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Bioavailability and absorption kinetics of nicotine following application of a transdermal system

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1 The absolute bioavailability and absorption kinetics of nicotine were investigated in 13 healthy adult male smokers following single and multiple applications of a nicotine transdermal system (NTS), designed to release nicotine at an approximate rate of 1.5 mg h^{-1} over 24 h. The absorption of nicotine from the single NTS application was calculated with reference to a simultaneous intravenous infusion (i.v.) of deuterium-labelled nicotine.

2 The mean input time (MIT) and mean absorption time (MAT) for nicotine following application of NTS for 24 h were 7.7 and 4.2 h, respectively.

3 Following NTS removal, the mean apparent nicotine elimination half-life was 2.8 h, compared with 2.0 h following i.v. nicotine, reflecting continued absorption of nicotine following NTS removal.

4 The mean amount of nicotine absorbed from the NTS after the 24 h application was 20.9 mg, which represents about 68% of the amount released from the system; the remaining 32% was lost from the system during daily activities.

5 The ratio of AUC values for the metabolite cotinine relative to nicotine was similar whether nicotine was administered transdermally or intravenously.

6 Following i.v. administration, the mean nicotine clearance was 72 l h^{-1} (coefficient of variation 29%). Since coefficients of variation in AUC values following NTS and i.v. treatments were similar, transdermal administration of nicotine was not associated with increased interindividual variability in plasma nicotine concentrations.

7 No significant changes were seen in the pharmacokinetics of nicotine between single and multiple applications of NTS.

8 As expected from the higher total plasma nicotine concentrations, the incidence of adverse effects was higher following simultaneous intravenous and transdermal administration of nicotine. The most frequently reported systemic side effects were nervousness and headache; mild itching was the most frequent topical effect.

Keywords nicotine transdermal pharmacokinetics absorption

Introduction

Variation in transdermal drug absorption can compound the changes in plasma drug concentrations that result from variation in drug clearance. In addition, the bioavailability of drugs administered transdermally is not influenced by first-pass hepatic metabolism, but could potentially be lowered by metabolism in the skin. Therefore, it is important to measure the effects of transdermal absorption on the bioavailability and disposition of drugs.

The Nicotine Transdermal System (NTS, Nicoderm®) contains a rate-controlling membrane that regulates the release of nicotine to and through the skin and ensures relatively constant plasma nicotine concentrations throughout the day. The study described here was undertaken to investigate the absolute bioavailability and absorption kinetics of nicotine and plasma cotinine concentrations following application of the NTS [1]. To account for any diurnal variation in clearance and to minimise interday variability which might affect plasma nicotine concentrations after transdermal application, i.v. infusion of nicotine-d2 and NTS were administered simultaneously for 24 h.

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Methods

Subjects

Thirteen subjects completed the study, 10 were Caucasian, two were black and one was Hispanic. Their mean (± s.d.) age was 32.7 ± 11.8 years, height 178.7 ± 8.9 cm, weight 75.8 ±11.1 kg and body mass index 23.8 ± 3.4 kg m^{-2}. Their mean (± s.d.) nicotine dependence as measured by Fagerström score [2] was 8.7 ± 1.1, and each subject smoked at least 1 pack of cigarettes/day.

All subjects gave written informed consent. The study protocol and consent form were approved by the Committee on Human Research of the University of California at San Francisco, where the study was conducted.

Study design

Subjects were admitted to the Drug Studies Unit at the University of California Hospital for the duration of the study. After 48 h of smoking abstinence, one NTS releasing approximately 1.5 mg nicotine h^{-1} over 24 h was applied to the upper outer arm of each subject for 24 h on Day 1. At the same time, nicotine-d2 was infused in a forearm vein at a rate of 0.2 μg min^{-1} kg^{-1} for 24 h. A 24 h washout period (Day 2) followed the removal of the NTS and end of the infusion. Every 24 h on days 3 to 7, each subject received a new NTS, applied to a previously unused skin site on the upper outer arm, upper chest, or upper back [3]. Subjects were not allowed to smoke or consume any other nicotine-containing products throughout the study, and compliance was tested at four randomly selected times each day with a carbon monoxide breath analyzer (Breathco Monitor, Vitalograph Ltd, Buckingham, England). Consumption of caffeine-containing beverages was also prohibited during the study.

Study medications

The NTS used has a surface area of 22 cm^2 and releases approximately 36 mg of nicotine over a 24 h wearing period (Nicoderm, ALZA Corporation, Palo Alto, California and Marion Merrell Dow Incorporated, Kansas City, Missouri and Cincinnati, Ohio, USA). This dose has been shown to provide plasma nicotine concentrations that decrease nicotine withdrawal symptoms in nicotine-dependent patients [4, 5].

The i.v. nicotine-d2 solution contained approximately 20 mg of 3′–3′-dideuteronicotine bitartrate dihydrate. Average plasma nicotine concentrations of about 10 ng ml^{-1} were to be provided by the infusion rate of 0.2 μg min^{-1} kg^{-1} [6].

Assay of plasma nicotine and cotinine

Heparinized blood samples were drawn before administration of i.v. nicotine-d2 infusion or application of NTS on Day 1 and on frequent occasions (total of 54 samples) during the study. Blood samples were centrifuged immediately; the plasma was removed, divided into two aliquots and frozen until assay.

