Drinking Coffee and Carbonated Beverages Blocks Absorption of Nicotine From Nicotine Polacrilex Gum

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Patients failing to obtain benefit from nicotine polacrilex gum in their efforts to quit smoking may be inadvertently blocking nicotine absorption. Effective nicotine absorption depends on the mildly alkaline saliva that is produced when buffering agents in the polacrilex are released along with nicotine as the polacrilex is chewed. We found that intermittent mouth rinsing with coffee or cola, but not distilled water, substantially reduced salivary pH and nicotine absorption. Because many commonly consumed substances were also found to be highly acidic, we recommend that patients do not ingest any substance during or immediately before nicotine polacrilex use.

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NICOTINE polacrilex (gum), when it is used properly, is an effective medication for the treatment of nicotine dependence.[1] Nicotine polacrilex can provide the following therapeutic effects: reduction of tobacco withdrawal symptoms[1,2]; reduction of the tendency to smoke cigarettes[1,3]; reduction of the effect of relapse factors, such as weight gain (at least while the polacrilex is being used)[1,4,5]; improvement in relapse avoidance[6,7]; and possibly reduction of urges to smoke.[1] However, all of these actions of nicotine are related to the dose level actually obtained; inadequate doses may produce no beneficial effect.[1,8] Often, it seems that patients use nicotine polacrilex with insufficient instruction either to enable them to obtain adequate dose levels or to achieve specific benefits they may expect.[9,10] Thus, for many patients who were unable to quit smoking with the use of nicotine polacrilex, the problem may have been failure to obtain the medication in sufficient doses and not medication failure per se.

When nicotine is placed in the mouth, the amount that is actually absorbed via the buccal mucosa is determined by the pH of the saliva, because nicotine is a weak organic base that is best absorbed in the nonionic form. The index of dissociation (pKa value) of nicotine is 8.0 when in aqueous solution at 25°C.[1] At a typical salivary pH of 7.0, only 10% of orally held nicotine is present in the nonionic form, rendering unbuffered nicotine polacrilex gum an unsatisfactory substrate for nicotine delivery.[11,12] Raising salivary pH to 8.0 results in 50% of the nicotine occurring in the nonionic form, which is satisfactory for clinical dosing. Therefore, 2-mg nicotine polacrilex is buffered with 10 mg of sodium bicarbonate and 20 mg of sodium carbonate, and 4-mg polacrilex (not commercially available in the United States) is buffered with 30 mg of sodium carbonate.

Chewing nicotine polacrilex releases nicotine and the buffering agent, thus enhancing effective nicotine absorption. The polacrilex does not, however, produce the sharp plasma level spike achieved when smoking cigarettes,[13] or even as quick an increase in plasma nicotine level as that produced by the use of smokeless tobacco products.[14] The buffered 2-mg formulation of nicotine polacrilex available by prescription in the United States can deliver a dose of nicotine somewhat less than that achieved by smoking a cigarette delivering a moderate nicotine level.[13,15] In fact, several studies have shown that, even in experienced polacrilex users, the actual amount of nicotine extracted from the 2-mg formulation is usually less than 1 mg, and only a portion (0.8 to 0.9 mg) of this nicotine is actually absorbed.[13,14,16] The amount extracted can also vary by such factors as chew rate.[17] Thus, anything that substantially reduces absorption could severely limit the efficacy of nicotine polacrilex.

Interviews with patients who seemed not to be achieving adequate doses of nicotine led to our hypothesis that nicotine absorption might be substantially impaired by the consumption of acidic beverages. We found that some of these patients drank coffee, fruit juices, or soft drinks, either while using the polacrilex or immediately before using polacrilex. A preliminary evaluation of the pH of whole-mouth saliva in a group of volunteers suggested that the consump-

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tion of an acidic beverage could substantially reduce salivary pH and that recovery could take as long as 20 minutes. This article describes our evaluation of the effects of oral pH manipulations on nicotine absorption.

