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Nicotine Gum: Chew Rate, Subjective Effects and Plasma Nicotine[1]

R. NEMETH-COSLETT,* NEAL L. BENOWITZ,†
NANCY ROBINSON* AND JACK E. HENNINGFIELD*[2]

*National Institute on Drug Abuse, Addiction Research Center, Baltimore, MD
†Division of Clinical Pharmacology and Experimental Therapeutics, Department of Medicine
San Francisco General Hospital, University of California, San Francisco

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NEMETH-COSLETT, R., N. L. BENOWITZ, N. ROBINSON AND J. E. HENNINGFIELD. *Nicotine gum: Chew rate, subjective effects and plasma nicotine.* PHARMACOL BIOCHEM BEHAV **29**(4) 747–751, 1988.—Two studies were conducted to assess the effects of varying the rate at which single pieces of nicotine gum (4 mg) were chewed. In each study, six cigarette-deprived volunteers were tested during four sessions. In each session, they were required to chew the gum for 10 min at varying rates; a variety of self-report and physiologic responses were recorded before and after chewing. All chewed gum was analyzed for amount of nicotine extracted, and blood samples were collected for nicotine analysis. Additionally, in Experiment 2, a measure of masticatory pressure was employed to assess the intensity of chewing and to empirically verify the number of chews. In both studies, we found a weak, but direct, relation between chew rate and the amount of extracted nicotine. Experiment 2 revealed a probable cause of the weaker than expected "dose-effect" function: subjects showed compensatory changes in behavior by chewing slower than instructed in the high rate conditions, and by chewing faster than instructed in the low rate conditions. Thus, despite instructions to vary chew rates across an 8-fold range, actual chew rate varied by only 2.2-fold. Intensity of chewing remained constant across conditions. Taken together, the findings suggest that rate of chewing nicotine gum can make a difference in the amount of nicotine extracted from the gum; however, compensatory changes in chew rate may attenuate attempts to systematically vary nicotine dose in this manner.

Nicotine gum Plasma nicotine level Humans Nicotine dependence Dose manipulation
Compensation Cigarette smoking

RECENT findings suggest that a major determinant of the efficacy of nicotine chewing gum is the dose which is administered. For instance, two studies have shown little or no effect of 2 mg nicotine gum on cigarette smoking, but reliable decreases in smoking when 4 mg pieces of gum were given [7,9], and, in one study [9], 8 mg (2 pieces of 4 mg gum) of nicotine in the form of the gum produced even greater decreases in cigarette smoking. Furthermore, plasma nicotine levels were a direct function of the nicotine gum dose level. In both of these studies, subjective effects were also directly related to the nicotine gum dose. Similarly, a recent study of the effects of nicotine gum on the signs and symptoms associated with tobacco withdrawal showed that whereas hourly administration (for 12 hours) of 4 mg gum reduced most measures of tobacco withdrawal, similarly administered 2 mg gum produced weak and generally non-significant effects [6]. The nicotine content of the gum, then, is a determinant of both the amount of nicotine administered as well as its efficacy on various behavioral and physiological measures.

The manner in which nicotine delivering gum is chewed (i.e., rate and vigor) could also alter the amount of nicotine extracted from the gum and, hence, alter its efficacy. Since preliminary data [8] had suggested such, chew rates were controlled in the three studies discussed above. It is plausible that the procedure contributed to the orderliness of the dose effect functions obtained in those studies. What remains uninvestigated, however, is whether or not chewing rate would make a systematic difference in the amount of nicotine extracted and hence the effects of the gum. If it did, such variation across subjects in basic research studies, or across patients in clinical applications, could limit the experimental control over dose or the intended therapeutic regimen respectively. The main purpose of the present study was to hold the nicotine content of the gum constant and assess the effect of varying the chew rate on amount of nicotine extracted, plasma nicotine levels, physiologic measures and subject ratings.

