Suppression of Nicotine Intake During Ad Libitum Cigarette Smoking by High-Dose Transdermal Nicotine

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ABSTRACT

Nicotine replacement therapy is believed to facilitate smoking cessation both by relieving withdrawal symptoms and by reducing the psychological reward from smoking. The latter might occur via down-regulation of nicotine receptors in the brain, which might require high levels of nicotine exposure. Our study examined the hypothesis that transdermal nicotine, dosed up to three times the doses currently recommended for smoking cessation, would suppress nicotine intake from ad libitum smoking in a dose-dependent manner. Eleven volunteers with no desire to quit smoking received placebo or 21, 42, and 63 mg/day transdermal nicotine, with and without cigarette smoking, in a blinded crossover study. Cigarette smoking was permitted as desired. Transdermal nicotine suppressed nicotine intake from cigarette smoking by 3%, 10% and 40% on average in the 21, 42 and 63 mg/day conditions. The number of cigarettes smoked per day declined from an average of 17.2 to 12.7 and the intake of nicotine per cigarette declined from 2.5 to 1.6 mg, comparing placebo and 63 mg nicotine conditions. Our study results suggest that high-dose transdermal nicotine has the potential to substantially suppress the intake of tobacco smoke and could be a useful strategy for smoking cessation therapy or for reducing the harm caused by smoking.

Nicotine medications are used to facilitate smoking cessation therapy and have been shown to increase cessation rates ~2-fold compared with placebo (Henningfield, 1995). However, absolute cessation rates remain low, ~25% to 30% at 1 year in treatment trials, and even less with typical use in the community (Tang et al., 1994; Fiore et al., 1994). The mechanism by which nicotine replacement therapy enhances smoking cessation is not completely understood. Nicotine replacement therapy almost certainly works in part by relieving withdrawal symptoms but probably also works by blocking the reinforcing effects of nicotine in cigarette smoke by binding to and desensitizing nicotine receptors in the brain (Benowitz, 1993; James et al., 1994). Experimental studies support the idea that nicotine replacement therapy may work in part by reducing the reinforcing effects of cigarette smoking, which would be consistent with the idea of receptor desensitization (Foulds et al., 1992; Levin et al., 1994).

Currently, nicotine replacement therapy is marketed as nicotine polacrilex gum, transdermal nicotine, nicotine nasal spray and nicotine inhalers. The levels of nicotine in venous blood produced by transdermal nicotine patches in doses of 21 mg/day are ~15 to 20 ng/ml, which are comparable to the levels found in the venous blood of light smokers (Benowitz, 1995). Nicotine intake from nicotine gum, nicotine nasal spray and nicotine inhalers is on average even lower than that delivered by nicotine patches (Benowitz et al., 1987, 1997).

When nicotine is absorbed slowly, as from nicotine patches, arterial and venous levels of the drug are expected to be in near-equilibrium and to be similar. However, when nicotine is absorbed quickly, as occurs when smoking a cigarette, arterial levels exceed venous levels severalfold. Thus, after smoking a cigarette, arterial blood nicotine levels, which reflect concentrations reaching the brain, reach levels as high as 50 to 100 ng/ml (Henningfield et al., 1990; Gourlay and Benowitz, 1997). If nicotine replacement therapy is working by desensitizing brain nicotinic receptors, it is reasonable to hypothesize that arterial levels comparable to those achieved in smokers are necessary for adequate desensitization.

There is evidence that currently recommended doses of nicotine replacement therapy are inadequate for many smokers. Higher doses (4 mg) of nicotine gum compared with lower doses (2 mg) enhance the likelihood of successful cessation in more dependent smokers (Tonnesen et al., 1988). Similar results have been reported with higher versus lower doses of transdermal nicotine, although not all studies have found the

ABBREVIATIONS: AUC, area under the plasma concentration-time curve; COHb, carboxyhemoglobin.
same results (Jorenby et al., 1995; Dale et al., 1995; Transdermal Nicotine Study Group, 1991). There is also evidence that matching levels of nicotine obtained from patch therapy with those obtained during base-line ad libitum smoking (done by adjusting patch doses to match levels of cotinine) enhances smoking cessation outcome (Sachs et al., 1995).

