

Chewing nicotine gum for 3 months: What happens to plasma nicotine levels?

McKENDREE E. McNABB, MD

Techniques that help patients stop smoking should also reduce their exposure to agents such as nicotine. The mean plasma nicotine levels in 50 subjects while they were still smoking and then while they were chewing pieces of gum containing either 2 or 4 mg of nicotine over a 12-week period of abstinence were 35, 9 and 23 ng/mL (217, 56 and 143 nmol/L) respectively. A small number of subjects given an unlimited supply of gum used 14 to 24 pieces of 4-mg gum daily and had plasma nicotine levels exceeding the levels achieved while smoking. There were no acute symptoms necessitating medical intervention associated with these excessive levels. Side effects were uncommon and usually controllable. When simple dosage rules are followed people who chew nicotine gum for a few months to stop smoking lower their exposure to nicotine.

Les méthodes adjuvantes pour cesser de fumer devraient diminuer la prise de nicotine par le sujet. Chez 50 personnes on a noté les nicotémies moyennes suivantes: 35 ng/mL (217 nmol/L) quand elles fumaient encore, 9 ng/mL (56 nmol/L) après 12 semaines d'abstinence tout en mâchant de la gomme à 2 mg de nicotine et 23 ng/mL (143 nmol/L) quand la gomme était à 4 mg. Les quelques sujets à qui on a permis de mâcher autant de gomme nicotinée qu'ils le voulaient en ont consommé par jour de 14 à 24 morceaux à 4 mg, ce qui leur a donné des nicotémies supérieures à celles observées au temps où ils fumaient, sans toutefois produire de symptômes aigus nécessitant un traitement médical. Les effets secondaires sont rares et habituellement faciles à corriger. Une posologie toute simple permet à ceux qui, afin de cesser de fumer, mâchent de la gomme nicotinée pendant plusieurs mois, de diminuer leur prise de nicotine.

Nicotine chewing gum is a simple self-administered agent designed to offer pharmacologic and behavioural rewards similar to those of cigarette smoking. It is meant to be used for 2 to 6 months to suppress withdrawal symptoms and prevent relapse in persons who have stopped smoking. The active ingredient of the gum is an extract of the tobacco plant bound to an ion exchange resin to provide controlled release of nicotine. The gum is also buffered to pH 8.5 to enhance buccal absorption of nicotine. Pieces of gum contain either 2 or

4 mg of nicotine. Thirty minutes of chewing releases 90% of the nicotine from the gum.

Nicotine chewing gum has been found to be more effective as an adjunct to smoking cessation efforts than placebo gum.¹⁻⁵ Since nicotine has both psychoactive⁶ and cardiostimulatory⁷ effects, the possible toxic effects of nicotine chewing gum will be of interest to physicians considering prescribing the gum. Chewing gum as a source of nicotine is inherently safer than smoking because the release of nicotine from the gum is slow and depends on the voluntary act of chewing⁸ and because the oral mucosa absorbs nicotine more slowly than the alveoli. Swallowing gum and saliva containing nicotine does not result in appreciable absorption of nicotine, and what nicotine is absorbed from the gastrointestinal tract is metabolized in a first pass through the liver.⁸ Peak levels of nicotine in plasma are reached after 25 minutes of chewing.^{9,10} The elimination half-life of nicotine in plasma is 120 minutes.¹¹

Plasma levels of nicotine in subjects chewing the gum have been measured in a laboratory study⁹ and on single occasions in the course of clinical use of the gum,¹⁰ but no study has compared plasma nicotine levels in subjects who are smoking with serial levels while they are chewing nicotine gum as desired during the first few months of smoking cessation efforts. This study tested the hypothesis that persons who chew nicotine gum as desired to control symptoms of withdrawal from smoking maintain levels of nicotine in the plasma that rarely exceed those produced by their smoking.