We conducted two experiments to determine whether intermittent rinsing with commonly consumed beverages would alter the serum nicotine level achievable with nicotine polacrilex. Both experiments used an adaptation of a standardized chewing procedure that we have found reliably to produce 40% to 60% nicotine extraction, with orderly patterns of absorption and subjective and behavioral effects.[2,16,17] The first experiment evaluated the effects of coffee and cola on nicotine absorption from 4-mg gum; the second experiment evaluated the effects of distilled-water mouth rinses. We show that acidification of the oral cavity by commonly consumed beverages may virtually eliminate absorption of nicotine extracted from polacrilex and that the effect is due to oral acidification and not simply to rinsing the mouth.

SUBJECTS AND METHODS

Subjects

Eight adult male cigarette smokers were paid volunteers participating in two experiments, with four subjects in each. They had smoked a mean of 17 cigarettes per day (range, 3 to 30) for a mean of 17.5 years (range, 10 to 26 years). The mean age of the subjects was 33 years (range, 26 to 39 years). In the two experiments, all the subjects were in good mental and physical health except for their nicotine dependencies. Each subject gave informed consent for participation in the study. The consent forms and the experimental procedures were approved by the local Institutional Review Board in accordance with the Department of Health and Human Services guidelines for the protection of human subjects.

Polacrilex and Mouth Rinse Solution

Volunteers were tested with polacrilex containing 4-mg nicotine. The 4-mg polacrilex formulation is not commercially available in the United States but is identical to that supplied by the manufacturer (Nicorette Division, Pharmacia, Helsingborg, Sweden) to other countries, including Canada and the United Kingdom. Two mouth rinse solutions were used in experiment 1: brewed coffee and a cola-flavored soft drink, both presented at room temperature. The mean pH of the cola was 2.57 (range, 2.30 to 2.76); the mean pH of the coffee was 5.24 (range, 4.86 to 5.45). In experiment 2, commercially distilled water with a mean pH of 6.62 (range, 6.09 to 7.27) was used. Although these beverages are not generally consumed in their entirety at room temperature, this procedure was safe and acceptable to the subjects and permitted a simple means of standardization; the fact that the cola was administered at higher temperature and the coffee at a lower temperature than those at which they are served outside the laboratory should not have substantially affected the pH values of the whole-mouth saliva.

Procedure for Experiment 1

A within-subjects or crossover experimental design was employed whereby each subject was repeatedly tested under several conditions. Such designs can yield definitive results with small numbers of research subjects.[18] The subjects were deprived of nicotine and caffeine for approximately 12 hours before testing. The 3-hour test sessions were begun at about 7:30 AM each test day and consisted of three 45-minute test cycles separated by 15-minute breaks. Test sessions were conducted at least 24 hours apart. During a test session, the subject sat in an easy chair. A research assistant presented the experimental manipulations and collected the data. A research nurse inserted the catheter for blood sampling, collected samples, and administered the nicotine polacrilex.

During each test cycle, blood pressure, heart rate, skin temperature, and subjective responses were measured before, during, and 20 minutes after polacrilex administration. Five-milliliter blood samples were collected immediately before administration of polacrilex and at 5 and 15 minutes after the 15-minute chewing cycle. The chewing rate was controlled by a taped sequence of 0.1-second–duration pure tones presented at 3-second intervals. The subjects were instructed to chew only at the tone and for the duration of the tone. During the chewing phase, the subjects were instructed to stop chewing after 50 seconds and rinse their mouths for 10 seconds with 20 mL of the test solution provided by the research assistant. The rinse solution, along with whole-mouth saliva, was then collected and chewing was resumed. This chewing and rinsing cycle was repeated every minute for 15 minutes. During the test cycles in which no rinse was given, the subject stopped chewing, sham-rinsed with his saliva for 10 seconds, expectorated, then resumed chewing.

