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PHARMACOKINETICS OF A TRANSDERMAL NICOTINE PATCH COMPARED TO NICOTINE GUM.

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A new transdermal nicotine delivery system (TBS-NCT)was investigated in laboratory and clinical studies with healthy cigarette smokers. Plasma nicotine concentration time profiles were characterized during and after 24-hr application of three doses of TBS-NCT and during and after a 6-hr regimen of nicotine polacrilex gum. Pharmacokinetic analysis revealed dose-related plasma concentrations for transdermal treatments, bracketing the concentrations obtained from nicotine gum. The TBS-NCT system was also well tolerated during a subsequent 4-week open trial and demonstrated a 40% success rate for smoking cessation during the course of the trial. Overall, the TBS-NCT system appears suitable for once-daily application as an aid in smoking cessation treatments.

INTRODUCTION

Nicotine replacement therapy has become an important part of smoking-cessation treatment programs. This development has resulted from recognition of the important role of nicotine in the maintenance of cigarette smoking behavior and the potential importance of nicotine withdrawal symptoms in relapse and treatment failure.

The first widely used method of nicotine replacement employed nicotine-containing chewing gum. Studies have shown that nicotine chewing gum can reduce symptoms of smoking withdrawal and improve smoking cessation success rates (1-3). However, nicotine gum has some unpleasant side effects for some individuals, including bad taste, nausea, heartburn, and hiccups (4). Other acknowledged disadvantages include that chewing gum may be socially unacceptable to some smokers or under some social circumstances and that it is contraindicated for people with dentures or other dental appliances.

A promising alternative method for nicotine substitution is the use of a transdermal nicotine patch. Following initial research that demonstrated the effectiveness of topical nicotine application to produce significant systemic levels of nicotine (5) and to reduce cigarette craving and preference for nicotine (6), a variety of different systems have been developed for the transdermal administration of nicotine. Studies of these have consistently demonstrated that transdermal nicotine systems can produce pharmacologically significant systemic levels of nicotine for 24-hour periods (7-12). Furthermore, studies demonstrate that transdermal nicotine can be an effective therapy in clinical smoking cessation trials (13-18).

Recently, a new transdermal nicotine patch system was developed (TBS-NCT, TBS Laboratories, Inc., Piscataway, NJ). The system is a 10-cm^2 patch that is constructed of three layers as follows. Nicotine and other excipients are first blended and dispersed in a polyacrylate adhesive solution. This solution is then coated onto an impermeable aluminized polyester backing, dried, and laminated to a silicon-coated polyester protective release liner. Patches are die-cut and individually packaged. Preliminary testing at TBS, Inc. demonstrated that the patch system delivered nicotine at a rate of 7.5 - 10.0 mg/10cm^2/day across human cadaver skin.

This new patch system was investigated in two studies reported here. The first was an inpatient clinical trial conducted to evaluate the

pharmacokinetics of this transdermal nicotine patch system in healthy normal cigarette smokers. In addition, the plasma nicotine concentrations resulting from administration of three different doses of transdermal nicotine were compared with nicotine levels associated with the typical pattern of administration of nicotine gum. Subjective craving for cigarettes and symptoms of nicotine withdrawal were measured to assess the relative effectiveness of each treatment during the acute, one-day treatment period. The second study was a four-week trial of patch system wearability and tolerability that also provided preliminary data regarding its efficacy for smoking cessation.

MATERIALS AND METHODS

Thirty-two healthy cigarette smokers (13 male and 19 female) participated in the two studies. Subjects' ages ranged from 20 to 60 years (Mean $\pm$ SD = 36 $\pm$ 8 years). All subjects had a normal medical history and were in good health, confirmed by physical examination and appropriate laboratory screening of blood and urine prior to participation. Criteria for exclusion included: history of cardiac disorder, hypertension, diabetes mellitus, peptic ulcer, liver or kidney disease, skin allergies or other skin disorders, allergy to adhesive products, and current pregnancy or breast feeding. Pregnancy tests were administered to all female subjects prior to acceptance into the study. Subjects were required to have smoked at least 20 cigarettes per day (at least 0.7 mg FTC delivery) for at least five years. Actual values were higher; cigarettes per day, 30 $\pm$ 13 cigarettes (range 20 - 70) and duration of smoking, 19 $\pm$ 9 years (range 6 - 45). Subjects also expressed a current desire to quit smoking and a willingness to attempt smoking cessation during the study.

