Pharmacokinetic Disposition of Multiple-Dose Transdermal Nicotine in Healthy Adult Smokers

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The pharmacokinetics and cardiovascular effects of nicotine and its major metabolite, cotinine, were characterized during repeated once-daily application for 5 days of a 30-cm^2 nicotine transdermal system, Nicotine TTS (Habitrol), to nine healthy, black, adult, male smokers. Subjects abstained from smoking throughout the study. Pharmacokinetic analysis indicated that nicotine was delivered from Nicotine TTS for the 24-hr application period averaging 0.76 mg/cm^2/24 hr, and at a relatively constant rate compared to other modes of drug administration. The transdermal clearance of nicotine, 1351 ml/min, coincided with reported values following intravenous nicotine administration; however, the terminal-phase half-life, 5.0 hr, did not. An analysis of the components of variance contributing to the variability in nicotine delivery from repetitive application of Nicotine TTS indicated that the *in vivo* transdermal permeation of nicotine is rate limited by both the device and the intrinsic skin conductivity. Clinical cardiovascular side effects were negligible as an apparent result of subclinical vasopressive nicotine concentrations, although drug activity with regard to other effects was manifested.

KEY WORDS: Nicotine TTS; transdermal pharmacokinetics and pharmacodynamics; components of variance.

INTRODUCTION

Nicotine in tobacco products has a well-established association with physical dependence. This dependence results in a withdrawal syndrome when these products are stopped, leading to early relapse in a significant number of cases. Nicotine replacement therapy offers a new approach to aid smoking cessation. Various therapies, including buccal and transdermal delivery, have been developed. Transdermal delivery of nicotine has been found efficacious in facilitating smoking cessation in association with behavioral modification programs (1–3). Nicotine replacement therapy reduces cigarette craving and withdrawal symptoms including negative affect and hypoarousal. Transdermal therapy offers advantages over buccal therapy due to the absence of repeated daily chewing of gum and associated gastrointestinal side effects.

Nicotine TTS (Habitrol) is a new transdermal drug delivery system designed to provide low but constant plasma nicotine concentrations over 24 hr during once-daily dosing. Transdermal maintenance of constant plasma nicotine concentrations has been shown to minimize cardiovascular side effects compared to the rapidly fluctuating concentrations associated with cigarette smoking (4).

The objective of this study was to characterize the plasma concentration–time profiles, the degree of accumulation, and the steady-state pharmacokinetics of nicotine and cotinine during once-daily application of a 30-cm^2 Nicotine TTS for 5 days in healthy, black adult, male smokers. Additionally, the cardiovascular effects resulting from Nicotine TTS were evaluated.

MATERIALS AND METHODS

Dosage Form

Nicotine TTS is a multilayered matrix system consisting of a reservoir of nicotine free base dissolved in Eudraget E100 acrylic copolymer surrounded with two polymer matrix layers, an aluminized polyester backing and an adhesive layer. It is designed to delivery nicotine to the systemic circulation at a nominal rate of 0.7 mg/cm^2/24 hr. A system with a contact surface area of 30 cm^2 and having a total nicotine content of 52.5 mg was used in this study.

Subjects

Nine subjects completed the study. All subjects were black male smokers, although race was not a selection criterion, whose average age was 29.6 years (range, 23–42 years), and average weight was 168.7 lb (range, 134–194 lb). All subjects were in good health on the basis of their medical history, physical examination, clinical laboratory tests, ECG, and chest X-ray. Each subject smoked at least 20 cigarettes per day.

Study Design and Procedures

This was an open-label, single-treatment period study which involved the application of a 30-mm^2 Nicotine TTS once daily for 5 consecutive days. Pharmacokinetic parameters were evaluated on the first and fifth days of system application. Cardiovascular measures were evaluated just prior to smoking cessation, after 2 days of abstinence but prior to drug administration, and on the fifth day of active treatment.

The study was conducted in a smoke-free area of the Clinical Research Unit (CRU) by personnel who were nonsmokers. Smoking and the use of nicotine-containing substances other than study medication were not permitted from 48 hr before application of the first system through 12 hr after removal of the last system. All subjects were instructed not to use any medication including over-the-counter products throughout the duration of the study.

After removing the release liner, the first Nicotine TTS system was applied to a clean, dry, hair-free, and tattoo-free area on the subject's back. No special preparation of the skin site was performed and no soap- or alcohol-containing preparation was permitted. At the end of 24 hr, the system was

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removed and replaced by a new system at a new site. A total of five systems was applied to the back of each subject. The skin sites were rotated according to a predetermined pattern and each site was used only once. System adhesion was evaluated at each visit to assure that the system was maintained in place securely during the required time interval.