Salivary samples were collected for 1 minute immediately before polacrilex administration. Saliva collected after each rinse was pooled for later pH measurement. Subjects were instructed not to swallow either saliva or the rinse solutions during the chewing cycles. The pH measurements were made within an hour after the end of the test session. The chewed polacrilex was collected and frozen for later analysis of residual nicotine content. The venous blood samples were stored on ice during the test session and were centrifuged immediately after the test session. The serum was then frozen for subsequent analysis using a high-performance liquid chromatographic method that had a detection limit of 1 μg/L; the high degree of precision of the assay was indicated by its average coefficient of variation of 6.5%.[19]

The order of rinse conditions was determined according to randomly assigned Latin-square sequences to ensure comparable presentation of all conditions to each subject. Thus, each of the three oral rinse conditions was established on four test sessions, with the conditions of the first test session being repeated on the fourth. The first session was used as a training day for the subject, and the results were excluded from the analysis (resulting in a 3×3 Latin square for each subject). This procedure resulted in 12 observations (four subjects × three sessions) at each oral rinse condition. Both individual and group analyses of the data were performed, and each period was analyzed separately. Two-way and three-way analyses of variance on the dependent variables were performed to determine significance of the experimental effects.

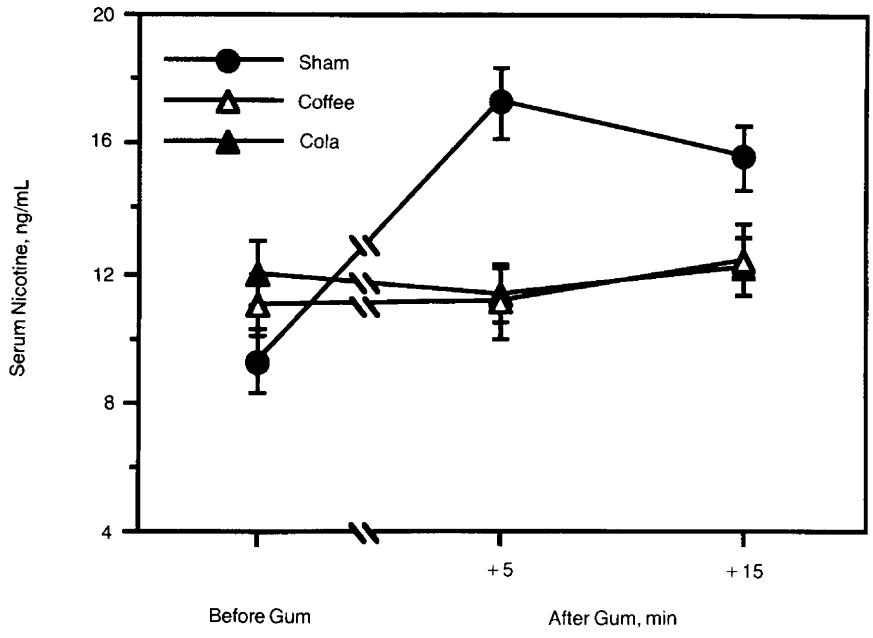
Procedure for Experiment 2

The general procedures of experiment 1 were used with the following changes. Volunteers participated in four test cycles on one test day. A sham rinse condition and distilled water (20 mL at room temperature) rinse condition were each tested twice in four subjects. The order of the sham rinse and distilled water rinse conditions was randomly determined for the first two test cycles and then repeated for the last two.

RESULTS

Experiment 1

Rinsing with coffee or cola acidified the saliva and virtually eliminated measurable levels of nicotine absorption. As shown in the Figure, changes in mean plasma nicotine levels were statistically insignificant over time after either a cola or a coffee mouth rinse. However, after the sham rinse, plasma nicotine levels increased significantly by 7.96 ng/mL 5 minutes after administra-



Serum nicotine levels as a function of rinse condition. Samples were taken immediately before administration of 4-mg nicotine polacrilex gum and 5 and 15 minutes after gum administration.

tion ($P<.01$) and by 6.30 ng/mL 15 minutes after administration ($P<.05$), when the data were analyzed by means of a two-way analysis of variance for dependent variables.

