

Original

Amantadine can Ameliorate Lower Urinary Tract Dysfunction and Nocturnal Polyuria in Patients with Parkinson Disease and Vascular Parkinsonism

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SUMMARY

Background : Amantadine is a drug used for patients with Parkinson's disease (PD) and vascular parkinsonism (VP). These patients often have lower urinary tract symptoms (LUTS) and nocturnal polyuria (NP). Thus, we investigated the effect of amantadine on these in parkinsonian patients.

Methods : Twenty-two patients with LUTS, including 13 with PD and nine with VP, were recruited. We performed a urinary questionnaire, frequency-volume chart, and residual urine (RU) measurement before and after daily administration of 150 mg and 300 mg amantadine.

Results : Before amantadine administration, mean daytime urinary frequency was 9.07 (standard error [SE], 0.64), nighttime urinary frequency 2.89 (0.24), urinary urgency per week 24.2 (6.69), urge incontinence per month 15.1 (9.94), urine volume per void 145.6 (12.6) mL, and residual urine volume 12.5 (6.30) mL. After daily 150 mg amantadine administration, mean daytime and nighttime urinary frequency, urinary urgency, and urge incontinence decreased to 6.9 (0.42), 1.97 (0.21), 13.0 (3.58), and 14.2 (10.2), respectively, and urine volume per void increased to 174.1 (11.3) mL. NP (N=8) was ameliorated in six patients. No patient had side effects. After daily 300 mg amantadine administration (N=8), mean daytime and nighttime urinary frequency, urinary urgency, and urge incontinence decreased to 6.90 (0.33), 1.69 (0.10), 5.88 (1.61), and 2.31 (0.61), respectively, and urine volume per void increased to 180.2 (15.0) mL. NP (N=4) was ameliorated in two patients. One patient developed hallucination, and two patients developed flashing sensation.

Conclusion : Amantadine has beneficial effects on LUTS and NP in patients with VP and PD.

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Lower urinary tract symptoms (LUTS) are common non-motor dysfunctions in patients with Parkinson's disease (PD)^{1~7}. In LUTS, storage symptoms, such as daytime urinary frequency, nighttime urinary frequency (nocturia), urinary urgency, and urge incontinence, are common in PD patients^{3,5~7}. Some studies report that nighttime urinary frequency is the most common among the storage symptoms in PD patients^{3,5~7}.

Vascular parkinsonism (VP) accounts for 2.5–5% of parkinsonism cases⁸. LUTS is common in patients with VP, as well as in those with other diseases of Parkinson's syndrome and cerebrovascular diseases. A recent systematic review showed that the patients with VP present more commonly with symmetrical gait difficulties, postural instability, falls, dementia, pyramidal signs, pseudobulbar palsy, and LUTS (urinary incontinence) than patients with PD⁹.

LUTS impairs the quality of life and also disturbs many areas of life, such as sleep and daily-activity, and generally results in a risk of serious adverse consequences such as fall, fracture, depression, and cognitive impairment^{10~12}. These disturbances and risks may be higher in patients with PD or VP, because these patients commonly have not only LUTS but also motor, sleep, and cognitive disturbances.

In addition, recent reports show that nocturnal polyuria (NP) is a cause of LUTS (nighttime urinary frequency) in older patients¹³. NP is reported to occur in some neurological diseases, such as VP¹⁴ and PD¹⁵, which contributes to LUTS and increases the risk of adverse consequences due to LUTS. Thus, LUTS and NP in patients with PD or VP must be prevented sufficiently. However, there is no disease-specific medication for LUTS and NP in patients with PD or VP.

Amantadine is 1-amino-adamantanamine, a salt of the symmetric 10-carbon primary amine, and is an antiviral for the treatment of influenza and a drug used for patients with PD and VP. Although its precise mechanism of action is uncertain, it is thought to be based on interaction with dopamine, by enhancing the release and inhibiting the reuptake of dopamine and by changing dopamine receptor affinity, and on NMDA glutamate receptor blockade, which normalizes the activities of the glutamatergic corticostriatal and subthalamic-pallidal pathways¹⁶. In addition, amantadine is reported to have other various clinical effects such as

reducing levodopa-induced dyskinesia¹⁷, improving pathological gambling and punting¹⁷, ameliorating depression¹⁸, preventing postoperative central sensitization¹⁹, and reducing pain¹⁹. Additionally, amantadine is thought to have noradrenergic, serotonergic, anti-cholinergic, and anti-opioid effects^{17~21}. It is also known that these effects are associated with neuro-muscular control of the lower urinary tract system. Actually, in clinical application, we experience that the treatment of amantadine ameliorates not only parkinsonism but also LUTS and NP, simultaneously.