EXPERIMENT 1

METHOD

Subjects

Six male cigarette smokers with histories of drug abuse

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[2]Requests for reprints should be addressed to Jack E. Henningfield, Ph.D., NIDA, Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224.

resided on a residential research ward. In brief, their mean ages were 32.3 years, they reported smoking a mean of 30 cigarettes a day for a mean of 18.1 years, and each subject smoked cigarette brands which delivered a mean of 1.03 mg nicotine per cigarette. No subject reported prior exposure to nicotine gum. Measurement of carbon monoxide (CO) in samples of expired air indicated that all subjects regularly inhaled tobacco smoke and were dependent on nicotine as judged by their scores on the Fagerstrom Tolerance Questionnaire (FTQ) (mean score 7.5) [2].

Procedure

Cigarette smoking was not permitted for 10 hr prior to and during sessions (mean presession CO levels were 14.8 ppm; SEM were ±1.06). Consumption of caffeine-containing products was not permitted for 12 hr prior to the session. At all other times, subjects were free to smoke their usual brand of cigarettes.

Each subject participated in 4, 1-hr experimental sessions which were scheduled 1–3 days apart. Before and immediately following each session, a 10 ml blood sample was collected. Sitting blood pressure, heart rate and skin temperature were monitored at 5-min intervals throughout the hour and five psychometric instruments were administered to characterize the subjective effects of varying the chewing rate. Briefly, these questionnaires consisted of visual line analog scales designed to measure the "positive" and "negative" effects of the gum, a short form of the Addiction Research Center Inventory (ARCI), the Single Dose Questionnaire (SDQ), a tobacco oriented questionnaire and an observer version of the SDQ [4].

Each subject was informed that participation in the study required that he remain seated in a test room and chew a piece of gum which may or may not contain nicotine, for 10 min. He was required to chew (bite) the gum once at the sound of each computer-generated tone. In the actual course of the study, each subject was always given one piece of 4 mg nicotine gum per test session. The chew rate varied, randomly, within subjects and rates across sessions included: 1 chew every sec, every 2 sec, every 4 sec, or every 8 sec. Subject compliance was monitored by an attending nurse. Gum chewing began at 10 min post-session onset and continued, uninterrupted at the rate set by the computer-generated tone, for 10 min, after which time the gum was collected and frozen for assay.

Data Analyses

Data from measures of blood pressure, heart rate, skin temperature, plasma nicotine level and amount of nicotine extracted from the gum were entered both as change scores (post-gum chewing values subtracted from pre-gum chewing values) and absolute post-gum chewing values and were analyzed separately in a one-way analysis of variance for repeated measures. Subject and observer ratings of drug effect, dose strength, feel drug, drug liking, subject ratings of equivalence to cigarettes and positive and negative analog scale scores were analyzed separately using post-gum chewing values. Subject ratings of desire to smoke as well as MBG, PCAG and LSD scale scores were analyzed as change scores (post-session values subtracted from presession values). Finally, both individual and group Pearson Correlation Coefficients were obtained to assess the relationship between the amount of nicotine extracted from the gum and plasma nicotine change values.

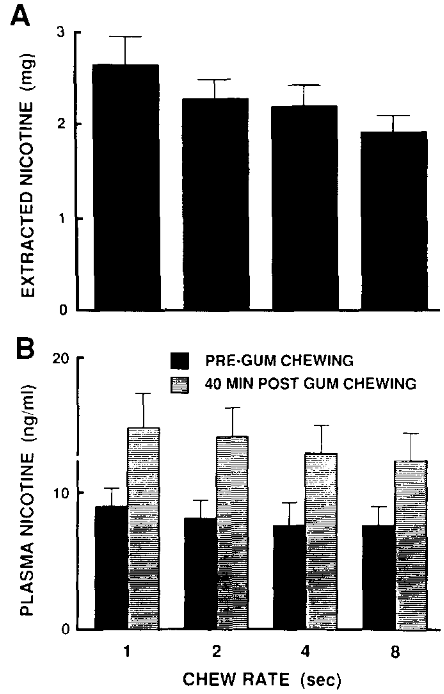

FIG. 1. Panel A shows amount of nicotine extracted as a function of chew rate from gum containing 4 mg nicotine in Experiment 1. Bars show mean data (n=6) and brackets show 1 SEM. The amount of nicotine extracted at the 1 chew every 8 sec rate was significantly less than the amount of nicotine extracted at the 1 chew every sec rate ($p<0.05$). Panel B shows pre-gum chewing (solid bars) and 40 min post-gum chewing (striped bars) plasma nicotine levels (ng/ml) for the subjects represented in Panel A. Nicotine plasma levels were significantly higher post-gum chewing when compared to pre-gum chewing levels; however, they were not significantly increased as a function of chew rate, nor correlated with amount of nicotine extracted from the gum.