The mean baseline salivary pH level was 7.06. The mean pH of the collected saliva was 5.66 after the 5.24-pH coffee rinse, 3.18 after the 2.57-pH cola rinse, and 7.78 after the sham rinse. These values showed that the polacrilex produced a weak, but consistent, effect in the direction of increasing the pH, but that the main effect on oral pH was determined by the pH of the mouth rinse.

A "tingle" is commonly reported by patients using nicotine polacrilex. The mean tingle score on a visual line analogue scale (scored 0 to 100) was 42 after the sham rinse, 25 after coffee, and 24 after cola; however, the number of subjects was not adequate to reveal a significant effect on this measure. Scores on scales of possible positive or negative effects of nicotine polacrilex showed similar trends as tingle scores but also were not significantly changed. All other subjective and physiologic measures were virtually unchanged across conditions.

Residual nicotine levels in the chewed polacrilex samples were compared with the nicotine levels of an identical number of unchewed polacrilex samples to provide an estimate of nicotine extracted in each condition. The nicotine analysis procedure (performed by Merrell Dow Research Institute, Cincinnati, Ohio) obtained an average of 4.18 mg from unchewed samples of the 4-mg polacrilex formulation. Subjects extracted an average of 2.05 mg (range, 1.83 to 2.59 mg) in the sham rinse condition, 1.72 mg (range, 1.33 to 3.29 mg) in the coffee rinse condition, and 1.51 mg (range, 1.31 to 1.85 mg) in the cola rinse condition. These differences were not significant.

Experiment 2

The distilled water rinse in experiment 2 produced a small decrease in salivary pH when compared with the sham rinse condition but did not block nicotine absorption as the cola and coffee rinses had in experiment 1. The pH of the expectorant after polacrilex was used was 7.84 (range, 7.48 to 8.41) in the sham rinse condition and was 7.34 (range, 6.97 to 7.56) in the distilled water rinse condition. Rinsing with distilled water produced only a small decrease in the amount of nicotine extracted from the polacrilex: 1.50 mg (range, 1.28 to 1.67 mg) was extracted in the distilled water rinse condition and 1.84 mg (range, 1.53 to 2.20 mg) was extracted in the sham rinse condition.

After the sham rinse, plasma levels of nicotine increased by a mean of 4.0 ng/mL 5 minutes after administration and by a mean of 1.75 ng/mL 15 minutes after administration from the mean preadministration value of 11.63 ng/mL (not significant). After the distilled water rinse, plasma nicotine levels increased by a mean of 3.0 ng/mL 5 minutes after administration and by a mean of 4.1 ng/mL 15 minutes after administration from the preadministration mean value of 7.88 ng/mL ($P<.05$). The difference in absolute nicotine levels across the sham vs distilled water rinses was significant 5 minutes after administration ($P<.05$) and not at other time points. There were no significant changes in other physiologic responses or in subjective response measures.

IMPLICATIONS FOR COMMON INTERVENTION

Commonly Consumed Substances Are Acidic

The present results have implications for instructing patients in effective use of nicotine polacrilex as well as for identifying the factors that might lead patients either to stop using the polacrilex or to relapse to tobacco use. The Table gives the pH values of several commonly consumed substances; all, except the tap water, are more acidic than typical whole-mouth saliva. All of these substances should, therefore, be avoided during or immediately before nicotine polacrilex use. Solid foods should be similarly avoided because they may be acidic, and because residual acidic food particles remain in the mouth for several minutes.[20] We also conclude that nicotine polacrilex use should be delayed at least 15 minutes after food or liquid consumption. This recommendation is based on the results of a study from our laboratory that showed that full recovery to baseline pH of the whole-mouth saliva required that amount of time after oral acidification.[21]