Clinical trials and experimental studies have reported, in smokers who do not quit, reduction of smoking rates during nicotine patch use compared with placebo therapy (Hurt et al., 1990; Transdermal Nicotine Study Group, 1991; Pickworth et al., 1994; Hartman et al., 1991). Transdermal nicotine treatment has been reported to reduce the pleasure, satisfaction and taste from cigarette smoking when a cigarette is smoked (Foulds et al., 1992; Levin et al., 1994). We reasoned that higher doses of nicotine replacement therapy than have been previously tested might be even more effective at reducing the appeal and/or psychological reward of cigarette smoking.

Based on these considerations, we examined the hypothesis that transdermal nicotine would suppress nicotine intake from ad libitum cigarette smoking in a dose-dependent manner. We administered doses of transdermal nicotine up to three times those currently recommended for smoking cessation and measured intake of nicotine and carbon monoxide from concurrent cigarette smoking.

**Methods**

**Subjects.** The subjects were 12 healthy men, ages 21 to 49 (mean, 41 ± S.D. 6 years), recruited by newspaper advertisements. They smoked an average of 29 cigarettes per day (range, 14 to 40), and had plasma levels of cotinine (the proximate metabolite of nicotine) while smoking of at least 150 ng/ml (mean, 340 ± 88 ng/ml; range, 168 to 434 ng/ml) and were determined not to be trying to quit or reduce smoking. Subjects had smoked for an average of 25 years (range, 9 to 34) and had no desire to quit. Subjects were judged to be in good health based on medical history, physical examination, blood tests and electrocardiogram. Exclusion criteria were any chronic illness or medication use and drug or alcohol abuse.

**Study protocol.** The study was a crossover, placebo-controlled, single-blind study. Subjects were admitted to the Clinical Study Center at San Francisco General Hospital for 21 days. The first day was for acclimatization. The next 20 days consisted of four treatment blocks, each lasting 5 days. Each day, subjects wore three patches, consisting of some combination of placebo and 21-mg nicotine patches (Nicoderm; Alza, Palo Alto, CA). The experimental treatment blocks consisted of 0, 1, 2 and 3 21-mg nicotine patches, representing average daily doses of 0, 21, 42 and 63 mg nicotine/day. Higher doses were gradually escalated over 3 days to allow tolerance to develop to potentially toxic effects of nicotine. Thus, for subjects in the 21 mg/day treatment, they received 21 mg for all 5 days. In the 42-mg treatment condition, subjects received 21 mg the first day and 42 mg on the second through fifth days. In the 63-mg treatment condition, subjects received 21 mg on day 1, 42 mg on day 2 and 63 mg on days 3 through 5. The sequence of treatments was balanced across subjects using latin squares.

For the first four subjects, all patches were applied simultaneously at 8:00 each morning. Two of these subjects experienced signs of nicotine toxicity, including nausea, dizziness and headache on the highest dose treatment. In one of these subjects, some patches in the high-dose condition were not administered due to nausea, so his data were excluded from the final data analysis. The other subjects received all patches as scheduled. Nicotine toxicity in the two subjects was seen at 2 to 4 hr after application of the patches, consistent with the expected time of peak plasma concentration. To avoid the peak developed from multiple patches applied simultaneously, for the next eight subjects, patches were applied at intervals: the first at 8:00 A.M., the second at 12:00 noon and the third at 4:00 P.M. With this schedule of patch application, no subject experienced symptoms of nicotine toxicity.

On days 1 through 4 of each treatment block, the subjects were allowed to smoke their own brand of cigarettes ad libitum. On day 5, they abstained from smoking. The no-smoking condition began at 8:00. On days 4 and 5 of each treatment block, plasma levels of nicotine, cotinine and carboxyhemoglobin were measured every 4 hr. Cigarette consumption was determined each day by counting cigarette butts.

Details of the cardiovascular and endocrine responses to transdermal nicotine with and without cigarette smoking in these subjects are presented elsewhere (Zevin et al., 1998).

