

Ropinirole does not affect plasma arginine vasopressin levels in patients with advanced Parkinson's disease

Motomi ARAI

Department of Neurology, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka, Japan

Correspondence to: Motomi Arai, MD., PhD.
Department of Neurology, Seirei Mikatahara General Hospital,
3453 Mikatahara-cho, Hamamatsu, Shizuoka 433-8558, Japan.
TEL: +81-53-4361251; FAX: +81-53-4380652; E-MAIL: arai-m@sis.seirei.or.jp

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Abstract

OBJECTIVES: Several cases of syndrome of inappropriate antidiuresis induced by anti-Parkinson agents have been reported. Our previous study demonstrated that pergolide and pramipexole stimulated elevation of plasma arginine vasopressin (AVP) levels in some patients with Parkinson's disease (PD), but that levodopa/carbidopa (300/30 mg/day) did not affect plasma AVP levels in treatment-naïve PD patients. On the basis of the binding profile of ropinirole to monoamine receptors, we hypothesized that ropinirole does not stimulate AVP secretion. The aim of this study was to test this hypothesis.

METHODS: Inclusion criteria were patients with probable PD suffering from a wearing-off phenomenon and who had been treated using levodopa/carbidopa with or without entacapone, but not with other classes of anti-Parkinson agents. Patients were excluded if they had at least one condition that could be associated with high AVP levels. Ropinirole was initiated at 0.5 mg 3 times daily, and daily dosages were increased by 1.5 mg/day on a biweekly basis up to 6 mg/day. Plasma AVP levels were determined every two weeks. Effects of escalating ropinirole dosage on plasma AVP levels were evaluated using a one-way analysis of variance for repeated measures, an a priori Dunnett multiple comparison test, and a regression analysis.

RESULTS: Of 16 patients enrolled, 11 patients (four males and seven females) completed the study. There was no statistically significant dose-response relationship between the ropinirole dosage and plasma AVP levels.

CONCLUSION: A minimal therapeutic dosage of ropinirole did not affect plasma AVP levels in patients with PD taking levodopa.

Abbreviations:

ANOVA - analysis of variance
AVP - arginine vasopressin
CI - confidence interval
LED - levodopa equivalent dose
PD - Parkinson's disease

INTRODUCTION

Non-ergot dopamine agonists are commonly used as an add-on therapy to levodopa to treat motor complications in patients with advanced Parkinson's disease (PD); however, it can also produce undesirable side effects. Several cases of syndrome of inappropriate antidiuresis induced by anti-Parkinson agents have been reported, including one reported by us (Arai & Iwabuchi 2009; Tomita *et al.* 2005). Increased arginine vasopressin (AVP) secretion, independent of plasma osmolality, presents a possible mechanism (Arai 2012). Our previous study demonstrated that pergolide and pramipexole stimulate elevations of plasma AVP levels in some patients with PD (Arai 2011). In contrast, monotherapy with levodopa/carbidopa (300/30 mg/day) does not affect plasma AVP levels in treatment-naïve patients with PD (Arai 2012).

Animal studies suggest that AVP-producing neurons are stimulated to release AVP through dopamine D4 receptors (Azdad *et al.* 2003), alpha-1 adrenoreceptors (Willoughby *et al.* 1987), and serotonin 5-HT_{2A} or 5-HT_{2C} receptors (Jørgensen *et al.* 2003). Pergolide and pramipexole have an affinity for some of these receptors, whereas ropinirole has no affinity for alpha-1, 5-HT_{2A}, and 5-HT_{2C} receptors (Millan *et al.* 2002). Moreover, ropinirole has an hD4/hD2 selectivity comparable to that of dopamine (Coldwell *et al.* 1999). Thus, we hypothesized that ropinirole does not stimulate AVP secretion. To test this hypothesis we investigated the relationship between ropinirole dosage and plasma AVP levels in patients with PD.

METHODS

Participants and study protocols

The current study was conducted between March 2010 and March 2012. Inclusion criteria were as follows: (1) patients who fulfilled the diagnostic criteria for probable PD (Gelb *et al.* 1999), (2) those who had been treated using levodopa/carbidopa with or without entacapone, (3) those who had not been treated with other classes of anti-Parkinson drugs or surgery for PD, and (4) those suffering from a wearing-off phenomenon. Patients were excluded if they had at least one condition that could be associated with high AVP levels, namely, previous ingestion of antidepressants, lung disease, heart failure, orthostatic hypotension, plasma hyperosmolality, or nausea within a day before AVP determination.

The initial ropinirole dose was 0.5 mg 3 times/day after meals (1.5 mg/day), which was increased by 1.5 mg/day on a biweekly basis up to 6 mg/day. When adverse effects occurred, ropinirole dosage was decreased or discontinued on the basis of the patient's decision. After the study period, titration was flexible. Plasma AVP levels were determined before and every two weeks after ropinirole initiation. Levodopa/carbidopa and entacapone dosage was maintained during

the study period. A total daily levodopa equivalent dose (LED) was calculated according to Thomlinson (Tomlinson *et al.* 2010).

Each patient provided written informed consent before enrollment in the study. The study protocol was approved by the Ethical Committee of Seirei Mikatahara General Hospital and was conducted in accordance with the Declaration of Helsinki.

AVP determination

Approximately 10 mL of venous blood was drawn in the morning from each patient in a sitting position while in the "on" state. Plasma AVP levels were determined by radioimmunoassay (Mitsubishi Chemical Medience Corporation, 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.