Because effective nicotine absorption from polacrilex requires that oral pH be raised above typical levels, nicotine absorption may be attenuated not only by the use of substances that sharply reduce oral pH but also by those that simply mitigate the alkalinizing effect of the polacrilex. In this regard, another study from our laboratory showed that use of several brands of commonly used chewing gum, but not sugarless brands, significantly lowered oral pH.[21] Therefore, patients who feel that they must use chewing gum along with the polacrilex, either to reduce sticking or to improve flavor, should use sugarless gum and should be advised that they may require additional doses of nicotine polacrilex to obtain the same levels of nicotine.

Control Over Nicotine Dose When Using Polacrilex

One intent of this article is to help clinicians achieve greater control over

pH of Substances at 22°C, in Descending Order*

Substance	pH
Tap water	7.74
Chocolate milk	6.76
Whole milk	6.72
Skim milk	6.58
Chicken soup	6.54
2% lowfat milk	6.53
Distilled water	6.02-7.28
Coffee	4.86-5.45
Tomato juice	4.37
Beer	4.00-4.60
Soy sauce	3.92
Apple juice	3.88
Orange juice	3.81-3.89
Ketchup	3.66
Pineapple juice	3.64
Mustard	3.34-4.87
Diet cola	3.32-3.36
Lemon-lime soda	3.22-3.28
Grape juice	3.17
Cola	2.30-2.76

*A range of values indicates that two or more commercially available brands were tested.

the blood levels of nicotine obtained by their patients who have been prescribed nicotine polacrilex. Nicotine polacrilex is a drug delivery system in which nicotine is bound in an ion exchange complex and incorporated into a polacrilex resin base.[22,23] This configuration was devised to preclude accidental overdosage that might occur if the nicotine were too freely available, and to enable regulation of intake by the properly instructed patient.[12,23]

This report and previous reports from laboratory studies and clinical trials provide practical information that should enable clinicians to improve their control over nicotine intake by patients. It is clear, for example, that carefully instructed patients generally absorb only 0.8 to 0.9 mg of nicotine per polacrilex unit (2-mg formulation) and may absorb much less if they do not use it properly.[10,13,14] It has also been demonstrated that the chewing rate itself is a determinant of nicotine release from the polacrilex.[17] Swallowed nicotine not only is largely unabsorbed[1] but may also contribute to side effects, such as nausea and hiccuping.[24] There is also growing evidence that persons at greater levels of nicotine intake from tobacco use may benefit from higher doses of nicotine given in polacrilex therapy.[1]

The foregoing observations have led to rationally based strategies for individually determining nicotine polacrilex dosage. For example, Cooper and Clayton[25] reported 40% abstinence rates at 1 year of follow-up of heavy smokers treated in a nicotine polacrilex–based treatment program. These authors had recommended that the daily number of nicotine polacrilex doses be 60% to 80% of the usual numbers of cigarettes smoked per day.[25] Another strategy may be termed the "nicotine reduction therapy" formula, which specifies the initial number of 2-mg nicotine polacrilex units taken per day based on the typical daily cigarette intake of the patient, ie, 20 cigarettes per day equals 10 to 14 doses, 30 cigarettes per day equals 14 to 18 doses, and 40 cigarettes per day equals 18 to 22 doses. Regardless of the initial dosing strategy, however, follow-up of patients is recommended to determine if dose adjustments should be made and to determine if inadequate absorption is occurring because of factors such as those discussed in this report.

