ORIGINAL ARTICLE

Levodopa in combination with carbidopa does not affect plasma arginine vasopressin levels in treatment-naïve older patients with Parkinson's disease: A before–after study

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Submitted: 2011-11-12 Accepted: 2012-01-11 Published online: 2012-03-10

Key words: **Parkinson's disease; levodopa; carbidopa; vasopressin; syndrome of inappropriate antidiuresis**

Neuroendocrinol Lett 2012; **33**(1):34–36 **PMID:** 22467109 NEL330112A02

Abstract

OBJECTIVE: Several cases of syndrome of inappropriate antidiuresis (SIAD) induced by antiparkinson agents have been reported. Our previous study demonstrated that in some patients with Parkinson's disease (PD), pergolide and pramipexole stimulate elevations of plasma arginine vasopressin (AVP) levels even at doses that are lower than the ordinary maintenance dose. Although mean plasma AVP levels are significantly higher in treated PD patients than in treatment-naïve patients, neither disease severity nor levodopa/carbidopa dosage (range, 300/30–850/85 mg) correlates with plasma AVP levels. However, the effects of levodopa/carbidopa monotherapy on plasma AVP levels in older patients remain unknown. To address this issue, a 14-day before–after study was conducted.

METHODS: Subjects in this study were consecutive treatment-naïve patients with a diagnosis of possible PD who visited our clinic from November 2008 to September 2009. Patients had no conditions that could be associated with high plasma AVP levels. Twenty-five patients were treated with levodopa/carbidopa (100/10 mg) 3 times a day. A paired t-test was used to compare plasma AVP levels before and 14 days after initiation of treatment.

RESULTS: Five patients dropped out of this study. In the remaining 20 patients (8 males and 12 females), no significant differences were observed between mean plasma AVP levels before and during treatment with levodopa/carbidopa.

CONCLUSION: Monotherapy with levodopa/carbidopa (300/30 mg/day) does not affect plasma AVP levels in older PD patients and seems less likely to cause SIAD.

Abbreviations:

AVP	- arginine vasopressin
GABAergic	- gamma-aminobutyric acid-mediated
PD	- Parkinson's disease
SIAD	- syndrome of inappropriate antidiuresis

INTRODUCTION

Several cases of syndrome of inappropriate antidiuresis (SIAD) induced by antiparkinson agents have been reported, including one reported by us (Arai & Iwabuchi 2009). There are 3 possible mechanisms by which antiparkinson agents cause SIAD: the agents can stimulate arginine vasopressin (AVP) secretion, reset the osmostat, thereby lowering the threshold for AVP secretion, and enhance AVP activity in the kidney. Plasma AVP levels were determined only in 3 reported cases and were found to be elevated (Arai & Iwabuchi 2009; Tomita *et al.* 2005; van Laar *et al.* 1998). Thus, increased AVP secretion, independent of plasma osmolality, accounts for antiparkinson agent-induced SIAD, although other possibilities cannot be excluded.

Several lines of evidence from animal studies suggest that dopamine stimulates AVP release from AVP-producing neurons in the supraoptic nucleus (Forsling & Williams 1984) by activating dopamine D2-like receptors (Yang *et al.* 1991). Dopamine inhibits gamma-aminobutyric acid-mediated (GABAergic) transmission on AVP-producing neurons by activating presynaptic D4 receptors, a class of D2-like receptors, on GABAergic terminals, resulting in AVP release (Azdad *et al.* 2003). AVP release is also stimulated through activation of alpha-1 adrenoreceptors (Willoughby *et al.* 1987) and serotonin 5-HT2A, 5-HT2C, or 5-HT3 receptors (Jørgensen *et al.* 2003). Our patient was treated with several antiparkinson agents, leading to increased plasma AVP levels. SIAD was resolved only after pramipexole dosage was reduced, suggesting that pramipexole was the offending agent (Arai & Iwabuchi 2009). Our previous study demonstrated that mean plasma AVP levels are significantly higher in treated patients with Parkinson's disease (PD) than in treatment-naïve patients. Furthermore, we showed that pergolide (range, 500–1000 μg/day) and pramipexole (range, 0.5–3 mg/day) stimulate elevations in plasma AVP levels in some PD patients (Arai 2011). Pramipexole has high selectivity for D4 receptors with an hD4/hD2L pKi ratio of 13, and is likely to increase AVP secretion (Arai & Iwabuchi 2009).

Levodopa is the most effective drug for relieving the motor signs and symptoms of PD. Clinical data suggest that levodopa does not hasten, but may slow down disease progression (Fahn *et al.* 2004). Moreover, because of its lower propensity for causing hallucinations, confusion, and drowsiness, levodopa is preferred over dopamine agonists in older PD patients. When levodopa 175 mg is injected intravenously, dopamine converted from levodopa in the blood suppresses AVP release at the posterior pituitary level in young healthy individuals (Lightman & Forsling 1980). Our previous study showed that plasma AVP levels do not correlate with levodopa/carbidopa dosage (range, 300/30–850/85 mg/day) in PD patients treated with more than one antiparkinson agent (Arai 2011). However, the effects of levodopa/carbidopa monotherapy on plasma AVP levels in older PD patients remain to be elucidated. To address this issue, we compared plasma AVP levels before and 14 days after initiation of treatment with levodopa/carbidopa (300/30 mg/day) in PD patients who had no prior exposure to levodopa or a dopamine agonist.