Thus, we hypothesized that amantadine ameliorates LUTS and NP and investigated the effect of amantadine on them in patients with PD or VP.

PATIENTS and METHODS

Twenty-two parkinsonian patients with LUTS, including 11 male and 11 female, with a mean age of 72.5 years (standard deviation [SD], 6.4), were included in these studies. Of these patients, 13 had Parkinson's disease (PD; median Hoehn & Yahr 2.78), and nine had vascular parkinsonism (VP). PD and VP were diagnosed after clinical examination, magnetic resonance imaging (MRI) according to clinical diagnostic criteria^{22,23}, as well as the results of cardiac I-metaiodobenzylguanidine (MIBG) testing. Furthermore, in cases of PD, it was possible to confirm the initial clinical impression after patients were started on parkinsonian medication, and their responses could be assessed. Patients with severe cognitive impairment, major depression/psychiatric disorder, or other diseases known to influence lower urinary tract function, such as diabetes mellitus, spondylosis, and prostate hypertrophy, as well as those receiving medication for lower urinary tract problems, were excluded.

We performed a detailed urinary questionnaire, frequency-volume chart/bladder diary, and measurement of residual urine (RU) by echography before and one month after daily administration of 150 mg amantadine. In addition, we addressed an insufficient effect for 150 mg amantadine in a cohort of patients with an increase of amantadine. One month after daily administration of 300 mg amantadine, we repeated the questionnaire, the chart/diary, and the measurement of RU. We also observed any side effects or changes of neurological and mental manifestations. This study was ap-

proved by the Ethics Committee of Chiba University and Dokkyo Medical University and was conducted according to the principles of the Declaration of Helsinki. All participants gave their informed consent before commencement of the studies.

Symptoms of LUTS were evaluated with a non-validated questionnaire that is used routinely in our departments. Storage symptoms consisted of urinary urgency, daytime urinary frequency, nighttime urinary frequency (nocturia), and urge/stress/mixed incontinence. Urinary frequency was defined as more than eight times per daytime period and twice or more per night. Voiding symptoms consisted of hesitancy, slow stream, intermittency, straining, feeling of incomplete emptying, and urinary retention. Volumes voided, as well as the time of each micturition and information about fluid intake, were recorded in a frequent-volume chart (bladder diary) for 2–3 successive days. Nocturnal polyuria (NP) was defined as a nocturnal urine volume exceeding 33% of the 24-h urine output. Nocturnal urine volume was defined as the total volume of urine passed between the time the individual goes to bed with the intention of sleeping and the time of waking with the intention of rising. The terminology of LUTS conformed to the standards proposed by the International Continence Society²⁴.

Statistical analyses were performed using commercial software (Excel Statistics Ver. 6.0; Esumi Inc., Tokyo, Japan). The results of the evaluation of LUTS, bladder daily volume, and residual urine volume before and after amantadine administration were compared by a paired *t*-test (parametric) or Wilcoxon signed-rank test (nonparametric). Differences in the results in each group were assessed with ANOVA and multiple comparisons. Associations between categorical variables were examined by a Chi-square test for independence. Significant results were considered with caution for *p* values marginally less than 0.05.

