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The short-term effect of nicotine chewing gum in patients with Parkinson's disease

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Abstract Because of the inverse association of cigarette smoking with the risk of Parkinson's disease, we performed a short-term, double-blind, randomized controlled trial of nicotine polacrilex resin gum in patients with this disease. Forty-eight subjects were randomly assigned to chew either nicotine gum or placebo gum three times at 2-h intervals, with evaluation of symptoms before and after the trial. The nicotine gum was reasonably well tolerated, but there were no substantial differences in Parkinson's disease symptoms between the two treatment groups.

Key words Parkinson's disease · Nicotine

Introduction

Epidemiological studies have repeatedly shown an apparent protective effect of cigarette smoking on the development of Parkinson's disease, with smokers having approximately half the risk of non-smokers (Baron 1986). Several lines of evidence suggest that nicotine in the smoke could be responsible for these effects. Nicotine readily crosses the blood-brain barrier, is concentrated in brain tissue (Sershen and Lajtha 1979), and stimulates increased activity of dopaminergic nigrostriatal neurons (reviewed in Baron 1986). In several studies (Lichtensteiger et al. 1979; Kaakkola 1981; Lapin et al. 1987; Janson et al. 1988), but not all (Fuxe et al. 1977), nicotine caused turning behavior in rodents with unilateral striatal lesions, indicating behavioral consequences of this augmentation of dopaminergic activity. Finally, there is evidence (albeit inconsistent) from animal models of parkinsonism that nicotine may exert a beneficial or protective effect (Perry et al. 1987; Janson et al. 1988; Sershen et al. 1988; Owman et al. 1989; Shahi et al. 1990; Fung et al. 1991; Behmand and Harik 1992; Carr et al. 1992). Nicotine may thus have potential as a therapeutic agent in Parkinson's disease, either to enhance dopaminergic functioning, or to prevent nigrostriatal degeneration. Indeed, in short-term, mostly uncontrolled studies there have been indications of a beneficial effect of cigarette smoking or nicotine on the symptoms of Parkinsonism (Moll 1926; Marshall et al. 1966; Ishikawa and Miyatake 1993; Fagerström et al. 1994).

Nicorette is a nicotine-containing polacrilex resin chewing gum used principally to promote smoking cessation. We report here the results of a short-term study of the administration of Nicorette gum to non-smoking patients with Parkinson's disease. Our goals were to assess the tolerance to this drug by patients with Parkinson's disease and to investigate its short-term effects prior to consideration of longer-term investigation of nicotine administration in Parkinson's disease.

Materials and methods

The research described here was approved by the institutional review board at Dartmouth Medical School. Forty-eight patients were recruited from among Parkinson's disease patients followed in neurology clinics at Dartmouth-Hitchcock Medical Center, the Veterans Administration Medical Center in White River Junction, Vermont, and the practives of two community neurologists in New Hampshire and Vermont. All subjects carried a diagnosis of idiopathic Parkinson's disease made by a neurologist and had mild-to-moderate termor, rigidity and/or bradykinesia. None of our patients had significant "on-off" phenomenon or dementia, and all were ambulatory. All patients were taking one or more medication(s) for the treatment of Parkinson's disease and most were taking L-dopa/carbidopa. No patients were taking drugs known to cause an extrapyramidal syndrome, including metaclopromide, phenothiazines, thioxanthenes or butyrophenones. Patients currently using tobacco in any form were excluded, as were those with unstable or incapacitating parkinsonism, or with any significant neurological co-morbidity. Patients were not enrolled if they had potential contraindications to nicotine use, including uncontrolled hypertension, active coronary artery disease, known serious cardiac arrhythmias, or active peptic ulcer disease.