**Biochemical analysis.** Plasma nicotine and cotinine concentrations were determined by gas chromatography (Jacob et al., 1981) modified for simultaneous extraction and analysis of cotinine and cotinine on a capillary column (Jacob et al., 1991). Carboxyhemoglobin was measured using a Ciba-Corning 2500 Co-oximeter (Ciba-Corning, Boston, MA).

**Data analysis.** The primary response measures were cigarette consumption, plasma nicotine concentrations and blood carboxyhemoglobin concentrations. To assess cigarette smoke exposure in the various nicotine patch conditions during ad libitum cigarette smoking, plasma nicotine and blood carboxyhemoglobin concentrations were compared while receiving transdermal nicotine (day 4) and during transdermal nicotine treatment without cigarette smoking (day 5).

The dose exposure level of a drug or chemical can be estimated by the area under the plasma-concentration time curve (AUC) after exposure. Assuming that the clearance of a drug or chemical for an individual is constant over time, which can be assumed to be the case for nicotine based on our prior studies, doses for an individual can be compared across treatments by comparing AUC values. In our studies, smoking occurred on day 4 but not on day 5, whereas patches were administered on both days. On day 4, nicotine levels were approximately at steady state because individuals had been taking patches and smoking for at least 3 days. Steady state was supported by the finding that plasma nicotine concentrations at 8:00 at the beginning of day 4 and then 24 hr later (at the end of day 4) were similar. Day 5, however, was not a steady state condition, as there was residual nicotine and carbon monoxide from cigarette smoking on day 4. These levels from smoking decline gradually over the day, as determined by the elimination half-life. To determine the AUC in a non-steady state condition, the area under the plasma nicotine concentration time curve needs to be extrapolated to infinite time after the end of the treatment, and the contribution of initial values needs to be subtracted. The AUC extrapolation from a particular terminal concentration is given by $C_{t}/K$, where $C_{t}$ is the terminal plasma concentration and $K$ is the elimination rate constant ($K = \ln(2)/t$). For our study, the plasma nicotine AUC on both day 4 and day 5 in various treatment conditions was estimated as: $AUC_{0-24} = C_{0}/K + C_{t}/K$, where $AUC_{0-24}$ is the area under the plasma concentration time-curve circumscribed within 24 hr, $C_{0}$ and $C_{t}$ are plasma nicotine concentrations at 0 and 24 hr, and $K$ is the elimination rate constant. The elimination rate constant was estimated for individuals from an intravenous nicotine study performed at a different date. One subject had not received such an infusion, and his elimination rate constant was taken as the average value for the other subjects. For AUC of carboxyhemoglobin, the simple steady state $AUC_{0-24}$ value on day 4 was used.

The actual dose of nicotine taken in from cigarette smoking was estimated using the AUC for plasma nicotine concentration in combination with the clearance of nicotine, which had been determined previously by an infusion of intravenous nicotine, as mentioned above. The dose was estimated as $AUC \times$ clearance (Benowitz et al., 1991). Because the cigarettes smoked per day were also re-
corded, we could estimate the intake of nicotine per cigarette smoked in the various treatment conditions.

The differences in plasma nicotine AUC (ΔAUCNIC) or other nicotine related values between days 4 and 5 and the absolute COHb AUC on day 4 were taken as the measures of cigarette smoke intake in different nicotine patch treatments. The extent of suppression of nicotine intake from cigarette smoking during various patch conditions was computed as

$$\Delta \text{AUC}_{\text{NIC}} (\text{NIC patch}) = \frac{\Delta \text{AUC}_{\text{NIC}} (\text{placebo patch})}{\Delta \text{AUC}_{\text{NIC}} (\text{placebo patch})}$$

The main hypothesis, that tobacco smoke intake would be suppressed in a dose-related manner by transdermal nicotine, was tested by repeated measures analysis of variance, comparing the four patch dose treatment conditions. The presence of a dose response was examined by orthogonal contrast test (Dixon, 1992). Individual comparisons were by the Tukey post test.

