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Controlled dosing of nicotine via an *I*ntranasal *N*icotine *A*erosol *D*elivery *D*evice (INADD)

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Abstract. The present report describes an *I*ntranasal *N*icotine *A*erosol *D*elivery *D*evice (INADD) employing an artist's airbrush as aerosolizer and precise, electromechanical control of spray duration. It was designed for the administration of controlled doses of nicotine in a laboratory setting and has been used successfully in over 30 smokers and nonsmokers of both genders. In the present study, nicotine was administered to 12 male smokers at three different doses (0.05 mg, 1.00 mg, and 2.00 mg), and at the same dose (1 mg) on three different occasions. The low dose produced a minimal change in plasma nicotine, while the high dose produced a peak increment of around 16 ng/ml. The medium dose reliably produced a peak increment of around 8–9 ng/ml on all three occasions. Nicotine in plasma showed a sharp rise followed by a slower decline, mimicking the pattern associated with cigarette smoking. Physiological and biochemical responses showed significant dose-response relationships. Subjective reports suggested that aerosol dosing was somewhat aversive, but it is unclear whether this effect is intrinsic to the method or due to other factors. The device described in this report answers the need for a safe and easy means of controlling nicotine dose. Moreover, since nicotine administration via aerosol is novel for both smokers and non-smokers, minimizing the contributions of behavioral tolerance and habituation to the dosing vehicle, it lends itself to the comparison of the pharmacological effects of nicotine between experienced and naive subjects.

Key words: Aerosol – Nicotine – Controlled dosing – Cortisol response – Physiological response – Subjective response – Smokers

The difficulty of controlling nicotine dose continues to be a limiting factor in research on cigarette smoking and nicotine dependence. Attempts to control dosing by means of changing the nicotine available in cigarette smoke are confounded by the smoker's well-documented ability to adjust nicotine intake (behavioral compensation) over wide differences in nicotine content or delivery (USDHHS 1988). Furthermore, depending on how it is smoked, the same cigarette can deliver varying amounts of nicotine to different smokers or to the same smoker at different times. The problem is clearly relevant to the understanding of nicotine dependence, as nicotine's psychoactive effects vary with dose–low doses being associated with alertness and stimulation, and high doses with calming and sedation (Ashton et al. 1978; Warburton and Wesnes 1978; Golding and Mangan 1982; Rose et al. 1983; Henningfield and Woodson 1989).

In a review of the problem, Pomerleau et al. (1989a) identified some of the criteria that should be met for a nicotine dosing method to be considered satisfactory for the study of cigarette smoking: 1) the method should be safe and easy to use; 2) specified doses should be accurately and reproducibly delivered; and 3) the pharmacokinetics of the dosing method should resemble those of cigarette smoking, since a sharp rise in plasma nicotine followed by a gradual decay is the pattern believed responsible for the unique reinforcing effects of cigarette smoking (Pomerleau and Pomerleau 1984).

Although nicotine can be administered intravenously in precisely controlled amounts (Benowitz et al. 1982; Feyerabend et al. 1985), the procedure is invasive and requires considerable care as bioavailability is complete and irrevocable; typically, dosing is conducted in dedicated in-hospital research settings. At the other extreme, the control of dosing by delimiting smoke inhalation (e.g., pre-determining the parameters of puffing topography) is safe on an acute basis and has enjoyed some degree of success (Zacny and Stitzer 1986; Gilbert et al. 1989; Pomerleau et al. 1989b; Cherek et al. 1991); furthermore, such techniques are highly acceptable to smokers, and the dosing kinetics are equivalent to ordinary smoking. Unfortunately, the approach does not lend itself to the study of either never-smokers or ex-smokers–groups whose investigation may shed light on

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the nature of nicotine reinforcement or the persistence of adaptation to nicotine.

About ten years ago, Russell et al. (1983) devised a nicotine nasal solution technique; although subjective effects resembled those produced by cigarettes, nicotine absorption varied widely. More recently, Perkins et al. (1986) described the use of a nasal-spray pump procedure to deliver metered doses of nicotine in aqueous solution. The data for the three subjects for whom nicotine levels were sampled suggested fairly good control over dosage, and there seemed to be consistency in dosing among the three subjects; though the sample was limited, the rise and decay of the plasma nicotine curve resembled the usual pattern for cigarette smoking. The present report describes an *I*ntranasal *N*icotine *A*erosol *D*elivery *D*evice (INADD) that employs an artist's airbrush as aerosolizer and precise, electromechanical control of spray duration. Dose-response characteristics for the INADD are described for 12 subjects, systematically showing plasma nicotine increments as well as subjective, physiological, and biochemical responses to nicotine delivery at three different dose levels. The same dose was also administered on three different occasions to determine whether comparable increments in plasma nicotine could be reliably reproduced.

