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Transdermal nicotine: reduction of smoking with minimal abuse liability

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Abstract. Cigarette consumption as well as the physiologic, performance and subjective effects of the nicotine patch were evaluated in ten subjects who smoked ad libitum while residing on a residential research ward for 30 days. Nicotine transdermal systems ("patches") delivering a total of 0, 22 or 44 mg per 24 h were applied daily at a constant dose during each 7-day condition; the order of dosing conditions was varied according to a randomized, double-blind, crossover design. Nicotine patches significantly but modestly reduced spontaneous smoking and significantly increased venous plasma nicotine levels. Self ratings of patch liking, satisfaction with cigarettes and the ability to identify the patch condition did not change as a function of the nicotine dose, indicating minimal abuse liability. There were no consistent changes in the puffing pattern measures; however, in all patch conditions, subjects with extensive histories of illicit drug use smoked cigarettes faster than subjects with histories of occasional drug use. Small changes in resting heart rate, pulse and blood pressure occurred when the nicotine patch was worn. Thus large changes in venous plasma nicotine levels engender only modest changes in ad libitum cigarette consumption, measures of abuse liability and cardiovascular effects. These findings are consistent with the notion that the addictive and toxic effects of nicotine are partially determined by the rate of drug administration.

Key words: Transdermal nicotine – Smoking

Transdermal nicotine administration is effective as an aid to quitting cigarette smoking, reducing tobacco withdrawal symptoms, and reducing cigarette smoke intake in cigarette smokers attempting to quit smoking but who have not successfully quit (Fagerstrom et al. 1992; Palmer et al. 1992). The effects of 15 mg nicotine, delivered transdermally ("patch") over 16 h, on ad libitum cigarette smoking were compared to placebo in a study by Foulds et al. (1992). Although no reduction in cigarette consumption was found, a small decrease in expired air carbon monoxide (CO) was observed. There was no evidence of an adverse interaction between cigarette smoking and the active nicotine patch condition. The present study evaluated the generality of these findings by testing two doses of transdermal nicotine against placebo; with the high dose condition (44 mg per 24 h) being substantlly higher than the dose used by Foulds et al. (1992).

Another purpose of this study was to evaluate the possibility that higher transdermal nicotine doses would have increased abuse potential. Because there is already published research demonstrating that intravenous or smoked nicotine meets criteria as an abusable drug (Henningfield et al. 1985; US PHS 1988), the availability of a very slow release nicotine delivery system provided an opportunity to compare its abuse potential to that of the rapid delivery systems previously studied.

Materials and methods

Subjects

Ten male cigarette smokers volunteered to participate in the study in response to local newspaper advertisements. They were paid approximately $800 for their participation. For the duration of the experiment, they resided on the clinical ward of the Addiction Research Center. The mean age of the subjects was 33.1 years (range: 20–35) and their mean weight was 76.2 kg (59.5–87.3). Their score on the Fagerstrom Tolerance Questionnaire (Fagerstrom 1978), a measure of nicotine dependence, averaged 8.1 (7–10) and each subject smoked over a pack of cigarettes per day (mean = 23.3, range 20–35). The FTC nicotine yield of their cigarettes averaged 1.2 mg (1.1–1.3). The subjects' self-reported drug histories indicated that five ("users") had extensive histories of drug abuse (lifetime experience averaged 4.6 illicit drugs used repeatedly; frequent current use); whereas the other five subjects ("occasional users") had less extensive drug histories (lifetime experience limited to occasional marijuana and cocaine; little current use). None of the subjects had tried to quit smoking within the past year and none expressed a current interest in stopping smoking at the time of their admission to the study. Before their participation in the study, the subjects

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gave informed consent that had been approved by the hospital institutional review board and met Department of Health and Human Services guidelines.