Methods

Observations on 50 subjects selected from a larger group attending a smoking cessation clinic form the basis of this report. The subjects were selected because they abstained from smoking while using nicotine chewing gum and had at least four determinations of their plasma nicotine levels. Forty of the subjects attended a veterans hospital clinic and 10 a community-based clinic. An additional 19 subjects were selected from a group of nonabstinent clinic participants because they gave evidence of smoking and chewing the gum on the same day and also had had several plasma nicotine measurements. All 69 subjects had plasma nicotine levels of at least 15 ng/mL (93 nmol/L) after smoking a cigarette. The subjects' ages ranged from 29 to 67 years with a mean of 47; 34 were women. The mean number of years the subjects had smoked cigarettes was 27. At the start of the study the subjects were smoking a mean of 34 cigarettes daily (standard deviation 12.6). The mean nicotine yield of cigarettes smoked was 0.91 (ranging from 0.20 to 1.78) mg, according to 1981 tables of the Federal Trade Commission. All participants gave written consent to a protocol that called for chewing nicotine gum for 6 months as well as having venous blood sampled once while smoking and on four

From the pulmonary section, Little Rock Veterans Administration Medical Center and the college of medicine, University of Arkansas, Little Rock

Reprint requests to: Dr. McKendree E. McNabb, The John L. McClellan Memorial VA Medical Center, 4300 W 7th St., Little Rock, AR 72205, USA

occasions during the period the patient was to chew the gum and abstain from smoking. The study was approved by the University of Arkansas' human research advisory committee.

The initial blood sample was drawn within 2 minutes of completing smoking an afternoon cigarette. On the day of sampling the person had been asked to smoke no more or less than usual before the test, and the time of smoking coincided as nearly as possible with a natural urge to smoke. Participants were then asked to chew pieces of gum containing either 2 mg or 4 mg of nicotine. The first 11 persons were allowed to chew as many pieces daily as desired, but the remaining subjects were limited to 15 pieces daily. Subjects were not advised to limit chewing of the gum to times when experiencing urges to smoke, as recommended by the distributing firm, but were allowed to chew the gum continuously if they wished. They were given their choice of the 2- or 4-mg gum. Supplies of the gum and participation in the study were offered without expense to the subjects. Over the first 3 months of participation four blood samples were obtained during afternoon clinic visits. No attempt was made to standardize the number of pieces of gum chewed before the blood sampling or the time elapsed since the last piece of gum was chewed, but these variables were recorded on each occasion.

Carbon monoxide levels in the breath were measured electrochemically with a meter calibrated daily with gas containing 60 parts per million (ppm) of carbon monoxide. Subjects were designated abstinent from smoking if they so stated and demonstrated a level of carbon monoxide in alveolar air of less than 9 ppm, a nonsmoker's level.¹² Since nicotine cannot be inhaled without inhaling carbon monoxide, and since the elimination time of nicotine from plasma is half or less of that of carbon monoxide from blood and alveolar gas, the determination that alveolar carbon monoxide is at a nonsmoker's level verifies that any smoking-generated nicotine has been eliminated from the plasma.^{13,14}

Plasma nicotine levels were determined by gas chromatography,¹¹ with ethyl nornicotine as the internal standard. The technique was standardized with the use of known quantities of nicotine in calf serum. The coefficient of variation based on multiple replicate determinations was 4%. The paired *t* statistic was used for analysis of the plasma nicotine data.

On each clinic visit information concerning side effects was recorded on a checklist. Before the study, participants were reminded that nicotine could cause nausea, vomiting, stomach discomfort, lightheadedness, palpitation or chest pain.

Results

Of the 50 subjects who successfully abstained from smoking during the study 20 chewed the 2-mg gum and 30 the 4-mg gum. The former chewed a mean of 9 pieces daily and the latter 12 pieces (those free to use as much as they wished chewed 14 to 24 pieces per day). Plasma nicotine levels were measured from 187 blood samples drawn during the four visits. The levels correlated significantly with the dose of nicotine in the gum

chewed before the blood sampling on the day of the clinic visit ($r = 0.73$, $p < 0.001$). The mean lag between having started to chew the last piece of gum and having a blood sample taken was 95 minutes for those chewing the 2-mg gum and 60 minutes for those chewing the 4-mg gum; the standard deviations were 94 and 58 minutes respectively. The mean plasma nicotine levels at each visit ranged between 15.7 and 18.9 ng/mL (97.3 and 117.2 nmol/L); the overall mean levels for those chewing the 2- and 4-mg were 9.4 and 22.5 ng/mL (58.3 and 139.5 nmol/L) respectively.