RESULTS

Gum Nicotine Extraction

Figure 1, Panel A shows that the amount of nicotine extracted from the gum was significantly increased as a function of chew rate, $F(3,15)=3.48$, $p<0.05$. The greatest amount (mean 2.66 mg) was extracted at the fastest chew rate and the least (mean 1.93 mg) was extracted at the slowest chew rate.

Plasma Nicotine Levels

As shown in Fig. 1, Panel B, the slight variations in post-session plasma nicotine levels represented weak, but non-significant increases in plasma nicotine level as a direct function of chew rate. Mean post-session plasma nicotine values were, however, uniformly significantly increased above mean presession values, $F(3,15)=10.15$, $p<0.05$.

Extracted Nicotine and Plasma Nicotine Levels

Across subjects, there was no correspondence between amount of nicotine extracted from the gum and subsequent plasma nicotine levels ($r=-0.04$). However, within subjects, there was wide variation in the correlation between extracted nicotine and plasma nicotine level change scores, ranging from −.29 to .85. Three subjects showed a positive correlation and three subjects show a negative correlation.

Physiologic Effects

Blood pressure, heart rate and skin temperature showed a significant change over time in all chew rate conditions; there was no significant change as a function of chew rate. Systolic and diastolic blood pressures tended to peak 5 min after gum chewing with an average increase of 1.3 mmHg and 2.7 mmHg across rate, respectively. Heart rate generally increased an average of 4.7 beats per min within 10 min after gum chewing. Skin temperature was not significantly affected by chew rate and increased an average of 1.6°C 5 min post-gum chewing.

Subject Ratings

Mean subject ratings of desire to smoke, equivalence to cigarettes, dose strength and drug liking were not significantly affected by chew rates (Tobacco and Single Dose Questionnaires). Occasional symptoms, reported verbally to the nurse observer, were nausea and jaw fatigue. Hiccupping also occurred in 3 subjects. These effects were somewhat more pronounced following the fastest rate of chewing. Scores on the MBG and PCAG scales did not significantly vary as a function of chew rate. However scores on the LSD scale ("Dysphoria") were significantly elevated at the 1 chew per sec rate when compared to scores obtained at the other three chewing rates. When positive and/or negative effects were noted on the visual line analog scales, they tended to be most pronounced within the first 5 min after gum chewing. There was, however, no significant effect of chew rate on either the mean positive or negative scale scores.

EXPERIMENT 2

Although the results of Experiment 1 did confirm that chew rate could make a difference in amount of nicotine extracted from the gum, the magnitude of the effect was weaker than expected on the basis of the instructed 8-fold variation of chew rate. In Experiment 2, we replicated the procedure of Experiment 1 and also included a measure of masticatory pressure to assess compliance with gum chewing instructions. Additionally, a third blood sample at 5 min post-gum chewing was collected.

METHOD

Subjects

Six male cigarette smokers, with histories of drug abuse who did not serve in Experiment 1, resided on a residential research ward. In brief, their mean ages were 32 years, they reported smoking a mean of 25.8 cigarettes a day for a mean of 19.3 years, and each subject smoked cigarette brands which delivered a mean of 1.11 mg nicotine per cigarette. No subject reported prior exposure to nicotine gum. Measurement of carbon monoxide (CO) in samples of expired air indicated that all subjects regularly inhaled tobacco smoke and were dependent on nicotine as judged by their scores on the Fagerstrom Tolerance Questionnaire (FTQ) (mean score 7.8) [2].

