Pharmacokinetics of Multiple Daily Transdermal Doses of Nicotine in Healthy Smokers

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The plasma concentration–time profiles and pharmacokinetics were characterized for nicotine and its major metabolite, cotinine, after multiple daily application of a nicotine user-activated transdermal therapeutic system (UATTS) to nine healthy smokers. The volunteers abstained from smoking 24 hr prior to and during the course of the study. A 10-cm^2 system (designed to deliver 75 $\mu g/cm^2/hr$) was applied every 24 hr for 5 days, with serial blood samples taken on Days 1 and 5 and after system removal on Day 5. Generally, the nicotine UATTS was well tolerated. Predose nicotine concentrations on Days 3 to 5 indicated that steady state was reached by Day 3. The nicotine pharmacokinetic parameters for Day 1 and Day 5 were similar: the mean (SD) AUC(0–24) values for Days 1 and 5 were 271.7 (50.7) and 311.7 (55.0) ng · hr/ml, the mean (SD) C_{max} values were 16.3 (2.6) and 16.8 (2.9) ng/ml, and the median (range) T_{max} values on Days 1 and 5 were 12 (9–24) hr and 12 (0–24) hr, respectively. There was only slight or no accumulation of nicotine after multiple dosing as indicated by the Day 5 to Day 1 AUC and C_{max} ratios of 1.15 (0.09) and 0.98 (0.06), respectively. Overall, the UATTS system maintained relatively constant plasma nicotine concentrations and is suitable for once-daily application.

KEY WORDS: nicotine; cotinine; pharmacokinetics; multiple dose; transdermal delivery.

INTRODUCTION

Nicotine replacement therapy offers an effective approach to aid in smoking cessation. When administered transdermally, nicotine has been shown to enhance success either by reducing cigarette craving or by relieving withdrawal symptoms with few adverse side effects (1–7). A proper transdermal nicotine dosage form should have the capability of maintaining constant low concentrations of nicotine in the blood over an extended period of time.

The nicotine user-activated transdermal therapeutic system (Nicotine UATTS) used in this study has been shown to enhance abstinence from cigarette smoking after 3 weeks at nearly three times that of the placebo condition (7). This system is designed to maintain nicotine in a chemically stable form until activated immediately before application to the skin (8). The system is an oval, multilaminate, two-compartment unit containing nicotine dihydrochloride and sodium hydroxide (activator) separated by a breakable central seal. Mixing the two components converts the nicotine salt to the free base, which is then delivered across the rate-controlling membrane to the skin.

The system tested in the present study was loaded with 50-mg equivalents of nicotine free base designed to deliver drug over a 10-cm^2 area at a steady-state rate of 75 $\mu g/cm^2/hr$. The resulting plasma nicotine concentrations were expected to be comparable to the mean concentrations produced by the 2-mg gum (9) but substantially lower than peak concentrations achieved during cigarette smoking. When given as a single dose to healthy smokers, a mean (range) lag time of 6.0 (3.0–8.0) hr and a mean C_{max} (SD) of 15.1 (6.0) mg/ml was observed (10).

The purpose of this study was to examine the plasma concentration–time profiles, degree of accumulation, and steady-state pharmacokinetics for nicotine and its principal metabolite, continine, after daily application of a UATTS system for 5 consecutive days to nine healthy smokers.

MATERIALS AND METHODS

Clinical Procedures

This was an open-label, single-treatment study in which nicotine UATTS systems were applied once daily for 5 days. Each subject had a single system applied to a clean, dry, hair-free area on the upper chest or lower abdomen. The study was conducted in a smoke-free area of the study unit by non-smoking personnel. No smoking was permitted by the subjects from 24 hr before the first system application to 12 hr after the last system was removed.

Ten healthy male smokers were enrolled and nine subjects completed the study. Their ages were between 22 and 44 years (mean, 32.8 years) and their weights were between 59.2 and 98.7 kg (mean, 77.3 kg). All subjects had normal medical history, physical examination, laboratory screen, EKG, and chest X-ray at the screening visit. The physical examination, EKG, and laboratory tests were repeated at the close-out visit.

Prior to application, the nicotine UATTS systems were examined visually on each study day to confirm that they had not been accidentally activated. The center seals were then ruptured, the contents of the two compartments were mixed well, and the activated systems were applied. At the end of 24 hr, the systems were removed and replaced by a new system at a new site. Skin sites were rotated using a predetermined pattern, using each site only once. Each skin site was observed at 1, 12, and 24 hr after removal except for the system applied on Day 5, when the site was not inspected at 24 hr.