On the days when multiple blood samples were drawn (Days 1, 5, and 6), the subjects received a standardized light breakfast and fluids after the first blood sampling. On the intervening days (Days 2, 3, and 4), the subjects received a regular breakfast except for breakfast meats. Lunch, dinner, and a small snack were served on these days.

Cardiovascular effects were assessed by ECG upon entry into and completion of the study, and sitting blood pressure (by auscultation) and heart rate during the study. Blood pressure and heart rate were determined at −48 hr (Day -2) prior to smoking abstinence, Day 1 prior to drug administration, and on Days 2 to 6 prior to dosing. All cardiovascular measurements were at the same time of day. Subjects were observed carefully throughout the study for signs of drug activity and were questioned about the occurrence of any medical problems.

Sample Collection and Analysis

Venous blood samples (7 ml) were drawn via an indwelling catheter or by repeated venipuncture immediately before (0 hr) and at 1, 2, 4, 6, 9, 12, 16, 20, and 24 hr after system application on Days 1 and 5. Blood samples also were drawn at 10, 30, and 45 min, and at 1, 2, 4, 8, and 12 hr after removing the last system on Day 6. Predose samples were obtained on intervening Days 3 and 4, before application of the respective daily system.

Each blood sample was collected in a potassium oxalate blood collection tube and centrifuged. The plasma fraction was transferred into a labelled glass vial and frozen immediately at −20°C.

All spent transdermal systems used in the study were collected and analyzed for residual drug content. Systems were removed from the subject's back after 24-hr application and were transferred to plain glass tubes. The tubes were tightly sealed and stored frozen.

Plasma concentrations of nicotine and cotinine were assayed by capillary gas chromatography with nitrogen–phosphorous detection using an established method (5). The quantitation limits in plasma were 1 ng/ml for nicotine and 10 ng/ml for cotinine.

Residual drug content in recovered systems was estimated using standard high-performance liquid chromatography. The drug was extracted from the systems by shaking in 0.1 *N* HCl in methanol for 2 hr. The solution was then filtered and a 20-μl aliquot was injected onto a C_{18}-Novapak (Millipore/Waters Inc., Milford, MA) 30-cm × 3.9-mm-i.d. column. The mobile phase consisted of 200 ml acetonitrile, 600 ml water, 420 mg sodium lauryl sulfate, and 1 ml triethylamine adjusted to a final pH of 5.0 with glacial acetic acid; the flow rate was 1.0 ml/min. Nicotine was quantified by UV detection at 260 nm. The accuracy and precision of the method are as follows. For systems (n = 6) containing 17.1, 37.9, and 54.5 mg nicotine base, the average recoveries of nicotine were 100.0, 101.6, and 100.4%, respectively. The corresponding coefficients of variation were 0.61, 1.3, and 0.36%, respectively.

Pharmacokinetic Calculation

Plasma concentration–time profiles for nicotine and cotinine were characterized in terms of their maximum (C_{max}) and minimum (C_{min}) levels during the dosing interval, time to peak concentration (t_{max}), predosing levels on each study day, areas under the curve during the dosing interval [AUC(0–24)], and average concentration over the dosing interval (C_{avg}). Other pharmacokinetic parameters evaluated were the fluctuation index (FI), apparent accumulation ratio (ACR), apparent terminal-phase half-life ($t_{1/2\lambda}$), and apparent transdermal clearance (CL_{TD}).

Values for C_{max} and C_{min} were obtained by visual inspection of the plasma concentration–time profiles. T_{max} was taken as the sampling time at which C_{max} was observed. AUC(0–24) values between 0 and 24 hr after system application were calculated using the linear trapezoidal rule. C_{avg} values on Day 5 were obtained by dividing the AUC values by the dosing interval (24 hr). FI values were estimated using the expression

$$FI = [C_{max} - C_{min}]/[C_{avg}]$$

Accumulation ratios were calculated by dividing the Day 5 AUC(0–24) values by the corresponding Day 1 AUC(0–24) values. The $t_{1/2\lambda}$ was estimated from linear regression of the terminal log-linear phase of the plasma concentration–time curves after final system removal.

The amount of drug delivered by each transdermal system was estimated by subtracting the measured residual content from the labeled content for the 30-cm^2 system (52.5 mg nicotine base). CL_{TD} was estimated by dividing the total amount of nicotine delivered on Day 5 by the corresponding AUC(0–24).

