blood pressure nor in pulse rate.

Interpretation of results
Mirabegron 50 mg improves both urodynamic and patient – reported outcome variables in patients with NDO. The treatment with mirabegron was well tolerated with low incidence of AEs.

Concluding message
These data strongly support the hypothesis that mirabegron can be safely used in the treatment of NDO. Further research in order to identify appropriate dosage of mirabegron in this specific population is highly required.

	Group A			Group B			A vs B
	Baseline (±SD)	End of Treatment (±SD)	Difference *p*	Baseline (±SD)	End of Treatment (±SD)	Difference *p*	Kruskal-Wallis *p*
CC (ml)	183,5 ± 121,6	238,81 ± 150,56	0,1343	210,44 ± 135,34	167,56 ± 102,96	0,1733	0,0610
VFDC (ml)	127 ± 104,72	199,31 ± 143,55	0,0311	125,03 ± 81,92	89,41 ± 63,84	0,0695	0,0005
C (ml/1cm H_2O)	34,78 ± 26,65	59,06 ± 54,89	0,0515	34,73 ± 22,84	30,4 ± 26,98	0,2670	0,0041
p_{detmax} (cm H_2O)	71,91 ± 10,04	74,23 ± 11,04	0,5865	74,91 ± 13,03	71,47 ± 10,17	0,2380	0,3173
24PWT (ml)	763,97 ± 1092,7	567,25 ± 1012,7	0,1330	572,42 ± 792,99	922,81 ± 1095,65	0,3193	0,0561
I-QoL	43,92 ± 18,04	52,62 ± 19,5	0,0539	43,4 ± 24,27	36,78 ± 24,42	0,2340	0,0060
TS-VAS	50,43 ± 37,26	71,05 ± 27,12	0,0355	37,89 ± 38,18	38,48 ± 36,14	0,9066	0,0004
PPBC	4,06 ± 1,16	3,53 ± 1,22	0,0671	4,12 ± 1,32	4,47 ± 0,96	0,2771	0,0013

Table 1: Results – efficacy variables
(CC - cystometric capacity, VFDC - volume at first detrusor contraction, C – compliance, p_{detmax} - maximal detrusor pressure, 24PWT – 24hours pad weight test, I–QoL – I–QoL questionnaire, TS-VAS – Treatment satisfaction – visual analog scale, PPBC - Patient Perception of Bladder Condition)

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Disclosures

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