Procedures

Procedures were identical to those of Experiment 1 except that each subject had electrodes attached with electrode paste, ipsilaterally, at the temporomandibular joint and the temporalis muscle on their preferred chewing side. This placement of electrodes provided a measure of conductance (mV) through electromyelography (EMG), to determine if masticatory pressure was influenced by chew rate. To validate subject compliance with respect to chew rate, the time course of actual number of chews within each session was determined by on line computerized analysis of EMG data. Specifically, an instance of electrical activity exceeding an empirically calculated threshold was counted as one chew. Also included in Experiment 2 was a third blood sample, drawn 5 min after gum chewing.

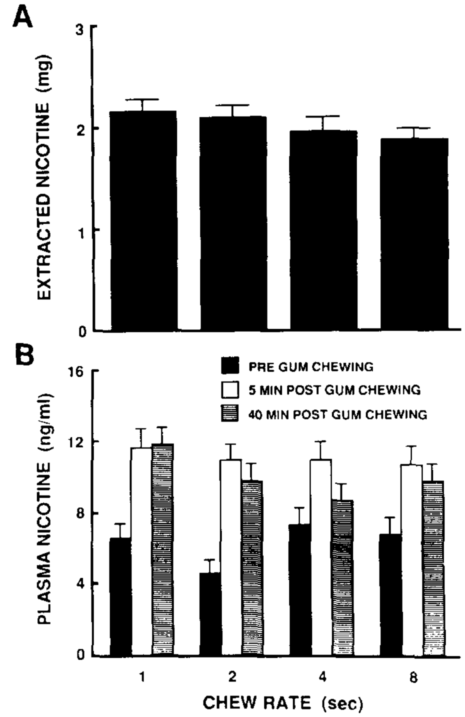

FIG. 2. Panel A shows amount of nicotine extracted as a function of chew rate from gum containing 4 mg nicotine in Experiment 2. Bars show mean data (n=6) and brackets show 1 SEM. The amount of nicotine extracted at the 1 chew every 8 sec rate was significantly less than the amount of nicotine extracted at the 1 chew every sec rate ($p<0.05$). Panel B shows pre-gum chewing (solid bars), 5 min post-gum chewing (open bars) and 40 min post-gum chewing plasma nicotine levels (ng/ml) for the subjects represented in Panel A. Nicotine plasma levels were significantly higher at both 5 min and 40 min post-gum chewing when compared to pre-gum chewing levels; however, at neither time point were plasma nicotine levels significantly increased as a function of chew rate, nor correlated with amount of nicotine extracted from the gum.

Data Analyses

All data was analyzed as in Experiment 1. In addition, Masticatory Pressure and number of chews per session were analyzed in a two-way analysis of variance [Rate (1 sec, 2 sec, 4 sec, 8 sec) × Time (first 5 min of gum chewing versus last 5 min)]. Finally, mean correlation coefficients were obtained to determine the relationship between actual number of chews, the amount of nicotine extracted from the gum, blood plasma level and subject ratings of positive effects (i.e., visual line analog scale data).

RESULTS

Gum Nicotine Extraction

Analysis of chewed gum revealed that nicotine was again extracted in a manner directly related to chew rate (Fig. 2, Panel A); however, the magnitude of this effect was weaker than in Experiment 1 and was not statistically significant. The greatest amount of nicotine (mean 2.16 mg) was extracted at the fastest rate and the least amount of nicotine (mean 1.88 mg) at the slowest chew rate.

Plasma Nicotine Levels

As in Experiment 1, analysis of blood samples revealed reliable increases in plasma nicotine levels in all conditions; again, however, these elevations were not significantly related to chew rate (Fig. 2, Panel B).

Physiologic Measures

Blood pressure, heart rate and skin temperature showed a significant alteration over time with no significant alteration as a function of chew rate.

Subject Ratings

Subject ratings of desire to smoke, equivalence to cigarettes, dose strength, and drug liking were not significantly affected by chew rate. Scores on MBG, PCAG and LSD scales were not significantly altered as a function of chew rate; LSD scale scores, however, approached significance ($p=0.07$). When positive and/or negative effects were noted on the visual line analog scales, they again tended to be most pronounced within the first 5 min after gum chewing. There was, however, no significant overall effect of chew rate on either the positive or negative scale scores.

