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Effects of Nicotine Chewing Gum on UPDRS Score and P300 in Early-onset Parkinsonism

Takako MITSUOKA, Yumiko KASEDA, Hiroshi YAMASHITA, Tatsuo KOHRIYAMA, Hideshi KAWAKAMI, Shigenobu NAKAMURA and Yasuhiro YAMAMURA*

The 3rd Department of Internal Medicine, Hiroshima University School of Medicine
**The Institute of Health Science, Hiroshima University School of Medicene*

ABSTRACT

It has been reported that nicotine shows some beneficial effects on Parkinson's disease. The purpose of the present study is to assess the therapeutic effects of nicotine chewing gum in patients with early-onset parkinsonism (EOP). The subjects were 8 patients with early-onset parkinsonism (male/ female = 4/ 4, mean age; 51.3 years). Four out of 8 patients had a history of smoking (smokers). To estimate the effects of nicotine gum, the scores on the Unified Parkinson's Disease Rating Scale (UPDRS) and auditory event-related potentials (ERPs) were studied before and after taking nicotine gum in the EOP patients. In smokers, UPDRS scores improved by more than 10 % and the P300 latency of auditory ERPs was shortened by more than 30 msec. In contrast, nicotine had no remarkable effects on UPDRS scores or auditory ERPs in non-smokers. We suggest that nicotine chewing gum may be a possible choice for the treatment of patients with EOP, especially when they are smokers.

Key words: *Early-onset parkinsonism, Nicotine chewing gum, P300, UPDRS*

Cigarette smoking is a risk factor for diseases of the respiratory and cardiovascular systems[5]. However, pure nicotine, the main pharmacologically active ingredient of cigarettes, shows some beneficial effects[19].

It has been reported that nicotine exhibits neuroprotective effects[1,13,18,47]. Negative associations have been demonstrated between tobacco smoking and neurodegenerative diseases, such as Parkinson's disease (PD)[4,14,19], Alzheimer's disease (AD)[33], and Gilles de la Tourette syndrome[31]. Particularly, a number of studies have shown that smokers have a lower incidence of PD than non-smokers[4,6,10].

In addition to long-term neuroprotective effects, nicotine has short-term therapeutic effects on parkinsonism[4,14,19] and cognitive dysfunction[26]. The short-term effect of nicotine may be related to the activation of neuronal heteromeric nicotinic acetylcholine receptor (nAChR)[28].

Cigarette smoking has been previously reported to relieve symptoms in patients with early-onset parkinsonism (EOP)[16,17,21]. Although the *Parkin gene* has recently been identified in familial EOP[22], EOP with an onset before 40 years old includes various types of parkinsonism. The heterogenous EOP, however, presents unique clinical features in common, which are different from late-onset Parkinson's disease (LOP), as follows: 1) occurrence in an autosomal recessive trait / or solitary occurrence; 2) higher frequency in females than in males; 3) average age of onset in early 20s; 4) parkinsonism and minor dystonia as the chief manifestation; 5) diurnal fluctuation of the symptoms and alleviation after sleep; 6) reduction in range of diurnal fluctuation with the development of dystonic posture; 7) accentuated deep reflex; 8) marked effect of L-dopa, invariably complicated by dyskinesias, or other adverse effects; 9) minimal autonomic failures; 10) absence of dementia; and 11) slow progression of the disease through life[45]. Neuropathological investigations have demonstrated the less extensive loss of dopaminergic neurons in EOP than in LOP[45]. In EOP, the administration of anti-parkinsonian drugs often produces diurnal fluctuation of parkinsonian symptoms accompanied by a drug-induced dyskinesia. Although the beneficial effect of smoking has been reported, cigarettes have not been recommended as a therapeutic agent because of its connection with respiratory[27] and cardiovascular diseases[11,30] probably due to ingredients other than nicotine. Pure nicotine is not related to respiratory disorders[42], and the side effects of nicotine gum

Address: The 3rd Department of Internal Medicine, Hiroshima University School of Medicine, 1–2–3 Kasumi, Minami-ku, Hiroshima, 734–8551, JAPAN
Phone: +81–082–257–5201, FAX: +81–082–505–0490

mainly consist of local irritable symptoms in the mouth, throat, and stomach[3].