Materials and methods

Subjects. Subjects were 12 male smokers recruited from the general community and paid for their participation. They were required to be between the ages of 21 and 40, with normal body weight (BMI 19–29), to be free from serious medical or psychiatric conditions, and to be using no prescription medications. Additional exclusion criteria were sinus conditions or upper respiratory difficulties. In order to obtain a distribution of subjects that would allow us to determine whether there were any differences between light and heavy smokers with respect to their ability to tolerate the procedure, subjects were telephone-screened using the Fagerstrom Tolerance Questionnaire (FTQ; Fagerstrom 1978), and an effort was made to include subjects across a wide range of scores.

Apparatus. The INADD is shown in Fig. 1. It consisted of a stainless-steel artist's airbrush (Olympus-Medea model HP–18BC) employed as aerosolizer, with duration of aerosol delivery determined by a Skinner pneumatic solenoid valve (Honeywell model V 52DB2100) that interrupted airflow from an air compressor (Thomas Industries model 600); pressure transients were measured via an in-line monitor (Omega model HP520). The device is an adaptation of a cocaine delivery system developed by Lukas et al. (1990); under FDA regulations, the administration of nicotine in this fashion qualifies as "unapproved use of an approved drug" (Kessler 1989; p 285). Duration of airflow to the airbrush was controlled via a manually-adjustable solid state timing unit. To prevent accidental administration, two functions were required for delivery–depression of an "enable" and an "administer" button. A plastic disposable nosepiece (Sarstadt #57.512 centrifuge tube) about 1 cm in length was cut open at one end and the inner wall of the other end was gouged out to fit snugly on the stainless steel nozzle of the airbrush. (The spray clutch was kept in the fully open position by a screw, and spray width was set so that none of the spray coated the inside of the plastic nosepiece.) About 150 µl of nicotine solution was placed in a 2 ml plastic reservoir attached to the airbrush. When a dose was to be administered, the subject inserted the nosepiece about 0.5 cm into the nostril. A dose was administered in less than 5 s and consisted of two 50 µl aerosol sprays (7 psi for 1 s), one spray into each nostril.

The nicotine solution for the nasal spray was prepared from doubly recrystallized nicotine tartrate and sterile 0.9% saline. Accuracy of specified nicotine concentrations was verified by HPLC (see below) prior to administration. The solution was buffered to a pH of 7.5 and contained menthol (0.1 mg/ml) to mask the smell of the nicotine. The solution was filtered through a "Milex-GS" (Millipore, Bedford, MA) filter unit (0.22 microns) in a laminar flow

