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Effects of Tyramine Administration in Parkinson's Disease Patients Treated With Selective MAO-B Inhibitor Rasagiline

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Abstract: Rasagiline is a novel, potent, and selective MAO-B inhibitor shown to be effective for Parkinson's disease. Traditional nonselective MAO inhibitors have been associated with dietary tyramine interactions that can induce hypertensive reactions. To test safety, tyramine challenges (50–75 mg) were performed in 72 rasagiline-treated and 38 placebo-treated Parkinson's disease (PD) patients at the end of two double-blind placebo-controlled trials of rasagiline. An abnormal pressor response was prespecified as three consecutive measurements of systolic blood pressure (BP) increases of $\geq$ 30 mm Hg and/or bradycardia of $<$ 40 beats/min. In the first study involving 55 patients with early PD on rasagiline monotherapy, no patients randomized to rasagiline (1 mg/2 mg; n = 38) or placebo (n = 17) developed systolic BP (SBP) or heart rate changes indicative of a tyramine reaction. In the second trial involving 55 levodopa-treated patients, 3 of 22 subjects on rasagiline 0.5 mg/day and 1 of 21 subjects on placebo developed asymptomatic, self-limiting SBP elevations $\geq$ 30 mm Hg on three measurements. No subject on 1 mg/day rasagiline (0/12) experienced significant BP or heart rate changes following tyramine ingestion. These data demonstrate that rasagiline 0.5 to 2 mg daily is not associated with clinically significant tyramine reactions and can be used as monotherapy or adjunct to levodopa in PD patients without specific dietary tyramine restriction. © 2006 Movement Disorder Society

Key words: Parkinson's disease; rasagiline; monoamine oxidase inhibitor; tyramine; pressor response; tolerability

Tyramine, an amino acid present in high concentrations in certain foods (e.g., cheese, red wine, chocolate), can generate surges of pressor amines when ingested, unless it is metabolized by the enzyme monoamine oxidase (MAO). The therapeutic use of nonselective MAO inhibitors has been limited by the need to restrict dietary tyramine intake to avoid potentially fatal elevations in blood pressure (BP) and reflex bradycardia.[1,2] Selective MAO-B inhibitors are relatively free of this limitation, because 90% of MAO activity in the intestine involves the MAO-A isoform. At higher dosages, however, MAO-B selectivity may be lost.[3–5] Selegiline, for example, may only be used at dosages up to 10 mg/day without dietary tyramine restrictions.[6,7] At dosages of 30 mg/day or higher, as were used when selegiline was first introduced as an antidepressant, serious cardiovascular side effects were observed.[8,9]

Rasagiline (N-propargyl-R-aminoindan) mesylate is a novel second-generation irreversible MAO-B inhibitor with high selectivity for the B-isoform. We previously reported two multicenter randomized double-blind placebo-controlled clinical trials of the efficacy and safety

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of rasagiline for Parkinson's disease (PD): one involving 404 patients with early, otherwise untreated PD (TEMPO study), and the other involving 472 levodopa-treated patients with advanced PD and motor fluctuations (PRESTO study).[10,11] In both studies, patients receiving rasagiline showed significant improvements in PD symptoms during 6 months of treatment compared to placebo, and rasagiline was well tolerated, even in the absence of dietary tyramine restrictions. Similarly, the 18-week LARGO study, a multicenter randomized double-blind parallel-group trial, demonstrated safety and efficacy in 687 levodopa-treated patients with moderate to advanced PD in the absence of dietary tyramine restriction.[12] We now report the results of oral tyramine challenges administered to a subset of participants at the end of the TEMPO and PRESTO studies.

PATIENTS AND METHODS

Patients

All patients completing the 26-week, placebo-controlled, double-blind phases of the TEMPO and PRESTO studies at sites equipped for intensive cardiovascular monitoring were offered participation in the substudy as an optional extension of the primary studies using a separate consent form, if they had no history of intracranial or systemic aneurysm, intracranial hemorrhage, or uncontrolled hypertension with systolic BP (SBP) $>$ 160 mm Hg or diastolic BP (DBP) $>$ 90 mm Hg. Patients participating at the end of TEMPO (n = 55) had been receiving rasagiline 1 or 2 mg or placebo once daily without other anti-PD therapy. Patients participating at the end of PRESTO (n = 55) had been receiving rasagiline 0.5 or 1 mg or placebo once daily in addition to levodopa and a wide variety of other anti-PD therapies, including dopamine agonists (n = 39), catechol-*O*-methyltransferase (COMT) inhibitors (n = 21), amantadine (n = 13), and selective serotonin reuptake inhibitors (SSRIs) (n = 11).

