Silver Acetate Mouth Spray As An Aid In Smoking Cessation: Results Of A Double-Blind Trial

Robert Morrow, MD, Peggy Nepps, PsyD, and Margaret McIntosh, MD

Background: We studied the use of an aversive technique to improve the outcome of smoking-cessation efforts. We hypothesized that a silver acetate mouth spray, which produces a strong aversive taste when cigarettes are smoked, would increase the quit rate among smokers.

Metbods: Our study was a double-blind, placebo-controlled trial that was carried out in a private family practice office in an urban area. We studied 42 smokers, who were recruited by advertisement and who were motivated to quit by self-report. They were randomly assigned active spray or placebo spray; all were given a written list of behavioral suggestions. The spray was to be used every 2 hours for 3 weeks during which time the subjects were to keep diaries of cigarette smoking and spray use. Biochemical measures (salivary thiocyanate and cotinine) were recorded at entry, at 3 weeks, and at 3 months.

Results: Thirty smokers completed the study. No differences were found between the two groups in quit rate or number of cigarettes smoked.

Conclusions: Silver acetate aversive spray did not increase quit rate among motivated smokers. (J Am Board Fam Pract 1993; 6:353-7.)

Silver acetate is a pharmaceutical ingredient used to deter cigarette smoking in several over-thecounter products. A heavy-metal salt, silver acetate produces an unpleasant taste when mixed with cigarette smoke and has been used in lozenges and chewing gum. A new preparation involves a proprietary method of solubilizing silver in a palatable mouth spray, permitting intermittent doses. This study examines the efficacy of this spray in increasing the quit rate of long-term smokers who report that they are eager to quit smoking.

Silver acetate therapy is an aversive technique, not a substitute, such as nicotine gum, nor a withdrawal blocker, such as clonidine. Aversive conditioning occurs when an aversive stimulus (e.g., noxious taste) is systematically and repeatedly paired with a behavior (e.g., smoking) that the subject wishes to eliminate.¹ Other aversive conditioning methods used in smoking cessation include rapid smoking and smoke holding. In general, aversive techniques are not effective when used alone in long-term treatments,² but they could have some utility when combined with other behavioral interventions.

Four placebo-controlled, double-blind studies have addressed the effectiveness of silver acetate in smoking cessation. Rosenberg³ tested the effects of a lozenge with silver acetate on 60 smokers who smoked an average of 18 cigarettes daily. At the end of 2 weeks, 11 of the 30 in the experimental group and 5 of 30 in the placebo group had quit smoking by verbal report only. Arvidsson,⁴ who studied 50 smokers, noted that the difference between a silver acetate group and a placebo group in reported number of cigarettes smoked was 10.6 and 18.4, respectively. In a large doubleblind study, conducted on 1000 subjects, Schmidt⁵ found that 31 percent of the silver acetate group and 25 percent of the placebo group had quit by self-report.

By relying on self-reporting in smoking-cessation studies, the number of subjects who indeed have stopped smoking has been overstated.⁶ One study by a committee of the British Thoracic Society⁷ found that 27 percent of those who claimed to have stopped smoking completely had biochemical evidence of smoking. Studies without biochemical measures can be unreliable.

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From the Department of Family Medicine, St. Joseph's Medical Center, Yonkers, NY (RM, MI), and the Department of Behavioral Medicine, Lancaster General Hospital, Lancaster, PA (PN). Address reprint requests to Robert Morrow, MD, 5997 Riverdale Avenue, Bronx, NY 10471.

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A 1963 report⁸ of a film editor chewing on photographic film to achieve an aversive dose of silver described the development of argyria, a blue-grey coloration of the skin, mucosa, and occasionally viscera. Argyria accompanies silver ingestion in large doses, described as 0.9 g⁹ to 25 g,⁸ at which point the body cannot clear the metal completely; otherwise, silver poses little apparent health risk at low doses. This safety has been demonstrated in a study by Jensen, et al.¹⁰ on serum silver levels, as well as levels in skin biopsy samples by autometallography in users of a silver acetate chewing gum (Tabmint). Reports of argyria from improper doses of silver acetate lozenges used for smoking cessation also indicated no systemic toxicity.11,12

Given the new availability of silver acetate in an oral spray, a randomized, placebo-controlled pilot study was instituted to find out whether the spray was efficacious in increasing quit rates among smokers motivated to stop smoking.

Methods

Given the probable efficacy of any single-component aversive technique, the spray was tested within the context of minimal behavioral change instruction.

Subjects

Subjects were recruited by advertisements in newspapers, by fliers in physicians' offices, and by word of mouth. The study was conducted during an 18-month period at a family practice office in a socially and ethnically integrated urban neighborhood. Participants were included if they smoked at least one pack per day for 5 years, were 18 years old or older, had no silver allergy, were not pregnant or nursing, and reported a desire to stop smoking. At the introductory visit the program was described, including randomization and placebo use, and a refundable deposit of \$25 was collected as an incentive to increase completion of the experimental protocol.