All experimental protocols were approved for protection of human subjects by the Institutional Review Boards of both the Veterans Affairs Medical Center, Durham and the Duke University Medical Center. Written informed consent was obtained from each subject prior to participation in these studies.

Pharmacokinetic Study

This was an open-label, single treatment study with random assignment of subjects to one of four experimental conditions. All experimental treatments were administered during one or two-day inpatient studies conducted in the Clinical Research Unit at Duke University Medical Center. All studies began at

0800 hrs following overnight smoking abstinence, which was confirmed by measurements of expired-air CO that yielded levels less than 8 ppm. Subjects were restricted to the ward during the study period and were closely supervised at all times to insure that they did not smoke. Meals were provided at regular times.

Three of the four experimental groups received either one, two, or three 10-cm^2 transdermal nicotine patches (TBS-NCT, TBS Laboratories, Inc., Piscataway, N.J.) in a study of 36 hrs duration. All patches were applied by one of the experimenters to the clean and bare skin of the subject's upper chest and were removed 24 hours later. Removed patches were collected in their original packaging and were returned to TBS, Inc. for subsequent analysis of residual nicotine. Subjects were studied for an additional 12 hours after removal of the nicotine patch(es). Blood samples were drawn at 2-hour intervals on the first study day, beginning immediately prior to patch application and continuing for 12 hours. Additional blood samples were drawn at 24 hrs of the study(when the patch or patches were removed) and afterward at 26, 28, 32, and 36 hrs.

The fourth treatment group received six pieces of nicotine gum (2 mg Nicorette®, Lakeside Pharmaceuticals, Cincinnati, OH), administered at hourly intervals from 8 AM until 1 PM. Each piece of gum was chewed according to standard package instructions for a period of 30 minutes. Afterward, the gum was collected for analysis of residual nicotine. Nicotine-gum subjects were studied for 12 hours. Blood samples were drawn every 15 minutes for the first hour, then at 1.5, 2, 4.5, 6.5, 8, 10, and 12 hours.

Blood samples were drawn from a superficial forearm vein using a heparinized catheter. The 5-ml samples were collected in iced glass tubes containing heparin. Samples were centrifuged immediately following collection (10 minutes at 2500 rpm) and plasma was separated and frozen at -20° C. Saliva samples (2-3 ml) were also collected at the time of each blood sample.

Expired-air CO was measured at 0800 and 2000 hrs on each day of study to confirm continued smoking abstinence. Subjects completed a 32-item inventory of withdrawal symptoms (19) at 0800, 1400, and 2000 hrs of each study day. Responses on this inventory provided scores representing subjective craving for a cigarette, experience of negative affect (tension and irritability), level of arousal, appetite, habit withdrawal, and three classes of somatic symptoms.

Clinical Investigation

All 32 of the subjects from the pharmacokinetic study also participated in a subsequent 4-week open trial to determine the wearability and potential side-effects of the TBS-NCT transdermal nicotine patch and to provide preliminary data regarding its effectiveness as an aid in smoking cessation. As mentioned above, all subjects had expressed a desire to quit smoking prior to participation.

