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BRIEF REPORT

PACED PUFFING AS A METHOD FOR ADMINISTERING FIXED DOSES OF NICOTINE

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Abstract — Smokers' ability to regulate nicotine intake by varying topographical parameters such as depth of inhalation and number of puffs makes it difficult to administer standardized doses of nicotine as delivered from smoking. A number of studies have claimed to control these parameters without confirming the effectiveness of such procedures by measures of plasma nicotine. The purpose of the present study was to determine whether specifying onset and duration of each puff would result in accurate dosing. Plasma nicotine boosts for five "paced puffers" were compared across two sessions and with similar data for five "free smokers." Neither between-subject consistency nor within-subject reproducibility was improved by this paced puffing procedure, despite apparent topographical control.

The ability of cigarette smokers to adjust nicotine intake has been well-documented (e.g., Pomerleau, Fertig, & Shanahan, 1983). The same cigarette can deliver widely varying amounts of nicotine to different smokers, or to the same smoker at different times, depending on topographical parameters (e.g., depth of inhalation, number of puffs, etc.; Herning, Jones, Benowitz, & Mines, 1983). Self-dosing — that is, the extent to which smokers regulate their smoke exposure via smoking topography — may be influenced by a variety of factors, including stress (Pomerleau & Pomerleau, 1987; Rose, Ananda, & Jarvik, 1983), task demand (Ashton, Watson, Marsh, & Sadler, 1970), arousal level (Agué, 1973), time of day (Agué, 1973), and time since last cigarette (Griffiths & Henningfield, 1982). Thus, the use of nicotine as an independent variable in research on the addictive and reinforcing properties of cigarette smoking is compromised by the phenomenon of nicotine regulation. Standardized research cigarettes of widely differing strengths are helpful in that they specify and delimit available nicotine, but their usefulness is undermined by the readiness with which smokers can compensate for such differences (Pomerleau et al., 1983). Techniques sufficiently similar to smoking to serve as a convincing model of normal smoking and sufficiently dependable to permit quantification of dose-response relationships, however, remain to be validated.

At least three criteria must be met if a method is to be regarded as a satisfactory tool for understanding the effects of nicotine *as delivered from smoking:* (a) The method must be safe, noninvasive, and easy to use; (b) the pharmacokinetics must resemble the spike-and-decay pattern that characterizes nicotine from ordinary smoking; and (c) specified doses must be reliably and reproducibly delivered as verified by assays of plasma nicotine, regardless of states such as stress or nicotine deprivation that might otherwise affect nicotine intake.

The simplest and most obvious approach — one that almost by definition satisfies the first two criteria — is to control one or more aspects of smoking topography by asking smokers

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to puff at regular intervals and/or to adjust puff duration in some fashion. A number of studies have employed variations on this theme (e.g., Griffiths, Henningfield, & Bigelow, 1982; MacDougall, Musante, Howard, Hanes, & Dembroski, 1986; Sult & Moss, 1986; Zacny & Stitzer, 1986) — without, however, verifying success by measuring plasma nicotine before and after smoking.

In the present study, five smokers were asked to smoke a high-nicotine research cigarette on two different days, puffing at fixed intervals and for a fixed duration, to determine whether pre- to postplasma nicotine increments could be held constant. Five smokers who had smoked the same high-nicotine cigarette in previous experiments on two different occasions, with no attempt to control or influence nicotine intake, provided information about variability under conditions of unrestricted self-administration.

METHOD

Subjects

Five male smokers recruited from the local community through newspaper advertizement were paid $50 for participating in this study. Only candidates who smoked at least 20 cigarettes per day and had smoked for at least five years were included. Subjects had a mean age of 33.0 ± 3.2 S.E.M. years and smoked a mean of 22.0 ± 3.4 cigarettes per day; mean nicotine yield from their preferred brands was 1.11 ± 0.13 mg. Mean level of plasma cotinine, a major nicotine metabolite that serves as an index of degree of dependence (Pomerleau et al., 1983), was 352.6 ± 91.8 ng/mL.

Plasma nicotine data for five male smokers who had been recruited by the same procedure and had participated in at least two previous experiments involving the smoking of a high-nicotine cigarette were randomly selected from our files to serve as a basis for comparison. In all cases, data from a control condition rather than a stressful condition were used. Mean age of these subjects was 46.8 ± 5.41 years. They smoked a mean of 37.0 ± 2.0 cigarettes per day; mean nicotine yield from their preferred brands was 1.15 ± .08 mg. Mean plasma cotinine level for these subjects was 362.8 ± 38.4 ng/mL. Interval between sessions was 27 ± 9 months. All control subjects and all but one experimental subject had at least two exposures to the research cigarettes in previous studies in our laboratory.