Statistical Analysis

Attainment of steady state was evaluated from predose concentration values utilizing analysis of variance (ANOVA). Subject and Day were regarded as factors. The components of variance associated with the amount of nicotine delivered transdermally were evaluated by mixed-effects ANOVA, where subject effects were regarded as a random factor and time-related effects (Day) as a fixed factor (6). The proportional contribution of intersubject and intrasubject variance was estimated. Any other comparison was by ANOVA with appropriate factors. A P value of 0.05 or less was considered to be statistically significant for both analyses.

RESULTS

Pharmacokinetics

Analysis of predose concentrations (Table I) on Days 1 through 5 demonstrated that nicotine steady state was attained by Day 2 and cotinine steady state by Day 4. Comparatively, nicotine levels on Days 2 to 5 were not statistically different. Cotinine levels on Days 4 and 5 were not

statistically different. Cotinine levels on Day 3 were significantly different from those on Day 4 ($P < 0.01$).

An average nicotine plasma concentration of 1.2 ng/ml and cotinine plasma concentration of 104 ng/ml were observed before Nicotine TTS application even though the subjects had abstained from smoking for 48 hr. After application of the system on Day 1, nicotine plasma levels showed no apparent change until 2 hr, demonstrating a 1 to 2-hr transdermal delivery lag time upon initial application (Fig. 1). This apparent lag time was not observed at steady state, indicating residual depot delivery from preceding application sites caused by dermal loading. Maximal concentrations of nicotine were only 9% greater at steady state than on the first day of dosing, while maximal cotinine concentrations increased by 70% at steady state (Fig. 2). T_{max} for nicotine was significantly reduced by 54% at steady steady compared to the first dose. T_{max} for cotinine was reduced by 35% at steady state; however, this difference was not statistically significant. The average degree of accumulation at steady state was 140% for nicotine and 240% for cotinine. After removal of the final Nicotine TTS on Day 6, plasma concentrations of both nicotine and cotinine exhibited a transient increase in concentration which dissipated within 1 hr. This transient increase in concentrations was attributed to a disturbance of the nicotine dermal depot caused by the mechanical distortion of the skin when the system was removed. Following this transient phase, both nicotine and cotinine plasma concentrations declined in the usual fashion. Nicotine's terminal-phase half life was 5 hr, which coincides with the attainment of steady state by Day 2, that is, by the time of the second dose application. Cotinine's terminal-phase half-life was 25 hr, which was based on measurements in only eight of the nine subjects. The cotinine half-life for Subject 6 was indeterminate. The average half-life of cotinine suggests that steady state was not actually achieved until Day 5, although plasma concentrations on Day 4 were within 7% of their expected final values. The transdermal clearance of nicotine was 1351 ml/min.

Table I. Nicotine and Cotinine Pharmacokinetic Parameters After Multiple Daily Dosing of Nicotine TTS

	Mean ± SD	
	Nicotine	Cotinine
Day 1		
C_{max}, ng/ml	15.3 ± 4.5	170.9 ± 50.7
t_{max}, hr	13.8 ± 5.4	21.3 ± 8.0
AUC (0–24), ng · hr/ml	233.0 ± 72.2	2994.1 ± 1173.7
Day 5		
C_{max}, ng/ml	16.7 ± 2.0	282.1 ± 67.1
t_{max}, hr	6.4 ± 2.7	13.9 ± 10.4
C_{min}, ng/ml	9.5 ± 2.4	233.8 ± 60.2
AUC (0–24), ng · hr/ml	310.5 ± 52.0	6141.3 ± 1464.9
C_{avg}, ng/ml	12.9 ± 2.2	255.9 ± 61.0
FI	0.6 ± 0.2	0.2 ± 0.1
ACR	1.4 ± 0.3	2.4 ± 1.2
CL_{TD}, ml/min	1351.0 ± 388.2	
$t_{1/2\lambda}$, hr	5.0 ± 1.2	25.0 ± 11.1
Predose concentrations, ng/ml		
Day 1	1.2 ± 1.1	104.0 ± 59.6
Day 2	9.9 ± 3.0	170.7 ± 50.5
Day 3	10.7 ± 2.9	207.9 ± 47.3
Day 4	11.1 ± 3.6	257.8 ± 58.8
Day 5	10.7 ± 3.3	258.6 ± 68.9

Nicotine Delivery from System Residual Content

The amount of drug remaining in each system after 24 hr of application was measured, and the amount delivered determined from the labeled drug content (Table II). The average transdermal delivery rate was 1 mg/hr, or 0.76 mg/cm^2/24 hr, which was in good agreement with the nominal rate. A components of variance analysis of the amount of nicotine delivered in 24 hr transdermally from multiple applications showed that an average (±SE) of 22.9 ± 2.40 mg was delivered, or 44% of the system's contents. No statistically significant time-related effects were detected, indicating the apparent absence of any time-related dermal alteration caused by systemic nicotine accumulation. A significant intersubject effect was found ($P < 0.001$). The population estimates of the intersubject and intrasubject standard deviations were 5.22 and 3.77 mg, respectively, with corresponding 90% confidence intervals of 3.55 to 9.24 and 3.14 to 4.76 mg. The proportional contribution of the intersubject variance was 65.7% of the total observed random variation.