The purpose of this study is to assess the therapeutic effects of nicotine gum on motor and cognitive functions in EOP patients. We evaluated patients with and without a history of smoking separately in order to elucidate the difference in response to nicotine between smokers and non-smokers.

SUBJECTS AND METHODS

1) Subjects

We examined eight patients with EOP (male/female = 4/ 4, mean age ± SD; 51.3 ± 5.21 years, mean age of onset 28.0 ± 11.8 years). The clinical background of the patients is given in Table 1. We included case 4 and 7, with an onset at the age of 41 and 43 respectively, because these patients manifested clinical characteristics of EOP. We divided the patients into two groups, smokers (N = 4) and non-smokers (N = 4). In the smoker group, three were smokers at the time of examination and one had a history of smoking. There was no statistical difference by t-test between the smokers and non-smokers of age at the onset and at the examination. The electrocardiogram result was normal in all patients. Informed consent was obtained before examination from all the patients.

2) Methods

The smokers were instructed to refrain from smoking from 9 p.m. on the day before the examination. The patients did not take any anti-parkinsonian drug, especially trihexyphenidyl, on the day of the examination. We evaluated their scores on the Unified Parkinson's Disease Rating Scale (UPDRS) and event-related potentials (ERPs), before and after chewing nicotine gum (nicotine 2.0 mg, masticated for 15 min).

ERPs were recorded using auditory odd-ball paradigm (rare; 2000 Hz, 20 %, frequent; 100 μHz, 80 %; 85 dBSL), and the subjects were asked to count the number of rare stimuli. The interstimulus interval was 1.5 s. ERPs were recorded from Pz electrodes referred to linked earlobe electrodes (A1A2) with a forehead ground. The impedance was below 5 kΩ. Analysis time was 1000 msec with a prestimulus period of 160 msec. The bandpass filter was 0.05–60 Hz. Artifact of electrooculogram over 100 (V was rejected.

The recording method was similar to that described in our previous report[20]. Two sessions of 30 responses were recorded and the reproducibility of ERPs was confirmed. The average waveforms of the first session were analyzed. The N100 component was defined as the largest negative peak between 65 and 135 msec, and P300 as the largest positive peak between 250 and 500 msec in responses induced by rare stimuli. We measured the peak latency and baseline to the peak amplitude of N100 and P300 components.

3) Data Analysis

To analyze individual data of UPDRS, we calculated % improvement = (Before-After) / Before × 100 for the evaluation of changes induced by nicotine gum. We defined the patient as a responder when the UPDRS scores decreased by more than 10% (% improvement > 10).

RESULTS

1) Scores of UPDRS (Table 2)

All the smokers were responders. The mean total score of UPDRS changed from 95.5 to 75.3 in the smoker group. In the responders, particularly cases 2, 3 and 4, the nicotine effect was more

Table 1. Clinical background of patients

Smokers

Case	Age	Sex	Smoking	Age of onset	Family History	Yahr	Sleep benefit	Diurnal fluctuation of symptoms	Dystonia	Dyskinesia
1	43	M	+ (before onset)	35	–	II	+	+	+	+
2	44	F	18 mg/day, 25yrs	24	Consang (+)	III	+	+	+	+
3	52	M	15 mg/day, 30yrs	39	–	II	+	+	+	+
4	55	M	2mg/day,37yrs	41	–	IV	+	+	+	–
mean ± SD	48.5 ± 5.92				34.7 ±7.59					

Non-smokers

Case	Age	Sex	Smoking	Age of onset	Family History	Yahr	Sleep benefit	Diurnal fluctuation of symptoms	Dystonia	Dyskinesia
5	45	F	–	12	Consang (+)	III	+	+	+	+
6	53	F	–	30	Consang (+)	III	+	+	+	+
7	54	F	–	43	Consang (+)	IV	+	+	+	+
8	57	M	–	36	–	II	+	+	+	+
mean ± SD	52.3 ± 5.12			30.3 ±13.2						