Apparatus

Subjects sat in an easy chair. An 18-gauge needle was inserted in the left median antecubetal vein; a 1 M length of extension tubing was run through a conduit in the wall to an adjacent room for unobtrusive withdrawal of blood. Between sampling, the line was flushed with heparinized saline to prevent clotting. Blood was centrifuged at 4 °C; frozen plasma aliquots were subsequently sent to the American Health Foundation (Valhalla, New York) for radioimmunoassay of nicotine (Hill, Haley, & Wynder, 1983).

During each session, subjects smoked a standardized high-nicotine (2.87 mg) research cigarette (Tobacco and Health Research Institute, University of Kentucky). Puff number and duration were measured using a gauge pressure transducer (LX 160-46; National Semiconductor). Pressure changes produced by inhaling through a modified cigarette holder were transmitted to the pressure sensor via flexible plastic tubing, where they were converted to digital electric signals. These parameters served as an index of compliance with experimental procedures.

Procedure

Experimental subjects were taught the paced puffing procedure, using the research cigarettes, during a screening session scheduled at least one day before the first experimental session.

Both experimental and comparison subjects were asked to smoke a cigarette in the usual manner one-half hour before the beginning of a session. Five minutes into each session, experimental subjects were instructed to take 3 s puffs every 30 s, for a total of 10 puffs over the course of 5 min. (These parameters were chosen for their resemblance to naturalistic topography observed in our laboratory during free-smoking sessions using the same cigarette.) Taped directions presented an alerting message ("Prepare to puff"), followed by a 3 s tone; subjects were asked to inhale throughout the duration of the tone. Blood was withdrawn for nicotine and cotinine assays 5 min before and immediately after the paced puffing procedure. For the comparison subjects, no instructions regarding puffing technique had been issued. As with paced-puffing subjects, blood was withdrawn 5 min before and immediately after a 5 min smoking interval.

RESULTS

Experimental subjects tended to be younger ($t = 2.2$, $p < .10$) and smoked significantly fewer cigarettes ($t = 3.81$; $p < .01$) than comparison subjects. Cotinine values did not differ significantly from those of the comparison subjects.

All experimental subjects took 10 puffs on each experimental day. Mean puff duration was $1.96 \pm .16$ s on the first day and $2.0 \pm .18$ s on the second. Comparison subjects took a mean of 9.0 ± 1.3 puffs on the second day, with a mean puff duration of $1.91 \pm .24$ s. (For day one, topography data were available for only three of the comparison subjects.) Variability in puff duration for day two did not differ significantly between paced puffers and free smokers, using an F test for equality of variances.

Mean changes in plasma nicotine for each of the two sessions are presented in Fig. 1. The difference between means for day one and means for day two for the experimental subjects showed a trend towards significance, using a paired t test ($t = 2.1911$, $p < .10$); no significant difference was detected for the comparison subjects. Variability of the absolute difference between the increments for the two sessions showed a trend towards being significantly greater for the paced puffers than for the free puffers ($F[4, 4] = 8.56$; $p < .10$).

Variability of day one plasma nicotine increments for the paced puffers was significantly smaller than variability for the free smokers ($F[4, 4] = 9.85$, $p < .05$). On the other hand, variability on day two showed a trend towards being significantly larger for the paced puffers than for the free smokers ($F[4, 4] = 8.20$; $p < .10$). Using the Pitman-Morgan test for equality of variances for correlated data, variability of nicotine increments for day one versus day two differed significantly for paced puffers ($r = + .95$, $p < .05$) but not for free smokers.

To assess within-subject consistency, increments for day one were correlated with increments for day two for both groups. In neither case was a significant correlation detected (paced puffers: $r = - .38$; free smokers: $r = + .10$).

DISCUSSION

Topographical measures confirm that manipulation of puff number and duration were successful. It is clear that for experimental subjects, variability in puff number was eliminated and variability in puff duration was reduced below that of comparison subjects, though not significantly.

Although variability in nicotine increments among paced-puffing subjects was reduced in the first session, this effect was not sustained during the second session. Within-subject consistency was not improved by the experimental manipulations as indicated by test-retest correlations (despite a bias to the contrary, since the interval between tests for the comparison subjects was considerably longer than that for the experimental subjects).