RESULTS

LUTS, NP, and RU in patients with PD and VP

Before amantadine administration, daytime urinary frequency was a complaint in 15 patients (68.2%, PD : VP = 53.8 : 88.9% ; *P* = 0.039), and mean daytime urinary frequency was 9.07 (standard error [SE] , 0.64) ; nighttime urinary frequency was a complaint in

19 patients (86.4%, PD : VP = 92.3 : 77.8% ; not significant [ns]), and mean nighttime urinary frequency was 2.89 (SE, 0.24) ; urinary urgency was a complaint in 17 patients (77.3%, PD : VP = 84.6 : 66.7% ; ns), and mean urinary urgency per week was 24.2 (SE, 6.69) ; urge incontinence was a complaint in 13 patients (59.1%, PD : VP = 61.5 : 55.6% ; ns), and mean urge incontinence per month was 15.1 (SE, 9.94) ; hesitancy was a complaint in six patients (27.3%, PD : VP = 7.7 : 55.6% ; *P* = 0.013), and mean hesitancy per week was 1.61 (SE, 0.69) ; slow stream was a complaint in eight patients (36.4%, PD : VP = 15.4 : 66.7% ; *P* = 0.013), and mean slow stream per week was 1.86 (SE, 0.72) ; intermittency was a complaint in four patients (18.2%, PD : VP = 7.7 : 33.3% ; ns), and mean intermittency per week was 0.52 (SE, 0.25) ; straining was a complaint in five patients (22.7%, PD : VP = 7.7 : 44.4% ; *P* = 0.043), and mean straining per week was 1.95 (SE, 0.89) ; feeling of incomplete emptying was a complaint in seven patients (31.8%, PD : VP = 15.4 : 55.6% ; *P* = 0.046), and mean feeling of incomplete emptying per week was 1.38 (SE, 0.60) ; and no patients had urinary retention.

A frequent-volume chart (bladder diary) was completed in 18 patients (81.8%, PD : VP = 9 : 9). Mean urine volume per void was 145.6 (SE, 12.6) mL, including mean daytime urine volume per void 136.9 (SE 11.6) mL and mean nighttime urine volume per void 187.3 (SE 21.3) mL. Eight patients (44.4%, PD : VP = 66.7 : 22.2% ; ns) had nocturnal polyuria, and mean nocturnal polyuria index (NPI) was 30.0 (SE, 2.47).

Mean residual urine volume was 12.5 (SE 6.30) mL.

LUTS after amantadine administration

One month after daily administration of 150 mg amantadine (*N* = 21), daytime urinary frequency was alleviated in 16 patients (76.2%), unchanged in four (19.0%, including three patients without daytime urinary frequency), and aggravated in one (4.8%). Mean daytime urinary frequency was decreased significantly to 6.9 (SE 0.42, *P* = 0.002). Nighttime urinary frequency was alleviated in 10 patients (47.6%), unchanged in 10 (47.6%, including 3 patients without nighttime urinary frequency), and aggravated in one (4.8%). Mean nighttime urinary frequency was decreased significantly to 1.97 (SE 0.21, (*P* = 0.001) (Figure 1). Urinary urgency was alleviated in 15 patients (71.4%) and

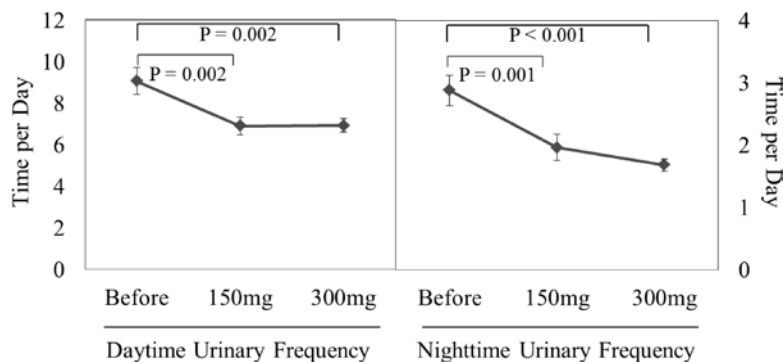


Figure 1 Daytime urinary frequency and nighttime urinary frequency before and after amantadine administration.

Amantadine ameliorates daytime and nighttime urinary frequency and urgency significantly in patients with PD or VP.

