The Titration Hypothesis Revisited: Nicotine Gum Reduces Smoking Intensity

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INTRODUCTION

Smokers alter puffing and inhalation patterns in response to changes in the characteristics of the cigarettes they smoke. Increasing ventilation or decreasing draw resistance increases smoking intensity (Dunn 1978; Sutton et al. 1978; Henningfield and Griffiths 1980). Shortening cigarette length increases puffing rate and the total number of cigarettes smoked (Goldfarb and Jarvik 1972; Gritz et al. 1976; Ashton et al. 1978; Russell et al. 1980a). When smokers take more puffs per cigarette, the intercigarette interval increases (Griffiths et al. 1982). When forced to smoke at more frequent intervals, they reduce puff volume (Gritz et al. 1983). Smokers who switched from middle to low tar cigarettes increased their puff size and a mathematically derived exposure index, but not the number of puffs, puff duration, interpuff interval, or butt length (Pawbone et al. 1978). Decreasing the machine-determined nicotine yield of cigarettes increased the number of cigarettes smoked in the 16 studies reviewed by Stepney (1980). Decreasing machine-determined nicotine delivery of cigarettes smoked increases puff volume (Adams 1978; Creighton and Lewis 1978; Herning et al. 1981; Gust and Pickens 1982). Only Dunn and Freiesleben (1978) reported no relationship between puff volume and decreased machine nicotine delivery.

These studies support the nicotine titration hypothesis. That is, smokers adjust their smoking patterns to obtain an optimal dose of nicotine from whatever cigarette they are smoking. Presumably, this dose produces some optimal blood or brain level of nicotine. Had nicotine blood levels been measured in these studies, the titration hypothesis might have been confirmed.

Studies where smokers were given cigarettes of different machine-determined yields and nicotine blood levels were obtained do not appear to support the titration hypothesis. When smokers are switched from mid-nicotine yield cigarettes to high machine yield cigarettes, nicotine blood levels are higher (Ashton et al. 1979,
when smokers are switched from mid- to low-yield cigarettes, the corresponding blood levels decrease (Russell et al. 1972; Ashton et al. 1979 1981; Benowitz et al. 1982). If smokers actually titrate, the nicotine blood levels for the different cigarettes should be similar. However, only Russell et al. (1972) found equal blood levels when cigarettes yielding 1.32 mg and 3.2 mg nicotine were compared. Hill and Marquardt (1980) noted similar nicotine metabolite levels (cotinine) when tar and nicotine machine yield were manipulated.

Thus, these cigarette-switching studies have adequately demonstrated that subjects change puffing patterns in the direction predicted by the titration hypothesis, but they have failed to show that the adjustment leads to similar blood levels. The interpretation of these studies is complicated because high- and low-yield commercial cigarettes contain equivalent amounts of nicotine (Renowitz et al. 1983), and blood nicotine or cotinine levels do not correlate with machine yield of nicotine in large samples of smokers (Russell et al. 1980b; Benowitz et al. 1982; Herning et al. 1983b).

Supplemental nicotine or pharmacological manipulations which modulate nicotine's effects or its excretion alter smoking patterns. Oral doses of nicotine or infusions reduced smoking (Johnston 1942; Lucchesi et al. 1967; Jarvik et al. 1970). Stolerman et al. (1973) found mecamylamine, a nicotine antagonist, increased smoking rate. Naloxone, an opiate antagonist, reduced the number of puffs on a cigarette as well as the number of cigarettes smoked per day (Karras and Kane 1980). The manipulation of urinary pH to alter nicotine excretion modified cigarette smoking (Schachter et al. 1977). Except for a study by Kumar et al. (1977, experimental alterations which either blocked nicotine effects or increased nicotine blood levels produced the expected changes in smoking behavior.