The subjects' mean plasma nicotine level within 2 minutes after smoking a cigarette was 35 ng/mL (217 nmol/L). On all four visits, and for both doses of nicotine, the mean levels while chewing the gum were lower than after smoking (Fig. 1). There were, however, 19 occasions when the levels were greater while chewing gum than after smoking (Fig. 2); all of these occurred in subjects chewing the 4-mg gum, although only 4 of the 19 were in people chewing 15 or fewer pieces daily. Four subjects accounted for 10 of the excessive levels.

A questionnaire inquiring about the six side effects of nausea, vomiting, stomach discomfort, lightheadedness, palpitation or chest pain was administered on 181 of the 187 clinic visits. There were 38 of 1086 possible affirmative answers. Nausea and stomach discomfort were recorded most frequently. Vomiting was reported only once, and lightheadedness, palpitation and chest pain were recorded rarely. Five subjects accounted for 23 (61%) of the complaints. Four of these subjects

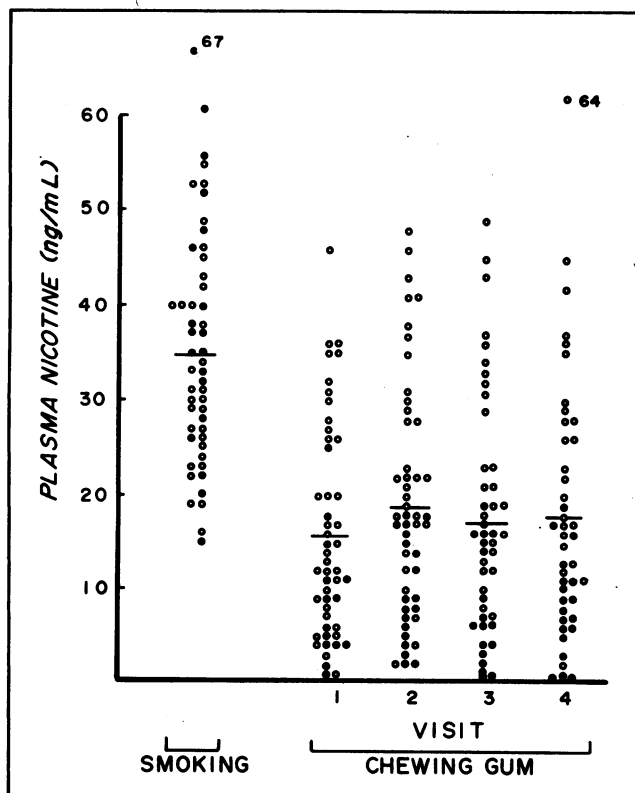


Fig. 1—Plasma nicotine levels while 50 subjects were still smoking, and while abstaining and chewing nicotine gum over a 3-month period. ○ = 4-mg gum; ● = 2-mg gum. Horizontal lines indicate mean values. There was no correlation between plasma nicotine levels during smoking and during use of gum.

continued to chew the 4-mg gum despite acknowledged side effects. The side effects never led the subject to seek medical attention. For 16 of the subjects reporting side effects the mean of all plasma nicotine levels during their use of the gum was 45% of their level while smoking (the baseline level). At the next clinic visit six subjects with nausea had a mean plasma nicotine level that was 60% of their baseline level. The mean of all the plasma nicotine levels of 32 subjects reporting no side effects was 61% of the baseline level. Among the 13 subjects who had excessive plasma nicotine levels the 4 with the highest plasma nicotine levels expressed as percentages of the baseline levels (154% to 258%, corresponding to absolute values of 37 to 64 ng/mL [229.4 to 396.8 nmol/L]) had no side effects.