Statistics

Statistical analyses were performed using JMP software (version 9.0.3, SAS Institute Inc., Cary, NC, USA). Results are expressed as the mean \pm standard deviation for continuous variables unless otherwise stated. Some statistical parameters are reported with 95% confidence intervals (95% CIs). Changes in plasma AVP levels during ropinirole dosage escalation were evaluated by one-way analysis of variance (ANOVA) for repeated measurements and an *a priori* Dunnett multiple comparison test. The relationship between ropinirole dosage and plasma AVP levels was assessed by regression analysis. A *p*-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the participants

A total of 16 patients, five males and 11 females, were initially enrolled. At the study entry, the mean patient age and disease duration were 62.3 \pm 7.5 years and 4.9 \pm 2.8 years, respectively. Two patients were evaluated to be at Hoehn–Yahr stage II and 14 at stage III. A "delayed-on" phenomenon was observed in two patients and peak-dose dyskinesia in three. No patient suffered from a "no-on" or "on-off" phenomenon. All patients were treated using levodopa (447 \pm 96 mg, range: 300–700 mg) in combination with carbidopa, and five patients were taking entacapone (range: 400–500 mg). Mean total LED was 492 \pm 118 mg (range: 300–700 mg).

One patient with a plasma AVP level of 8.4 pg/mL at baseline and multiple subpleural nodules demonstrated on chest CT scans, was excluded from the study. One patient was satisfied with the improvement using 3 mg of ropinirole and refused further dose escalation. Three patients discontinued ropinirole due to adverse effects: nausea in two patients and daytime sleepiness in one.

The remaining 11 patients, four males and seven females, completed the study. The mean age and disease

duration were 62.5 ± 7.7 years and 6.1 ± 2.1 years, respectively. One patient was evaluated to be at Hoehn-Yahr stage II and 10 at stage III. A “delayed-on” phenomenon was observed in two patients and peak-dose dyskinesia in three. All patients were treated using levodopa (464 ± 112 mg, range: 300–700 mg), and four patients were prescribed entacapone (range: 400–500 mg). Mean total LED was 518 ± 132 mg (range: 300–700 mg). Under treatment with 6 mg of ropinirole, nine patients were satisfied with improvement of the wearing-off phenomenon, and no patient suffered from worsening or appearance of dyskinesia. Serum sodium concentrations and plasma osmolality were unremarkable during the study period in all patients.

Ropinirole dosage and plasma AVP levels

Repeated measures ANOVA showed no significant changes in plasma AVP levels at different ropinirole dosages ($p=0.844$). The Dunnett test demonstrated no significant differences in the mean plasma AVP levels at each ropinirole dosage compared with the baseline value (Table 1). Regression analysis showed no correlation between ropinirole dosage and plasma AVP levels ($r=0.045$ [95% CI: -0.223 to 0.306], $p=0.747$).

DISCUSSION

The present study found no statistically significant dose–response relationship between ropinirole dosage and plasma AVP levels.

The small number of the participants was a limitation of this study. Because the manufacturer terminated production of the AVP determination kit in February 2012, we were unable to enroll more patients in the study. To increase the power of analysis with fewer subjects, the repeated measurement ANOVA was employed to reduce the error term. Moreover, the Dunnett test was used because it is designed to compare means of each treatment group with the mean of the control group and has better power than other multiple comparison tests.

In more than two-thirds of Japanese patients with advanced PD, 6–15 mg of ropinirole is needed to improve motor function and daily activities when used as an adjunct to levodopa (Mizuno *et al.* 2007). The mean daily dosage of levodopa in our preparatory investigation (Arai 2011) was larger than that reported by Mizuno *et al.* (2007) by approximately 140 mg, which was equivalent to 7 mg of ropinirole (Tomlinson *et al.* 2010). Thus, we generated the study protocol consisting of plasma AVP determinations with up to 6 mg/day of ropinirole. The mean daily dosage of levodopa in the present study was close to that observed in the preparatory investigation. In the present study, treatment with 6 mg of ropinirole ameliorated the wearing-off phenomenon in nine out of 11 patients, but did not affect plasma AVP levels. Although there is a possibility that higher dosages of ropinirole may stimulate AVP secre-

Tab. 1. Plasma arginine vasopressin (AVP) levels at different ropinirole dosages.

Ropinirole (mg/day)	Plasma AVP levels ^a (pg/mL)	p-value ^b
0	2.80 ± 1.48 (1.80–3.80)	–
1.5	2.98 ± 2.07 (1.58–4.37)	0.999
3.0	3.25 ± 2.44 (1.61–4.89)	0.954
4.5	2.78 ± 2.08 (1.38–4.17)	1.000
6.0	3.20 ± 1.72 (2.04–4.36)	0.971

^a Mean \pm standard deviation with 95% confidence intervals in parentheses.

^b Dunnett multiple comparison test using the baseline levels as a control.

tion, a minimal therapeutic dosage of ropinirole did not affect plasma AVP levels, which contrasts sharply with the observation that pramipexole caused elevation of plasma AVP levels in some patients with PD even at dosages that were lower than the ordinary maintenance dosage (Arai 2011; Tomita *et al.* 2005).

Despite these limitations, the results of this study suggested that treatment using a minimal therapeutic dosage of ropinirole was less likely to stimulate AVP secretion in patients with PD, who had been treated using levodopa.

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