Procedures

During their 30-day stay on the residential research ward, subjects had 24 h, unrestricted access to their usual brand of cigarettes from a computer-controlled dispenser that recorded the time of cigarette delivery. Subjects were allowed to smoke ad libitum throughout the study except that no smoking was allowed during the data collection periods. Once each day (1400 hours) subjects were required to smoke one cigarette through a puff monitor to enable measurement of the puffing behavior. During the first 3 experimental days, no patches were administered (baseline smoking phase) but cigarette consumption was monitored. On each of the following three days, two patches delivering a total of 0, 22 or 44 mg nicotine were applied, in ascending dose order to insure that the subjects could tolerate the various doses of nicotine. Daily, over the next 3 weeks, two patches delivering a total of 0, 22 or 44 mg of nicotine were applied to a new site on the arms (one patch on each) at 0900 hours. Each of the three dose phases lasted 7 days and were administered in random double-blind order. After the last patch was removed, subjects resided on the ward for an additional 3 days.

Nicotine patch

The nicotine and placebo patches were supplied by the Elan Pharmaceutical Corporation (Athlone, Republic of Ireland). The nicotine patches contained a total of 30 mg nicotine in a gel matrix with a circular surface area of 30 cm^2. A single patch released 75% (22 mg) of nicotine over 24 h and raised venous plasma nicotine levels to 12 ng/ml in abstinent smokers (Mulligan et al. 1990). The placebo patches were similar in appearance to the nicotine patches but contained no nicotine. On study days, one patch was applied to each arm: in the 22 mg condition (one placebo and one nicotine patch), no attempt was made to ensure that the active patch was placed on the same arm.

Dependent measures

All of the dependent measures were collected beginning at 1400 hours each day, about 5 h after the application of the patch. Study measures were collected in the following order: performance tasks (not reported), subjective measures, physiologic measures, expired carbon monoxide (CO), puff measures (smoke one cigarette), adverse events, concomitant medications, venous plasma sample, skin evaluation. Because smoking was permitted ad libitum, except for the cigarette smoked at 1400 hours each day, the time between the last cigarette and the collection of the physiologic, subjective and smoking measures was not controlled. However, the interval was always greater than 15 min (time for performance tasks) to preclude expired air CO determinations and possible other measures from being invalidated by more recent smoke exposure. The venous plasma sample was always collected 10 min after the subjects smoked the cigarette through the puff monitor.

Physiologic measures. The heart rate, systolic and diastolic blood pressure and oral temperature were obtained using an IVAC automated vital signs monitor (Ivac, San Diego, Calif.). Expired CO was measured using an Ecolyzer carbon monoxide monitor (National Draeger, Pittsburgh, Pa.).

Smoking measures. The number of cigarettes smoked in 24 h, the average butt weight and the time of day each cigarette was smoked were recorded. At 1400 hours, on the last 5 days of each patch condition (Mon-Fri), subjects smoked one cigarette using a cigarette holder attached to a pressure sensitive switch connected to a computer keyboard. The frequency and durational measures of puffing behavior included puff duration, number of puffs, cigarette duration, and interpuff interval.

Subjective measures. Each afternoon at 1400 hours, 5 h after patch application, subjects completed the Single Dose Questionnaire containing four scales rating the effects of the drug in the patch: drug detection ("feel drugs?"); drug liking (0–4 scale of "not at all to "awful lot"); drug identification (11 names of commonly used and abused drugs) and a symptom check list (Fraser et al. 1961). Visual analog scales (100 mm) were used to indicate: positive-negative effects of the patch, patch comfort, satisfaction with recently smoked cigarettes, and various characteristics of cigarettes: strength, draw, hotness, harshness, and taste.

Venous plasma levels. Blood samples (10 ml) were drawn from a prominent vein in the forearm seven times during the study: on admission, during a baseline smoking period, after the dose run up, on day 7 (always a Friday) of each of the three patch conditions, and prior to discharge from the ward. Blood collection occurred 10 min after the subject smoked a single cigarette through the puff monitor. The samples were centrifuged and the plasma was separated and kept frozen until an analysis for nicotine and cotinine levels using GC mass spectroscopy was performed (Mulligan et al. 1990).