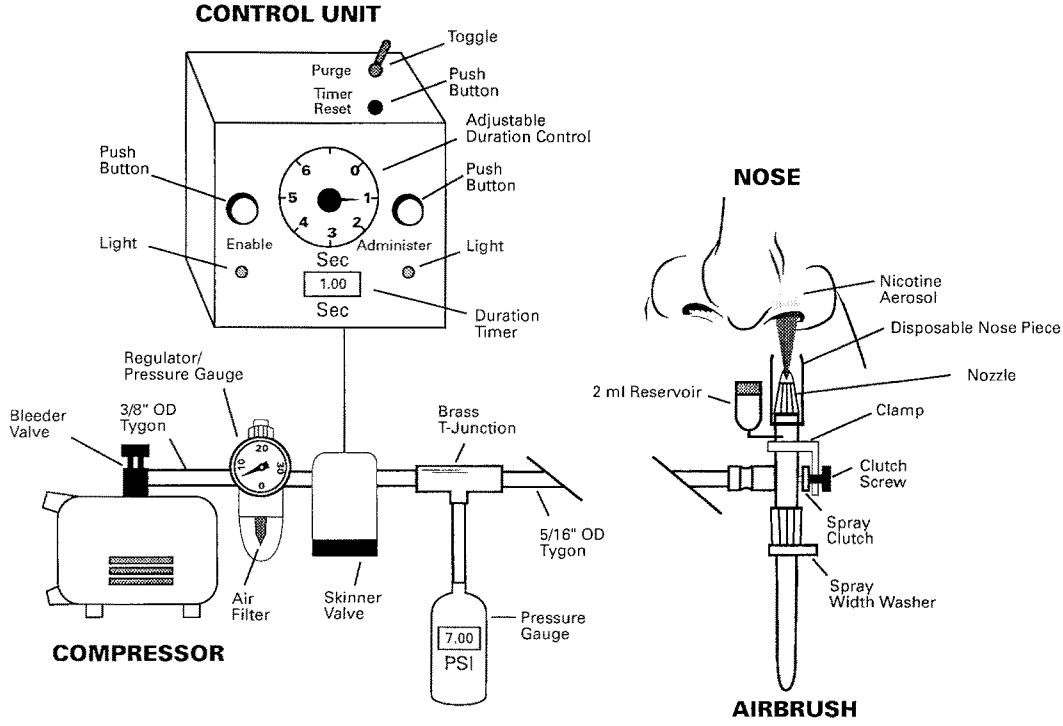

Fig. 1. INADD schematic diagram

sterile hood and aliquoted into 10 ml sterile injection bottles. The sterility of the solutions was confirmed by incubation studies with both thioglycolate and soy broth media. All components of the INADD that came in contact with the nicotine solution were disinfected by soaking them in a 10% Zepharin (benzalkonium) solution for about 3 h and rinsed thoroughly with sterile water several times before use. The concentrations of nicotine in spray were checked by spraying designated volumes into wide-mouth tubes for weighing and for subsequent assay by HPLC (see below). The coefficient of variation (CV = SD/mean × 100) for actual volume delivery and for nicotine delivery was less than 5%. The reproducibility and accuracy of volume delivery (minimum 10 test sprays) was checked every day prior to use.

Heart rate and digit skin temperature were monitored using a Grass model 7B polygraph. Galvanic skin response was measured using a J&J GSR Preamplifier Model T–68. Blood pressure was recorded using a Vitastat Automatic Blood Pressure Monitor Model 900–S. A Vitalograph BreathCO device was used to determine levels of carbon monoxide. (Calibration of physiological inputs was by physical simulation, utilizing pre-set numbers of electronic "R" waves, known concentrations of CO, etc.; the exception was blood pressure readings, whose accuracy was determined using manual sphygmomanometry.) All experimental sequences were controlled by an IBM AT computer located in the adjacent control room. Standardized instructions were delivered via an AMIGA computer equipped with a voice synthesizer; the AMIGA was also used to present visual analog scale (VAS) ratings (responses obtained via computer mouse) of desire to smoke, nausea, dizziness, and satisfaction compared with the usual cigarette (queried immediately after the nicotine dose). An indwelling 18-gauge catheter was inserted into a left antecubital vein and attached to an opaque 1 m length of infusion-exfusion tubing that ran through a channel in the wall to allow unobtrusive withdrawal in the control room; the line was heparinized, and samples were collected in standard EDTA vacutainer tubes. Samples were kept on ice during the session, then centrifuged at 4° C, with the plasma stored at −80° C until assayed. With the exception of the actual INADD spray administration, there was no subject/experimenter interaction during the course of a session.

Assays. Plasma nicotine and cotinine concentrations were determined by a slight modification of the high performance liquid chromatographic (HPLC) method of Hariharan et al. (1988). The isocratic method utilizes a C–18 reversed phase column (15 × 0.46 cm) and a mobile phase of citric acid-phosphate buffer containing triethylamine at pH 4.7. The ultraviolet detection was monitored at 256 nm. The interassay coefficient of variation was 6.5% for nicotine and 4.0% for cotinine. The detection limit of the assay was 1.0 ng/ml for nicotine and 3 ng/ml for cotinine. Plasma cortisol levels were quantitated by competitive protein binding assay; average interassay CV is 6.3% and intra-assay CV is 5.9%, with a 0.5 μg/dl limit of detection.

Procedure. The protocol for this study was approved by the Institutional Review Board of the University of Michigan Medical School. All subjects participated in a screening session in which the study was explained and informed consent obtained. They were then familiarized with the INADD procedure via the administration of two sprays of sterile 0.9% NaCl, one to each nostril.

The study design consisted of five sessions, identical in format except for the nicotine dose administered, and scheduled 2–3 days apart insofar as possible. During each of the first three sessions, presented in Latin square order, subjects received either an ultra-low dose (0.05 mg nicotine, intended to be physiologically and pharmacologically inert), a medium dose (1.00 mg nicotine), or a high dose (2.00 mg nicotine). The fourth and fifth sessions consisted of repetitions of the medium dose. Thus, the design actually incorporated two overlapping sub-experiments, with the first three sessions intended to test ability to achieve parametric dosing and to determine whether there was a linear relationship between dose administered and plasma levels achieved; and the three medium-dose sessions designed to test ability to reproduce, within and across subjects, comparable nicotine levels in plasma. All sessions were run double-blind.