The latter studies provide support for the nicotine titration hypothesis and support the use of supplemental nicotine as adjunct to smoking cessation therapy. Slow release buffered nicotine gum (Nicorette) now available provides the researcher another opportunity to test the nicotine titration hypothesis in controlled laboratory studies. The previous studies giving supplemental nicotine did not measure nicotine blood levels. Although smoking behavior changed, there is no evidence that the experimental manipulation produced similar nicotine blood levels. If subjects are indeed titrating nicotine, blood levels should be equal when supplemental nicotine and placebo are given. The present study evaluates whether smokers given placebo or nicotine gum reduce the intensity with which they smoke as compared with smokers given placebo and whether blood levels are reasonably similar on nicotine and placebo gum test sessions.
METHODS

Subjects

One female and five males served as subjects. They were 31.7 ± 3.3 (mean and standard deviation) years old. The subjects smoked 30.8 ± 7.4 cigarettes per day with 6.0 ± 26 of these cigarettes smoked in the morning. All subjects had smoked for at least 10 years and smoked their current brand for 2 years or more. The machine-determined nicotine yield of their current cigarette was 1.14 ± 0.19 mg. They smoked their current brand during each of the two ad lib smoking sessions.

Experimental Procedure

During each of two morning sessions, the subjects smoked their self-selected brand of cigarette while chewing either nicotine or placebo gum in a counterbalanced order. The subjects were asked to remain abstinent from cigarette smoking from the night before. The experimental sessions lasted 4 hours. The subject sat in a comfortable reclining chair during this time and either read or listened to music. During this period the subject could smoke at anytime. Before and 2 minutes after smoking, blood was drawn for nicotine terminations. Expired breath samples were collected 10 minutes after each cigarette and tested for carbon monoxide level. During smoking, puff and inhalation patterns were monitored (see below). During the first half hour of each hour the subjects chewed either placebo gum or gum containing 2 mg of nicotine in a buffered slow release resin (Nicorette, supplied by Merrell Dow) according to the instructions in the package insert. Before and 25 minutes after chewing, blood was drawn for nicotine levels. During a given morning session, each subject received four pieces of one type of gum or the other. The gum was administered in a double-blind fashion. The lab sessions were separated by 5 or more days. Heart rate and blood pressure were measured at half-hour intervals.

Measurement of Smoking Patterns

Puff volume and duration were measured by a single transducer flow meter. The flow meter consists of a plastic cigarette holder connected via flexible tubing to a Statham pressure transducer (Model PM5TC). Each cigarette smoked was precalibrated with known air flows, as in our previous studies (Herning et al. 1981 1983a,b). Inhaled volume and duration were measured by an Ambulatory Monitoring inductance plethysmograph Respitrace). The plethysmograph was calibrated with a Collins (Model 06031) water spirometer using the method described by Watson (1979).

The analog signals from the flow meter and plethysmograph were digitized every 40 ms from start of the puff for a period of 8 seconds. Puff and inhalation measures were numerically calculated from digital values. We calculated puff volume from flow using numerical integration which involves dividing the area under the flow curve into small trapezoids. These trapezoids are then added
together to obtain volume. Puff duration is the interval from start to end of puff where the flow values are non-zero. Inhaled volume is volume at maximal inhalation after a puff. The duration of inhalation is interval from start of the puff to maximal inhalation. Thus, it is half the actual duration of inhalation. Puff and inhalation duration were measured to the nearest 1/25 of a second while interpuff interval was measured to the nearest second.

Biochemical Measures

Blood samples were drawn from a forearm vein at half-hour intervals, immediately before smoking, and 2 minutes after the last puff. Samples were assayed for nicotine using the gas chromatographic method described by Jacob et al. (1981). An Ecolyzer (Series 2000) monitor was used to determine the CO levels from the expired breath samples.

Data Analysis Concerns

We hypothesized that the subjects would reduce the frequency and intensity of smoking when given nicotine gum compared to placebo. Since our hypothesis implied the direction each measure would change when the subjects chewed nicotine gum, one-tail probability values were appropriate for the t-test on these smoking measures. For example, our hypothesis tests especially for reduction in the number of cigarettes smoked on the nicotine gum day as compared to the placebo day.

