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ADMINISTRATION OF PROSULTIAMINE FOR HTLV-1-ASSOCIATED MYELOPATHY MAY IMPROVE NOT ONLY VOIDING SYMPTOMS BUT ALSO STORAGE SYMPTOMS BY DECREASING URINARY NERVE GROWTH FACTOR LEVELS

Hypothesis / aims of study
In patients with HTLV-1-associated myelopathy (HAM), the onset and clinical conditions of neurogenic bladder may vary. Treatment for HAM is mainly symptomatic, with some patients being inadequately treated. In those with long-standing HAM, detrusor underactivity may necessitate clean intermittent self-catheterization, which often decreases quality of life (QOL). Prosultiamine is expected to induce apoptosis of HTLV-1-infected cells. Therefore, we evaluated the clinical efficacy of prosultiamine for treating neurogenic bladder in HAM patients.

Study design, materials and methods
The study included 24 patients (7 men and 17 women) who had neurogenic bladder due to HAM, with or without spontaneous voiding. Patients received once-daily dosing with encapsulated oral prosultiamine 300 mg before breakfast for consecutive 12 weeks. Concomitant medications were continued in this study. Subjective symptoms were assessed using the Nocturia Quality of Life questionnaire (N-QOL) and Overactive Bladder Syndrome Score (OABSS). For objective findings, urodynamic studies (UDS) were conducted. Urinary nerve growth factor (NGF)/creatinine levels were determined to evaluate the association with OABSS. These evaluations were performed prior to the first dosing and at Week 12 of treatment. Three patients experienced mild gastrointestinal symptoms, but no other adverse reactions were reported. Statistical analyses were performed by the Wilcoxon signed rank test with statistical significance at $p<0.05$.

Results
Patients had a mean age of 60.2 years (range, 44-80 years) and disease duration of 20.9 years (range, 3-51 years). Sixteen patients were able to void spontaneously prior to the study.
The N-QOL results at baseline and Week 12 of treatment are shown in Fig. 1. Treatment with prosultiamine significantly improved both total and subscale converted N-QOL scores.
The OABSS results are shown in Fig. 2. Thirteen patients (54.2%) achieved a decreased total OABSS score after treatment. Overall, a statistical trend towards improvement relative to baseline was observed. For each item of the questionnaire, treatment resulted in a non-significant decrease in scores.
The UDS results are shown in Table 1. Bladder capacity and detrusor pressure improved. In patients who were able to void spontaneously, the max flow rate increased significantly. Detrusor-sphincter dyssynergia (DSD) was noted in 11 patients at baseline, of whom 5 (45.5%) had recovered from the condition at Week 12 of treatment. Detrusor overactivity (DO) was present in 15 patients at baseline and had resolved in 11 (73.3%) at Week 12. In addition, 2 patients became able to urinate.
Overall, the urinary NGF/creatinine level after treatment was not significantly different from that at baseline. However, in 11 (84.6%) of 13 patients with relief of OAB symptoms, the urinary NGF/creatinine level decreased significantly relative to that at baseline (19.5 ± 16.2 pg/mg at baseline vs. 12.7 ± 11.9 pg/mg post-dose; $P=0.0033$).

Interpretation of results
Treatment with prosultiamine increased both bladder capacity and detrusor pressure. The UDS showed that these increases lead to a significant elevation in the max flow rate. Additionally, DSD and DO, the most characteristic bladder dysfunctions in HAM patients, improved. These findings are consistent with improvements in subjective measures, N-QOL scores and OABSS. As to OABSS, it is very interesting that most of the patients achieving a better score than the baseline had a decreased urinary NGF/creatinine level, although no significant difference was found.
Prosultiamine is an agent originally intended to improve the distribution of vitamin B1 into tissues and cells. However, prosultiamine that distributes into tissues of the spinal cord or bladder may exert its effect at the tissue level. Prosultiamine is poorly understood in terms of disposition and/or metabolites, and the optimal dose, etc. In this study, no remarkable adverse reactions were reported; a higher dose of prosultiamine may have produced more improvement in test observations. These findings should be further analyzed in detail.

Fig. 1 Comparison of the converted N-QOL score before and after administration

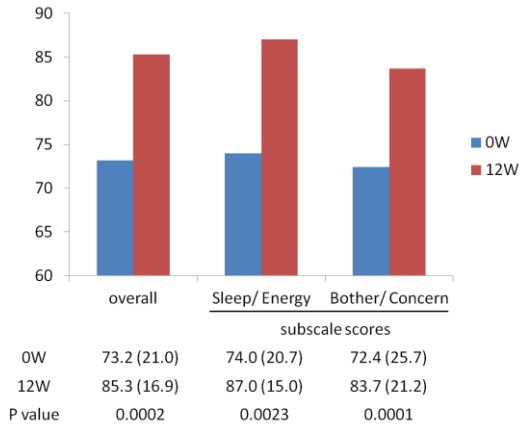

Fig. 2 Comparison of OABSS before and after administration

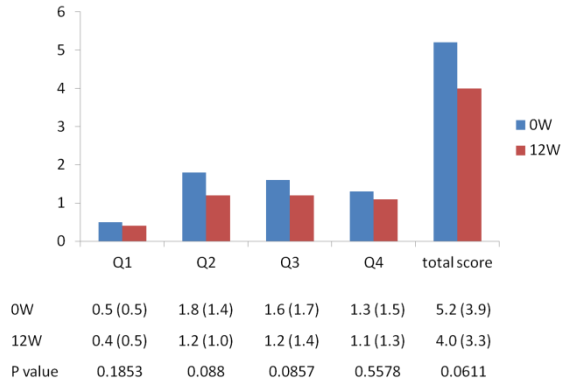

Table 1 Urodynamic study findings

	0W	12W	*P* value
Qmax (ml/sec)*	7.5±6.2	10.2±5.5	0.0057
Max bladder capacity (ml)	341.3±127.2	391.0±140.0	0.0066
Detrusor pressure (cmH2O)	16.8±.15.6	27.5±15.2	0.0001
Voided volume (ml) *	151.2±156.1	138.6±124.8	0.5223
Residual urine volume rate (%)*	60.2±31.8	55.8±32.1	0.452

*N=16 for patients able to void spontaneously prior to the study

Concluding message

Prosultiamine for oral use is a promising novel therapeutic agent for neurogenic bladder caused by HAM.

Disclosures

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