**Results**

Subjects smoked an average of 15.4 cigarettes per day on day 4 across the various treatment blocks (table 1). In the placebo patch (0 mg nicotine) condition, smokers smoked an average of 17.2 cigarettes per day, which was less than their usual average of 29 cigarettes per day. The number of cigarettes smoked was lowest on 63-mg nicotine patch compared with other treatment conditions, but the difference was not statistically significant.

Plasma nicotine concentrations throughout the day on day 4 (cigarette smoking plus transdermal nicotine) and day 5 (transdermal nicotine alone) are shown in figure 1. A rise in plasma nicotine concentration was observed between 4:00 A.M. and 8:00 A.M. at the end of day 4 in many subjects because they smoked cigarettes immediately after awakening about 7:00 A.M. in anticipation of the next day without cigarettes. The difference in AUC plasma nicotine concentrations on day 4 and day 5, and the estimated dose of nicotine taken in from cigarette smoking both decreased linearly with increasing nicotine dose (P < .05, orthogonal contrast test) (table 1, fig. 2). The average nicotine intake per cigarette fell from 2.5 mg with 0 mg nicotine patch to 1.6 mg with the 63-mg transdermal nicotine system (table 1), although the difference was not statistically significant (linear decrease by orthogonal contrast test, P = .08). The percent of suppression of nicotine intake from smoking averaged 3% (95% CI, −37% to 43%), 10% (95% CI, −31% to 50%), and 40% (95% CI, 6% to 74%) in the 21-, 42- and 63-mg nicotine patch conditions, respectively (P < .05), by orthogonal contrast test (fig. 3). Analysis of the three subjects who received all of their patches spaced throughout the day revealed no significant differences in cigarette consumption or degree of nicotine suppression.

Blood COHb levels during the course of 24 hr on days 4 and 5 of the various treatments are shown in figure 4. Average COHb levels during *ad libitum* cigarette smoking declined as

![Fig. 1. Plasma nicotine concentrations on day 4 (TDN + CS) and day 5 (TDN with no smoking). Data represent the mean values of 11 subjects.](Image)

**TABLE 1**

<table>
<thead>
<tr>
<th>Cigarette smoking, nicotine and carbon monoxide exposure in different nicotine patch dosing conditions</th>
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<tr>
<td><strong>Patch dose</strong></td>
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* n = 11, mean ± S.E.M.
*° Day 4, smoking combined with patch day.
*°° Day 4 minus day 5.
*°°° Different from each another, P < .05.
*°°°° Different from 0-mg patch condition, P < .05; Tukey’s post hoc test.
the dose of transdermal nicotine increased (P < .05) (table 1, fig. 5).

Discussion

Our study demonstrates that dosing with high doses of transdermal nicotine, up to 63 mg/day, is feasible and results in substantial suppression of nicotine intake from cigarette smoking, even in smokers who have no interest in quitting smoking.

The safety of high-dose transdermal nicotine, including details on cardiovascular and endocrine responses in our study, have been discussed in detail in another report (Zevin et al., 1998). That report found no difference in mean heart rate or blood pressure and no changes in the pattern of circadian variation in heart rate or blood pressure across various transdermal nicotine doses compared with smoking alone. Urinary epinephrine excretion was significantly higher with transdermal nicotine compared with placebo patch but was no higher in transdermal nicotine condition with smoking compared with smoking alone. These observations are consistent with a flat dose-response curve to the cardiovascular and hormonal effects of nicotine. An important observation in our study was that high-dose transdermal nicotine was much better tolerated when patch doses were spread out at 4-hr intervals so as to avoid the high peaks, seen at 2 to 4 hr after application, when multiple patches were applied at the same time. Thus, if high-dose nicotine is to be used therapeutically, we recommend that delivery be gradual so as to maintain more or less steady blood levels throughout the day.

The premise of our study was that high-dose transdermal nicotine could produce venous blood nicotine concentrations similar to arterial concentrations seen after cigarette smoking. The average venous plasma nicotine concentration in the 63-mg nicotine patch condition was \( \frac{55}{35} \) ng/ml. This level is within the range of arterial levels measured after cigarette smoking (Henningfield et al., 1990; Gourlay and Benowitz, 1997).