Cardiovascular Effects

No significant alterations in ECG were found. Comparisons of systolic and diastolic blood pressure and heart rate prior to cessation of cigarette smoking and after 2 days of abstinence resulted in no significant difference. Comparisons of blood pressure and heart rate after 2 days of abstinence from cigarette smoking and following the last Nicotine TTS dose (Day 6) resulted in a significant ($P < 0.01$) reduction in systolic blood pressure of an average 6.9 mm Hg. Diastolic blood pressure decreased an average 2.9 mm Hg which was not significant. Heart rate increased an average of 7.3 bpm, which was marginally significant ($0.10 > P > 0.05$). These changes were not considered clinically significant, although they may have pharmacological implications.

DISCUSSION

The plasma concentration–time profiles of nicotine derived from Nicotine TTS investigated in this study demonstrated characteristics of extended duration drug delivery relative to cigarette smoking or bucally administered nicotine (7). These observations are compatible with the expected characteristics of continuous transdermal nicotine delivery. The pharmacokinetic disposition of nicotine and cotinine when delivered transdermally were compared to the reported disposition following intravenous administration of nicotine (8) and cotinine (9). The observed average transdermal half-life was 2.5-fold greater than the 2-hr half-life found following intravenous nicotine administration. The total clearance observed following intravenous nicotine was reported as 1292 ml/min and within 5% of the value observed in this study. These findings suggest that the plasma concentration–time profile for Nicotine TTS is characterized by a "flip-flop" pharmacokinetic model where the terminal-phase half-life corresponds to the input rate half-life. The

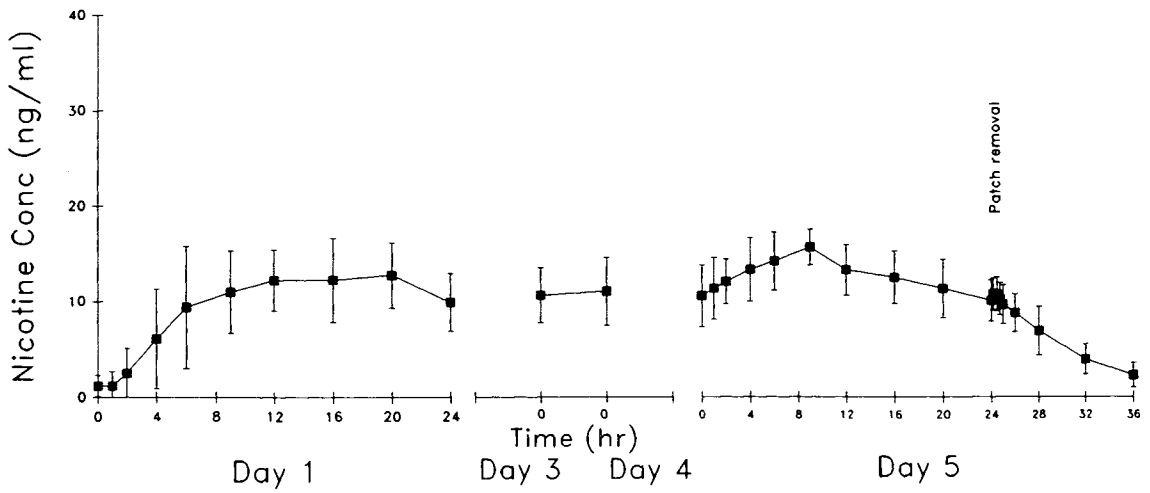

Fig. 1. Mean (±SD) plasma concentrations of nicotine (ng/ml) after once-daily application of 30-cm^2 Nicotine TTS to the backs of nine healthy smokers.

coincidence of clearance values suggests that nicotine does not exhibit transdermal first-pass extraction. The observed transdermal half-life of cotinine was 1.25-fold greater than the 20-hr half-life found after intravenous cotinine administration. The difference between cotinine half-lives is not considered significant, although the transdermal half-life may be marginally influenced by the nicotine input rate. Evaluation of cotinine's transdermal half-life was additionally compromised by the duration of plasma concentration monitoring following removal of the final dose.