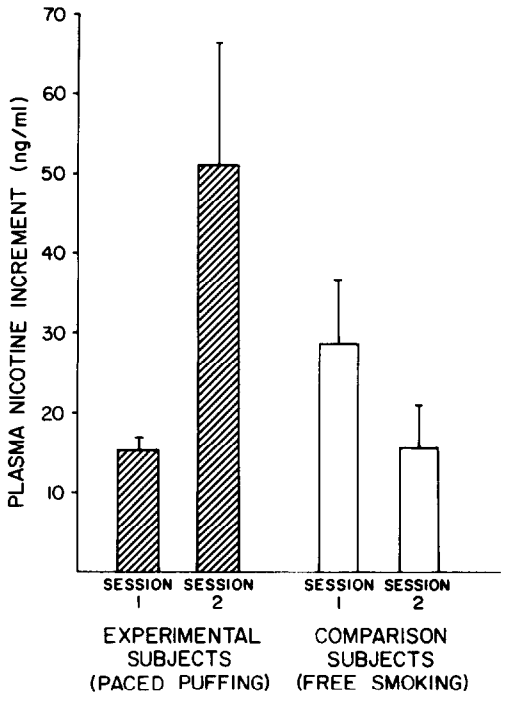

Fig. 1. Plasma nicotine increments (ng/mL) from smoking one high-nicotine (2.87 mg) cigarette (mean ± S.E.M.). Paced-puffing subjects (n = 5) versus free-smoking subjects (n = 5).

Since people who smoke may become heavier and more dependent smokers over time (Russell, 1974), the fact that the comparison subjects tended to be older than the experimental subjects may in part account for less stable intake in the latter. Cotinine levels, however, did not differ significantly for experimental and comparison subjects, suggesting no remarkable differences in degree of dependence. Moreover, to be considered satisfactory, a fixed-dosing method should overcome rather than perpetuate such differences.

In the present study, we wished to minimize deviations from normal smoking; consequently, attempts were made to control only two aspects of topography, number of puffs and puff duration. Other approaches may yield more consistent dosing; Zacny, Stitzer, Brown, Yingling, and Griffiths (1987), for example, were able to produce systematic changes in plasma nicotine as puff volume was varied, using a technologically sophisticated microcomputer/strain-gauge/auditory-feedback procedure. Nevertheless, the present results point to the need for verifying the effectiveness of any fixed-dosing method, however face-valid, using measures of plasma nicotine.

REFERENCES

Agué, C. (1973). Smoking patterns, nicotine intake at different times of day and changes in two cardiovascular variables while smoking cigarettes. *Psychopharmacologia,* **30,** 135–144.

Ashton, H., Watson, D.W., Marsh, R., & Sadler, J. (1970). Puffing frequency and nicotine intake in cigarette smokers. *British Medical Journal,* **3,** 679–681.

Griffiths, R.R., & Henningfield, J.E. (1982). Pharmacology of cigarette smoking behavior. *Trends in Pharmacological Sciences,* **3,** 260–263.

Griffiths, R.R., Henningfield, J.E., & Bigelow, G.E. (1982). Human cigarette smoking: Manipulation of number

of puffs per bout, interbout interval, and nicotine dose. *Journal of Pharmacology and Experimental Therapeutics,* **220,** 256–265.

Herning, R.I., Jones, R.T., Benowitz, N.L., & Mines, A.H. (1983). How a cigarette is smoked determines blood nicotine levels. *Clinical Pharmacology & Therapeutics,* **33,** 84–90.

Hill, P., Haley, N., & Wynder, E. (1983). Cigarette smoking as a risk for cardiovascular disease: 1. Biochemical analyses, carboxyhemaglobin, plasma nicotine, cotinine, and thiocyanate versus self-report smoking data. *Journal of Chronic Disease,* **36,** 439–449.

MacDougall, J.M., Musante, L., Howard, J.A., Hanes, R.L., & Dembroski, T.M. (1986). Individual differences in cardiovascular reactions to stress and cigarette smoking. *Health Psychology,* **5,** 531–544.

Pomerleau, O.F., Fertig, J.B., & Shanahan, S.O. (1983). Nicotine dependence in cigarette smoking: An empirically-based, multivariate model. *Pharmacology, Biochemistry & Behavior,* **19,** 291–299.

Pomerleau, C.S., & Pomerleau, O.F. (1987). The effects of a psychological stressor on cigarette smoking and subsequent behavioral and physiological responses. *Psychophysiology,* **24,** 278–285.

Rose, J.E., Ananda, S., & Jarvik, M.E. (1983). Cigarette smoking during anxiety-provoking and monotonous tasks. *Addictive Behaviors,* **8,** 353–359.

Russell, M.A.H. (1974). The smoking habit and its classification. *Practitioner,* **212,** 791–800.

Sult, S.C., & Moss, R.A. (1986). The effects of cigarette smoking on the perception of electrical stimulation and cold pressor pain. *Addictive Behaviors,* **11,** 447–451.

Zacny, J.P., & Stitzer, M.L. (1986). Effect of puff size instructions on puff volume. *Addictive Behaviors,* **11,** 17–23.

Zacny, J.P., Stitzer, M.L., Brown, F.J., Yingling, J.E., & Griffiths, R.R. (1987). Human cigarette smoking: Effects of puff and inhalation paramaters on smoke exposure. *Journal of Pharmacology and Experimental Therapeutics,* **240,** 554–564.