Participants were randomized to receive either nicotine-containing gum (2 mg nicotine in polacrilex resin) or placebo-containing gum. These were identical in appearance and similar in taste. One investigator, who did not perform clinical evaluations, as-

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Table 1 Baseline characteristics of subjects, by treatment assignment

Characteristic	Treatment group	
	Nicotine	Placebo
Number	25	23
Percent male	80%	70%
Mean age, years	62.3±16.5 years[a]	66.6±6.6 years
Percent ever smoked	44%	48%
Mean age at onset parkinsonian symptoms	59.0±9.9 years	58.6±9.0 years
Mean age at diagnosis of Parkinson's disease	60.5±10.2 years	59.6±8.4 years

[a] SD

Table 2 Adverse symptoms, by treatment assignment

Side-effect	Treatment group	
	Nicotine (n=25)	Placebo (n=23)
Dry mouth	2	1
Dizziness	4	4
Headache	1	0
Palpitations	1	0
Nausea	3	2
GI upset	3	1
Vomiting	2	0

Table 3 Blood pressure and pulse, by treatment group (mean± standard error)

	Treatment group	
	Nicotine	Placebo
Pulse		
Baseline	77.0±2.4	75.4±2.9
+2 h	77.9±2.8	77.7±2.7
+4 h	81.3±2.9	78.6±2.1
Systolic blood pressure		
Baseline	129.5±2.7	132.1±4.3
+2 h	131.1±3.5	129.3±4.1
+4 h	126.0±3.9	123.0±4.1
Diastolic blood pressure		
Baseline	84.0±2.1	81.2±2.0
+2 h	83.1±2.4	82.9±2.4
+4 h	79.0±1.9	76.8±2.1

signed participants to the two groups using a random number table. Participants took their medications as usual on the study day. Three pieces of gum were administered at 2-h intervals over $4^1/_2$ h, each piece chewed for 30 min. Blood pressure, pulse, adverse effects, and difficulties with gum chewing were monitored just prior to chewing the second and third pieces of gum.

The severity of each subject's parkinsonian symptoms was rated by one neurologist prior to receiving any gum, and just after chewing the third piece. All raters were blinded to the treatment assignment of their patients. The rating scale used was based on the motor examination portion of version 3.0 of the unified Parkinson's disease rating scale (Lang and Fahn 1959), which was modified to allow for separate grading of left- and right-sided findings of tremor, rigidity and coordination. By combining individual items, it is possible to construct subscales reflecting tremor, rigidity and bradykinesia as well as an overall score (see Appendix). The data from the rating scales were analyzed by calculating an overall score, as well as subscores for tremor, rigidity, and for bradykinesia. Higher scores reflect greater severity of symptoms.

One participant's evaluation was incompletely recorded initially. This subject was re-evaluated completely at a later date using the same protocol. Differences between study groups were tested using t-tests.

Results

Baseline characteristics of the participants are summarized in Table 1. The two groups were similar in terms of age, gender, number who smoked in the past, and age of onset of Parkinson's disease.

Overall, the gum was well tolerated by both groups. Side effects of dizziness, nausea, gastrointestinal upset, dry or burning mouth and palpitations were mild and occurred with approximately equal frequency in the nicotine and the placebo groups (Table 2). However, two nicotine subjects developed vomiting (around the time of eating) and chose not to continue in the study. One other participant receiving placebo developd severe chorea, apparently due to overmedication with L-dopa/carbidopa. Gum administration was discontinued for these three subjects, and the absence of post-treatment data prevented their inclusion in the analysis. There was no indication of adverse cardiovascular response to the nicotine (Table 3); at no observation time did the two treatment groups differ in pulse or blood pressure.

The Parkinson's disease scores are presented in Table 4. Both groups improved slightly in all subscores during the period of observation. This occurred to a similar extent in each group. At the end of the study, there were no statistically significant differences between the two groups in the overall motor score, or any of the components.