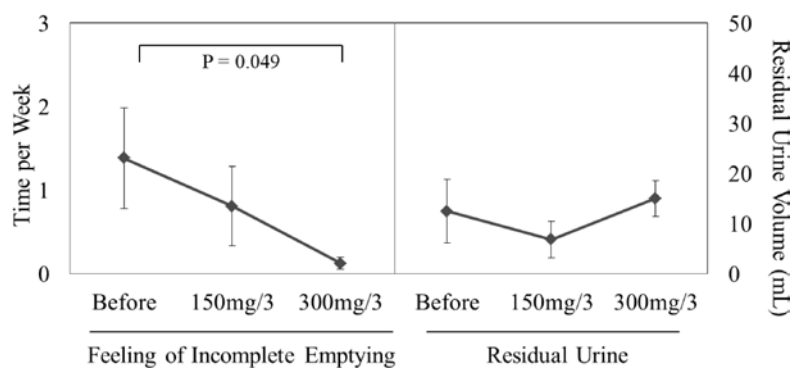


Figure 2 Feeling of incomplete emptying and residual urine before and after amantadine administration.

Amantadine ameliorates feeling of incomplete emptying as a post-voiding symptom significantly, but did not change residual urine volume in patients with PD or VP.

unchanged in six (47.6%, including five patients without urinary urgency). Mean urinary urgency per week was 13.0 (SE 3.58), which tended to decrease, but this change was not significant. Urge incontinence was alleviated in eight patients (38.1%) and unchanged in 13 (61.9%, including 9 patients without urge incontinence). Mean urge incontinence per month was 14.2 (SE 10.2), which tended to decrease, but this change was not significant. Hesitancy was alleviated in two patients (9.5%), unchanged in 18 (85.7%, including 13 patients without hesitancy), and aggravated in one (4.8%). Slow stream was alleviated in three patients (14.3%), unchanged in 17 (80.9%, including 13 patients without slow stream), and aggravated in one (4.8%). Intermittency was alleviated in three patients (14.3%) and unchanged in 18 (85.7%, including 17 patients without intermittency). Strain was alleviated

in three patients (14.3%), unchanged in 17 (80.9%, including 16 patients without strain), and aggravated in one (4.8%). However, mean hesitancy per week, slow stream per week, intermittency per week, and strain per week tended to decrease, but these changes were not significant. Feeling of incomplete emptying was alleviated in three patients (14.3%) and unchanged in 18 (85.7%, including 14 patients without slow stream). Mean feeling of incomplete emptying per week was decreased significantly to 0.81 (SE 0.47, $P=0.049$) (Figure 2).

One month after daily administration of 300 mg amantadine in PD patients showing an insufficient effect with daily 150 mg amantadine ($N=8$), compared with before amantadine treatment, daytime urinary frequency was alleviated in five patients (62.5%) and unchanged in three (37.5%, including two patients

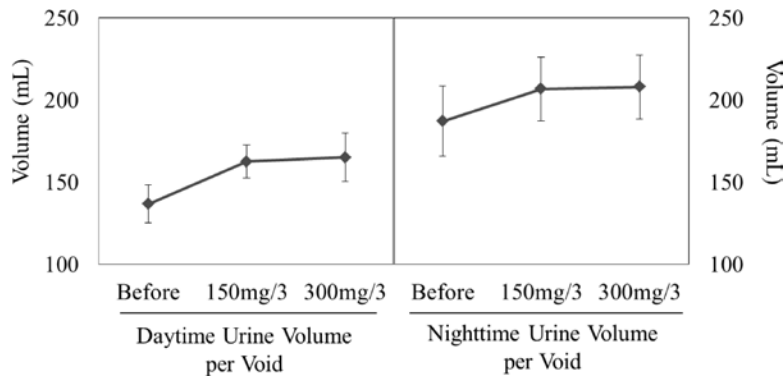


Figure 3 Daytime and nighttime void volume before and after amantadine administration.

Amantadine tended to increase both daytime and nighttime urine volume per void in patients with PD or VP.

without daytime urinary frequency). Nighttime urinary frequency was alleviated in three patients (37.5%) and unchanged in five (62.5%, including two patients without nighttime urinary frequency). Urinary urgency was alleviated in six patients (75.0%) and unchanged in two (25.0%, including one patient without urinary urgency). Urge incontinence was alleviated in five patients (62.5%) and unchanged in three (37.5%, including three patients without urge incontinence). Mean daytime urinary frequency was 6.90 (SE 0.33), mean nighttime urinary frequency 1.69 (SE 0.10), and mean urinary urgency per week 5.88 (SE 1.61); all were decreased significantly ($P=0.002, <0.001, 0.005$, respectively). Mean urge incontinence per month was 2.31 (SE 0.61), which tended to decrease, but this change was not significant. Hesitancy, slow stream, intermittency, strain, and feeling of incomplete emptying also were alleviated or unchanged. Mean hesitancy per week, slow stream per week, intermittency per week, strain per week, and feeling of incomplete emptying per week tended to decrease, but these changes were not significant.