On both blood sampling days (Days 1 and 5), fluids and a light breakfast were given to each subject between 8 and 9 AM. Lunch, dinner, and a small snack were served at 4, 10, and 14 hr, respectively, after dosing. Blood samples (10 ml) were drawn immediately before and at 1, 2, 4, 6, 9, 12, 16, 20, and 24 hr after system application on Days 1 and 5. Additional samples were drawn at 10, 30, and 45 min and at 1, 2, 4, 8, and 12 hr after removal of the system on Day 6.

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Daily predose samples were obtained on Days 3–5 before system application.

Analytical Method

Blood samples were collected in tubes with EDTA and centrifuged immediately. The plasma fractions were separated, transferred to glass tubes, and frozen immediately. The nicotine and cotinine plasma concentrations were performed using an established capillary gas chromatographic technique (11). The gas chromatographic assay had been previously validated with regard to precision, accuracy, specificity, sensitivity, and linearity. The quantification limits for nicotine and cotinine were 1 and 10 ng/ml, respectively.

Calibration curves were constructed daily by assaying plasma samples spiked with known amounts of drug and metabolite. Drug concentrations in the study samples were estimated by using these calibration curves. Quality-control samples prepared at the assay center were assayed at the same time as the study samples to demonstrate consistency in the performance of the analytical technique. Overall variability of the peak area ratios (N = 10) for the spiked standards ranged from 3.7 to 18.7% for nicotine and 3.7 to 16.1% for cotinine. Variability of the quality control samples (N = 10) ranged from 3.1 to 10.5% for nicotine and from 3.5 to 11.4% for cotinine.

Pharmacokinetic Calculations

All concentration values below the quantification limit were treated as zero in the calculation of mean data and pharmacokinetic parameters. The pharmacokinetic parameters were calculated as follows.

1. C_{max} (C_{min}): the highest (lowest) observed plasma concentration during the 24-hr dosing interval.
2. T_{max} (T_{min}): the time at which C_{max} (C_{min}) occurred.
3. $C_p(24)$: concentration at the time of system removal (24 hr).
4. AUC(0–24): the area under the plasma concentration–time curve during a dosing interval (0–24 hr), calculated by the linear trapezoidal rule.
5. T(lag): the time at which the first apparent increase in plasma concentration occurred on Day 1.
6. $T_{1/2}$: calculated from linear regression of the log-linear phase of the plasma concentration–time curve after final system removal, using the last three observable concentrations. $T_{1/2}$ was not determined if the coefficient of determination of the regression (r^2) was less than 0.95.

Statistical Analysis

The C_{max} and AUC(0–24) for Day 1 and Day 5 were compared by a two-sided, paired Student's t test. The T_{max} values for Day 1 and Day 5 were compared by the Wilcoxon signed-rank test. The predose concentration for Days 3 to 5 were compared by analysis of variance (ANOVA). All comparisons were performed using the commercially available computer program, STATGRAPHICS (Statistical Graphics Corporation, Rockville, MD, Version 3.0).

RESULTS AND DISCUSSION

Clinical Observations

Ten subjects were enrolled in the study; nine successfully completed the study. One subject discontinued partic-