Subjects were instructed in the application and use of the transdermal patch while they were participating as inpatients in the pharmacokinetic study. Subjects were asked to quit smoking beginning on the first day of patch use, which typically was the following day. Each subject received a total of 56 patches. Subjects were instructed to apply two patches to the skin of the upper chest each morning, varying the application sites daily. When patches were removed after 24 hours, subjects rated the level of itchiness and redness at each patch site using a 4-point scale consisting of 0 ("none"), 1 ("mild"), 2 ("moderate"), and 3 ("severe"). The removed patches were saved in their original packaging for later analysis of residual nicotine. Subjects completed cumulative weekly records of the number of patches that they had worn and the number of cigarettes that they had smoked, if any. Each subject was contacted by telephone on a weekly basis to confirm continued adherence to this protocol.

Only limited behavioral treatment interventions for smoking cessation were provided to accompany the nicotine patch. Subjects received a standardized package of written instructional materials to aid their efforts at smoking cessation, but no other clinical interventions were provided.

At the end of the 4-week trial, the subject returned for an exit physical examination. The subject returned all used and unused patches and rating sheets. Expired-air CO was measured to confirm each subject's report of smoking abstinence.

Analytical Method

The nicotine and cotinine plasma concentrations were measured by the Clinical Pharmacology Laboratories, San Francisco General Hospital and Medical Center, using an established capillary gas chromatographic technique (20) that has been previously validated for precision, accuracy, specificity, sensitivity, and linearity. Quantification limits for nicotine and cotinine were 1 and 10 ng/ml respectively.

All used nicotine patches and gum were returned to TBS Laboratories for nicotine residue analysis. Residual nicotine content in the used TBS-NCT

patches was extracted into methanol. Nicotine concentrations were then analyzed by gas chromatograph (Hewlett Packard HP-5890 II) following standard methods. Residual nicotine in nicotine gum was extracted into acidic water after gum was dispersed into fine particles by stirring in cyclohexane. Nicotine concentration in the aqueous phase was analyzed by HPLC (Hewlett-Packard HP-1090M with diode-array detector), using a method developed at TBS Laboratories.

Pharmacokinetic Calculations

Nicotine concentration values below the quantification limit were treated as 0.5 ng/ml in the calculation of pharmacokinetic parameters. The pharmacokinetic parameters were calculated as follows.

1. C_{max}, the highest plasma concentration observed during the dosing period.
2. t_{max}, the time of occurrence of the maximum concentration.
3. $AUC_{(0-24)}$, the area under the plasma concentration time curves calculated by trapezoidal rule.
4. $t_{1/2}$, the elimination half-life calculated from log-linear regression of plasma concentration over time after removal of patch or completion of oral dosing. The $t_{1/2}$ calculated for a subject was not used if the coefficient of determination for the regression (r^2) was less than 0.90.

RESULTS AND DISCUSSION

Nicotine Pharmacokinetics

Mean (SE) plasma nicotine concentration-time profiles associated with the three TBS-NCT patch treatments and with nicotine gum are presented in Figure 1. Immediately prior to patch application, average nicotine concentrations were less then 2 ng/ml, consistent with the required overnight smoking abstinence. Plasma concentration profiles indicate an initial linear absorption after patch application and resultant dose-related increases in nicotine concentration. Peak nicotine concentrations were observed at 8 hrs, after which time concentrations decreased slowly. Clinically significant plasma concentrations did remain after 24 hours of application, averaging 3.7 ng/ml, 6.3 ng/ml, and 8.2 ng/ml for the one, two, and three-patch treatments. Following removal of the patch(es), concentrations declined exponentially during the remaining 12 hours of study.