The intake of nicotine from \textit{ad libitum} cigarette smoking was suppressed on average by 40% with the high-dose patch, and suppression occurred in a dose-dependent manner. The dose-suppression curve is hyperbolic (fig. 3), suggesting that there is a dose of nicotine, not far exceeding the highest dose in our study, that would have almost completely suppressed nicotine intake. Previously, we studied nicotine intake from \textit{ad libitum} cigarette smoking during intravenous infusion of nicotine (Benowitz and Jacob, 1990). In that study, the average intravenous dose of nicotine was 35 mg administered over 14 hr, and the extent of suppression of nicotine intake from smoking was \( \frac{25}{35} \% \).

The number of cigarettes smoked per day in various patch conditions decreased proportionally less than the decrease in nicotine intake from smoking. This occurred because smokers had a tendency to take in less nicotine per cigarette as they were exposed to higher levels of transdermal nicotine. We have also observed this phenomenon in previous studies of \textit{ad libitum} cigarette smoking during urinary alkalinization and with concomitant intravenous infusions of nicotine (Benowitz and Jacob, 1990, 1985). Presumably, the cigarette smoking behavior persists as a highly conditioned behavior, whereas the body’s need for and intake of nicotine is more physiologically regulated.

Also of note is that the smokers smoked on average less (17 cigarettes per day) during the study than they did previously (29 cigarettes per day). Many of the common environmental cues to cigarette smoking are not present on the research ward, which probably explains why subjects smoked less. Thus, some caution in generalizing the findings of our study to smoking in naturalistic environments is warranted. On the other hand, since we have observed suppression of nicotine intake that exceeded the magnitude of suppression of cigarette consumption \textit{per se}, the same phenomenon is likely
to occur in a naturalistic situation where nonpharmacological factors play an even greater role in triggering smoking.

The most likely mechanism by which transdermal nicotine suppresses nicotine intake from cigarette smoking is desensitization of nicotine receptors, resulting in reduced nicotine-related reinforcement from smoking. Simple replacement of nicotine effects that would have been obtained from smoking is not an adequate explanation for our findings because subjects do not experience the pleasure or stimulation from patch use that they receive from smoking. Other researchers have reported that transdermal nicotine reduces the satisfaction and pleasure obtained from smoking a cigarette, which is consistent with the idea of receptor desensitization (Foulds et al., 1992; Levin et al., 1994). Alternatively, it has been suggested that some smokers may smoke to desensitize receptors; that is, the desensitized receptor state is perceived as desirable and reinforcing (Balfour, 1994). In either case, desensitization of nicotinic cholinergic receptors by high-dose transdermal nicotine could explain our results. Suppression of smoking to prevent toxicity from excessive nicotine appears not to be the explanation for our findings. None of the subjects who received nicotine patches spaced out across the day developed any symptoms of toxicity, which would have been expected, at least to some degree, if toxicity was limiting intake.

The implication of our study is that high-dose transdermal nicotine has the potential to substantially suppress the intake of tobacco smoke and could be a useful strategy for smoking cessation therapy or for harm reduction. Our subjects were not trying to quit smoking. Subjects who are motivated to quit are likely to have experienced a much greater reduction of smoke intake. Also, our study was conducted in subjects who were administered high-dose patches with smoking for only 2 or 3 days. Assuming that transdermal nicotine is working by reducing the reinforcing effects of nicotine from cigarette smoking, it may take more than 2 to 3 days to see the maximal effect, as the conditioned reinforcement from cigarette smoking diminishes.

Other studies support the idea that doses of nicotine higher than those currently marketed might increase smoking cessation rates (Dale et al., 1995). One study prospectively matched the dose of transdermal nicotine to the smoker’s precession cotinine level (Sachs et al., 1995). That study found a strong dose-response curve for the percent nicotine replacement and the percent successful cessation.

In conclusion, the present study demonstrates that high-dose transdermal nicotine has low acute toxicity if dosed appropriately and that transdermal nicotine suppresses nicotine and carbon monoxide intake during ad libitum cigarette smoking in smokers who are not trying to quit. Our observations suggest that clinical trials of high-dose transdermal nicotine to aid smoking cessation and/or to reduce the harm caused by smoking are warranted.

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