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# Increased plasma arginine vasopressin levels in dopamine agonist-treated Parkinson's disease patients

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**Key words**: Parkinson's disease; dopamine agonist; pergolide; pramipexole; levodopa; vasopressin; hyponatremia; side effects

## Abstract

Several cases of syndrome of inappropriate antidiuresis induced by antiparkinson agents have been previously reported. However, the effect of antiparkinson agents on plasma arginine vasopressin (AVP) levels remains unknown in Parkinson's disease (PD) patients. The aim of the present study is to determine plasma AVP levels in PD patients and the effects of antiparkinson agents on these levels. PD patients who visited our clinic between November 2008 and September 2009 were included in this study. Patients were excluded if they had at least one condition that could be associated with high AVP levels. PD patients who had been treated with antiparkinson agents participated in this study (treated PD group, n=76). De novo PD patients were also included (n=25). Mean plasma AVP levels were significantly higher in treated PD patients than those in treatment-naïve patients. Neither disease severity nor L-dopa dosage correlated with plasma AVP levels. Multiple linear regression analysis identified the male gender and pergolide dosage as weak independent predictors of high plasma AVP levels. While no difference in plasma AVP levels between genders in treatment-naïve patients was observed, mean plasma AVP levels were significantly higher in male patients than in female patients administered antiparkinson agents. Mean plasma AVP levels in pergolide users were significantly higher than those in dopamine agonist nonusers with corresponding disease duration and L-dopa/carbidopa dosage. In some patients, plasma AVP levels appeared to be dependent on pramipexole dosage. Dopamine agonists may cause increased plasma AVP levels in some PD patients.

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## INTRODUCTION

Several cases of syndrome of inappropriate antidiuresis (SIAD) induced by antiparkinson agents have been previously reported including one reported by us (Arai & Iwabuchi, 2009). Although our patient was treated with several antiparkinson agents, increased plasma arginine vasopressin (AVP) levels and SIAD resolved only after the pramipexole dosage was reduced (Arai & Iwabuchi, 2009). Several lines of evidence suggest the involvement of dopamine receptors in regulation of AVP release. First, intracerebroventricular injections of dopamine have been shown to stimulate AVP secretion in rats (Forsling & Williams, 1984). Second, AVP-producing neurons in rat hypothalamic explants have been shown to get depolarized by activation of D2-like receptors by dopamine (Yang *et al.* 1991). Third, D4 receptors are highly expressed in the supraoptic nucleus. Fourth, AVP-producing neurons receive both inhibitory GABAergic and excitatory glutamatergic innervations. Dopamine inhibits GABAergic transmission on AVP-producing neurons by activating presynaptic D4 receptors on GABAergic terminals, resulting in the facilitation of AVP release (Azdad *et al.* 2003). Given that pramipexole has a moderate affinity for human D4 receptors with a selectivity up to 13-fold over D2L receptors, it was hypothesized that pramipexole is a cause of SIAD (Arai & Iwabuchi, 2009). However, a study on humans has suggested that dopamine suppresses AVP release (Lightman & Forsling, 1980).

Pathological studies on brains of patients with Parkinson's disease (PD) have shown that AVP-producing neurons in the hypothalamus are mostly intact (Purba *et al.* 1994); however, only few studies have analyzed plasma AVP levels in PD patients. Sundquist *et al.* (1983) reported that no difference exists in mean plasma AVP levels between PD patients and patients with other neurological diseases. There is disagreement, however, whether AVP secretion on the head-up tilt test is intact (Niimi *et al.* 1999) or impaired (Adhiyaman *et al.* 2008) in PD patients with orthostatic hypotension. The validity of these studies remains doubtful because of the small study populations. Furthermore, the relationship between antiparkinson agents and plasma AVP levels remains unknown. The aim of this study was to determine plasma AVP levels in PD patients and the effects of antiparkinson agents on these levels.