Statistical analyses

In general, the results of the various dependent measures were evaluated by analysis of variance techniques for a repeated measure, within subject design. The main factors were: drug condition (three levels: placebo, 22 and 44 mg), time (seven levels: day of application) and illicit drug use history of the subjects (two levels: user and occasional user; between subjects factor). Where there was no significant effect as a function of subject history, the results of all ten subjects were pooled and the data were analyzed by a two-factor (drug condition and time) within-subjects, repeated measures analysis of variance. When these analyses were significant, post hoc tests were used to discriminate the differing conditions.

Results

Average daily cigarette consumption significantly decreased with increasing doses of patch-delivered nicotine [$F(2,18) = 18.6$; $P < 0.01$]. As illustrated in Fig. 1A, in the placebo patch condition (17.01 $\pm$ 1, mean cigarette/day $\pm$ SEM) there was a nonsignificant decrease in smoking compared to the baseline phase 1 levels (18.1 $\pm$ 1). However, compared to smoking rates during the placebo condition, each of the nicotine conditions significantly reduced spontaneous smoking (22 mg, 15.3 $\pm$ 1; 44 mg, 13.4 $\pm$ 1). There was a significant [$F(6,54) = 2.21$; $P < 0.05$] effect of time but the condition by time effect was not significant. On the first day of all patch conditions cigarette totals were the lowest of the 7 days.

The decrease in spontaneous smoking was most evident in the 18 h after the application of the active patches, as little smoking occurred from 0200 hours to 0800 hours. In the first 6 h of patch application, ad libitum smoking decreased from 5.6 (placebo) to 5.1 and 4.4 (22 and 44 mg conditions) cigarettes [$F(2,18) = 7.31$;

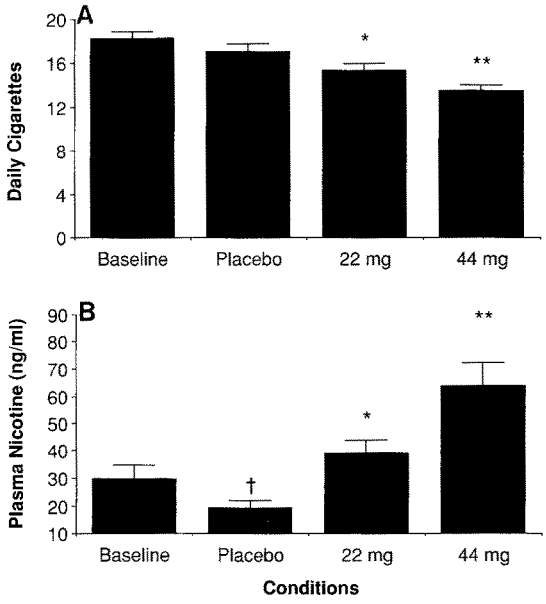

Fig. 1A,B. Mean (± SEM) ad libitum cigarette consumption by ten subjects wearing no patch (*Baseline*), or patches delivering a total of 0, 22 and 44 mg nicotine per day (**A**). Venous plasma nicotine concentrations (mean + SEM) on the last day of the patch conditions (**B**). *Asterisk* indicates mean is significantly different from placebo condition (* $P < 0.05$; ** $P < 0.01$; paired *t*-tests). *Dagger* indicates significant difference between placebo patch condition and baseline ($P < 0.05$, paired *t*-test)

$P < 0.01$]. Over the following 12 h, ad libitum smoking in the active patch condition was less than ad libitum smoking in the placebo patch conditions; during the final 6 h (0200–0800 hours) there was little smoking (average = 1.8 cigarettes) and no significant differences in spontaneous smoking among the patch conditions were observed.