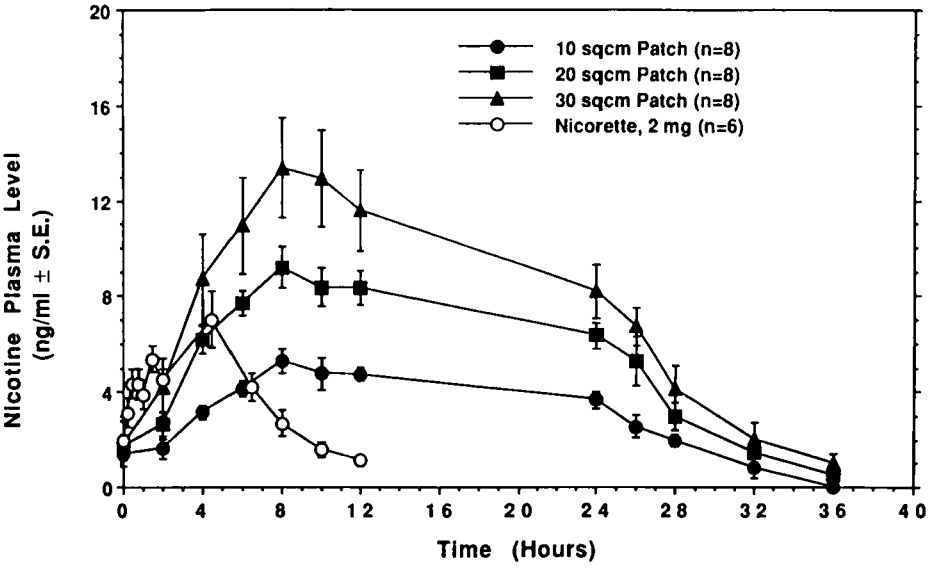

FIGURE 1.
Mean (SE) nicotine plasma concentration-time profiles for three doses of transdermal nicotine and nicotine gum.

Table 1 summarizes the results of nicotine pharmacokinetic analysis. A linear dose proportionality is clearly indicated for this transdermal patch system by the relative values of C_{max} and $AUC_{(0-24)}$ associated with the 1-, 2-, and 3-patch treatments. However, the values for t_{max} were comparable across dose, as were the values obtained for the elimination $t_{1/2}$ following patch removal. Thus dose apparently had no noticeable effect on either absorption or elimination.

By comparison with the transdermal nicotine treatments, the peak plasma concentration in the nicotine gum treatment (one 2-mg piece per hour) averaged 6.5 ng/ml, slightly higher than the maximum level obtained from one TBS-NCT patch. Concentration profiles suggest that nicotine absorption in the gum treatment was somewhat faster than in patch treatments, and the peak concentration was reached earlier. The $t_{1/2}$ was not calculated.

Subjective symptoms of withdrawal

All three nicotine patch treatments were associated with significant changes in subjective craving for cigarettes and in negative affect. However, statistical analysis did not reveal orderly differences related to transdermal

TABLE 1.

Summary of Pharmacokinetics

Parameter	Treatment			
	1 patch (10 sq cm)	2 patches (20 sq cm)	3 patches (30 sq cm)	Nicorette gum (6 pieces)
$AUC_{(0-24)}$ (ng•hr/ml)	95.0 ± 8.5	166.6 ± 14.1	232.7 ± 35.5	
$AUC_{(0-12)}$ (ng•hr/ml)				104.3 ± 19.1
C_{max} (ng/ml)	5.5 ± 0.6	9.4 ± 0.8	13.9 ± 2.3	6.5 ± 1.3
t_{max} (hr)	9.0 ± 0.7	10.5 ± 2.3	8.5 ± 0.5	4.6 ± 1.4
$t_{1/2}$ (hr)	3.7 ± 0.4	3.5 ± 0.5	3.6 ± 1.4	

Values expressed as Mean ± SE.

nicotine dose. Thus, results from the three nicotine patch treatment groups were combined. The data are summarized, averaged across the three patch doses, in Table 2.

Reported craving for a cigarette decreased significantly on Day 1 from 0800 hours (the time of patch application following overnight smoking abstinence) to 1400 and 2000 hours, after six and twelve hours of patch application ($p < .001$). Craving for cigarettes rose again significantly on Day 2, from 0800 hours (when the patch or patches were removed) to 1400 and 2000 hours. Reported negative affect followed a parallel time course, decreasing significantly following patch application on Day 1 from 0800 hours to 1400 and 2000 hours and increasing following patch removal at 0800 on Day 2 ($p < .001$). No treatment effects emerged for the other symptoms scales.