Electromyelography Measures

The recorded number of chews taken at each of the four specified rates varied significantly, $F(3,15)=3.68$, $p<0.05$. However, whereas subjects had been instructed to chew upon the sound of each tone which would have produced values of 600, 300, 150 and 75 chews at the 1 sec, 2 sec, 4 sec and 8 sec rates, respectively, the actual mean number of chews and resultant chew rates were 315 (1.9 sec), 282 (2.1 sec), 223 (3.7 sec), and 143 (4.2 sec), respectively.

Analysis of EMG data suggested that intensity of chews did not vary across conditions since there was no significant change in voltage as a function of chew rate; average values were 152.2 ($\pm$15.7) mV per chew. Additionally, there was no significant change in voltage within sessions, when values obtained from the first 5 min of the 10 min chewing bout were compared to values obtained from the last 5 min.

To assess the relationship among actual number of chews, amount of nicotine extracted from the gum, plasma nicotine level and subject ratings of positive effects, correlational analyses were conducted. Coefficients indicated that the only significant relationship was between plasma nicotine level and subject ratings of positive effects ($r=.41$, $p<0.05$). coefficients between number of chews and extracted nicotine, blood plasma, and positive effects were $r=.06$, .03 and .12, respectively. Coefficients between extracted nicotine with plasma nicotine and positive effects were .08 and .26, respectively.

GENERAL DISCUSSION

These experiments confirm that variation in instructed chew rate can alter the amount of nicotine extracted from the gum. The relatively small resultant changes in nicotine plasma levels (less than 6.1 ng/ml) were not sufficient to produce reliable changes in the measures of subjective and physiologic effects used in this study; however, it is possible that over the course of a day in which multiple pieces of gum were chewed, a cumulative effect of this factor could occur. The results of Experiment 2 suggest that subjects may chew the gum in such a manner that compensates for intended changes in dose extraction (e.g., by underchewing 53% at the fastest rate and overchewing 91% at the slowest rate).

Assays of chewed gum verified that all subjects extracted a portion of the total nicotine available from the gum. Although there was a tendency for subjects to extract more nicotine from the gum while chewing at the fastest rate, the amount extracted varied widely both within and across subjects. Determinants of this source of variation in administered dose remains to be identified. Another factor that is of likely import in the control of dose is the amount and/or rate of saliva swallowed during chewing, since nicotine not absorbed through the buccal mucosa is largely metabolized upon its first pass through the liver [1].

The analysis of plasma nicotine levels revealed that increases in plasma nicotine following the chewing of 4 mg nicotine gum were weakly, but not significantly, affected by chew rate. In retrospect, the small magnitude of this effect is not surprising since there was only a variation of 0.8 mg of nicotine extracted from the gum across conditions in Experiment 1 and 0.6 mg difference in amount of nicotine extracted in Experiment 2. Similarly, since there was no significant change in blood plasma nicotine level as a function of chew rate, it is not surprising that other physiologic and self-reported measures remained relatively stable.

It is also possible that the observed compensatory changes reflect an effort to control nicotine dose, since analogous compensation is observed when cigarette smokers are given cigarettes of varying yield to smoke [3,10]. However, since the present subjects had no prior experience with the gum chewing and rates remained stable throughout the 10 minute duration of the chewing bout, it seems more likely that gum chewing rates themselves are relatively stable within subjects and resistant to instructional change.

The only subject rating which was significantly affected by chew rate was an elevation in "dysphoria" as measured by the LSD scale scores in Experiment 1. The increase in dysphoria was only obtained at the highest (one chew every sec) rate and is a finding which is consistent with higher nicotine dose effects found in other studies [4]. Alternatively, it is possible that this effect may have been due to the physical demands of the high chew rate condition.

A possible clinical implication of such findings is that patients may require more careful and explicit instructions regarding chew rate. Since, as Hughes and his co-workers have shown, anticipated effects can alter gum self-administration, it is possible that an explanation of the likely consequences of increasing or decreasing chewing rates would ensure compliance. Clearly, however, insofar as control over nicotine dose is important in both research and clinical applications involving nicotine gum, further study of variables that determine the actual delivered dose should be of benefit. Such studies should contribute to better specification of the parameters which should be controlled for optimal therapeutic nicotine gum dosing regimens in the treatment of tobacco dependence.

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