Subjects completed a questionnaire with the assistance of one of the investigators (MM) or an assistant. Data regarding age, eating habits, smoking habits and history, earlier cessation attempts, reasons for quitting, motivation, and belief in the effectiveness of the proposed intervention (silver acetate spray with behavioral suggestions) were collected. Subjects then received diaries to use for 1 week of cigarette self-monitoring before actual inclusion into the study; those unable to keep a diary for 1 week were excluded from further analysis.

At the second office visit, subjects received a 3-week supply of diaries for recording use of the spray, as well as numbers of cigarettes smoked. These diaries were attached to the spray bottle and cigarette pack, and the subject would tick off each spray and cigarette when used. Use of the spray was taught to the study subjects, and saliva samples were taken for measurement of cotinine and thiocyanate. A list of behavioral suggestions was given and reviewed, and a quit day was assigned for 7 days after this visit. A supportive approach was taken with all subjects, encouraging them to succeed in total cessation of smoking. At this point subjects were randomized to active or placebo group by code; neither they nor the investigators had access to the randomization code for the spray bottles, which were otherwise not discernably different.

The post-treatment office visit occurred 3 weeks later; diaries and salivary samples were collected, and a follow-up questionnaire was administered.

A follow-up visit took place 2 months after the third visit, and a questionnaire about smoking behavior was administered. A third salivary sample was taken. The \$25 deposit was then refunded.

The Spray

We used a proprietary formulation of silver acetate suspended in an alcohol-water mix. This spray contained 0.5 percent silver acetate (500 mg/100 g). Each spray delivered a measured volume of spray, and the subjects were prescribed a total daily dose of 4 mg of silver salt. A total dose of 0.9 to 25.0 g of silver salt taken during the course of 6 months has been calculated to produce argyria.^{8,9} Each bottle of spray contained approximately 15 mL, or 75 mg of silver acetate solution.

The subjects were instructed to spray their mouths, aiming at the back of the tongue, with one or two sprays every 2 hours while awake. One extra spray daily was permitted. Most subjects did not use the second bottle of spray in the 3 weeks of treatment, so no subject received a silver salt body burden greater than 150 mg during the course of study, yielding a safety factor much greater than tenfold.

Biochemical Measures

Salivary thiocvanate and cotinine (a metabolite of nicotine) levels were chosen as biochemical markers to confirm diary reports of smoking cessation. Saliva was collected at three different times, frozen, and analyzed in batches by the American Health Foundation, Valhalla, NY, Saliva was chosen as a body fluid because it is easy to collect, its collection is sufficiently acceptable to the subjects (versus venipuncture), and it is sufficiently resilient to documenting persistent cessation. As opposed to venous cotinine, which drops off in 24 hours, and exhaled carbon monoxide, which has an even briefer half-life, salivary cotinine persists for several days after smoking cessation. Our test points were 2 weeks and 10 weeks after assigned quit dates.

Statistical analysis was performed on data from the two groups and several small subgroups. The statistician was blinded as to which was the active group and which was the placebo group.

This study was reviewed by the Human Experimentation Review Committee of St. Joseph's Medical Center in Yonkers, NY.

Results

Fifty-two smokers were recruited to complete questionnaires and smoking diaries prior to initiating the study. Those who did not complete this task were not included in the study. Forty-two smokers thus made up the research cohort; they were randomized to an active group or a placebo group. Fourteen subjects in the treatment group and 16 in the control group completed all appointments, diaries, and biochemical measures. Table 1 summarizes the demographics, smoking behaviors, and motivation of the two groups; no differences in sex, age, number of cigarettes smoked, or motivation were found. Motivation was selfassessed using a seven-point scale (seven = high motivation). There were 5 dropouts from the silver acetate group, and 7 from the control group. Two subjects in the silver acetate group and 1 in the placebo group stopped smoking, as confirmed by cotinine and thiocyanate levels. No statistical test for significance is appropriate to compare this small group of quitters.

The data were first analyzed including subjects who did not complete treatment. A linear regression and correlation was done with the outcome measure as a ratio of the measured variables —

Table 1. Characteristics of Subjects.