Procedures

The general designs for the tyramine challenges in TEMPO and PRESTO were similar. Immediately following completion of the week 26 visit activities in either study, within 24 hours after the last rasagiline dose, subjects enrolled in the tyramine substudy for TEMPO and for PRESTO had baseline BP and heart rate (HR) monitored with an automated sphygmomanometer every 10 minutes for 30 minutes. They consumed a low-tyramine meal, followed by an oral dose of tyramine hydrochloride (75 mg for subjects from TEMPO and 50 mg for subjects from PRESTO) mixed in applesauce, yogurt, or ice cream. Following tyramine administration, BP and HR monitoring was continued every 5 minutes for 2 hours, then every 15 minutes for a third hour. Twelve-lead ECGs were also obtained 30 minutes prior and 3 hours after tyramine ingestion. Subjects who experienced persistent elevations in BP, bradycardia, or adverse events had additional extended monitoring. All patients and investigators remained blinded to rasagiline treatment assignment during performance of the substudy.

Outcome Measures

The prespecified primary endpoint for the tyramine challenge study was the proportion of subjects who exhibited either an increase in SBP $\geq$ 30 mm Hg from mean baseline value documented by at least three consecutive measurements, or a reduction in heart rate to $<$ 40 bpm for three measurements over 10 minutes, with or without clinically significant changes on ECG. These criteria have been used in tyramine pressor testing as the standard for approximately 40 years.[13–15] In addition to these fairly strict hemodynamic criteria, we also evaluated the incidence and frequency of adverse reactions and the number of patients requiring antihypertensive therapy during the substudy. Upon completion of the PRESTO substudy, a cardiovascular specialist (W.B.W.) performed a blinded review of all BP changes, also looking for those that might reflect pressor responses but did not meet the prespecified endpoint. Subjects in this category demonstrated concordant elevations in both SBP and DBP starting from at least 30 to 40 minutes after ingestion of tyramine and subsiding after 2 hours, with a concomitant decrease, or no change, in heart rate.

Statistical Methods

Kruskal–Wallis tests, χ^2 tests, and Fisher's exact tests were used to compare the baseline characteristics of subjects who participated in the substudies with those who did not participate. These tests were also used to compare baseline characteristics by treatment group for those who participated in the tyramine challenge. The number of patients in each treatment group reaching the endpoint was compared using a Cochran–Armitage trend test. The level of significance was set at 0.05, and all tests were two-sided.

RESULTS

The distribution of patients, baseline characteristics by treatment group, and a comparison of participants with nonparticipants in each study are shown in Tables 1 and 2. In the TEMPO substudy, subjects who received rasagiline 2 mg/day had significantly higher baseline SBP

TABLE 1. *Baseline characteristics of tyramine challenge participants*

	TEMPO Monotherapy Study			PRESTO Adjunctive Study		
	Placebo (n = 17)	Rasagiline 1 mg (n = 19)	Rasagiline 2 mg (n = 19)	Placebo (n = 21)	Rasagiline 0.5 mg (n = 22)	Rasagiline 1 mg (n = 12)
Caucasian, n (%)	15 (88)	18 (95)	18 (95)	20 (95)	20 (91)	12 (100)
Male, n (%)	10 (59)	14 (74)	9 (47)	17 (81)	16 (73)	6 (50)
Age, yr (SD)	62 (9)	62 (11)	62 (12)	65 (9)	63 (8)	60 (7)
PD duration, yr (SD)	0.9 (0.7)	0.8 (0.7)	1.3 (1.6)	10.6 (5.4)	9.6 (5.8)	8.0 (5.4)
Levodopa dose, mg/day (SD)	0	0	0	898 (578)	747 (421)	733 (338)
Standing SBP, mm Hg (SD)	121 (9)	123 (10)	129 (14)	116 (17)	119 (18)	123 (25)
Supine SBP, mm Hg (SD)	127 (12)	129 (14)	132 (16)	119 (12)	121 (18)	124 (24)
Standing DBP, mm Hg (SD)	77 (8)	78 (8)	79 (8)	71 (10)	74 (10)	74 (12)
Supine DBP, mm Hg (SD)	74 (7)	77 (7)	78 (7)	73 (10)	74 (8)	75 (10)

compared to the placebo group. In the PRESTO substudy, treatment groups were similar in all relevant clinical characteristics. Those who participated in the PRESTO substudy had significantly lower baseline supine SBP and standing DBP compared with those who did not participate. There were no significant differences in the baseline characteristics between participants and nonparticipants for the TEMPO substudy.

None of the 55 subjects from the TEMPO study experienced the prespecified endpoint of three consecutive measurements of SBP increases of $\geq$ 30 mm Hg or heart rate reduction $<$ 40 bpm over 10 minutes. One subject from the placebo group and one from the rasagiline 2 mg/day group complained of headaches but without hemodynamic changes or temporal relationship suggestive of a tyramine response.