We also hypothesized that nicotine blood levels would be equal on both test days. Thus, in such a test the area under the nicotine blood level curves (AUC) on both sessions should be equal. This statistical test is a test of the null hypothesis. Such a test presents some statistical problems. The lack of differences, if observed, could be due to excessive variability in the measures or to no actual difference in the means. One cannot be sure. One method to protect against this problem is basing the test against the null hypothesis by adjusting the probability levels to make finding a difference easier. Thus, for the test on nicotine AUC, a probability level of 0.10 was used. An additional problem in testing whether nicotine blood levels are equal revolves around the issue of what is a biologically significant difference in levels. Certain differences in the WC may be found, but are they biologically important? Thus, testing the titration hypothesis has some practical problems.

RESULTS

The area under the curve (AUC) for nicotine tended to be higher during the nicotine gum session (2945 ng•min•ml⁻¹) as compared to the placebo gum session (1925 ng•min•ml⁻¹). This difference was significant (t=2.16, df=1,5, p<.10) at the increased probability level. That is, our test subjects appear not to be titrating. The individual nicotine curves are presented in figures 1, 2, and 3. Before it was concluded that the subjects were not titrating, an unexpected complication was noted. Three of the subjects had
FIGURE 1. Nicotine blood level curves for Subjects 1 and 2. Bars indicate placebo or nicotine gun chewing periods.
FIGURE 2. Nicotine blood level curves for Subjects 3 and 4. Bars indicate placebo or nicotine gun chewing periods.
FIGURE 3. Nicotine blood level curves for Subjects 5 and 6. Bars indicate placebo or nicotine gun chewing periods.
higher blood nicotine levels on the gum day. These subjects smoked all or the majority of their cigarettes during the nicotine session while actually chewing the nicotine gum. Both the active and placebo gum have an alkaline buffer which increases buccal absorption of the nicotine. These subjects were perhaps obtaining more nicotine with the gum than they might have without chewing it. We tested for this possibility. A two factor analysis of variance with gum (placebo versus nicotine) and smoking period (chewing versus not chewing) as factors was used to test for any differential increase in nicotine blood levels while chewing gum. The increase in nicotine blood levels with smoking was significantly (F=4.4, df=1,53, p<.05) larger when the subjects were chewing gum (8.0 mg/ml) than when they were not chewing (5.1 mg/ml). Thus, regardless of the type of gum, nicotine blood level increased more during periods of gum chewing. Under such unexpected nicotine delivery conditions, titration may have been difficult.

Smoking patterns were modified by the nicotine gum. The mean number of cigarettes smoked during the 1-hour session was significantly less (t=2.23, df=5, p<.05, one-tailed) for the nicotine gum (4.3) than the placebo gum session (5.3). Mean interpuff interval, puff volume, puff duration, inhaled volume, and inhaled duration are listed in table 1 for all subjects on both test sessions. The means are calculated from all puffs during a given session. To simplify the analysis of these measures, a single exposure index (EI) was calculated for each session from equation (1).

$$EI = \sum_{i=1}^{N} EI_i$$  \hspace{1cm} (1)

where N equals the number of cigarettes smoked.

Each EI is calculated by (2) for each cigarette.

$$EI_i = (b_0 + b_1 \cdot MDOSE_i + b_2 \cdot NP_i + b_3 \cdot IPI_i + b_4 \cdot PV_i + b_5 \cdot PD_i + b_6 \cdot IV_i + b_7 \cdot ID_i)$$  \hspace{1cm} (2)

$MDOSE_i$ = machine determined yield for cigarette i
$NP_i$ = number of puffs for cigarette i
$IPI_i$ = interpuff interval for cigarette i
$PV_i$ = puff Volume for cigarette i
$PD_i$ = puff duration for cigarette i
$IV_i$ = inhalation volume for cigarette i
$ID_i$ = inhalation duration for cigarette i