## METHODS

### Patients

Patients clinically diagnosed with PD who visited our clinic between November 2008 and September 2009 were included in this study. PD diagnosis was made according to the following criteria: presence of at least two of the four cardinal PD signs (akinesia, rest tremor, rigidity, and postural instability), absence of any findings on magnetic resonance imaging that indicated other causes of parkinsonism, and an efficacious response to L-dopa. Patients with at least one condition that could be associated with high AVP levels, including lung disease, heart failure, orthostatic hypotension, hyperosmolar hyperglycemia, nausea within a day before AVP determination, or previous ingestion of antidepressants were excluded from the study. PD patients treated with antiparkinson agents were allowed to participate in this study (treated PD group; n = 76). All patients were treated with standard release L-dopa/carbidopa (range 300/30–850/85 mg). Fifteen patients were taking entacapone (range 200–700 mg) and 8 were taking selegiline (range 2.5–5.0 mg). Pergolide (range 500–1000 μg) and pramipexole (range 0.5–3 mg) were administered in 5 and 22 patients, respectively. Echocardiography showed normal valvular function in all patients administered pergolide. Dosages of antiparkinson agents were maintained at the same levels for at least 1 month prior to AVP determination. Demographics and plasma AVP levels in pergolide and pramipexole users were compared with those of treated PD patients with corresponding disease duration and administered L-dopa/carbidopa but not dopamine agonists (dopamine agonist nonusers). PD patients with no prior antiparkinson treatment were also included in this study (*de novo* PD group; n = 25).

When treated PD patients administered pramipexole were found to have high AVP levels, the pramipexole dosage was reduced. On the other hand, when treated PD patients not administered dopamine agonists developed motor fluctuations during the study period, pramipexole was administered. Plasma AVP levels were determined in these patients before and 2 weeks after pramipexole dosages were changed.

All diagnostic and treatment procedures were carried out after obtaining informed consent from each patient. The study was approved by the Ethical Committee of Seirei Mikatahara General Hospital.

### AVP determination

Approximately 10 mL of venous blood was drawn from each patient in the sitting position while in the "on" state. Plasma AVP levels were determined using a radioimmunoassay (Mitsubishi Chemical Medience, Tokyo, Japan) at a commercial laboratory. Normal range of plasma AVP levels in the laboratory was 0.3–3.5 pg/mL when plasma osmolality was within a range of 270–295 mOsm/kg. Since no significant association of age with plasma AVP levels was observed (Duggan *et al.* 1993), this normal range was used as a reference in this study.

### Statistics

Statistical analyses were performed using software (StatView version 5.0, SAS Institute). Even if the dosage of the antiparkinson agents was changed during the study period, only the initial data were used for analyses unless otherwise specified. Data are shown as the mean ± standard deviation for continuous variables. The unpaired Student's *t*-test or Welch test was used for comparisons of means between the two groups. Differences between frequencies were assessed using the Fisher's exact test. Stepwise multiple regression analysis was performed to identify any independent predictors of plasma AVP levels. $F \geq 4.0$ was considered significant. Possible dependent variables that were tested included gender, age, disease duration, and L-dopa/carbidopa, selegiline, entacapone, pergolide, and pramipexole dosages. Spearman rank correlation analysis was used to assess the relationship between Hoehn-Yahr stage and plasma AVP levels. $p<0.05$ was considered statistically significant.

## RESULTS

### Characteristics of the study population

The treated PD group comprised 29 male and 47 female patients. One patient was evaluated at Hoehn-Yahr stage I, 4 at stage II, 58 at stage III, and 13 at stage IV. The *de novo* PD group comprised 10 male and 15 female patients. Six patients were evaluated at Hoehn-Yahr stage I, 10 at stage II, and 9 at stage III.