In the PRESTO study, 4/55 patients had elevations in systolic BP by $\geq$ 30 mm Hg for three consecutive measurements after the tyramine challenge. None of these patients demonstrated reflex bradycardia or ECG changes. Three of the patients were receiving rasagiline 0.5 mg/day, and one was receiving placebo (Fig. 1). None of these patients reported any associated symptoms and interventions were not required. No patient taking rasagiline 1 mg/day experienced the prespecified endpoint. Three additional patients in the PRESTO substudy, all receiving placebo, had nonsustained BP elevations suggestive of a possible pressor response as determined by the blinded review of the BP changes. However, these changes did not meet the prespecified endpoint criteria (Fig. 2).

Among the patients from the PRESTO study who experienced sustained SBP elevation $\geq$ 30 mm Hg, the increase in SBP started at greater than 110 minutes after tyramine intake and did not entirely subside within 2 hours. One subject (Fig. 1B) had BP fluctuations throughout the monitoring period and maintained elevated SBP readings for approximately 4 hours. Another subject (Fig. 1C) experienced significant SBP changes at two different intervals, at 2 and 6 hours after tyramine administration. There was no statistical difference relative to placebo in the proportion of patients in each treatment group who demonstrated the prespecified endpoint ($P = 0.81$). There were no significant group differences in mean BP changes following tyramine challenge. All groups had a temporary decrease in SBP and DBP of 6 to 8 mm Hg as expected after a meal (data not shown). All subjects in both substudies completed the substudy protocol.

TABLE 2. *Baseline characteristics of substudy participants and nonparticipants*

	TEMPO Monotherapy Study		PRESTO Adjunctive Study	
	Participants (n = 55)	Nonparticipants (n = 349)	Participants (n = 55)	Nonparticipants (n = 417)
Caucasian, n (%)	51 (93)	332 (95)	52 (95)	379 (91)
Male, n (%)	33 (60)	224 (64)	39 (71)	266 (64)
Age, yr (SD)	62 (11)	61 (11)	63 (8)	63 (10)
PD duration, yr (SD)	1.0 (1.1)	1.0 (1.2)	9.6 (5.5)	9.2 (5.3)
Levodopa dose, mg/day (SD)	0	0	801 (471)	793 (443)
Standing SBP, mm Hg (SD)	125 (11)	127 (16)	119 (19)	122 (18)
Supine SBP, mm Hg (SD)	130 (14)	130 (17)	121 (17)	128 (17)
Standing DBP, mm Hg (SD)	78 (8)	79 (9)	73 (10)	77 (10)
Supine DBP, mm Hg (SD)	76 (7)	78 (9)	74 (9)	76 (9)

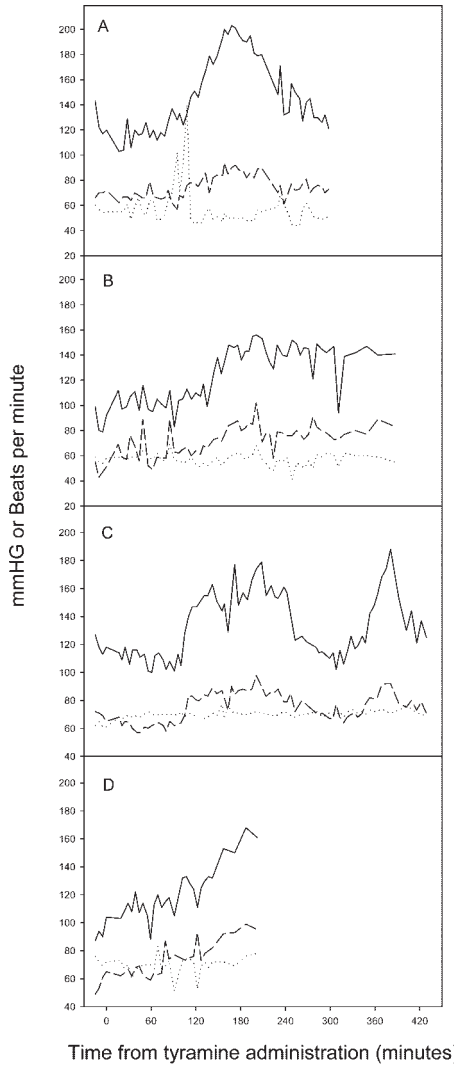

FIG. 1. Systolic blood pressure (solid lines), diastolic blood pressure (dashed lines), and heart rate (dotted lines) in the four patients (**A**–**D**) who experienced the prespecified endpoint (an increase in SBP ≥ 30 mm Hg from mean baseline value documented by at least three consecutive measurements, or bradycardia < 40 bpm for three measurements over 10 minutes). Three of these patients (A–C) were receiving rasagiline 0.5 mg/day; the fourth (D) was taking placebo. Tyramine was administered at time = 0.