From the analysis of the components of variance, the intrasubject variance represents the variance associated with within-subject variation in transdermal drug delivery, variation in labeled system content due to the manufacturing process, and analytical variation in the assessment of residual drug content in the transdermal system. The variation in transdermal delivery from a system where nicotine is exclusively rate controlled by the device would thus represent the sum of the above sources of variation. The expected proportion of intrasubject variance relative to total random variance for such a system would be close to unity, since the total random variance would be independent of intersubject variance. The observed 34% proportional intrasubject variance for Nicotine TTS suggests that the transdermal delivery of nicotine from Nicotine TTS is only partially controlled by the device. The *in vivo* Nicotine TTS delivery rate is thus dependent on the interaction of the permeation of nicotine from the device and the permeation of nicotine through the skin. Since differences in individual intrinsic skin permeabilities are partially expressed, optimal therapeutic efficacy may require individualized dose titration. Individualizing doses is supported by the intersubject variation seen in this study.

The predominant clinical cardiovascular activity of nicotine mimics sympathetic stimulation. The observed corresponding reduction in systolic blood pressure, maintenance of vascular tone, and increase in heart rate are not entirely consistent with the known activity of nicotine. These findings suggest possible reflex compensation in heart rate at subclinical vasopressor nicotine levels in response to a reduction in cardiac stroke volume. A 12% reduction in stroke volume has been reported after 10 days of multiple dosing

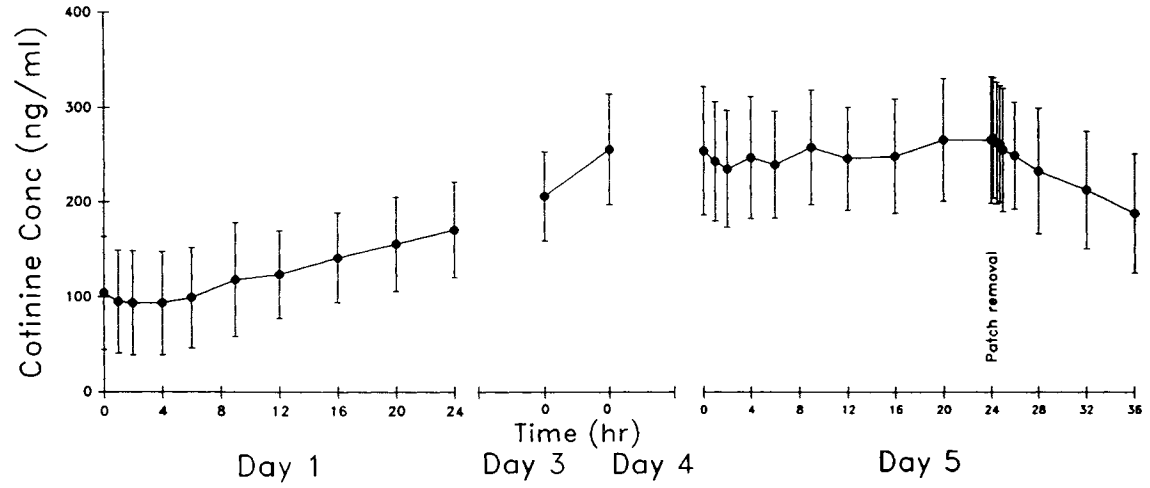

Fig. 2. Mean (±SD) plasma concentrations of cotinine (ng/ml) after once-daily application of 30-cm^2 Nicotine TTS to the backs of nine healthy smokers.

Table II. Nicotine Delivery from Nicotine TTS (30 cm^2) After Five Repetitive Applications

Subject no.	Amount delivered (mg; mean ± SD)	Average delivery rate (mg/hr)
1	19.9 ± 4.2	0.8
2	24.5 ± 2.9	1.0
3	35.6 ± 1.8	1.5
4	23.3 ± 2.0	1.0
5	24.5 ± 3.8	1.0
6	18.2 ± 2.8	0.8
7	22.4 ± 3.1	0.9
8	21.6 ± 6.6	0.9
10	16.5 ± 4.2	0.7
Mean		0.96
SD		0.23

with transdermal nicotine from a similar transdermal nicotine system (4).

In conclusion, Nicotine TTS delivers nicotine transdermally at a relatively constant rate compared to other modes of drug administration, resulting in an average steady-state nicotine concentration of 13 ng/ml and cotinine concentration of 256 ng/ml. Mechanistically, the *in vivo* permeation of nicotine from Nicotine TTS is rate limited by both the device and the intrinsic skin conductivity. Clinical cardiovascular side effects of Nicotine TTS appear to be negligible as a result of subclinical vasopressive concentrations of nicotine.

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