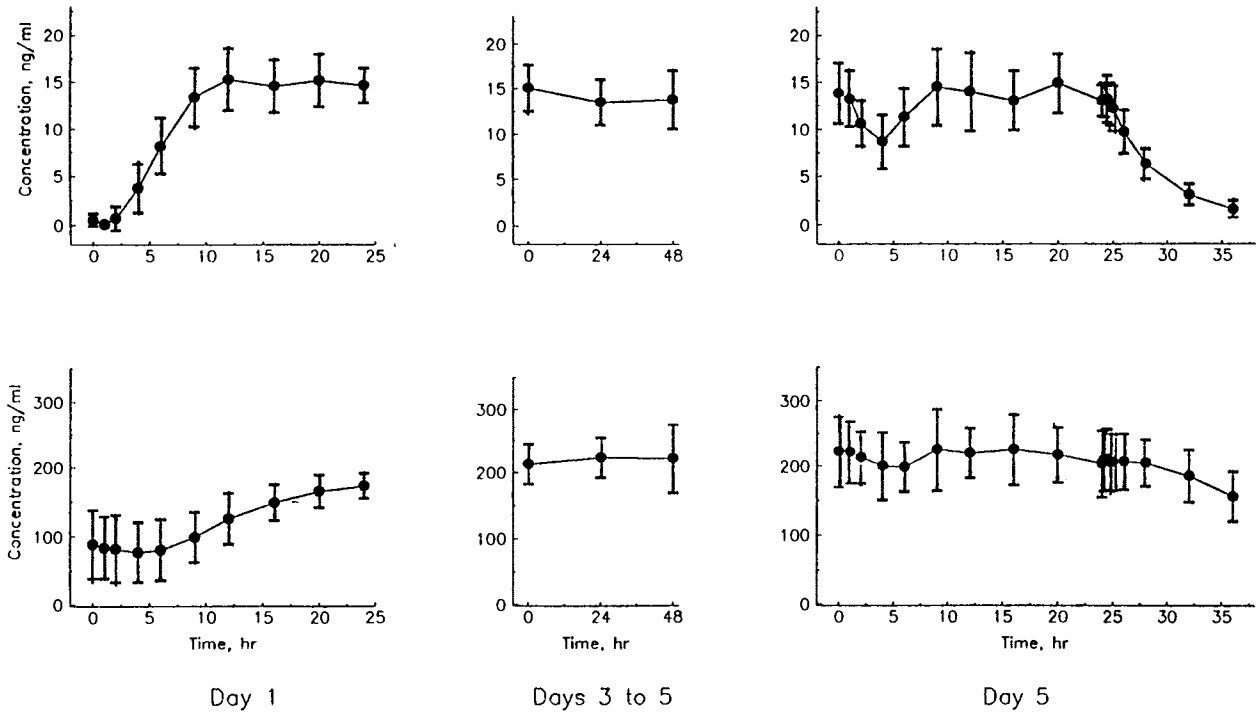

Fig. 1. Mean and SD plasma concentration–time profiles of nicotine (upper panels) and cotinine (lower panels) after multiple daily transdermal dosing of nicotine.

ipation because of complaints of headache and nausea. One subject reported intermittent headaches and nausea, and experienced one episode of vomiting, but was able to complete the study. Barely perceptible erythema was noted for almost half of the application sites, which resolved in 1 to 2 days. One subject exhibited moderate erythema and slight edema at each of the five sites. The erythema was observed up to 12 days after removal of the systems. Three application sites were associated with mild pruritus in two different subjects. Overall, the nicotine UATTS was well tolerated by the subjects in this short-term multiple-dose study. A long-term study using the same system has been reported (12).

Nicotine Pharmacokinetics

Mean (SD) plasma concentrations of nicotine before system application on Day 1 were 0.5 (0.6) ng/ml, consistent with the subjects having not smoked any cigarettes since the previous evening (Fig. 1). There was no apparent increase in plasma concentrations after application of the system for a median of 4 hr (range, 1–4 hr; Table I). Nicotine concentrations then increased and achieved a maximum concentration of 16.3 (2.6) ng/ml at 12 hr after dosing (range, 9 to 24 hr). At 24 hr on Day 1, nicotine concentrations had declined slightly, and were 14.7 (1.8) ng/ml.

Predose nicotine concentrations on Days 3, 4, and 5 were similar, with values of 15.1 (2.5), 13.5 (2.5), and 13.8 (3.2) ng/ml, respectively. There were no statistically significant differences ($P > 0.05$) between the predose concentrations, demonstrating that steady state was achieved by Day 3.

Plasma nicotine concentrations on Day 5 showed an initial decline over 4 hr before increasing to relatively constant levels. The initial fall in concentrations is consistent with clearance of the drug from the previous dose combined with a lag in delivery from the newly applied system. The C_{max} concentrations were 16.8 (2.9) ng/ml and the C_{min} (trough) concentrations were 7.9 (2.3) ng/ml. The C_{max}-to-C_{min} ratio on Day 5 was 2.19 (0.34), demonstrating some fluctuation in nicotine concentration over the 24-hr dosing period. At 24 hr on Day 5, the plasma concentration was 13.0 (1.7) ng/ml. This concentration remained constant for 10 min to 1 hr after system removal and then declined. An elimination half-life of 3.6 (0.8) hr was consistent with previously reported results (10).

The 4-hr median T_{min} on Day 5 (range, 4 to 16 hr) corresponded well with the 4-hr median lag time on Day 1 (range, 1 to 4 hr) and with the value of 6 hr (range, 3–8 hr) reported in a previous study for the UATTS system (10). The median T_{max} was 12 hr for both Day 1 and Day 5, with ranges of 9–24 and 0–24 hr, respectively. The difference was not statistically significant ($P > 0.05$), suggesting consistent absorption characteristics on Days 1 and 5.