Because of experimenter error, physiological data were not collected on one subject during his high-nicotine session. Consequently, his high-nicotine session was rerun following the fifth experimental session. Since the original high-nicotine session happened to be his session 3, this circumstance resulted in minimal disruption of the Latin square sequence. Nicotine levels were similar for the original and the repeat high-nicotine session; all analyses presented in this paper include data from the repeat session for this subject.

Testing began at 0830 hours following overnight abstinence from smoking; compliance was assessed preliminarily by a breath CO reading of < 20 ppm and later verified by baseline nicotine values. The subject rested quietly for 15 min after a patent line was established. Blood samples for nicotine and cotinine, blood pressure readings, and VAS responses were obtained at baseline (minute 0, immediately before aerosol administration) and every 5 min thereafter until minute 30. For the administration of the nicotine dose, the subject placed the nosepiece into a nostril, signaled readiness, and took a "strong, steady sniff" for about 1 s coincident with delivery of the aerosol spray. Within 5 s, a second spray was administered to the other nostril in the same manner. The subject was instructed to inhibit sneezing and not to blow his nose for 5 min (a tissue was used to catch drainage, when necessary). After the dose, and when not responding to the VAS queries, the subject sat quietly and read.

Data analyses. Nicotine data were subjected to a full time-course factorial ANOVA, with drug dose (low, medium, and high) and time (minutes 0, 05, 10, 15, 20, 25, and 30) as repeated measures. Base-to-peak scores for physiological and subjective data were computed and subjected to a one-way ANOVA. Trend analyses were included as appropriate to verify that a dose-response relationship had occurred.

Results

Subjects had a mean (± SEM) age of 24.5 ± 5.5 years. Their mean weight was 75.3 ± 7.9 kg, mean height 1.8 ± 0.1 M, and mean Body Mass Index (kg/m^2) 23.5 ± 2.7. The had smoked a mean of 17.5 ± 6.1 cigarettes/day for a mean of 8.4 ± 6.4 years. Mean Fagerstrom TQ (range 1–11) was 5.3 ± 2.5.

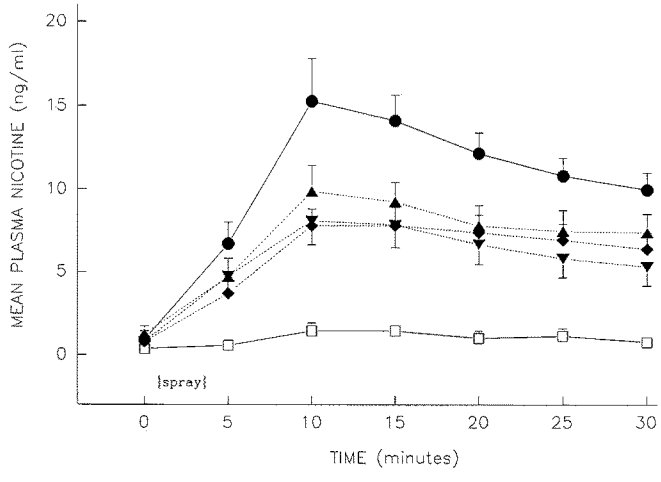

Fig. 2. Plasma nicotine levels (mean ± SEM) for all sessions (N = 12). Nicotine: (□) 0.05 mg; (▼) 1.00 mg; (●) 2.00 mg; (◆) 1.00 mg; (▲) 1.00 mg