The decrease in spontaneous smoking paralleled an increase in venous plasma nicotine levels [Fig. 1B). During the baseline phase, venous plasma nicotine levels averaged 29.6 (± 5.2 SEM) ng/ml. In the placebo patch condition, plasma nicotine levels decreased to 18.7 (± 3.3) ng/ml; venous plasma nicotine levels significantly increased as a function of the nicotine content of the patch [$F(2,5) = 6.68$; $P < 0.01$]. The plasma nicotine levels in the 22 and 44 mg patch conditions, 39.2 (± 4.7) and 63.4 (± 8.5) ng/ml, respectively, were significantly higher than those during the placebo condition ($t = > 3.5$; $P < 0.01$).

During baseline smoking, afternoon (1400 hours) expired air CO levels averaged 22 ± 1 ppm. During the placebo patch condition, the expired air CO concentration was 18 ± 1 ppm. This was a nonsignificant decrease. During the active patch conditions, expired CO averaged 18 ± 1 (22 mg) and 16 ± 1 (44 mg). The levels during the high dose condition were significantly less than those during the baseline smoking ($t = 3.6$; $P < 0.01$).

Subjective effects

Subjects evaluated their liking for the drug in the patch using the drug liking scale of the Single Dose Questionnaire [*F*raser et al. 1961). No significant differences in liking as a function of dose condition, time, or drug history were observed. Further, there were no significant changes in the subjects' rating of the overall "positive" or "negative" effects on a visual analog scale. These scores remained near a neutral level regardless of the patch condition. Visual analog ratings for cigarette satisfaction, harshness, draw and taste did not change as a function of the patch dose or time.

Subjects were unable accurately to identify the dose condition. For example, the placebo patch was identified as tobacco 35% of the time and as a blank 51% of the time. On the other hand, the 44 mg patch condition was identified as a blank 44% and as tobacco-like 41% of the time.

Physiologic measures

As shown in Table 1, the resting heart rate was slightly higher during the 22 and 44 mg patch conditions. Heart rate varied as a function of the patch condition [$F(2,18) = 7.98$; $P < 0.01$]; however, there was no significant effect for time or the interaction between dose and time. Systolic and diastolic blood pressure were slightly higher when subjects wore the 22 mg but not the 44 mg patches. There was a small but significant change [$F(2,18) = 3.66$; $P < 0.05$] in diastolic blood pressure as a function of the patch condition. A small increase in pressure occurred during the week the subjects wore the 22 mg patch. However, changes in diastolic blood pressure did not change as a function of time, nor was the dose by time interaction significant. There were no significant changes in oral temperature.

Puffing pattern

As shown in Table 2, the nicotine content of the patch did not significantly affect the average or total puff duration on the daily test cigarette. Total puff duration averaged 13 s and single puff duration averaged 1.7 s across all conditions. In the high dose (44 mg) patch condition, drug users took significantly fewer puffs than occasional users. Total time to smoke a cigarette was not significantly decreased as a function of the nicotine content of the

Table 1. Physiologic effects of transdermal patches

	Placebo	22 mg	44 mg
Heart rate[a] (beats per min, BPM)	74.5±1.2	78.3±1.3	75.5±1.3
Systolic blood pressure[a] (mm Hg)	121.3±1.2	124.8±1.3	121.5±1.2
Diastolic blood pressure[a] (mmHg)	68.3±0.8	70.8±0.9	69.9±0.9
Oral temperature (°C)	36.7±0.02	36.8±0.03	36.8±0.03

Values are mean±SEM for 10 subjects taken from daily measures on each subject

[a] ANOVA indicates significant ($P<0.05$) dose effect $F(2,18)>3.66$)