The AUC(0–24) for Day 5, 311.7 (55.0) ng · hr/ml, was slightly larger than that on Day 1, 271.7 (50.7) ng · hr/ml, with a Day 5-to-Day 1 ratio of 1.15 (0.09). The statistically significant difference between the AUC values for the two days indicates that slight accumulation occurred during multiple dosing. However, the mean C_{max} on Day 5, 16.8 (2.9) ng/ml, was similar to that on Day 1, 16.3 (2.6) ng/ml, and the difference was not statistically significant ($P > 0.05$). The mean (SD) ratio of C_{max} for Day 5 to Day 1 was 0.98 (0.06). The ratio of $C_p(24)$ on Day 5 to Day 1 was 0.89 (0.11).

Table I. Mean and SD Nicotine and Cotinine Pharmacokinetic Parameters After Multiple Daily Dosing of Nicotine UATTS

	Nicotine		Cotinine	
	Mean	SD	Mean	SD
Day 1				
$C_p(24)$, ng/ml	14.7	1.8	173.3	18.1
$C_{max}(0–24)$, ng/ml	16.3	2.6	173.9	18.5
$T_{max}(0–24)$, hr[a]	12.0	(9–24)	24.0	(20–24)
AUC(0–24), ng · hr/ml	271.7	50.7	2948.9	734.4
Lag time, hr[a]	4.0	(1–4)		
Day 5				
$C_p(24)$, ng/ml	13.0	1.7	204.0	49.6
$C_{max}(0–24)$, ng/ml	16.8	2.9	240.1	49.1
$T_{max}(0–24)$, hr[a]	12.0	(0–24)	9.0	(0–20)
$C_{min}(0–24)$, ng/ml	7.9	2.3		
$T_{min}(0–24)$, hr[a]	4.0	(4–16)		
C_{max}/C_{min} ratio	2.19	0.34		
AUC(0–24), ng · hr/ml	311.7	55.0	5174.9	1042.6
$T_{1/2}$, hr	3.6	0.8	16.9	4.2
Ratios (Day 5/Day1)				
$C_p(24)$	0.89	0.11	1.2	0.3
AUC(0–24)	1.15	0.09	1.9	0.9
C_{max}	0.98	0.06	1.4	0.3
Predose levels, ng/ml				
Day 1	0.5	0.6	88.5	49.7
Day 3	15.1	2.5	212.8	30.7
Day 4	13.5	2.5	223.1	30.9
Day 5	13.8	3.2	222.0	53.0

[a] Median (range).

Cotinine Pharmacokinetics

Plasma concentrations of cotinine before UATTS application on Day 1 averaged 88.5 (49.7) ng/ml. Since cotinine has a reported elimination half-life of 20 hr (13), these data are also consistent with the volunteers having not smoked for 24 hr. Plasma concentrations continued to decline over 0 to 6 hr before increasing to achieve a maximum level of 173.9 (18.5) ng/ml at 20 to 24 hr after system application (median, 24 hr).

Predose cotinine concentrations on Days 3, 4, and 5 were 212.8 (30.7), 223.1 (30.9), and 222.0 (53.0) ng/ml, respectively. These values were not significantly different ($P > 0.05$), demonstrating that steady state was achieved by Day 3.

The maximum concentrations of cotinine achieved during the dosing interval on Day 5 averaged 240.1 (49.1) ng/ml. These values were observed between 0 and 20 hr (median, 9 hr). The half-life for the two subjects meeting the calculation criteria for $T_{1/2}$ were 19.9 and 13.9 hr and were consistent with a previously reported half-life of 20 hr (13).

The AUC(0–24) for Day 5, 5174.9 (1042.6) ng · hr/ml, was significantly greater than that for Day 1, 2948.9 (734.4) ng · hr/ml, with the Day 5/Day 1 ratio being 1.9 (0.9). The Day 5-to-Day 1 ratios for $C_p(24)$ and C_{max} were 1.2 (0.3) and

1.4 (0.3), respectively. These observations are consistent with accumulation of cotinine during multiple dosing. Given an elimination half-life of 20 hr for cotinine, accumulation during once-daily dosing is expected. It has been reported that cotinine exerts little, if any, pharmacological effect at 300 ng/ml, the level associated with moderate smoking (13).

In conclusion, this study demonstrated that the shape of the plasma profiles on both Day 1 and Day 5 were consistent with an initial lag in drug delivery of approximately 4 hr after application of the system. The profiles were also consistent with an extended duration of release of the drug from the system since nicotine concentrations were maintained at relatively constant levels following the onset of drug absorption. Steady-state conditions for nicotine were established by Day 3; the extent of accumulation was negligible or small. This is consistent with the short elimination half-life of nicotine. Accumulation of cotinine was more apparent, due to a longer half-life value. However, this degree of accumulation is consistent with that found in regular smokers.

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