Table 2. Change in UPDRS by administration of nicotine gum in each patient

Smokers

Case	1		2		3		4		average	
	B	A	B	A	B	A	B	A	B	A
<Symptoms and Signs>										
Rigidity	14	7	7	0	7	7	7	0	9.1	3.5
Tremor	0	0	0	0	0	0	0	0	0	0
Akinesia	9	9	9	9	9	0	18	9	11.3	3
Demmentia	0	0	0	0	0	0	0	0	0	0
Postural abnormality	0	0	6	6	3	3	6	6	3.9	3.9
Depression	5	5	5	5	0	0	5	0	3.5	2.5
Seborrhea	2	2	2	2	0	0	4	4	2	2
Sialorrhea	0	0	2	2	0	0	6	4	2	1.5
Blephalospasm	0	0	4	2	0	0	0	0	1	0.5
Mask faces	2	2	2	2	1	1	3	2	2	1.8
(subtotal)	32	25	37	28	20	11	49	25	34.5	22.3
(% improvement)		+22		+24		+45		+49		35.3
<Activity>										
Dressing	5	5	5	5	0	0	10	10	5	5
Eating	0	0	0	0	0	0	21	21	5.3	5.3
Walking	10	0	10	10	10	10	20	10	13	0.8
Getting out of bed	0	0	0	0	0	0	12	12	3	3
Turning in bed	0	0	0	0	0	0	8	8	2	2
Getting out of chair	0	0	0	0	0	0	10	10	2.5	2.5
Climbing stairs	2	0	0	0	2	2	2	2	1.5	1
Use of toilet	6	6	0	0	0	0	12	12	4.5	4.5
Bathing	6	6	6	6	0	0	12	12	6	6
Speech	10	10	10	10	10	10	30	20	15	12.5
Handwriting	0	0	5	5	0	0	10	10	3.8	3.8
(subtotal)	39	27	36	36	22	22	147	127	61	53
(% improvement)		+31		0		0		+14		+13.1
(Total)	71	52	73	64	42	33	196	152	95.5	75.3
(% improvement)		+27		+12		+21		+22		+21.2

Non-smokers

Case	1		2		3		4		average	
	B	A	B	A	B	A	B	A	B	A
<Symptoms and Signs>										
Rigidity	7	7	0	0	7	14	14	7	7	7
Tremor	0	0	5	5	0	0	0	0	1.3	1.3
Akinesia	18	18	0	0	18	18	18	18	13.5	13.5
Demmentia	16	16	0	0	8	8	8	8	8	8
Postural abnormality	6	6	3	3	3	3	6	6	4.5	4.5
Depression	0	0	0	0	5	5	5	5	2.5	2.5
Seborrhea	2	2	2	2	0	0	0	0	1	1
Sialorrhea	0	0	0	0	0	0	0	0	0	0
Blephalospasm	2	2	0	0	0	0	0	0	0.5	0.5
Mask faces	2	2	1	1	2	2	2	2	1.8	1.8
(subtotal)	53	53	11	11	43	50	46	39	38.3	38.3
(% improvement)		0		0		–16		+15		0
<Activity>										
Dressing	5	5	0	0	15	15	5	5	6.3	6.3
Eating	7	7	0	0	21	21	7	7	8.8	8.8
Walking	20	20	10	10	30	30	10	10	17.5	17.5
Getting out of bed	12	12	0	0	18	18	6	6	9	9
Turning in bed	8	8	0	0	12	12	4	4	6	6
Getting out of chair	10	10	5	5	15	15	5	5	8.8	8.8
Climbing stairs	4	4	0	0	6	6	2	2	3	3
Use of toilet	6	6	0	0	18	18	6	6	7.5	7.5
Bathing	6	6	0	0	18	18	6	6	7.5	7.5
Speech	0	0	0	0	20	20	10	10	7.5	7.5
Handwriting	15	15	5	5	15	15	5	5	10	10
(subtotal)	93	93	20	20	188	188	66	66	91.75	91.75
(% improvement)		0		0		0		0		0
(Total)	146	146	31	31	231	238	119	112	131.8	131.8
(% improvement)		0		0		–3		+5		0