The 19 subjects who chewed the gum but did not abstain from smoking on the days of their clinic visits had a mean baseline plasma nicotine level of 28 ng/mL (173.6 nmol/L) (Fig. 3) and a mean baseline carbon monoxide level of 32 ppm. The mean of 43 plasma nicotine levels on days of both smoking and chewing gum was 23 ng/mL (142.6 nmol/L); the mean carbon monoxide level then was 24 ppm. Only 2 of these 19 subjects converted to abstinence and completed the protocol; the remainder dropped out before making the required number of visits. In 228 opportunities to record side effects these 19 subjects gave 23 affirmative answers. Four accounted for 14 of the 23 complaints; three of these four did not abstain from smoking even temporarily. The fourth person, after a failed first effort

at cessation, returned for a second effort and subsequently did not record any side effects. The only one of these four subjects found to have plasma nicotine levels that exceeded the baseline level achieved the excess levels by smoking more.

Discussion

When administering psychoactive and cardiostimulatory drugs physicians are careful to follow rules for prescribing and sometimes monitor blood levels. Need they be so meticulous in administering nicotine gum to help patients stop smoking? In this study liberal use of the gum was encouraged. More gum was used per subject per day than in other reported clinical trials.^{1,3} In general the subjects were not influenced in their selection of the 2-mg or 4-mg gum by their previous level of smoking. There was no correlation between the baseline nicotine levels and the subsequent levels while the subjects were chewing the gum, and some subjects with the highest baseline levels elected to chew the 2-mg gum, whereas others with low baseline levels, 20 ng/mL (124 nmol/L) or less, chose the 4-mg gum (Fig. 1). Thus, the average of 9 pieces of 2-mg gum daily for 20 subjects and 12 pieces of 4-mg gum for 30 subjects represented what the subjects themselves found to be required in quitting smoking. Despite the minimal restriction of gum use the plasma nicotine levels never exceeded those produced by smoking in the subjects using the 2-mg gum. On average, users of the 4-mg gum had levels lower than their baseline, and only 19 of 114 (17%) plasma levels exceeded the baseline levels. Accounting for these excesses were a small number of

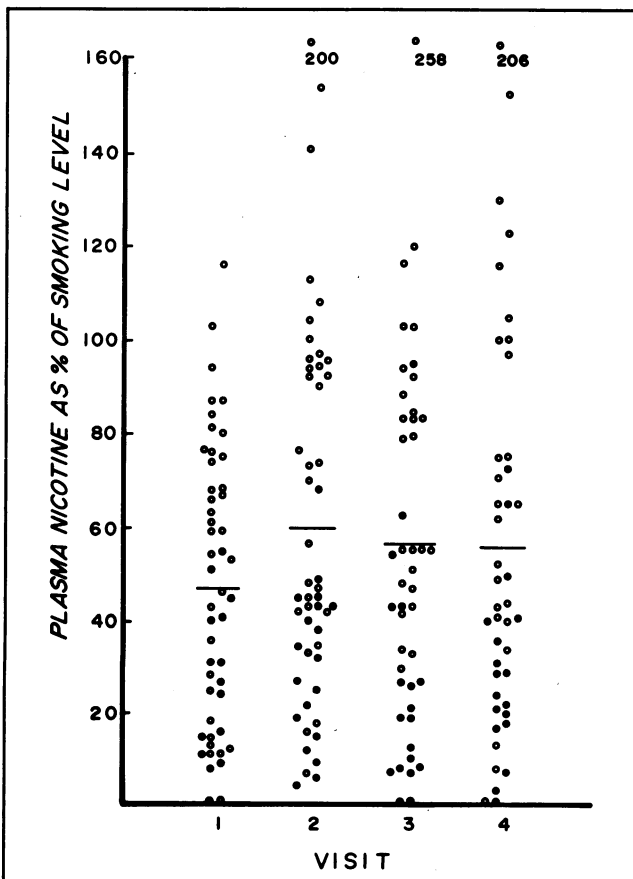


Fig. 2—Plasma nicotine levels during use of gum, expressed as percentages of levels during smoking.