Characteristics	Silver Acetate	Placebo
Women	6 (44%)	9 (57%)
Men	8 (57%)	7 (43%)
Mean age (years)	50.4	49.9
Pretreatment cigarettes smoked per day	34 (SD 12)	32 (SD 11)
Motivation (1+7 scale)	6	6

thiocyanate, cotinine, and reported number of cigarettes smoked — at each of the two outcome times (post-treatment and follow-up) to the measurement at the initial time. The use of a ratio allows each subject to be his or her own control and thereby measures individual change over time and not just change in the group mean. There were no significant differences found. The data were then reanalyzed using only the 30 subjects who completed treatment. This analysis was done with simple comparisons of means and standard deviations and analysis of variance utilizing SAS.13 The results once again showed no significant differences. Analysis of variance was performed for differences between groups at the three time periods using both the absolute measures and the ratio measures as outcomes, and there were no significant differences between the groups on any of the tested outcomes.

The initial mean number of cigarettes smoked daily by the treatment group was 34 (SD = 12); for the control group it was 32 (SD = 11). At posttreatment, reported number of cigarettes for the treatment group was 12 (SD = 9) compared with 16 (SD = 12) for the control group. Both groups showed a significant decrease in mean daily cigarettes between initial and the first post-treatment follow-up visit, but the two groups had no significant difference between them, demonstrating no difference in reported smoking behavior between groups. A 2-month follow-up visit, with the study group and placebo group both reporting means of 16 (SD = 12), showed no difference between the two groups.

Several subjects reported smoking behavior that was at variance with biochemical values; that is, they appeared biochemically to be smoking much more than they reported by diary. Reanalysis of the data with these subjects excluded did not change the results. An analysis of the correlation between reported numbers of cigarettes smoked and biochemical values showed that a particular stated number of cigarettes did not predict a particular value of thiocyanate or cotinine, nor could the biochemical values be correlated with a single quantity of cigarettes smoked. These indices appear to be of more value in separating smokers from nonsmokers rather than in exactly quantifying smoking behavior. Not surprisingly, a positive correlation was found between the cotinine and thiocyanate values.

The strongest relation was found between group and reported spray use. The treatment group used the spray significantly less often than the control group, 4.2 times daily versus 7.3 times daily (t = 3.059, P < 0.005). The treatment group therefore did not comply with their instructions to spray every 2 hours.

A number of other relations were examined to determine whether any other variables explained change in smoking behavior during the study period. Motivation, sex, years of smoking, and final satisfaction were all examined, with no significant relation found.

Discussion

This study failed to show an increase in quit rates for motivated smokers who used the silver acetate spray. The quit rate was relatively low -2 out of 30 subjects - although a small change in those who quit would have a large effect on percentages given the small group size. No significant difference in number of cigarettes smoked was found between the active and placebo groups; both groups claimed to have decreased their smoking throughout the study.

The sample population for this study was small, so modest improvements in quit rates might not have been found. If the effect was only 10 to 20 percent, more than twice as many subjects would have been needed to demonstrate a treatment effect.

Noncompliance is also a possible explanation for the failure to demonstrate an effect. The treatment group did not use the spray as often as directed and thus reduced their aversive-conditioning experience. One might speculate that this poor compliance was due to the aversive component; a number of patients commented that they knew their group assignment (active or placebo) as soon as they smoked their first cigarette. Silver acetate as an aversion is self-administered. It provides no positive feedback, but rather provides self-punishment for an addiction. Punishment can indeed be a strong tool for behavioral change, although it can also engender sabotage and overt defiance, especially when self-administered. Punishment likewise does not address the discomfort of stopping a difficult and complex behavior; it indeed adds to physical discomfort. The lack of benefit from this aversive therapy is not a surprise in this context.

In clinical applications in general, punishment can make behavior less likely to occur, but results are at best temporary. When repeated, the same punishment tends to lose effectiveness quickly. More important is that punishment techniques alone teach people what not to do (i.e., smoke), but not how to achieve that goal. Aversive strategies might have utility within the context of a broader, multicomponent therapeutic approach that combines aversion with support and skill building. Although this trial provided a list of behavioral suggestions, more intensive and extensive behavioral therapy would enhance success.

The decline in the number of cigarettes reported smoked by both groups is intriguing; even a placebo intervention appears to be of modest benefit for smokers motivated to quit. The results do point to both the strength and the weakness of measuring salivary cotinine and thiocyanate. In particular, cotinine persists in saliva for many days after smoking has ceased. This persistence reduces the value of this measure in quantifying smoking behavior, but it also makes cheating more difficult. It is probable that the imperfect correlations between salivary thiocyanate and cotinine on the one hand and self-reported smoking behavior on the other reflect inaccurate recording of smoking behavior, given the wellknown limitations of self-report. Nevertheless, it is possible (albeit unlikely) that biological variance in nicotine metabolism and salivary secretion could have contributed to the total variance.

Summary

This small pilot study did not reveal any benefit from the use of silver acetate as an aversive therapy. A larger sample study could be necessary to establish any important benefit from this approach as a single treatment. Future studies are also needed to evaluate the utility of this product, if any, within broader, multicomponent treatment approaches.

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