The mean age and disease duration in the treated PD group were more than those in the *de novo* PD group by 1.1 years and 4.5 years, respectively (Table 1). Because of orthostatic hypotension, 13 patients were not included in the treated PD group. The mean age of the excluded patients was 83.5 years. When the excluded patients were combined with the treated PD group, the mean age of

this combined group was 73.4 years, 2.8 years more than the mean age of the *de novo* PD group.

Serum sodium concentrations and plasma osmolality were normal in all patients.

**Plasma AVP levels in treated and de novo PD patients**

In the treated PD group, plasma AVP levels ranged from 0.8 to 30.2 pg/mL. Six patients had high plasma AVP levels (more than 10 pg/mL), however, chest and abdominal CT scans were negative for ectopic AVP-producing tumors. Thirty of 76 patients (39.5%) had plasma AVP levels more than 3.5 pg/mL. Mean plasma AVP levels were significantly higher in the treated PD patients than in the treatment-naïve patients (Table 1). The mean disease duration of the treated PD group was significantly longer than that of the *de novo* PD group (Table 1). However, simple regression analysis demonstrated that plasma AVP levels did not correlate with disease duration ($r$=0.05, $p$=0.964) or L-dopa/carbidopa dosage ($r$=0.160, $p$=0.169). Furthermore, Hoehn-Yahr stage and plasma AVP levels did not show a correlation (Spearman rho=0.174, $p$=0.133).

Multiple linear regression analysis revealed that male gender (standardized regression coefficient β=0.268, $p$=0.016) and pergolide dosage (β=0.261, $p$=0.019) were independently associated with plasma AVP levels (adjusted $R^2$=0.136). However, disease duration, age, and L-dopa/carbidopa dosage were not associated with plasma AVP levels.

There were no significant differences in the mean age, disease duration, and L-dopa/carbidopa dosages of the male and female patients of the treated group (Table 2). Mean plasma AVP levels, however, were significantly higher in the males of the treated group than those in the females (Table 2). In contrast, within the *de novo* PD group no significant difference was observed in mean plasma AVP levels between male and female patients (2.50 ± 1.07 vs 2.58 ± 1.52 pg/mL, respectively; $p$=0.887).

**Plasma AVP levels in PD patients administered pergolide**

Since the mean disease duration was 11.6 years among pergolide users, nonusers of dopamine agonists with disease duration of 7 years or more served as controls. Significant differences between pergolide users and controls in terms of the gender ratio, mean age, disease duration, or L-dopa/carbidopa dosage

**Tab. 1.** Statistical comparisons of demographics and plasma AVP levels between treated and untreated PD patients.

| Group | No. of patients | Gender M/F | Age (year) | Duration (year) | AVP levels (pg/mL) |
|---|---|---|---|---|---|
| Treated | 76 | 29/47 | 71.7±9.3 | 6.2±3.7 | 4.32±4.78 |
| Untreated | 25 | 10/15 | 70.6±8.5 | 1.7±0.9 | 2.55±1.33 |
| *p*-value | — | 0.999 | 0.607 | 0.001 | 0.005 |

**Tab. 2.** Statistical comparisons of demographics, L-dopa dosage, and plasma AVP levels between male and female patients in the treated PD group

| Gender | No. of patients | Age (year) | Duration (year) | L-dopa (mg) | AVP levels (pg/mL) |
|---|---|---|---|---|---|
| Male | 29 | 69.7±9.6 | 6.8±4.0 | 459±178 | 6.15±6.91 |
| Female | 47 | 73.0±8.9 | 5.9±3.6 | 413±153 | 3.19±2.16 |
| *p*-value | — | 0.136 | 0.341 | 0.238 | 0.032 |

**Tab. 3.** Statistical comparisons of demographics, L-dopa dosage, and plasma AVP levels between pergolide users and controls.

| Subgroup | No. of patients | Gender M/F | Age (years) | Duration (years) | L-dopa (mg) | AVP levels (pg/mL) |
|---|---|---|---|---|---|---|
| Pergolide | 5 | 3/2 | 68.8±6.8 | 11.6±2.9 | 600±187 | 8.56±7.87 |
| Control | 16 | 6/10 | 75.0±6.7 | 9.5±3.0 | 528±141 | 3.51±2.36 |
| *p*-value | — | 0.611 | 0.087 | 0.189 | 0.368 | 0.029 |

