Nicergoline Improves Dysphagia by Upregulating Substance P in the Elderly

Taku Nakashima, MD, PhD, Noboru Hattori, MD, Mafumi Okimoto, MD, Jitsuro Yanagida, MD, and Nobuoki Kohno, MD

Abstract: Dysphagia induces silent aspiration, which is a known risk factor for aspiration pneumonia in the elderly. Dysphagia is associated with impaired substance P secretion. Because nicergoline was recently reported to enhance substance P secretion, it may improve dysphagia by upregulating substance P; however, roles for nicergoline in this process have not been demonstrated. We therefore compared the effects of nicergoline on serum substance P and dysphagia with the effects of imidapril, an angiotensin-converting enzyme (ACE) inhibitor whose efficacy in improving dysphagia and preventing pneumonia has been previously demonstrated.

We randomly assigned 60 elderly patients with both dysphagia and a previous history of pneumonia to receive either imidapril (5 mg/d; n = 30) or nicergoline (15 mg/d; n = 30) for 6 months. Primary outcomes were the effects of these drugs on the substance P level and dysphagia 4 weeks after the start of treatment. Secondary outcome was the effect of these drugs on pneumonia recurrence during the 6 months of treatment.

Significant elevations of serum substance P were obtained by both medications after 4 weeks of treatment. Patients whose dysphagia was improved showed significantly increased serum levels of substance P. There was no statistically significant difference in the overall proportion of patients who showed improvements in dysphagia and pneumonia recurrence with imidapril or nicergoline treatment. Nicergoline, but not imidapril, seemed to be more effective at improving dysphagia and elevating serum substance P in patients with dementia.

In conclusion, nicergoline has a comparable effect to ACE inhibitors for improving dysphagia. Nicergoline might be a novel regimen for the treatment of dysphagia in the elderly who are not treatable with ACE inhibitors.

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Abbreviations: ACE = angiotensin-converting enzyme, CT = computerized tomography, SP = substance P, SPT = swallowing provocation test.

INTRODUCTION

Despite recent medical advances, pneumonia is still a major cause of death worldwide.[7,18] Pneumonia is one of the most common health problems, particularly in the elderly, and is ranked as the fourth leading cause of death in Japan.[5] The major risk factor predisposing elderly individuals to pneumonia is silent aspiration of oropharyngeal contents that are colonized by pathogenic microorganisms.[6] Aspiration itself is strongly associated with impaired swallowing and coughing reflexes during senescence.[6,8,9,12,22] Therefore, most cases of pneumonia in the elderly are categorized as aspiration pneumonia.[17]

Multiple strategies have been proposed to prevent aspiration pneumonia, including improvement of oral hygiene, swallowing training, and dietary changes. In addition, pharmacologic interventions to prevent aspiration pneumonia have been attempted. Among these interventions, angiotensin-converting enzyme (ACE) inhibitors have been evaluated in a few clinical studies to determine their effects on preventing pneumonia, particularly aspiration pneumonia.[3,4,7,22] In addition to their basic function in blocking the conversion of angiotensin I to angiotensin II, ACE inhibitors reduce substance P (SP) degradation. Because SP is a neurotransmitter that promotes swallowing reflex in animal models, and decreased SP secretion is associated with depressed swallowing reflex in humans, ACE inhibitors upregulate the impaired reflex. Consistent with this suggested mechanism, ACE inhibitors, but not angiotensin-receptor blockers, improve the swallowing reflex by increasing serum SP levels in patients with symptomless dysphagia.[2] In fact, Sekizawa et al[13] reported that ACE inhibitors reduced the risk of pneumonia by one-third compared with other drugs used for treating hypertension and stroke. However, another study[14] reported no significant difference in the incidence of pneumonia in hypertensive elderly patients treated with ACE inhibitors or calcium channel blockers. More recent studies have indicated that ACE inhibitors are effective in preventing pneumonia among Asian populations[11] but not in populations worldwide.[19] Thus, ACE inhibitors may be effective for preventing aspiration pneumonia in Asian populations, particularly in individuals with hypertensive stroke.[16]

Nicergoline, an ergot alkaloid derivative, has a broad spectrum of action; it induces vasodilation and increases arterial blood flow, enhances cholinergic and dopaminergic neurotransmission in the brain, and inhibits platelet aggregation.[21] Due to these pleiotropic effects, nicergoline is widely used throughout the world in patients suffering from cerebrovascular and balance disorders. Because nicergoline enhances the function of dopaminergic neurotransmitters in the brain, thereby inducing the secretion of SP,[10] it may also enhance swallowing reflex. Based on this notion, we hypothesized that nicergoline may be effective at improving dysphagia by upregulating SP. To test this hypothesis, we conducted the current study. In addition, we compared the effects of nicergoline with those of imidapril, a known ACE inhibitor that effectively prevents pneumonia in Asian populations.