NP after amantadine administration

One month after daily administration of 150 mg amantadine, mean urine volume per void ($N=19$) increased (over 10%) in 13 patients (68.4%) and was unchanged in six (31.6%). Mean daytime urine volume per void ($N=19$) increased (over 10%) in 14 patients (73.7%) and was unchanged in six (26.3%). Mean nighttime urine volume per void ($N=18$) increased

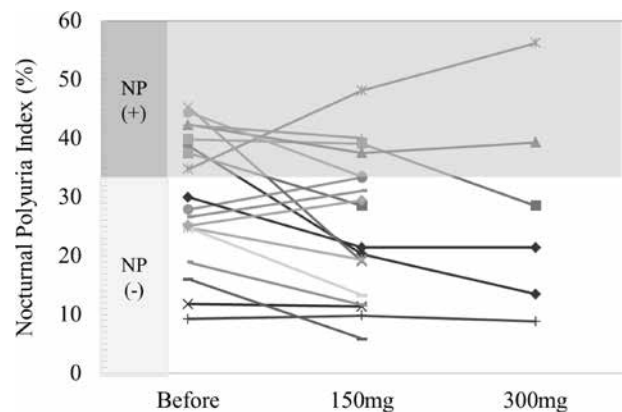


Figure 4 Nocturnal polyuria index (NPI) before and after amantadine administration.

Amantadine tended to decrease NPI and ameliorated NP (NPI >33%) in each patients with PD or VP.

(over 10%) in nine patients (50.0%), was unchanged in six (33.3%), and decreased in three (16.7%). Mean urine volume per void was 174.1 (SE, 11.3) mL, including mean daytime urine volume per void 162.6 (SE 10.1) mL and mean nighttime urine volume per void 206.8 (SE 19.5) mL, and tended to increase but not significantly (Figure 3). NP ($N=8$) was alleviated in six patients (75.0%), unchanged in one (12.5%), and aggravated in one (12.5%). Mean NPI was 25.1 (SE, 2.66) and tended to decrease but not significantly (Figure 4).

After daily administration of 300 mg amantadine, compared with before amantadine treatment, mean urine volume per void and mean daytime urine volume per void increased (over 10%) in five patients (83.3

%) and was unchanged in one (16.7%) (N=6). Mean nighttime urine volume per void increased (over 10%) in three patients (50.0%), was unchanged in two (33.3%), and decreased in one (16.7%) (N=6). Mean urine volume per void was 180.2 (SE, 15.0) mL, including mean daytime urine volume per void 165.3 (SE 14.9) mL and mean nighttime urine volume per void 208.1 (SE 19.5) mL, and tended to increase, but these changes were not significant (Figure 3). NP (N=4) was alleviated in two patients (50.0%) and unchanged in two (50.0%). Mean NPI was 28.0 (SE, 3.84) and tended to decrease, but this change was not significant (Figure 4)

RU after amantadine administration

One month after daily administration of 150 mg amantadine, RU volume was 6.84 (SE, 3.63) and tended to decrease but not significantly. One month after daily administration of 300 mg amantadine, RU volume was 15.0 (SE, 3.60) and tended to decrease, but this change was not significant.

Other symptoms after amantadine administration

After daily administration of 300 mg amantadine, one patient with mild cognitive dysfunction developed exacerbation of hallucination, and two patients developed flashing sensation.

DISCUSSION

Our study reports, for the first time, that amantadine ameliorates LUTS in patients with PD or VP, and, in detail, it ameliorates daytime urinary frequency, nighttime urinary frequency, and urinary urgency, as storage symptoms, and the feeling of incomplete emptying, as a voiding symptom. Amantadine also ameliorated NP in patients with PD or VP. In addition, these results show that there is a difference between LUTS in patients with PD and VP. Patients with VP present more commonly with daytime urinary frequency, as a storage symptom, and hesitancy, slow stream, straining, and feeling of incomplete emptying, as voiding symptoms.