Although these preliminary data lacked experimental controls, the observed changes suggest that transdermal nicotine administration may reduce at least some of the subject symptoms of smoking withdrawal during the period of application. Comparisons with nicotine gum treatment could not be properly made, however, because the first symptom rating was made one hour after gum treatment had been completed.

TABLE 2.

Subjective Withdrawal Symptoms During the 24 hours of Patch Application (Day 1) and 12 hours Following Patch Removal (Day 2).*

	Day 1			Day 2		
Time	0800	1400	2000	0800	1400	2000
Craving for Cigarettes	33.3 (1.6)	25.4 (1.3)	24.1 (1.4)	22.0 (1.4)	28.0 (1.5)	27.3 (1.4)
Negative Affect	16.7 (1.0)	13.2 (0.6)	13.3 (0.8)	12.8 (0.7)	16.8 (1.0)	15.8 (0.9)

* Values (Mean and SE) averaged across 1, 2, and 3-patch treatments (N = 25). These scales have different maximum ranges, from 7 to 42 for Craving for Cigarettes and from 7 to 21 for Negative Affect.

Clinical Observations from 4-week Trial

Twenty-five subjects (11 males, 14 females) completed the 4-week protocol and provided complete data. Overall compliance was good, with 87.5% of patches applied as instructed. Fifteen of 25 subjects wore all 56 patches and only one subject showed less than 67% compliance in wearing the patches.

Skin reactions were generally very mild and subjects tolerated patches well. In 22 of 25 subjects (88%), average reported itchiness ratings were less than or equal to 1.0 ("mild") and no subject reported average ratings greater than 1.66. Average ratings of redness at the site of patch application were less than or equal to 1.0 ("mild") in 19 of 25 subjects (76%), and no subject reported average ratings greater than 1.16.

Ten of the 25 subjects (40%) reported complete smoking abstinence for the entire duration of the four-week trial. These subjective reports of clinical success were confirmed in each case by measurements of expired-air CO that yielded levels less than 8 ppm at the time of the exit physical examination, indicating that the subject had not smoked that day.

Residual Nicotine in Used Patches

The analysis of residual nicotine in used patches provided estimates of nicotine delivery to the skin. These provided further support for linear dose

proportionality associated with the three patch treatments. Estimated values (Mean ± SE) for nicotine delivered were 9.0 ± 1.0, 15.8 ± 0.8, and 25.0 ± 2.7 mg, for the one, two, and three-patch treatments respectively.

CONCLUSIONS

The pharmacokinetic study determined that the 10 cm^2 TBS once-a-day transdermal nicotine patch does deliver significant nicotine doses in vivo to healthy cigarette smokers. Plasma nicotine concentrations resulting from the 1 and 2-patch treatments were roughly equivalent to the plasma concentrations obtained in subjects who chewed six pieces of 2-mg nicotine gum at a rate of one piece per hour. Three TBS-NCT patches yielded plasma concentrations roughly twice those obtained from the regimen of nicotine gum administration.

All three doses of transdermal nicotine produced significant reductions in subjective reports of craving and negative affect that were maintained for the 24 hrs of patch application. As expected, subjective craving rose again within six hours following removal of the patch systems. Thus, the patch treatments were associated with reduction in clinical symptoms of smoking cessation or nicotine withdrawal.

Clinical observations from the four-week trial suggest that the TBS-NCT patch system has acceptable levels of wearability, associated with minimal skin irritation or reddening. Compliance with patch application and removal was also acceptable and results for smoking cessation in this trial (40% success at four weeks) are encouraging. This is especially encouraging given the minimal level of adjunctive behavioral intervention that accompanied the trial.

In conclusion, the TBS-NCT transdermal nicotine patch system should provide suitable doses of replacement nicotine that would be effective in the production and maintenance of smoking abstinence in cigarette smokers. Further studies will examine its clinical effectiveness for smoking cessation using a placebo-controlled, double-blind protocol in larger populations.

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