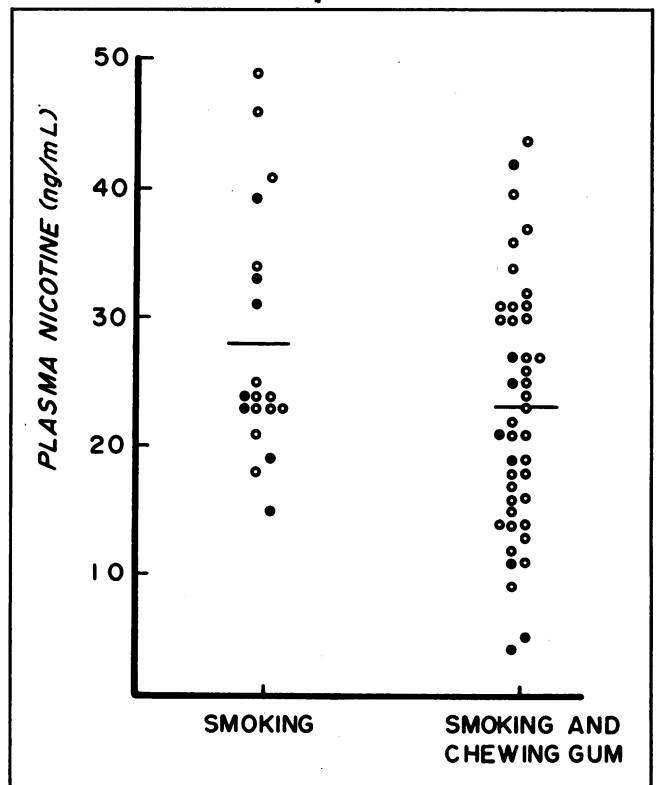


Fig. 3—Plasma nicotine levels of 19 nonabstinent subjects during smoking and during both use of gum and smoking.

individuals who in the earliest period of the study were allowed to chew up to their tolerance of the mechanical burden of chewing. Side effects were uncommon and not related to nicotine levels in blood samples taken during clinic visits. Subjects never required medical attention for side effects and with few exceptions continued chewing the gum even after reporting such effects.

The experience reported here offers evidence that physicians can prescribe nicotine chewing gum for smoking cessation with confidence in its safety. There seems to be no need for monitoring plasma nicotine levels or for rigid dose schedules.

The plasma nicotine levels of our subjects using the 4-mg gum were consistent with those found in other studies and confirm that nicotine levels do not rise over time. In a study of 43 clinic participants the mean plasma nicotine level produced by the use of 2-mg gum was 10.7 ng/mL (66.3 nmol/L).¹⁵ Studying the use of 4-mg gum by 21 subjects the same authors found peak and trough levels of 25.9 and 18.6 ng/mL (160.6 and 115.3 nmol/L).¹⁰ Peak and trough baseline nicotine levels in the latter subjects were 31.1 and 24.9 ng/mL (192.8 and 154.4 nmol/L). In a laboratory study nine subjects chewed gum hourly to produce mean trough levels of 11.2 ng/mL (69.4 nmol/L) for 2-mg gum and 23.2 ng/mL (143.8 nmol/L) for 4-mg gum.⁹ Mean plasma nicotine levels higher than those seen here for nicotine gum were found with smoking regular cigarettes,¹⁵⁻¹⁷ low-nicotine filter cigarettes^{16,17} and ultra-low-nicotine cigarettes,¹⁷ dipping smokeless tobacco¹⁸ and snuffing tobacco.¹⁹

Although nicotine gum is not intended to be used concurrently with smoking, 19 subjects did this for a limited time. Their plasma nicotine levels never exceeded the baseline levels except in one, whose breath carbon monoxide levels indicated increased smoking. This is consistent with a previous report indicating no trend toward excessive nicotine levels in persons smoking as desired while on a regimen of chewing nicotine gum.¹⁵ Together these reports suggest that persons alter their smoking to regulate nicotine in the plasma to accustomed levels.

While this study indicates that liberal provision of nicotine in gum seldom leads to excessive plasma nicotine levels, certain prescribing rules should be followed to ensure a greater margin of safety. Noninhalers should be advised that their efforts can be successful without the use of nicotine gum or with proprietary gum. Other subjects should begin with 2-mg gum and not use more than 15 pieces a day. Only 2-mg gum should be used for minimal inhalers and subjects smoking 15 or fewer cigarettes per 24 hours. No more than 12 pieces per 24 hours of 4-mg gum should be prescribed.

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