Table 2. Puffing pattern

Measure		Placebo	22 mg	44 mg
Puffs/cigarette	U	7.4± 0.6	7.1± 0.5	6.3± 0.5[a]
	O	9.3± 0.7	9.5± 0.5	9.0± 0.6
Average puff duration (s)	U	1.7± 0.1	1.8± 0.2	1.7± 0.1
	O	1.7± 0.1	1.6± 0.1	1.5± 0.1
Total puff duration (s)	U	12.2± 0.9	11.2± 0.7	10.6± 0.8
	O	15.7± 1.3	14.6± 0.9	12.9± 0.9
Total smoking time (s)	U	189 ±24.3[a]	182 ±27.3[a]	156 ±21.0[a]
	O	327 ±22.1	334 ±17.2	333 ±20.2

Values are the means of 5 subjects with extensive histories of drug use, users (U) and 5 with less extensive histories, occasional users (O). Measures from each subject are the means for the last 5 days of each patch condition

[a] Indicates value is significantly ($P < 0.05$, critical values, studentized range) different from occasional users.

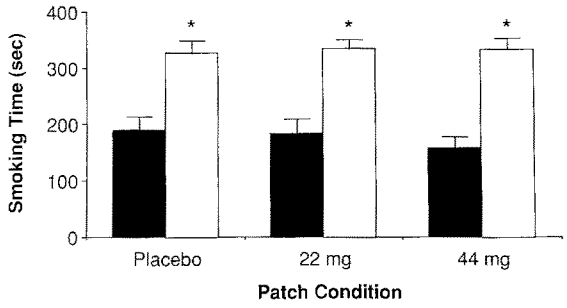

Fig. 2. Mean (± SEM) time to smoke a cigarette in subjects ($n = 5$) with extensive drug abuse histories (*filled bars*) and in subjects ($n = 5$) with less extensive histories (*open bars*). *Asterisk* indicates the mean is significantly different between groups ($P < 0.05$, studentized range)

patch. However, on this smoking measure, the drug use history of the subject was a significant factor [$F(1,8) = 7.56$; $P < 0.05$]; across all the dose conditions the drug users smoked faster than the occasional users [Fig. 2].

Skin reactions

The subjects evaluated the overall patch comfort daily using a 0 to 100 mm visual analog scale. There were no significant effects as a function of dose, time or the dose by time interaction. The experimenters also evaluated the patch sites for: erythema, dryness, pruritus, burning, edema, and weeping using an intensity scale of 0 (none) to 3 (severe). In general, these symptoms increased as a function of the dose and the day of the dose phase. Immediately after the removal of the patch, the skin seemed less affected than 6 h later, when the skin reaction was maximal. The swelling and itching subsided over 24 h but the application site was evident for up to 5 days after the removal of the patch. All subjects reported itching and had some evidence of skin irritation at the high dose condition. On day 5 of the 44 mg condition, two of the subjects had skin reactions that were rated as severe. These reactions necessitated that one subject withdraw from the study 1 day early. Both subjects were treated with topical anti-inflammatory cream and one subject was given an antihistamine (diphenhydramine, 25 mg).

Discussion

The main results of the present study were that transdermal nicotine significantly decreased ad libitum cigarette smoking without causing similar changes in measures of abuse liability, puffing patterns or cardiovascular parameters.

In the present study, transdermal nicotine patches, but not placebo patches, significantly reduced spontaneous smoking. Daily average cigarette consumption in the 44 mg dose condition decreased 29% (versus baseline) or 21% (versus placebo patch). During the 22 mg patch condition, a smaller (18.6% and 9.5%, respectively) decrease in spontaneous smoking occurred. Our findings are consistent with those of Hartman et al. (1991), who reported that transdermal nicotine, but not placebo, reduced smoking in a 1-day study on psychiatric inpatients with no desire to quit. However, results of the present study differ from those of Foulds et al. (1992), who reported no decrease in smoking between the placebo and nicotine patch conditions, and a significant difference between the placebo and the no patch conditions. In that study, the no patch condition lasted a full week, whereas in the present study the baseline period was 3 days. Furthermore, the present study was conducted in a residential, closely supervised institutional setting where the patches were worn 24 h per day. The Foulds et al. (1992) study was conducted on outpatients who wore the patch for 16 h per day. Thus, the experimental setting may account for some of the difference seen in ad libitum smoking, the main outcome measure.