B: before takin nicotine gum
A: after takin nicotine gum
% improvement = (B–A)/B

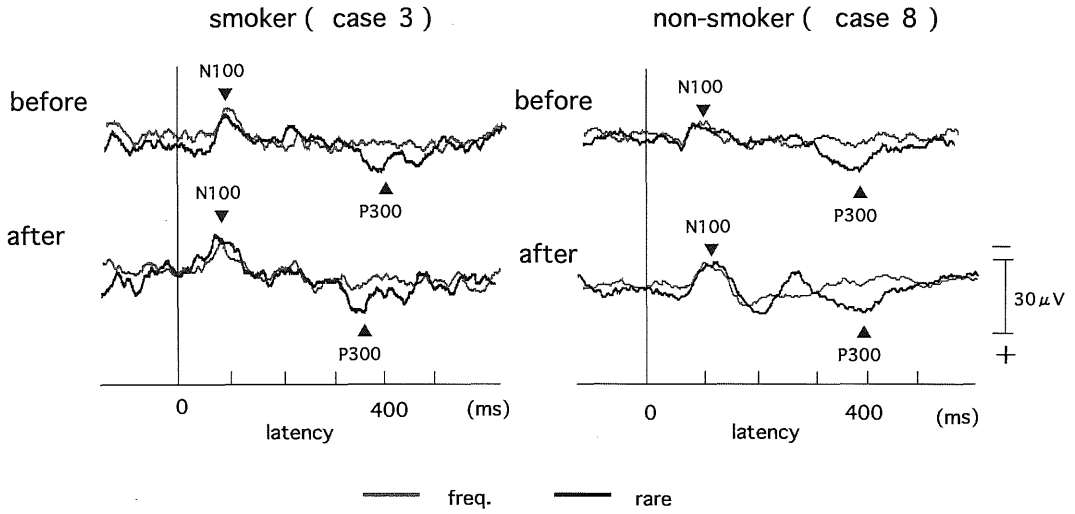

Figure. Change of the event-related potentials by nicotine gum. Representative ERP wave forms of smoker (case 3) and non-smoker (case 8) before and after administration of nicotine gum. The latency of P300 is shortened after the administration of nicotine gum only in the smoker. Gray and black lines show waves obtained with frequent and rare stimuli, respectively.
before: before taking nicotine gum
after: after taking nicotine gum

Table 3. Mean value of latencies and amplitudes of ERPs components before and after administration of nicotine gum

Smokers

	UPDRS	N100 lat. (ms)			P300 lat. (ms)			N100 amp. (μV)		P300 amp. (μV)	
case	% improvement of UPDRS	B	A	B–A	B	A	B–A	B	A	B	A
1	+27*	79	95	–16	348	318	+30**	–2.4	–3.56	11.7	9.34
2	+12*	79	71	+8	385	354	+31**	–3.6	–10.5	12.9	9.92
3	+21*	89	92	–3	400	357	+43**	–2.87	–2.91	9.34	13.6
4	+29*	107	96	+11	433	403	+30**	–3.24	–1.98	6.4	6.23
average	+25*	98	94	0	416.5	380	+33.5**	–3.03	–4.74	10.1	9.77
SD	7.63	13.2	11.8	0	35.3	34.8	6.35	0.51	3.89	2.87	3.02

Non-smokers

	UPDRS	N100 lat. (ms)			P300 lat. (ms)			N100 amp. (μV)		P300 amp. (μV)	
case	% improvement of UPDRS	B	A	B–A	B	A	B–A	B	A	B	A
1	0	90	87	+3	372	371	+1	–1.25	–0.6	6.17	4.33
2	0	90	93	–3	379	370	+9	–2.49	–3.26	4.67	6.3
3	–3	122	88	+34	353	367	–14	–1.85	1.95	10.5	10.3
4	+5	95	86	+9	393	390	+3	–1.11	–4.64	17.9	12.2
average	–1	99.3	89.33	+10.8	368	369.3	–0.2	–1.68	–1.64	9.81	8.28
SD	3.32	15.3	3.11	16.3	16.6	10.5	9.78	0.63	2.92	5.93	3.6

B: before taking nicotine gum
A: after taking nicotine gum
% improvement = (B–A)/B
* responder % improvement > 10
** P300 latency shortened by more than 30 ms.

remarkable in the symptom category than in the activity one. Akinesia, rigidity and gait disturbance appeared to be good targets for the improvement brought about by nicotine administration (Table 2).

2) ERPs (Table 3)

Table 3 presents the mean latencies and amplitudes of ERP components before and after the administration of nicotine chewing gum. The figure shows the representative ERP waveforms of a

smoker (case 3) and a non-smoker (case 8) before and after administration of nicotine gum. A slight shortening of N100 and remarkable shortening of P300 were observed in case 3 (smoker) in response to rare stimuli, while not in case 8 (non-smoker). No distinct P300 was recognized either in smokers or non-smokers in response to frequent stimuli. P300 latency was shortened by more than 30 msec (> 10%) in all responders (smokers). However, it was not shortened after administration of control gum without nicotine.