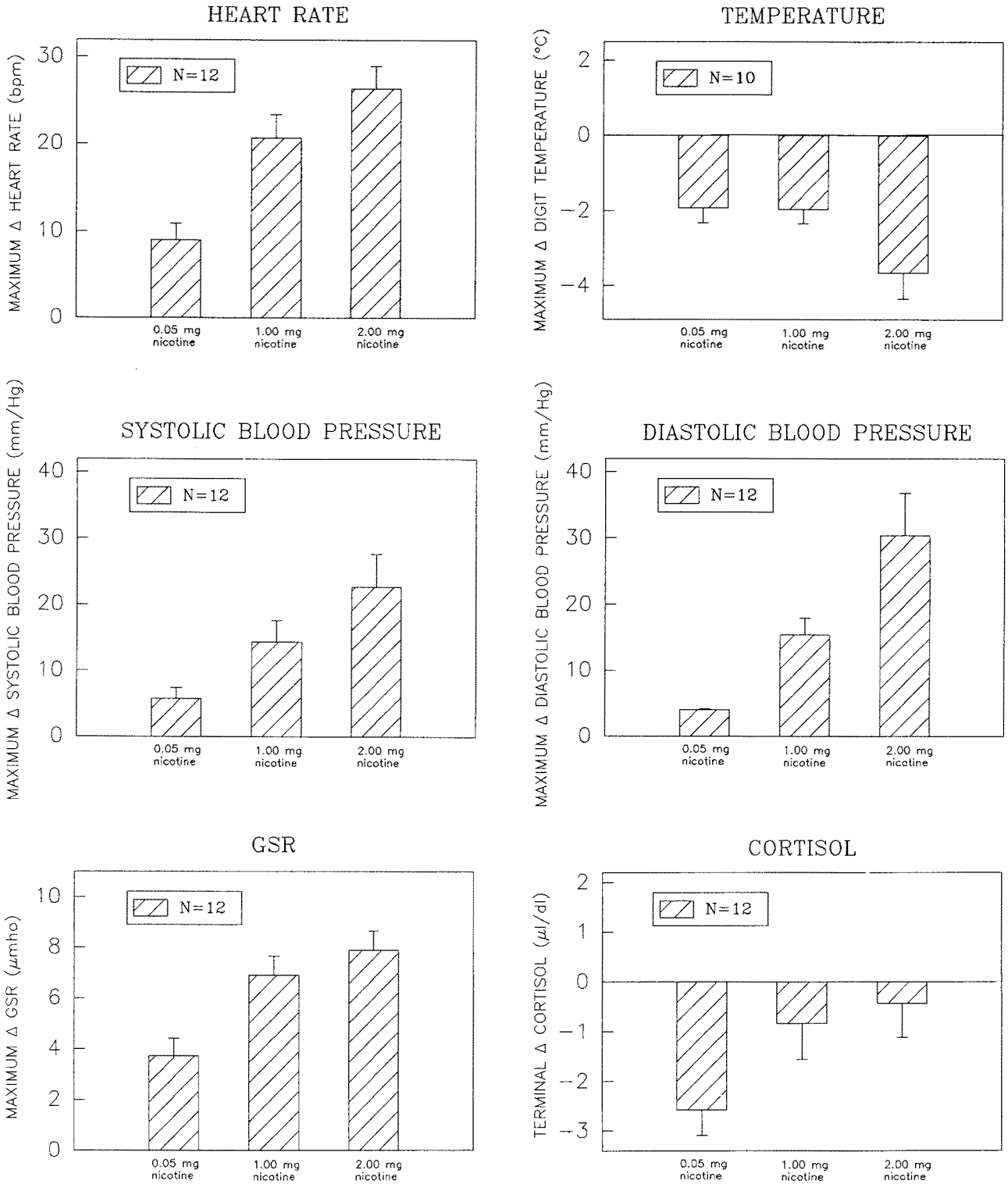

Fig. 3. Physiological and biochemical responses (mean ±SEM to parametric doses of nicotine ($N=12$): base-to-peak changes in heart rate, skin temperature ($N=10$), systolic and diastolic blood pressure, and GSR, and end-of-session changes in cortisol

The highest baseline nicotine level of any subject for any of the five sessions was 6.2 ng/ml, indicating compliance with the overnight deprivation procedure. No differences were observed between light versus heavy smokers in the ability to tolerate the procedure. Nicotine levels for all five sessions are shown for all subjects in Fig. 2.

Plasma nicotine increments following parametric dosing procedure (sessions 1, 2, and 3)

Time course analysis for the low-, medium-, and high-nicotine sessions showed highly significant effects for dose [$F(2,20)=37.45$, $P<0.0001$), time [F (5,50) = 21.25, $P<0.0001$), and dose × time [$F(10,100)=6.28$, $P<0.0001$).

When each of the three dosing curves was subjected to trend analysis, a significant linear trend was detected for the medium [F (1,10) = 15.70, P = 0.005] and the high [F (1,10) = 66.52, P < 0.0001] doses, but not for the low dose. Base-to-peak changes were minimal for the low dose (1.6 ± 0.5 ng/ml), 7.9 ± 1.4 ng/ml for the medium dose, and 15.6 ± 2.6 ng/ml for the high dose. With respect to within-subject parametric dosing, for all 12 subjects the lowest nicotine increment was associated with the low dose session and the highest with the high dose session. The between-subjects CV for the high nicotine session was 57%.

Plasma nicotine increments following dosing replicability procedure (sessions 2, 4, and 5)

Time course analysis for the three medium-nicotine sessions showed a highly significant time effect [F (6,60) = 30.56, P < 0.0001]. No significant effects were detected for dose. Mean (± SEM) nicotine increment was 7.9 ± 1.4 ng/ml for the first exposure to the medium dose, 8.1 ± 1.1 to the second, and 9.8 ± 1.1 for the third. Between-subject CVs for the three sessions were 63%, 47%, and 38%, averaging 49%. Within-subject CVs across the three sessions (comparing nicotine boost over three sessions for each subject), ranged from 5% to 52%, averaging 28%. The weight range of the subjects was 62 – 89 kg, and a determination was made of whether heavier subjects achieved smaller boosts in plasma nicotine by virtue of having received lower doses of smoke per kilogram of body weight. Pearson correlation coefficients of weight with nicotine boost for each of the three medium nicotine sessions were $r = -0.277$, $r = -0.186$, and $r = -0.341$ (all NS).