There was an orderly and significant increase in venous plasma nicotine levels as a function of the patch condition, from 18.7 (placebo) to 39.2 (22 mg) and 63.4 ng/ml (44 mg). Foulds et al. (1992) also reported a significant increase in venous plasma nicotine levels in the subjects wearing a nicotine patch (34 ng/ml) compared to a placebo patch (25 ng/ml). Plasma nicotine levels increased by 85% (22 mg) and 215% (44 mg) in the active patch conditions in the present study and by only 36% in the Foulds et al. (1992) study. The venous plasma nicotine levels produced by the 22 mg patch during ad libitum smoking were within the range commonly observed by people who smoke about 1 1/2 packs of cigarettes per day. These levels were generally lower than the peak increase in arterial blood following the smoking of a single cigarette by tobacco deprived cigarette smokers (Henningfield et al. 1990).

Smoking behavior is regulated by a complex array of physiologic and psychologic factors including plasma nicotine levels (Henningfield 1984). The degree to which people vary their cigarette smoking in response to supplemental nicotine intake has been studied by several techniques. For example, plasma levels of nicotine were enhanced by the administration of nicotine gum (Ko-

zlowski et al. 1975; Russell et al. 1976; Ebert et al. 1984), and after intravenous nicotine administration (Lucchesi et al. 1967; Henningfield et al. 1985) and after a transdermal nicotine patch (Foulds et al. 1992). Such supplemental nicotine administration generally produced diminished smoking, although the effect was not robust. Moreover, regulation of nicotine intake was imperfect; regardless of the venous plasma nicotine level, smoking persisted at rates that increased plasma nicotine. Our results confirm and extend previous findings. Although venous plasma nicotine levels increased by 215% in the high dose condition, smoking was reduced by only 21%. These results and those of other studies emphasize that nicotine blood levels only partially regulate the behavior of smoking.

Overall, afternoon expired CO did not differ significantly as a function of the patch condition in the present study. During the 44 mg condition, expired CO decreased to 16 ppm, which was not significantly different from the placebo value (18 ppm), but differed significantly from the baseline values (22 ppm). The later result bolsters the observation by Foulds et al. (1992) that afternoon expired CO was reduced in the nicotine patch condition.

There were no differences in puffing patterns as a function of the nicotine dose. The mean number of puffs (9.3/cigarette) and the mean time to smoke a cigarette (327 s) in subjects with no extensive drug use histories were similar to the smoking patterns reported elsewhere [US PHS 1988; Foulds et al. 1992). Regular users of illicit drugs smoked faster, and in the high dose condition, took fewer puffs per cigarette. Similarly, subjects with a history of alcoholism smoke faster than those without that history (Keenan et al. 1990). Alcohol use was equivalent in the groups of the present study; these were distinguished by the use of opiates, stimulants other than cocaine, and by the frequency of current drug use. Data from small sample studies must be conservatively interpreted, but it appears that regular drug users, like alcoholics, smoke faster than occasional users.

The patch did not increase measures of abuse liability in either the regular or the occasional drug users. The nicotine patch did not increase scores on the drug liking question of the Single Dose Questionnaire (Fraser et al. 1961), a widely used instrument for assessing potential abuse liability (Jasinski 1977; Jasinski et al. 1984). Furthermore, there were no significant changes in the positive/negative effects scale, which was near neutral in all patch conditions. In fact, subjects were unable to accurately the nature of the patch condition, providing little evidence for psychoactivity (Jasinski and Henningfield 1989). Even in the high dose condition, the patch was identified as a blank 44% of the time and as "tobacco-like" only 41%. Foulds et al. (1992) similarly reported that subjects were unable to distinguish nicotine from placebo patches and that the patch exerts minimal subjective effects, but they did not use measures of established validity for abuse potential. Taken together, these data provide no evidence that the nicotine patch has significant potential for abuse. These results differ from those after rapid intravenous injections and smoking where nicotine is reinforcing (Henningfield et al. 1985). Benowitz and Jacobs (1990) reported no definitive subjective effects after slow intravenous nicotine infusions, whereas Henningfield et al. (1985) reported marked drug liking after an intravenous bolus of nicotine. These results are consistent with the hypothesis that rate of nicotine administration is a determinant of its abuse liability (Henningfield and Keenan 1993). A caveat is that our subjects were tolerant to nicotine; the possibility that the nicotine patch may possess significant abuse liability in non-tolerant subjects is not ruled out by the present study.