There are a few reports that compare LUTS in patients with PD and VP. A recent systematic review⁹⁾ and some reports^{25,26)} show that patients with VP present more commonly with urinary incontinence than

patients with PD. Although our study evaluated a small group, there was a difference between LUTS in patients with PD and VP. In PD, it is well known that storage symptoms are common, resulting from central disinhibition of the micturition reflex and abnormal bladder sensation by a PD specific pathology, and that voiding symptoms are not common, although voiding disorder frequently exists in the background¹⁻⁷⁾. Our results are similar with the findings in the previous studies. On the other hand, details of LUTS in patients with VP and the pathophysiology are not well known. There is no report that evaluates the voiding symptoms, except indwelling catheter in patients with VP. In the central nervous system, there is a brain lesion associated with both storage function and voiding function²⁷⁾. It is thought that various LUTS occur according to the vascular lesion in patients with VP. In our study, daytime urinary frequency and many kinds of voiding symptoms are more common in patients with VP than in patients with PD. These findings suggest that patients with VP present more commonly with not only storage symptoms but also with voiding symptoms than patients with PD.

In our study, amantadine tended to increase both daytime and nighttime urine volume per void and significantly ameliorated daytime and nighttime urinary frequency and urinary urgency in patients with PD or VP. Amantadine also ameliorated feeling of incomplete emptying as a post-voiding symptom in those patients. Amantadine is reported have various effects such as activation of dopamine action, blockage of the glutaminergic (NMDA) receptor, activation of noradrenaline (NA) action, activation of serotonin (5HT) action, blockage of opioid receptors (particularly δ receptor), and blockage of cholinergic receptors¹⁶⁻²¹⁾. Single administration of a drug with dopamine action, such as levodopa or a dopamine agonist, is reported to accelerate micturition reflex short-term after the administration²⁸⁻³¹⁾. However, single administration of apomorphine elicited a dose- and time-dependent biphasic effect on bladder storage function³²⁾. It is also shown that chronic repeated administration of levodopa ameliorates storage disorder³³⁾. Thus, chronic repeated dopamine action by amantadine is associated with amelioration of storage and voiding disorders in patients with PD or VP. An NMDA receptor blocker inhibits spinal

neuronal response and spinal reflex responses to urinary bladder distension by blocking glutaminergic excitatory transmission in the central micturition reflex pathway^{34~36}. Thus, blockage of the NMDA receptor by amantadine is associated with amelioration of storage disorders in patients with PD or VP. NA and 5HT inhibits the micturition reflex mainly by activating descending inhibitory transmission in the central micturition reflex pathway^{34,35}. Thus, activation of NA and 5HT action by amantadine is associated with amelioration of storage disorders in patients with PD or VP. Opioids activate not only antinociceptive systems but also pronociceptive systems in the micturition reflex pathways and may modulate the micturition reflex^{34,35}. Thus, anti-opioid action by amantadine is associated with amelioration of storage and voiding disorders in patients with PD or VP. The central cholinergic system inhibits and/or activates micturition reflex^{34,35}. Thus, anti-cholinergic action by amantadine is associated with amelioration of storage and voiding disorders in patients with PD or VP.

Amantadine also tended to decrease NPI and ameliorated NP in patients with PD or VP. NP is reported in some neurological diseases such as VP and PD^{14,15}. However, the pathophysiology of NP in those neurological diseases is not evaluated fully. In previous reports, NP is associated with decreases in the daily changes of antidiuretic hormone (ADH) secretion^{14,15}. The secretion of the pituitary hormones is controlled by hypothalamic hormones, which are synthesized by neurosecreting cells whose activity is modulated by different neurotransmitters such as dopamine, NA, and 5-HT^{37,38}. Thus, it is thought that dopamine, NA, and 5-HT actions by amantadine modulate circadian ADH secretion and ameliorate NP in patients with VP and PD.

In conclusion, amantadine has beneficial effects on LUTS and NP in patients with PD and VP. Amantadine can become a useful alternative for LUTS and NP in patients with PD and VP, as well as for motor dysfunction.

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