Physiological and biochemical effects of parametric doses of nicotine delivered via INADD

Physiological and biochemical data are presented in Fig. 3. Physiological data are in line with the expected dose-related effects of nicotine. Heart rate showed a significant dose-related response to nicotine [dose effect: F (2,22) = 13.93, P < 0.0001; linear trend: F (1,11) = 28.93, P < 0.0005), as did systolic blood pressure [dose effect: F (2,22) = 8.84, P < 0.005; linear trend: F (1,11) = 13.14, P < 0.005], diastolic blood pressure [dose effect: F (2,22) = 10.40, P < 0.001; linear trend: F (1,11) = 17.37, P < 0.005], and GSR [dose effect: F (2,22) = 14.43, P < 0.0001; linear trend: F (1,11) = 35.53, P < 0.0001]. Because of equipment problems, peripheral skin tem-

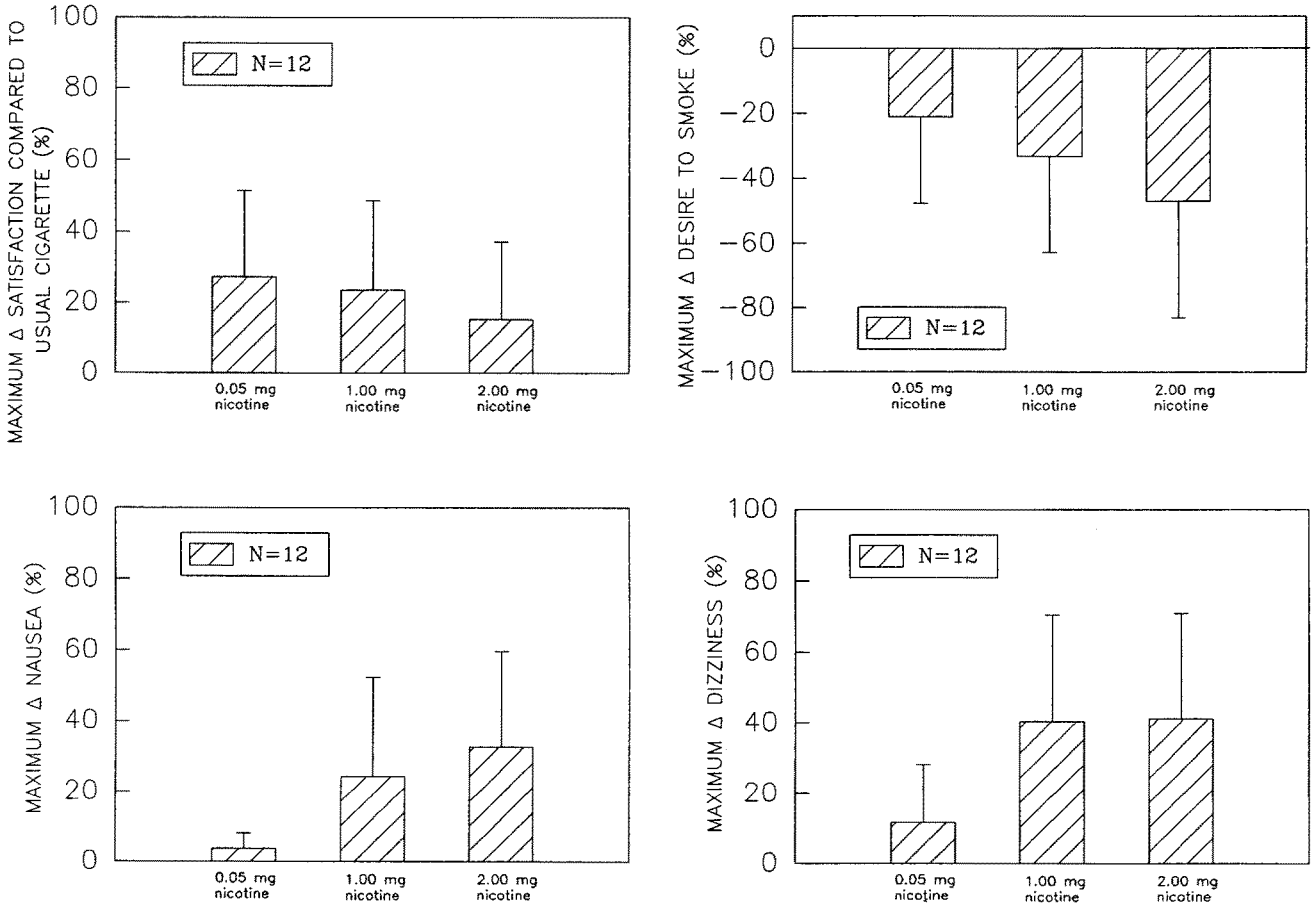

Fig. 4. Subjective responses (mean ± SEM) to parametric doses of nicotine (expressed as % of a 100 mm line). Satisfaction with nicotine aerosol as compared with usual-brand cigarette; change in rating of desire to smoke 5 min after nicotine administration; base-to-peak changes in nausea and dizziness (N = 12)

perature data were available for only ten subjects; temperature showed a trend towards a dose-related decrease [dose effect: F (2,18) = 3.40, P = 0.0559; linear trend: F (1,9) = 3.66, P = 0.0879].

Cortisol showed a strong secular trend downward in the control (0.05 mg nicotine) condition, and the values shown in the cortisol panel indicate the level reached at the 30 min end point. (Subtracting values from the control session for each subject clearly reveals that the stimulation of cortisol by nicotine opposed the secular trend, and that it had not reached its full effect by the end of the session, at least for the high dose.) Nevertheless, cortisol showed a significant dose-related response to nicotine [dose effect: F (2,22) = 4.88, $P < 0.05$; linear trend: F (1,11) = 8.31, $P < 0.05$].

Subjective effects of parametric doses of nicotine delivered via INADD

Subjective responses to the low, medium, and high doses of nicotine aerosol are shown in Fig. 4. Subjects rated the aerosol administration as about a quarter as satisfying as their usual cigarette, with satisfaction decreasing as concentration increased, though not significantly. There was a significant dose-related impact on desire to smoke, pre- to post-dosing [dose effect: F (2,22) = 3.44, P = 0.0503; linear trend: F (1,11) = 5.21, $P < 0.05$]. There were also significant dose-response relationships for peak nausea [dose effect: F (2,22) = 8.14, $P < 0.005$; linear trend: F (1,11) = 15.93, $P < 0.005$] and peak dizziness [dose effect: F (2,22) = 9.03, $P < 0.005$; linear trend: F (1,11) = 11.03, P = 0.01].