**Tab. 4.** Statistical comparisons of demographics, L-dopa dosage, and plasma AVP levels between pramipexole users and controls.

| Subgroup | No. of patients | Gender M/F | Age (years) | Duration (years) | L-dopa (mg) | AVP levels (pg/mL) |
|---|---|---|---|---|---|---|
| Pramipexole | 22 | 10/12 | 65.8±8.1 | 7.0±3.3 | 475±196 | 4.46±3.95 |
| Control | 23 | 8/15 | 74.8±8.3 | 7.6±2.3 | 476±151 | 3.27±2.25 |
| *p*-value | — | 0.550 | 0.001 | 0.444 | 0.983 | 0.215 |

were absent. Nevertheless, mean plasma AVP levels were significantly higher in pergolide users than those in the controls (Table 3).

## Plasma AVP levels in PD patients administered pramipexole

Since the mean disease duration was 7.0 years in the pramipexole users, dopamine agonist nonusers with disease duration of 5 years or more served

as controls. Significant differences between pramipexole users and controls in terms of gender ratio, mean disease duration, or L-dopa/carbidopa dosage were absent (Table 4). Mean plasma AVP levels in pramipexole users were higher than those in controls; however, the difference was not statistically significant (Table 4).

Pramipexole dosage was reduced in two patients because of high AVP levels. On the other hand, pramipexole was administered to four patients because of motor fluctuation development during the study period. In these six patients, plasma AVP levels appeared to be related to the pramipexole dosage (Figure 1). In one patient, mild hyponatremia developed with increased plasma AVP levels after the pramipexole dosage was increased from 1 mg to 2.5 mg (Figure 1, Case 5). Pramipexole dosage and plasma AVP levels appeared to be correlated (Spearman rho=0.488); however, the correlation was not statistically significant ($p$=0.106).

## DISCUSSION

The present study demonstrated that mean plasma AVP levels increased in the treated PD group but were within the normal range in the *de novo* PD group. A larger number of patients with progressive supranuclear palsy and multiple

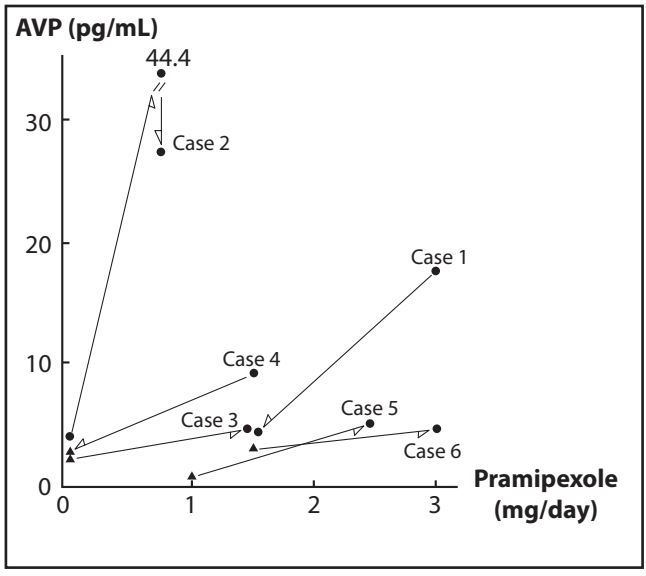


**Fig. 1.** The effect of pramipexole dosage on plasma AVP levels. The change in plasma AVP level is shown for individual patients. The arrow indicates the time course; circles indicate high plasma AVP levels and triangles indicate normal AVP levels. Plasma AVP levels appear to be dependent upon the pramipexole dosage in some patients.