METHODS

Patients

Among consecutive treatment-naïve patients who visited our clinic with resting tremors or bradykinesia from November 2008 to September 2009, 25 patients fulfilled the diagnostic criteria for possible PD (Gelb *et al.* 1999) and were included in this study. All patients were treated with standard release levodopa/carbidopa (100/10 mg) 3 times a day.

All diagnostic and treatment procedures were conducted after obtaining informed consent from each patient. This 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 on the morning before treatment, and 2 to 3 hours after ingestion of levodopa/carbidopa 14 days after treatment initiation. Plasma AVP levels were determined by radioimmunoassays (Mitsubishi Chemical Medience, Tokyo, Japan) in a commercial laboratory. The 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 is observed (Duggan *et al.* 1993), this normal range was used as a reference in this study.

Statistical analyses

Statistical analyses were performed using a software (StatView version 5.0, SAS Institute). Data are represented as the mean ± standard deviation for continuous variables. Changes in plasma AVP levels, serum sodium concentrations, and plasma osmolality after treatment with levodopa/carbidopa were assessed using a paired *t*-test. An unpaired Student's *t*-test was used to compare mean AVP levels between male and female patients. $p<0.05$ was considered statistically significant.

RESULTS

Ten male and 15 female treatment-naïve patients were diagnosed with possible PD (Gelb *et al.* 1999). Six patients were evaluated to be at Hoehn-Yahr stage I, 10 at stage II, and 9 at stage III. Their mean age and disease duration were 70.6 ± 8.5 years and 1.7 ± 0.9 years, respectively. None of the 25 patients had previously ingested antidepressants or had conditions that could

Tab. 1. Effects of levodopa/carbidopa on plasma AVP levels, serum sodium concentrations, and plasma osmolality.

	Before Tx	During Tx	*p*-value
AVP (pg/mL)	2.35 ± 1.37	2.46 ± 1.44	0.627
Na (mEq/L)	139.7 ± 4.1	139.8 ± 3.1	0.870
Posm (mOsm/kg)	286.0 ± 4.7	288.0 ± 3.5	0.345

Tx: treatment with levodopa/carbidopa 100/10 mg 3 times a day
AVP, plasma arginine vasopressin level; Na, serum sodium concentration; Posm, plasma osmolality.

be associated with high plasma AVP levels, including lung disease, heart failure, orthostatic hypotension, hyperosmolar hyperglycemia, or nausea within a day of plasma AVP determination.

These 25 patients were treated with standard release levodopa/carbidopa (100/10 mg) 3 times a day. Five patients dropped out of the study because of nausea or self-judged insufficient efficacy. The remaining 20 patients (8 males and 12 females) showed improved akinesia with this treatment and were analyzed. The mean age and disease duration were 71.7 ± 7.4 years and 1.8 ± 0.9 years, respectively. Three patients were evaluated to be at Hoehn-Yahr stage I, 9 at stage II, and 8 at stage III. No significant differences were observed between mean plasma AVP levels, serum sodium concentrations, and plasma osmolality before and during treatment (Table 1). In addition, no significant differences were observed in mean plasma AVP levels between male and female patients during treatment (2.85 ± 1.71 vs. 2.19 ± 1.24 pg/mL, respectively; p=0.330).

Of the 20 patients analyzed, 4 were lost to follow-up. The remaining 16 patients received regular treatment with levodopa/carbidopa for more than 2 years and fulfilled the diagnostic criteria for probable PD (Gelb *et al.* 1999).

DISCUSSION

The present study demonstrated that monotherapy with levodopa/carbidopa (300/30 mg/day) had no effect on plasma AVP levels in previously untreated older PD patients. Although our previous study demonstrated significantly higher mean plasma AVP levels in male patients than in female patients who were administered antiparkinson agents (Arai 2011), no gender differences were observed in this study.

There are 3 major limitations to the present study. First, eligibility was restricted to treatment-naïve patients with shorter disease durations, which presents a diagnostic challenge given that the accuracy of diagnosis improves with time and repeated assessments. Of the 20 patients who were analyzed in this study, 16 were followed up for more than 2 years and fulfilled the diagnostic criteria for probable PD (Gelb *et al.* 1999). However, it is possible that the study population analyzed in the present study contained atypical parkinsonism cases. Second, the study timeframe of 14 days may have been insufficient. However, in most reported cases of SIAD induced by antiparkinson agents, hyponatremia developed within 14 days after initiation or dose escalation of the offending agent. Moreover, our previous study showed that plasma AVP levels changed 14 days after pramipexole dosages were changed in PD patients (Arai 2011). Thus, we believe that the study timeframe of 14 days was long enough. However, the potential long-term effects of levodopa on plasma AVP levels remain uncertain. Third, there is a possibility that higher doses of levodopa stimulate AVP secretion. Plasma AVP levels are elevated in some PD patients receiving pergolide or pramipexole even at doses lower than the ordinary maintenance dose (Arai 2011). On the other hand, monotherapy with levodopa/carbidopa (300/30 mg/day) seems suitable as an initial treatment for PD because it relieves motor symptoms with low frequency of unwanted effects (Fahn *et al.* 2004). Treatment with levodopa/carbidopa at this dosage is less likely to stimulate AVP secretion.

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