Discussion

Plasma nicotine levels resulting from dosing using INADD exhibited a sharp rise followed by a gradual decay; the level and pattern were comparable to that commonly observed for cigarette smoking. Extrapolation of the pharmacodynamics of nasal nicotine to that of cigarette smoking, however, should be made with caution; although venous blood levels may look similar, arterial blood levels, which are believed to be more closely related to pharmacological effects, could be different.

Though the overall pattern was similar to that obtained by Perkins et al. (1986) using a nicotine aerosol pump method, the plasma nicotine increments from the 1 mg and 2 mg doses in the present study were two-thirds and three-quarters, respectively, of that reported by Perkins. The relationship between dosing and the plasma nicotine rise was nearly proportional in the present study; in Perkins' study, the plasma nicotine response to the lower doses was proportional, but the response to the highest dose was somewhat attenuated. These minor discrepancies may be due to plasma nicotine data being available for only three subjects in Perkins' study, or they could come from procedural variations between the two procedures, e.g., the administration of two sprays within 5 s versus ten sprays over 5 min, resulting in a total dose volume of 0.1 ml in the present study versus 1.8 ml in Perkins's study. Moreover, the pH in Perkins's study (6.1) was lower than that of the present study (7.5), which might have diminished transfer of the highest dose in his study.

Repeat administration of the medium dose in separate sessions produced plasma nicotine time courses that were not significantly different from one another, indicating consistency of dosing. Moreover, within the weight range in the present study (62–89 kg), plasma nicotine from aerosol dosing was not affected in any systematic way by body weight. These reliability results are in keeping with those of Perkins et al. (1989), who, in a subsequent study, ascertained the consistency of the aerosol pump spray approach on nicotine boost using a sample of three smokers given four doses of nicotine aerosol spaced 20 min apart (a dose was 6 sprays over 3 min, resulting in total dose volume of 1.08 ml).