METHODS

Patients

Between January 2009 and February 2009, we screened all patients aged 65 years or older who visited the outpatient setting of

From Department of Respiratory Medicine (TN, MO, JY), Hiroshima General Hospital of West Japan Railway Company, Hiroshima; Department of Molecular and Internal Medicine (NH, NK), Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan.
Dr. Nakashima's current address: Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan.
The authors have no funding or conflicts of interest to disclose.
Reprints: Taku Nakashima, MD, PhD, Department of Pathology, University of Michigan Medical School, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200 (e-mail: tnaka@eos.ocn.ne.jp).
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Hiroshima General Hospital of the West Japan Railway Company. After obtaining written informed consent from each patient or his or her family, we assessed 72 patients who had previous history of pneumonia within the last 2 years for enrollment eligibility. Patients who presented obvious malignancy (n = 2), had a previous history of laryngopharyngeal surgery (n = 1), or were already taking ACE inhibitors and/or nicergoline (n = 1) were excluded from the study. In the remaining 68 patients, the presence of dysphagia was examined in the outpatient setting by a simple 2-step swallowing provocation test (SPT), as described below. Eight patients (8 of 68, 11.8%) who showed normal swallowing function were excluded. Clinical characteristics of the eligible patients, including age, sex, medical treatment history, coexisting illnesses, and daily living activities, were recorded at the time of enrollment. Coexisting illnesses included the following: diabetes mellitus, with an HbA1c value of 6.5% or higher and/or using hypoglycemic drugs; hypertension, with a systolic blood pressure of 160 mmHg or higher, a diastolic blood pressure of 95 mmHg or higher, and/or using antihypertensive drugs; and hyperlipidemia, with a total cholesterol level of 240 mg/dL or higher and/or using lipid-lowering drugs. A brain computerized tomography (CT) scan was performed on all patients, and the results were evaluated by an expert radiologist who was blinded with respect to the medications that the patients were taking.

Study Design

This study was designed as a randomized, open-label, active-controlled, parallel-group prospective pilot study. This study was approved by the Institutional Review Board of Hiroshima General Hospital of the West Japan Railway Company and registered with the UMIN Clinical Trials Registry (number UMIN000001216) before enrollment of the first patient. Following enrollment, patients who participated in the study were randomly assigned to receive either the ACE inhibitor imidapril (5 mg/d; n = 30), or nicergoline (15 mg/d; n = 30) for 6 months. The patients were assigned to each treatment group using computer-generated permuted block randomization. Sealed envelopes containing the prescription for the appropriate medication were delivered to and opened by an independent pharmacist after informed consent was obtained from each patient. Researchers were completely blind with respect to the group assignments before the envelopes were opened. The 2-step SPT was repeated 4 weeks after the start of treatment. In addition, serum samples were obtained before administration of the drugs and again 4 weeks after the start of treatment. All patients were evaluated for 6 months after the start of treatment. During the 6 months of the treatment period, the patients were contacted monthly by medical staff or when the patients presented any symptoms. Pneumonia was diagnosed based on the Japanese Respiratory Society guidelines.[20] The primary outcomes of the study were the effect of the treatment on the serum levels of SP and dysphagia 4 weeks after the start of treatment; the secondary outcome was the pneumonia recurrence during the 6 months of the treatment period.

Evaluation of Swallowing Function

The severity of underlying dysphagia was evaluated by a simple 2-step SPT as described by Teramoto et al.[15] As a first-step SPT, the swallowing reflex was observed after injection of 0.4 mL of distilled water using a 5 Fr nasal catheter (Atom Medical Co., Tokyo, Japan) placed at the lowermost margin of the nasopharynx (behind the palatine uvula). The amount of time elapsed from water injection to the beginning of the swallowing reflex was measured by 2 independent observers who were blinded with respect to the medications that the patients were taking. The SPT was considered abnormal when the time elapsed between water injection and swallowing was greater than 3 seconds. Following evaluation of the first-step, the swallowing reflex was observed again after injection of 2.0 mL of distilled water (second-step). Based on the results of the 2-step SPTs, patients were categorized into 3 groups: 1) normal swallowing function: patients who showed normal results in the SPTs upon injection of both 0.4 mL and 2.0 mL of water; 2) moderate swallowing dysfunction: patients who showed abnormal results in the first-step SPT with the injection of 0.4 mL of water but showed normal results in the second-step SPT with injection of 2.0 mL of water; 3) severe swallowing dysfunction: patients who showed abnormal results in the SPTs upon injection of both 0.4 mL and 2.0 mL of water. Showing improvement in swallowing reflex upon injection of either 0.4 mL (first-step) or 2.0 mL (second-step) of distilled water after treatment was considered to be an "improvement in dysphagia."