COMMENT

Whole-mouth saliva is the intermediary between the nicotine released from polacrilex and absorption through the buccal mucosa. Because the volume of whole-mouth saliva is typically only a few milliliters,[26] its pH can be readily be altered. When unaffected by other substances or stimulated by chewing, salivary pH values are commonly about 6.9 to 7.3,[12,27,28] which is too low for efficient transmucosal nicotine absorption.[1] Stimulated salivary flow, as occurs when chewing or at the sight of certain foods, includes saliva released from the parotid gland, which is alkalinized with bicarbonate; this source of bicarbonate, along with that released by nicotine polacrilex, can raise the pH of acidic solutions held in the mouth.[12,29] However, as shown in this report, the overall effect of commonly consumed beverages is to lower drastically the pH of whole-mouth saliva. Such acidification can virtually eliminate absorption of nicotine. The pronounced adverse impact on absorption produced in a single dose of polacrilex suggests that the clinical consequences of the effect might be magnified by the number of times during the day that a person used the polacrilex along with an acidifying substance.

Individuals vary in their salivary flow rates and such variation can also affect the buffering capacity of the oral cavity.[30-32] Because rates of swallowing are directly related to the volume of whole-mouth fluid,[26] differences in salivary flow rates may contribute to individual variability in amount of nicotine absorbed from polacrilex. Therefore, patients should not adjust their chewing technique simply based on variations in salivation; considerable variation, both within and across individuals, is independent of chewing technique and is expected. Moreover, patients who complain of excess salivation should be questioned to determine if their chewing technique is in accord with one of those widely recommended[24,33,34]; for example, effective nicotine release can be achieved if the patient chews the polacrilex once every 3 to 10 seconds until a tingling sensation results and repeats this cycle every few minutes. It may be important to remind individuals with high salivary flow rates to refrain from swallowing for about 1 minute immediately after a bout of chewing. (Preliminary data from our laboratory suggest that 40 seconds is sufficient for effective absorption of oral nicotine.)

The high frequency of coffee and tea drinking in cigarette smokers [1,35] suggests that the opportunities for occurrence of this adverse interaction to occur would be numerous. Similarly, because many people consume coffee, tea, fruit juices, and fruit during the first few hours of the day, the amount of nicotine obtained from the first few doses of nicotine polacrilex each day could also be severely reduced. This effect might be especially pronounced because of the apparent importance of early-morning nicotine intake in cigarette smokers for whom nicotine polacrilex therapy is indicated.[36]

The role of salivary pH in nicotine delivery is not limited to the polacrilex vehicle. The alkaline smoke from pipes and cigars permits effective transmucosal absorption, whereas nicotine from the more acidic cigarette smoke is poorly absorbed unless inhaled into the lungs.[1] Analogously, manufacturers of smokeless tobacco adjust both alkalinizing capacity and nicotine content by mixing differing kinds of tobacco and additives.[1,37,38] This practice is used to manufacture products in which the amount and speed of nicotine delivery can be varied according to the specific marketing intent for the product; for example, "starter" smokeless tobacco products are low in both nicotine concentration and pH, whereas "maintenance" products are higher in nicotine concentration and pH.[1,38]

Helping people to abstain from tobacco is widely acknowledged as one of the most important single contributions that health professionals can make to improve public health.[39] Many clinical trials have confirmed that a wide range of behaviorally and pharmacologically based strategies are of demonstrated efficacy to help people achieve abstinence.[1,40] This is not to imply that tobacco dependence is an easy disorder to treat; it is not, but even low-intensity efforts by health professionals can help many people quit.[1,9,39,41] For some tobacco users, pharmacologic therapy can enhance the achievement and maintenance of abstinence.[1] Unfortunately, many tobacco users who have at-

tempted to achieve abstinence with nicotine polacrilex–based pharmacotherapy have inadvertently received the equivalent of placebo therapy because they did not know what dose they should take, did not understand how to control the dose, and/or may have engaged in a behavior such as concurrent coffee or carbonated beverage drinking that defeated the absorption of nicotine. This report should provide clinicians with information that can enhance their efforts to help people abstain from tobacco by improving their control over the dose of nicotine administered when using nicotine polacrilex.

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