Table 4 Parkinson's disease scores, by treatment group (mean±standard error)

Score	Treatment group			
	Nicotine (n=23)		Placebo (n=22)	
	Baseline	Completion	Baseline	Completion
Overall	[a]12.4 ±1.4	[a]10.2 ±1.5	11.1 ±1.4	8.6 ±1.2
Tremor	0.74±0.14	0.50±0.11	0.54±0.20	0.30±0.12
Rigidity	0.85±0.12	0.58±0.10	0.91±0.17	0.59±0.13
Bradykinesia	[a]7.1 ±0.8	[a]6.3 ±0.9	5.8 ±0.8	4.7 ±0.7

[a] n=22 because of missing data

Discussion

This randomized, double-blind, placebo-controlled trial demonstrates that nicotine is reasonably well tolerated by patients with Parkinson's disease. The vomiting that occurred with two participants given nicotine seemed to be precipitated by eating directly before or after chewing gum. However, there were no statistically significant differences between the treatment groups in parkinsonian symptoms.

While the randomized double-blind design of our trial ensures a valid assessment of the effect of short-term use of the gum, there are several limitations to our investigation. One is the natural variability in the severity of symptoms which could have obscured a true effect of the gum. Also, despite detailed instructions on proper chewing techniques given orally and in writing, gum-chewing proved to be difficult for some of the participants, particularly those with dentures. This could have affected the speed and completeness with which nicotine was released from the resin. Other methods of administering the drug, such as transdermally, might be more reliable and less cumbersome. Finally, interpretation of our findings would have been facilitated if we had had a measurement of the effective dose experienced by our subjects (e.g. serum or salivary nicotine or cotinine).

It is unlikely that we failed to detect a substantial short-term effect because of inadequate study power. The scale we used appears to be a sensitive one, and samples smaller than ours appear large enough to detect the modest difference in symptom severity that would be expected from 2 years' progression of the disease (Fahn and Bressman 1984). The administration of nicotine to parkinsonian patients is not new. In 1926, Moll gave between 1/10 and 1/5 of a grain of nicotine intravenously three times daily for 2–3 weeks to 13 patients with postencephalitic parkinsonism. The study was not controlled or blinded and the data reported were qualitative. Rigidity was reported to improve transiently, although there was no apparent effect on tremor or sialorrhea. More recently, 2 mg nicotine base given intravenously to five parkinsonian patients was followed by a reduction in tremor; administration of 1 mg resulted in a slight increase (Marshall and Schnieden 1966). In an uncontrolled series investigation, cigarette smoking was associated with a consistent symptomatic improvement in six patients with Parkinson's disease (Ishikawa and Miyatake 1993). Most recently, Fagerström and colleagues (1994) reported improvement in parkinsonian symptoms with a combination of nicotine gum and a nicotine patch, evaluated in two patients during a double-blind crossover study.

The time required for nicotine gum to have any clinically noticeable effect in parkinsonism is likely to be longer than the few hours we used in our investigation. Indeed, in one of the first double-blind, controlled studies of L-dopa for Parkinson's disease, a single intravenous dose was given, and there was no significant benefit in comparison to saline (Fehling 1966). Subsequent controlled studies (Cotzias et al. 1967; Brogden et al. 1971) clearly showed the necessity of sustained treatment with larger doses for a therapeutic effect. Similarly, an extended trial with nicotine is likely to be necessary to establish the ultimate therapeutic efficacy of this drug for fixed lesions. Longer-term study would also be required to determine if nicotine offered protection against the deterioration of nigrostriatal neurons, as has been suggested (Baron 1986). Our data indicate that such a trial would be feasible, although nausea appears to be a problem with nicotine polacrilex gum when taken around the time of meals.

Appendix: components of Parkinson's disease rating scale

Tremor (right and left)

Rigidity of major joints (right and left)

Bradykinesia
- finger taps (right and left) (thumb tapped against index finger)
- hand movements (right and left) (opening and closing hands)
- rapid alternating hand movement (right and left) (pronation-supination)
- foot agility (heel taps lifting entire foot)
- arising from chair
- gait
- body motion

Other
- speech
- facial expression
- posture
- postural stability
- salivation

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