DISCUSSION

These tyramine challenges from the TEMPO and PRESTO study revealed observations not previously described in this patient population. They showed no statistically significant interactions between rasagiline and high doses of oral tyramine in patients with Parkinson's disease. This finding is in agreement with the clinical outcomes in the TEMPO and PRESTO trials in which rasagiline was not associated with hypertensive reactions during 26 weeks of double-blinded treatment in 404 patients with early PD and in 472 patients with levodopa-related motor fluctuations, in the absence of dietary tyramine restrictions.[10,11]

Typically, tyramine-induced pressor reactions occur as concordant and sustained elevations in both systolic and diastolic BP starting 30 to 40 minutes after ingestion and subsiding after 2 hours or less.[13,16,17] The patients from the PRESTO study who experienced prespecified SBP

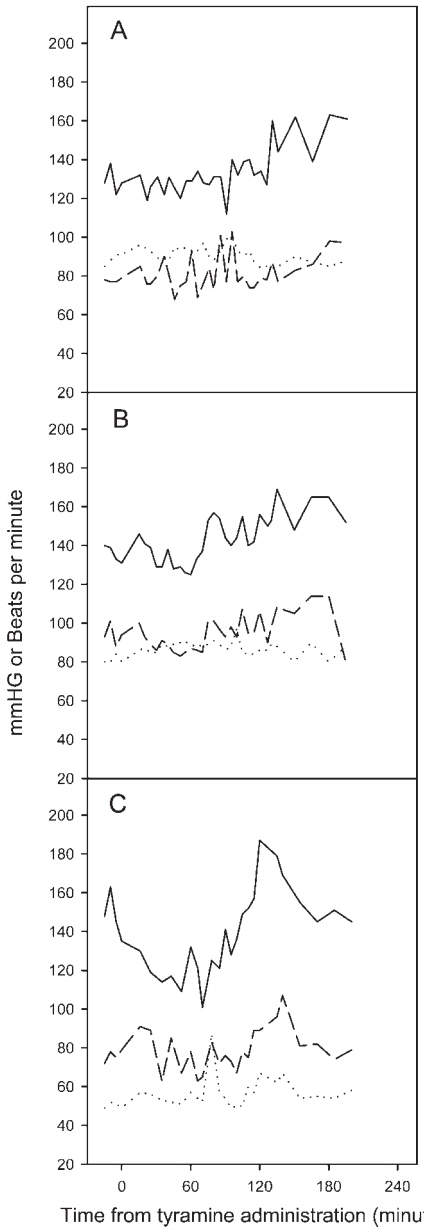

FIG. 2. Systolic blood pressure (solid lines), diastolic blood pressure (dashed lines), and heart rate (dotted lines) in three patients (**A**–**C**) who had SBP elevations suggestive of a possible pressor response, but did not meet the prespecified endpoint. All three were receiving placebo. Tyramine was administered at time = 0.

elevations ≥ 30 mm Hg during the tyramine challenge did not demonstrate such a pattern of BP changes. The patient who experienced BP fluctuations throughout the monitoring period and maintained elevated SBP readings for almost 4 hours raises the possibility that the changes may have been due to other confounding factors, such as motor fluctuations or dose failures with associated tremors or rigidity of the upper arm during the monitoring period. Detailed information regarding the PD *on*/*off* status of the subjects during the substudy, however, was not systematically collected. The patient who demonstrated a biphasic increase in SBP at different intervals, about 2 and 6 hours after tyramine administration, was also atypical for a tyramine-related event. The second hypertensive response 6 hours after administration of tyramine would be inconsistent with the half-life of tyramine. The heterogeneity of the BP responses in this small number of patients suggests that some of the BP changes likely reflect autonomic instability in PD patients rather than an interaction between tyramine and rasagiline. Indeed, the diurnal and postprandial lability of blood pressure in patients with PD have been reported and may increasingly be observed with the use of ambulatory BP monitoring devices.[18,19] In addition, the absence of any reactions in PRESTO patients taking rasagiline 1 mg/day and in the TEMPO patients taking 2 mg/day of rasagiline reveals no dose response and is inconsistent with the impact of tyramine and monoamine oxidase inhibition from earlier studies of the nonselective inhibitors.[1,20] Since confounding factors may be involved in patients with Parkinson's disease, it is possible that the prespecified endpoint of systolic BP elevation ≥ 30 mm Hg and noninvasive BP monitors susceptible to artifact in rigid or tremulous arms may not have been appropriate in this population of patients.

These data further support the overall safety profile of rasagiline. They demonstrate that rasagiline can be safely used in patients with early or advanced PD, with or without concomitant anti-PD therapies, without dietary tyramine restrictions.

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APPENDIX

Parkinson Study Group TEMPO and PRESTO Tyramine Substudy Investigators and Coordinators who participated in this study and authored this report are as follows.

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