The $b_0$, $b_1$ . . . $b_7$ were derived from a multiple regression of the above measures used to predict the increase blood nicotine levels in a large sample (N=104) of smokers used in our previous study (Herning et al. 1983b). Thus, the $b_i$'s were calculated from an independent sample of subjects. The $b_i$'s were 15.35, 8.35, -0.18, -0.25, 0.12, -3.06, -4.46, and 0.59, respectively.
<table>
<thead>
<tr>
<th>Subject Number</th>
<th>Type of Gum</th>
<th>No. of Cigarettes</th>
<th>No. of Puffs</th>
<th>Interpuff Interval (sec)</th>
<th>No. of Gum ettes</th>
<th>Puff volume (ml)</th>
<th>Puff Duration (sec)</th>
<th>Volume Inhaled (L)</th>
<th>Inhaled Duration (sec)</th>
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<tbody>
<tr>
<td>1</td>
<td>Placebo</td>
<td>6</td>
<td>51</td>
<td>51.5±17.7</td>
<td>49.1±16.1</td>
<td>2.2±0.6</td>
<td>0.68±0.22</td>
<td>2.7±0.5</td>
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<td></td>
<td>Nicotine</td>
<td>4</td>
<td>36</td>
<td>54.1±20.2</td>
<td>58±20.6</td>
<td>2.4±0.6</td>
<td>0.46±0.16</td>
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<td>2</td>
<td>Placebo</td>
<td>8</td>
<td>74</td>
<td>37.4±20.0</td>
<td>54.9±15.8</td>
<td>1.8±0.5</td>
<td>0.67±0.15</td>
<td>4.6±1.2</td>
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<tr>
<td></td>
<td>Nicotine</td>
<td>7</td>
<td>73</td>
<td>29.6±15.3</td>
<td>41.7±15.4</td>
<td>1.7±0.7</td>
<td>0.44±0.12</td>
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<td>6</td>
<td>43</td>
<td>54.2±35.3</td>
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<td>1.8±0.7</td>
<td>0.45±0.10</td>
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<td>38</td>
<td>45.7±27.1</td>
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<td>Nicotine</td>
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<td>48</td>
<td>29.6±17.1</td>
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<tr>
<td>5</td>
<td>Placebo</td>
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<td>22</td>
<td>71.8±28.0</td>
<td>65.8±24.5</td>
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<td>1.14±0.64</td>
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<tr>
<td></td>
<td>Nicotine</td>
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<td>66.1±42.9</td>
<td>83.2±28.6</td>
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<tr>
<td>6</td>
<td>Placebo</td>
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<td>46</td>
<td>45.5±28.6</td>
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<tr>
<td></td>
<td>Nicotine</td>
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<td>33</td>
<td>38.1±30.2</td>
<td>18.6±6.7</td>
<td>1.1±0.4</td>
<td>0.58±0.23</td>
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</tr>
<tr>
<td>Placebo</td>
<td>5.3±1.7</td>
<td>45.0±17.5</td>
<td>49.3±14.8</td>
<td>47.2±14.6</td>
<td>1.8±0.4</td>
<td>0.68±0.35</td>
<td>4.1±1.1</td>
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</tr>
<tr>
<td>Nicotine</td>
<td>4.3±1.5</td>
<td>41.3±18.0</td>
<td>43.1±16.5</td>
<td>49.9±19.6</td>
<td>1.9±0.5</td>
<td>1.03±0.70</td>
<td>3.8±0.8</td>
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</table>
The EI for the placebo session (81.6) was significantly larger ($t=2.14, \ df=5, P<.05$) than the corresponding EI (63.6) for the nicotine gum session. The area under the curve for CO tended to be lower on the nicotine session (2222 PPM•sec) than the placebo session (2606 PPM•sec), but the difference in means was not significant. Although CO did not clearly indicate increased smoking on the placebo day, it paralleled the EI measure. The values for each subject are plotted in figure 4. Points below the diagonal line indicate an increase in the intensity of smoking on the placebo day. Points above the diagonal line indicate an increase in the intensity of smoking on the nicotine day. Distance from the diagonal line indicates the magnitude of change. The plots are remarkably similar. Subject 4 is the only smoker not reducing his smoking behavior while on the nicotine chewing gum.