Measurement of Serum SP Levels

Serum samples were centrifuged and stored at −30°C until they were processed for the analysis of SP levels using a commercial kit (R & D Systems, Minneapolis, MN), according to the manufacturer's protocols.

Statistical Analysis

Results are reported as median values and interquartile ranges. Groups were compared using the Mann-Whitney U test

TABLE 1. Baseline Characteristics of Study Participants

Characteristic	Imidapril No. (%) (n = 30)	Nicergoline No. (%) (n = 30)	P
Age, yr, median (IQR)	80.0 (77.0–84.3)	79.0 (75.5–83.0)	0.66
Female sex	7 (23.3)	7 (23.3)	1.00
Coexisting illness			
Diabetes mellitus	16 (53.3)	10 (33.3)	0.19
Hypertension	20 (66.7)	21 (70.0)	1.00
Hyperlipidemia	11 (36.7)	11 (36.7)	1.00
Dementia	11 (36.7)	12 (40.0)	1.00
Parkinson disease	4 (13.3)	3 (10.0)	1.00
Bedridden	15 (50.0)	16 (53.3)	1.00
PEG	2 (6.7)	6 (20.0)	0.25
Smoking			
Current smoker	3 (10.0)	3 (10.0)	1.00
Ex-smoker	21 (70.0)	18 (60.0)	0.59
Medical treatment			
Statin	5 (16.7)	3 (10.0)	0.71
Angiotensin-receptor blocker	3 (10.0)	3 (10.0)	1.00
Calcium channel blocker	14 (46.7)	12 (40.0)	0.80
Levodopa and amantadine	2 (6.7)	3 (10.0)	1.00
Brain CT findings			
Lacunar infarction	22 (73.3)	20 (66.7)	0.78
Brain atrophy	19 (63.3)	24 (80.0)	0.25
Post-stroke	5 (16.7)	6 (20.0)	1.00

Abbreviations: IQR = interquartile ranges, PEG = patients who had percutaneous endoscopic gastrostomy.

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	Imidapril (n=30)		Nicergoline (n=30)	
	Before	After	Before	After
Normal swallowing function – no.	0	8	0	12
Moderate swallowing dysfunction – no.	15	15	12	11
Severe swallowing dysfunction – no.	15	7	18	7
Patients who showed improvement in swallowing reflex – no. (%)	15 (50.0)		19 (63.3)	

FIGURE 1. The effects of imidapril and nicergoline on dysphagia. According to a 2-step swallowing provocation test to measure swallowing function, patients were categorized into 1 of 3 levels of swallowing function (described in the Methods section).