system atrophy were probably included in the *de novo* PD group than that in the treated PD group. However, the extent to which the possible heterogeneity of the study population affected the findings of this study remains unknown since there is an almost complete lack of knowledge about plasma AVP levels in parkinsonism-plus disorders. The mean age of the treated PD patients was not significantly different from that of the *de novo* PD patients despite the treated PD patients having a longer averaged disease duration. This apparent discrepancy probably is attributed to the exclusion of a large number of PD patients with higher ages and orthostatic hypotension from the treated PD group. Differences in AVP levels could be related to the disease process itself and not the antiparkinson agents. However, this possibility is less likely since plasma AVP levels did not correlate with disease duration or disease severity.

Multiple regression analysis identified pergolide dosage and the male gender as weak independent predictors of high plasma AVP levels. However, low adjusted $R^2$ value indicates that these predictors leave a considerable amount of variability in the observed plasma AVP levels unexplained.

Increased plasma AVP levels in pergolide users are unlikely to be related to the disease process because plasma AVP levels were significantly higher in pergolide users than those in the controls with corresponding disease duration and L-dopa dosage.

Plasma AVP levels appear to be dependent on pramipexole dosage in some patients. Thus, pergolide and pramipexole facilitate AVP secretion in some PD patients. In contrast, plasma AVP levels did not correlate with L-dopa/carbidopa dosage in treated PD patients.

While no differences in plasma AVP levels between genders in the treatment-naïve patients were observed, mean plasma AVP levels were significantly higher in male than in female patients administered antiparkinson agents. Thus, there is a possibility that antiparkinson agent-induced AVP secretion is inhibited by estradiol (Swenson *et al.* 1998).

AVP-producing neurons in the supraoptic nucleus are stimulated to release AVP through dopamine D2-like receptors (Yang *et al.* 1991), alpha-1 adrenoreceptors (Willoughby *et al.* 1987), and serotonin 5-HT2A or 5-HT2C receptors (Jorgensen *et al.* 2003). Activation of D4 receptors facilitates AVP release (Azdad *et al.* 2003). Pergolide has a moderate affinity for D4 and alpha-1 receptors and a high affinity for 5-HT2A receptors while pramipexole has a

moderate affinity for D4 receptors (Millan *et al.* 2002). Activation of these receptors may stimulate AVP secretion in some PD patients.

In the present study, none of the treated PD patients developed hyponatremia despite the existence of increased plasma AVP levels on the initial examination. Some mechanisms probably attenuate actions of AVP to prevent water retention and hyponatremia when plasma AVP levels are inappropriately increased. First, when high plasma AVP levels are sustained for significant periods of time, the binding capacity of the V2 receptor is downregulated and AVP-induced antidiuresis is attenuated (Tian *et al.* 2000). Second, the action of AVP in the collecting duct is inhibited by activation of both D4 (Li & Schafer, 1998) and adrenergic alpha-2 receptors (Edwards & Brooks, 2001); pergolide and pramipexole have moderate affinity for both of these receptors (Millan *et al.* 2002). Third, the mean daily sodium intake of PD patients is almost the same as that of the age-matched controls, but the mean daily water intake of PD patients is only 57% of that of the controls (Ueki & Otsuka, 2004). Such a state of latent water depletion in PD patients could prevent the development of hyponatremia. If the abovementioned mechanisms fail to work for some reason, SIAD would develop. Therefore, patients administered antiparkinson agents should be monitored for serum sodium concentrations, especially in the first few weeks of therapy and during dosage increase.

Because a vast majority of treated PD patients were at Hoehn-Yahr stages III and IV, it was impossible to include untreated PD patients as controls whose disease severity and duration matched the treated PD patients. The small number of patients taking dopamine agonists is another limitation of this study. Furthermore, combined effects of antiparkinson agents were not adequately evaluated. Despite these limitations, the results of this study indicate that dopamine agonists may cause increased plasma AVP levels in some PD patients.

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