Between-subject variability in plasma nicotine was considerably higher than within-subject variability in the present study, suggesting that each subject obtained a characteristic nicotine boost. This is consistent with previous observations of individual variability in nicotine pharmacokinetics (Benowitz et al. 1982; Feyerabend et al. 1985; Pomerleau et al. 1989b). Specifically, Benowitz (1991) has noted that even in the case of intravenous nicotine administration (where bioavailability is fully controlled), there can be up to fourfold differences in nicotine metabolism in smokers. While the level of variability for the present aerosol dosing method is somewhat greater than was found for intravenous nicotine administration procedures (see review by Pomerleau et al. 1989b), the difference does not necessarily reflect deficient dose control. A possible explanation is that rapid administration of nicotine increases the potential for between-subject variation in the rate of distribution, thus exaggerating variability in plasma nicotine levels measured shortly after dosing.

Physiological and biochemical effects were linearly related to INADD dosing. Heart rate boost and blood pressure increases were proportional to nicotine dose to a striking degree. In the only other published test of a similar method (Perkins et al. 1986), dosing via a nicotine aerosol pump resulted in nicotine-produced elevations, but physiological effects did not show a close correspondence to dose magnitude, with values for the intermediate and high doses overlapping (possibly because of the attenuated plasma nicotine increment at the highest dose level). In the present study, galvanic skin response, which reflects nicotine's general enhancement of sympathetic tone (Benowitz 1988), showed a linear relationship to nicotine dose; digit temperature, which reflects nicotine's vasoconstrictive actions, showed a dose related trend. Cortisol, which has been recently implicated in feedforward modulation of sensitivity to nicotine (Pomerleau and Pomerleau 1990b), exhibited stimulation that was related to the nicotine dose (overcoming the strong downward secular trend typical of plasma cortisol at this time of day; Pomerleau and Pomerleau 1990a).

Subjective effects in the present study were significantly related to aerosol dose with respect to ratings of desire

to smoke, nausea, and dizziness. These findings can best be interpreted by comparison with values from a study of cigarette smoke inhalation in smokers assessing some of the same subjective effects (Cherek et al. 1991). In Cherek's study, dosing was in four intervals ranging from sham smoking, which produced no nicotine boost, to the highest nicotine concentration, which yielded a plasma nicotine increment of 19 ng/ml: ratings of nausea increased as a function of nicotine dose, ranging from a low of nearly zero to a high of about 8% of scale maximum at the highest dose (compared to 33% for the high dose. associated with a plasma nicotine increment of 16 ng/ml in the present study); ratings of dizziness increased from a low of about 4% to a high somewhat more than 30% (compared to 41% for the high dose in the present study). These results indicate that even in subjects accustomed to the dosing via cigarette smoke, aversive components are experienced, albeit with less intensity than for the aerosol dosing method. Since the present procedure provided minimal opportunity for habituation to the aversive aspects of aerosol dosing (data were based on a series of 7 sprays–2 saline sprays followed by 5 nicotine sprays), the finding that nicotine dosing by means of a novel method was more aversive than usual cigarette smoking should not be particularly surprising. Whether smokers would adapt to nicotine aerosol dosing after repeated exposure, and the degree to which such dosing would become pleasurable, remain to be determined.

The approach to the delivery of nicotine via intranasal aerosol described herein meets most of the requirements indicated for a nicotine dosing method for studying cigarette smoking. Accuracy of dosing was confirmed, both by resulting increases in plasma nicotine level and by corresponding dose-related effects on known markers of nicotine's physiological and neuroendocrine activity. Subjective reports suggested that aerosol dosing was somewhat aversive, but it is not clear whether this effect is intrinsic to the method or due to nicotine administration per se (cf Cherek et al. 1991), or alternatively if it was due to insufficient opportunity for behavioral tolerance and adaptation to occur. The method has been tested in more than 30 subjects without serious ill effect. A recent exploration of the subjective effects and overall safety of the method was conducted in ten smokers and ten never-smokers (unpublished manuscript): Non-smokers reported fairly intense nausea and dizziness (necessitating termination of the session in three subjects) at doses that produced plasma nicotine levels in the order of 12 ng/ml; when dosage was reduced to produce a level of 7.5 ng/ml, subjective and physiological effects for non-smokers were similar in magnitude and duration to those observed for smokers receiving doses producing around 12 ng/ml.

A feature of the INADD approach is that nicotine administration via aerosol is novel for all subjects–smokers as well as non-smokers–thereby minimizing the contributions of behavioral tolerance and habituation to the dosing vehicle. In addition to flexible dose manipulation, the potentially confounding contributions of several thousand compounds in tobacco smoke are eliminated. Thus, the method lends itself to the investigation of the response to nicotine in populations who have never used nicotine as well as in those who have administered it extensively, providing a technological basis for systematic explorations of vulnerability to nicotine use and susceptibility to nicotine dependence. These features were exploited in the above-mentioned examination of differences in sensitivity to nicotine in smokers and never-smokers (unpublished manuscript).

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