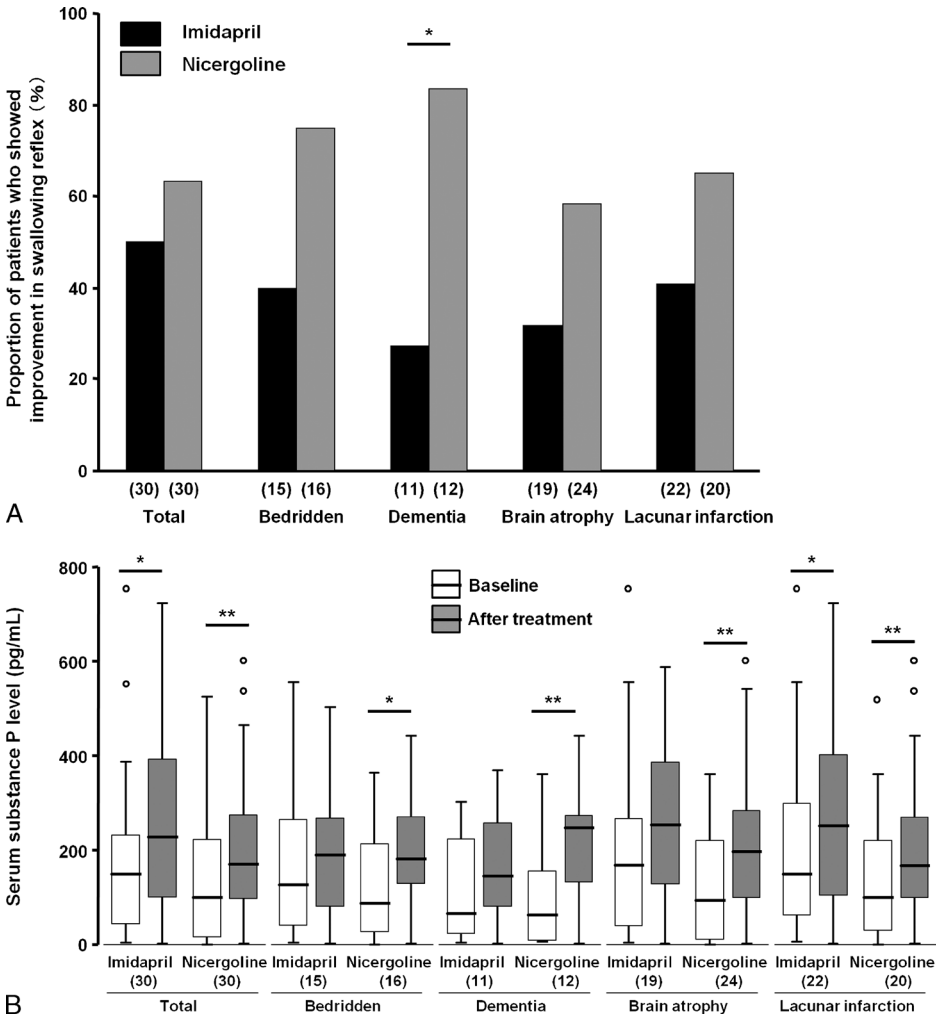

FIGURE 2. The effects of imidapril or nicergoline on dysphagia and serum substance P levels. A. The proportion of patients who showed improvement in dysphagia after 4 weeks of treatment. Dysphagia was evaluated using a simple 2-step swallowing provocation test. Values in parentheses indicate the numbers of patients belonging to each group. *$p < 0.05$, **$p < 0.01$ between treatment with imidapril or nicergoline. B. Serum substance P levels at baseline and after treatment with imidapril or nicergoline. Box-whisker plots show 25th and 75th percentiles (boxes) and 10th to 90th percentiles (whiskers). Thick lines and circles denote median values and outliers, respectively. Values in parentheses indicate the numbers of patients belonging to each group. *$p < 0.05$, **$p < 0.01$ between serum substance P levels at baseline and after treatment.

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or the chi-squared test. Differences between paired parameters were evaluated using the Wilcoxon test. Differences were considered statistically significant when p values were < 0.05. All analyses were performed using SPSS for Windows (v. 12.0, SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics and Pneumonia Recurrence

The characteristics of the 60 patients who participated in the study are shown in Table 1. There were no differences in age, sex, coexisting illness, medical treatment, or brain CT findings between patients treated with imidapril or nicergoline. All patients completed the 6 months of the treatment period, and no adverse drug reactions were observed. During the 6 months of the treatment period, 9 of 30 patients in the imidapril group (30%, all male) and 5 of 30 patients in the nicergoline group (17%, 4 male and 1 female) developed pneumonia recurrence. There was no significant difference in the pneumonia recurrence rate between the imidapril and the nicergoline groups.

Effects of Nicergoline on Dysphagia

The effects of imidapril and nicergoline on dysphagia were evaluated using a simple 2-step SPT (Figure 1). There was no statistically significant difference in the overall proportion of patients who showed improvements in dysphagia with imidapril or nicergoline treatment. However, subgroup analysis showed some differences between patients treated with imidapril or nicergoline (Figure 2A). The effect of nicergoline for improving dysphagia was significantly better in patients with dementia, compared with imidapril.

Effects of Imidapril and Nicergoline on Serum Levels of SP

To assess whether the administration of imidapril and/or nicergoline affects SP secretion, we measured serum SP levels before and 4 weeks after the start of treatment. Comparing the nicergoline and imidapril groups, there were no significant differences in the serum SP levels at baseline (p = 0.50) or after treatment (p = 0.49). Both imidapril and nicergoline significantly increased serum levels of SP (Figure 2B). It is noteworthy that the patients whose dysphagia was improved as assessed by SPT showed significantly increased serum levels of SP (Figure 3). By contrast, the patients whose dysphagia failed to improve did not show significant increases in serum levels of SP (see Figure 3). Subgroup analysis indicated that nicergoline, but not imidapril, significantly elevated serum levels of SP, particularly in patients who were bedridden, had dementia, or showed brain atrophy (see Figure 2B).