Heart rate ($F=4.65, \ df=9,45, P<.05$) increased over the smoking session from a pre mean of 62.9 to a maximum of 69.2. No difference in the increase was observed on the two test sessions. The changes in systolic blood pressure over a given session or over both sessions were not statistically significant from the pre test. Diastolic blood pressure increased with smoking from a pre mean of 69.3 to a maximum level of 75.2. This increase, although significant ($F=3.17, \ df=9,45, p<.05$), was similar on both test sessions. The maximal increase for both heart rate and diastolic blood pressure occurred at the 2-hour sample. No further increases were observed.

DISCUSSION

Nicotine chewing gum reduced the frequency and intensity of smoking in our subjects. The change in smoking behavior was reflected in a composite index of number of puffs, inter-puff interval, puff volume, puff duration, inhaled volume and duration. A decrease in carbon monoxide was also observed, but the difference in CO AUC between sessions was not statistically different. The composite exposure index appeared to be the more sensitive of the two measures. Since the composite index weights all aspects of smoking behavior, individual differences in regulation can be taken into account. However, a very simple measure of smoking, that is, number of cigarettes smoked, was also significantly reduced. Whether smoking behavior measures were simple or complex, our subjects smoked less on the nicotine gum session than on the placebo session.

The reduction in smoking is similar to that found by Johnston (1942) and Lucchesi et al. (1967) with intravenous doses of nicotine and by Jarvik et al. (1970) with nicotine tablets. It is unclear why Kumar et al. (1977) did not find such a reduction in smoking intensity. One possible reason is that the subjects in the Kumar experiment were not abstinent before testing as were the subjects in other studies and thus were relatively nicotine satiated at the time of testing.
FIGURE 4. The CO AUC values (top) and exposure index values (bottom) are plotted for each subject on both test sessions. The placebo session values are plotted on the x-axis and nicotine session values are plotted on the y-axis. Each point is labeled with a subject number. Values below the diagonal indicate increased smoking intensity on the placebo day.
In previous studies testing the titration hypothesis by administering supplemental nicotine while the subjects were free to smoke, nicotine blood levels were not measured. If subjects are titrating, one might expect the nicotine blood levels to be similar in sessions where supplemental nicotine was given and sessions where no supplemental nicotine was administered. Despite variability, the nicotine levels were higher in the nicotine gum session at the 0.1 level of significance. The increase in nicotine levels was due to half the subjects smoking their cigarette while chewing gum on nicotine sessions. The gum (both placebo and nicotine) changed the pH of the mouth which resulted in increased nicotine absorption. The increased nicotine absorption may have made titration more difficult.

Since only six subjects were tested, these results may not generalize to a heterogeneous sample of smokers. Different results might be obtained with less dependent or older, more dependent smokers. Our sample of smokers were in their late twenties and early thirties, had smoked for 10 years, and were now smoking one and a half to two packs a day.

In our study, the nicotine AUC was different between sessions. However, differences in nicotine blood levels between the two experimental sessions did not produce significant cardiovascular changes between sessions. Thus, it could be argued that the differences in blood levels between sessions were not physiologically meaningful. Smokers may have a range of blood levels which are sufficient to produce the cardiovascular and subjective effects they desire or to reduce the withdrawal symptoms they seek to avoid. Precise titration to identical blood levels may not be necessary.

SUMMARY

Supplemental nicotine gum reduced the intensity of smoking in six one-and-a-half to two-pack-a-day smokers. The study involved two 4-hour self-paced smoking sessions where nicotine and placebo chewing gum were administered in a double-blind fashion. Puff volume, puff duration, inhaled volume, inhaled duration, and interpuff interval were calculated for each puff on each cigarette. Blood was drawn for nicotine levels at regular intervals as well as before and after each cigarette. Cardiovascular measures were made at regular intervals. The nicotine gum reduced smoking frequency and intensity as predicted by the titration hypothesis. Precise titration (i.e., equal nicotine blood levels on both test days) was confounded by changes in smoked nicotine delivery produced by the gum. The gum, whether placebo or active, increased smoked nicotine absorption. However, while nicotine blood levels were slightly higher on nicotine gum day, the differences may not be biologically meaningful since heart rate and blood pressure increases were similar on both days. Difficulties testing the titration hypothesis are discussed.
REFERENCES


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