In the present study, the patch did not significantly change subjective measures of cigarette smoking. There were no significant differences on the five visual analog questions that queried satisfaction with cigarettes. These results differ somewhat from those of Foulds et al. (1992), where there were no significant differences on individual items but there was a small but statistical difference in "total severity of unpleasant symptoms".

It has been estimated that approximately 50% of patients wearing the nicotine patch smoked at least a few cigarettes a day [Food and Drug Administration 1992). A newspaper article reported that five patients suffered myocardial infarctions while smoking cigarettes and wearing nicotine transdermal patches (Hwang and Walholtz 1992). This report raised the concerns that concurrent patch use and cigarette smoking may be highly cardiotoxic. The present results provide little support for this theory. In our study, only small increases in heart rate and blood pressure occurred, and none of the subjects complained of nicotine-related toxicity during the study. Our results are consistent with those of Benowitz and Jacobs (1990), who reported minimal cardiovascular changes during slow intravenous infusions of nicotine to subjects who were allowed to smoke freely. Ad libitum smoking did not cause symptoms of nicotine toxicity in subjects that wore the nicotine patch and smoked at daily rates equivalent to those of the present study (Foulds et al. 1992). These studies provide little evidence that adverse cardiovascular effects would occur from concomitant smoking and nicotine patch use. These laboratory findings are consistent with recent epidemiologic observations of a remarkably low incidence of serious cardiovascular adverse events (33 reported to the Food and Drug Administration) occurring in the approximately 3 million patch users in the United States (Food and Drug Administration 1992). It was estimated that approximately 2250 myocardinfarctions would have been expected had these people continued smoking unabated. There is little basis to assume that people unmotivated to quit and showing little reduction in smoke intake, as occurred in our study, would incur a cardioprotective effect by use of the nicotine patch.

Although there were no significant changes in the subject-rated comfort of the patch, erythema and swelling occurred in all subjects at the high dose condition. In two subjects, exudative reactions occurred. These findings are similar to those reported by others [Fagerstrom et al. 1992) that nicotine patches cause skin reactions in up to 74% of subjects (Hurt et al. 1990). Reactions as serious as

those of two subjects in this study occur in about 4% of patients wearing patches delivering 20 mg nicotine daily (Fagerstrom et al. 1992). The increasing severity of the reaction and the systemic complaints in the high dose condition of the present study suggest that nicotine could have induced a contact allergy. Such a response was noted by Eichelberg et al. (1989) and occurs during continuous transdermal application of clonidine, estrogen and (to a lesser extent) nitroglycerin. It has been proposed that the allergic response is to the nicotine-hapten formed as the drug is absorbed through the skin (Eichelberg et al. 1989). The result of our study that the response increased over dose and time of application tends to support that proposal.

In summary, the results of the present study indicate that transdermal nicotine delivery systems safely increase plasma levels of nicotine but have minimal abuse liability. The increase in venous plasma nicotine engendered by the active patch led to small but significant decreases in ad libitum smoking, indicating that simply raising the plasma level of nicotine has minimal effects on ad libitum smoking in subjects with no desire to quit. Finally, our data support the notion that the speed and route of nicotine administration are important determinants of its addictive and toxic effects.

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