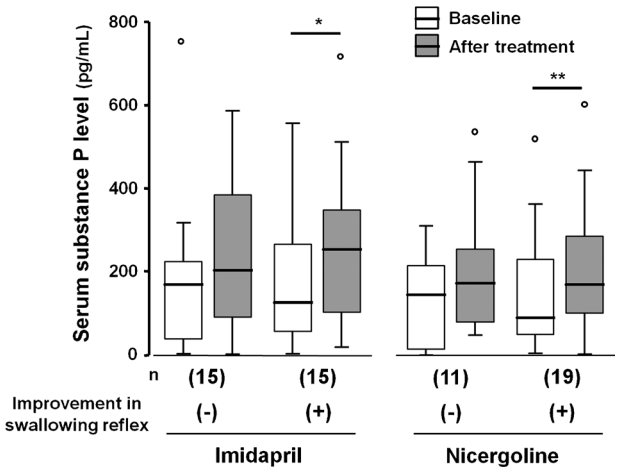

FIGURE 3. Association between improved dysphagia and changes in serum substance P levels before and after treatment. Box-whisker plots show 25th and 75th percentiles (boxes) and 10th to 90th percentiles (whiskers). Thick lines and circles denote median values and outliers, respectively. *p < 0.05, **p < 0.01 between serum substance P levels at baseline and after treatment.

DISCUSSION

In the present study, nicergoline showed a comparable effect to ACE inhibitors for improving dysphagia in patients with both dysphagia and a previous history of pneumonia. In addition, nicergoline increased serum levels of SP as effectively as imidapril, and this effect correlated with improved dysphagia as assessed by SPT. With regard to pneumonia recurrence, there was no statistically significant difference between the imidapril or nicergoline groups.

Because nicergoline has a broad spectrum of action,[21] multifactorial mechanisms may underlie the improvement of dysphagia. However, we also observed an increase in serum levels of SP in patients treated with nicergoline. Most recently, Nishiyama et al[10] also demonstrated that nicergoline significantly increases the serum levels of SP when compared with control. As shown in Figure 3, our results suggested that the improvement of dysphagia was strongly associated with increased SP. SP may promotes the swallowing reflex, and its secretion is enhanced by dopamine.[22] Because nicergoline enhances dopaminergic neurotransmitter function in the brain, we believe the mechanism underlying the improvement in dysphagia is primarily due to an enhancement in dopamine metabolism induced by nicergoline.

In the current study, we also found an extremely high proportion of abnormal swallowing reflex (60 of 68, 88.2%) in elderly patients with a previous history of pneumonia. Teramoto et al[17] have also reported the high incidence of swallowing disorders in elderly patients with a history of pneumonia. In the report by Teramoto et al, more than 80% of patients aged 70 years and older had abnormal swallowing function. In the current study, the median age of participants was 80 years old. Therefore, our results agree with this notion.

Subgroup analysis showed differences in the efficacy of nicergoline and imidapril to improve dysphagia and elevate serum SP levels. Among patients with dementia, treatment with nicergoline seemed more effective at improving dysphagia than treatment with imidapril. A significant increase in serum levels of SP was also observed with nicergoline treatment in this group of patients.

There are some limitations of the current study. First, untreated patients were not included as a control group. However, based on the efficacy of imidapril in preventing pneumonia in a Japanese population, we believe that the comparison between nicergoline and imidapril provides sufficient data concerning the influence of these drugs on the pneumonia recurrence rate in patients enrolled in this study. In addition, as described above, Nishiyama et al[10] have already demonstrated that nicergoline significantly increases serum SP when compared with control.

As a second limitation, the occurrence rate of pneumonia in the present study was extremely high compared with that in previous studies.[1,11,13,14,16,19] This discrepancy may be due to differences in the characteristics of the patients enrolled in this

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study. In this study, all patients had a previous history of pneumonia, and more than half of the patients were bedridden; this proportion of bedridden patients was apparently higher than that in previous studies. An extremely high incidence of pneumonia in bedridden patients has been reported by Nakajoh et al.[9] Finally, the number of patients in the present study was small. Further studies with more patients are necessary.

In conclusion, our results reveal that nicergoline improves dysphagia by upregulating SP. There was no statistically significant difference in the overall proportion of patients who showed improvement in dysphagia and pneumonia recurrence with imidapril or nicergoline treatment. Among patients with dementia, treatment with nicergoline seems to be more effective at improving dysphagia and elevating serum levels of SP when compared with imidapril. Considered as a whole, our results suggest that nicergoline might be a novel regimen for the treatment of dysphagia in elderly Japanese patients.

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