DISCUSSION

Parkinsonian symptoms were ameliorated and P300 latency was shortened by nicotine gum in 4 out of 8 patients with EOP, and all the responders were smokers. However, in LOP patients nicotine gum was not effective either on parkinsonian symptoms or P300 latency[21].

1) Effects of nicotine on parkinsonian symptoms

In CNS, nicotinic cholinergic neurons are distributed throughout the brain, with a high concentration of nAChR in the hypothalamus, hippocampus, thalamus, mid-brain, brainstem and various areas of the cortex[25]. In LOP, high affinity nicotinic binding sites are decreased, especially in the nigrostriatal pathway[24,43], which plays a crucial role in the initiation of voluntary movements[29]. Nicotine stimulates presynaptic nAChR at dopaminergic terminals in the striatum[44,46] and in dopaminergic neurons in the substantia nigra[2], which accelerates the release of dopamine. Smoking[16] and nicotine chewing gum[21] have been previously reported to relieve symptoms in EOP, but not in LOP. The different response to nicotine between EOP and LOP may be related to a less prominent neuronal loss in the nigrostriatal dopaminergic system and the relatively preserved presynaptic nAChR in dopaminergic neurons in EOP.

2) Comparison between smokers and non-smokers

In the present study, all four responders were smokers or had a history of smoking. Their UPDRS scores decreased by more than 10 % after chewing nicotine gum. It has been reported that the number of nAChR in CNS is increased in smokers compared with non-smokers[36]. Smokers are likely to be more sensitive to nicotine because of the increase in CNS nAChR. The effect of nicotine gum on parkinsonian symptoms in smokers could be associated with the accelerated release of dopamine induced by nicotine[46]. Another possibility may exist: smokers are more tolerant to nicotine and can bear the side effect better than non-smokers.

3) Effects of nicotine on cognitive functions

Nicotine also stimulates the release of norepinephrine (NE) from the frontal cortex and thalamus, and the release of acetylcholine from the hippocampus and frontal cortex[38]. Recent studies have indicated that the nicotinic network plays a major part in higher cognitive functions[9,12,37]. In LOP, cognitive impairment is accompanied by a decrease of nAChR in CNS[39]. The beneficial effect of nicotine on learning and memory has been demonstrated by psychological tests of the cognitive function[8]. Nicotine is thought to be particularly effective in ameliorating memory and attentional deficits in AD[34,35]. In the present study, P300 latencies were shortened by more than 30 msec (> 10%) after chewing nicotine gum in smokers, but not in non-smokers. The favorable change in P300 latencies in smokers could be related to increased nAChR on NE neurons in smokers compared with non-smokers[36].

4) Pharmocokinetics of nicotine gum

Nicotine gum is available in two forms, 2 mg and 4 mg. About half of the nicotine (0.86 mg) is absorbed into the blood stream from the 2 mg gum[7], and the blood level of nicotine is maintained to 4.3 ng/ ml, when a piece of 2 mg nicotine gum is chewed hourly for 12 hours[7]. Routine clinical trials with 5–10 pieces of 2 mg nicotine gum/ day have revealed that the mean successful rate to stop smoking is 22% after a 1-year-follow-up even in highly dependent smokers[15,23,40,41]. Furthermore, Newhouse et al[35] examined the quantitative effects of nicotine in PD patients using a transdermal patch with doses of 14 mg/ day for 2 weeks. They suggested that nicotine appeared to improve the performance of PD patients during the period of the examination and 2 weeks after the examination. Thus, a therapeutic nicotine concentration may possibly be maintained without serious side effects by a usual dosage of 5–10 pieces 2 mg nicotine gum in EOP patients too.

In the present study, we focused on the short-term effects of nicotine. However, another possible beneficial effect would include neuroprotection[4,28,32]. Nicotine may act as a neuroprotective agent to prevent the progression of degenerative process in PD including EOP. Further studies are needed to elucidate the underlying mechanism.

In conclusion, we suggest that nicotine gum could be a possible choice for treatment of EOP patients, especially in smokers.

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