Plasma concentrations of nicotine and cotinine (labelled and unlabelled) were measured using a GC–MS method [7]. The lower limits of quantification of the plasma assays were 0.5 ng ml^{-1} and 5.0 ng ml^{-1} for nicotine and cotinine, respectively, whether labelled or unlabelled. Within-day coefficients of variation (CV) of the nicotine assay, varied from ± 8.6% to ± 2.6% over the concentration range of 1.2 to 30.0 ng ml^{-1}. Those for cotinine varied from ± 11.6% to ± 3.3% over the concentration range of 8.1 to 293.8 ng ml^{-1}. The between-day CVs for nicotine and cotinine varied from ± 11.9% to ± 7.7% and from ± 15.0% to ± 9.6%, respectively, over six-fold concentration ranges.

Determination of residual nicotine content and delivered dose from NTS

After the 24 h application period, each NTS was removed from the skin and wrapped immediately in aluminum foil. The wrapped system was returned to its pouch, which was then sealed and placed immediately in a freezer. The residual nicotine contents of all used systems were assayed; the nicotine content of control (unworn) systems was also assayed to provide an estimate of the initial content of worn systems. Following removal of the NTS at the end of Day 1, any nicotine remaining on the skin surface at the application site was removed by swabbing the area with a gauze pad saturated with 0.1% w/v phosphoric acid. The gauze pad was wrapped in aluminum foil and frozen until assayed for nicotine.

The delivered dose of nicotine was calculated as the difference between the mean nicotine content of control (unworn) systems ($n = 6$) minus the residual amount of nicotine remaining in each used system and any nicotine remaining on the skin surface (as measured in the gauze swabs).

Determination of amount of nicotine infused

The volume of infused drug solution was determined by weighing the infusion bottle before and after the infusion. The concentrations of nicotine in the infusate were determined by GC-MS assays of 3 to 5 ml aliquots of the infusion solution before and after the infusion.

Pharmacokinetic analysis

Non-compartmental methods Plasma nicotine and cotinine concentrations below the quantification limits of the assay were assigned a value of zero. Maximal plasma concentrations (C_{max}) and corresponding times (t_{max}) values following NTS application or the start of the i.v. infusion of nicotine-d2 were determined for the first 24 h NTS application on Day 1 (single dose), and for the fifth consecutive 24 h NTS application on Day 7 (multiple dose). Minimal plasma concentrations (C_{min}) were also determined on Day 7. Apparent elimination rate constants (k) of nicotine and cotinine for the i.v. and NTS treatments were estimated by linear regression of log-transformed plasma concentrations following the end of the i.v. infusion on Day 1 and NTS removal on Day 7, respectively. Apparent half-life values for nicotine and cotinine were calculated as $0.693/k$. AUC (0, 24) values of nicotine and cotinine were determined on Day

1 and Day 7 by the linear trapezoidal method. For both NTS application and i.v. infusion, the Day 1 AUC values were calculated as the sum of AUC $(0, t)$ and the area extrapolated from the final plasma concentration at time t divided by k. Values of AUC and AUC (0, 24) for nicotine and cotinine on Day 1 were corrected for nicotine and cotinine concentrations on plasma prior to NTS application. The average nicotine and cotinine concentrations (C_{av}) were calculated from AUC (0, 24) divided by 24, for Day 1 and Day 7.

Drug concentration ratios for both nicotine and cotinine were calculated as ratios of AUC (0, 24) Day 7: AUC (0, 24) Day 1; a ratio > 1 is considered representative of accumulation [8]. The ratio of AUC (0, 24) Day 7: AUC Day 1; a ratio equal to one demonstrates linear kinetics. Cotinine-to-nicotine Day 1 AUC ratios for NTS and i.v. infusion and Day 7 AUC (0,24) ratios were determined as indices of nicotine metabolism.

The clearance (CL) of nicotine was calculated from the total amount of nicotine infused intravenously divided by AUC following i.v. infusion. The total amounts of nicotine absorbed following single and multiple NTS applications were calculated as CL multiplied by AUC for Day 1 and by AUC (0, 24) for Day 7, respectively.

Compartmental model for intravenous infusion A two-compartment open model [9] was fitted to plasma nicotine-d2 concentrations observed after i.v. administration. Noncompartmental methods were used to establish time invariance of clearance. The input rate for intravenous infusion (infusion rate) was deconvoluted using the point-area method and the terminal slope as the disposition rate constant.

Nicotine absorption from NTS Mean residence times (MRT), mean input times (MIT), and mean absorption times (MAT) were determined by moment analysis. The area under the first moment curve (AUMC) was determined using the linear trapezoidal rule for the intravenous and NTS treatments. MRT_{iv} was calculated using an MIT_{iv} of 12 h (half the infusion time) for i.v. infusion and MIT_{NTS} calculated from mean nicotine *in vitro* release rates for NTS [10]. Mean absorption time (MAT) for NTS was calculated as MRT_{NTS} minus MRT_{iv}. Assuming transdermal absorption is a first order process, the absorption half-life (HL) for NTS was calculated as $0.693 \times MAT$. The cumulative fraction of nicotine absorbed from NTS was estimated using the Loo-Riegelman method [11].

Determination of the amount of released nicotine not absorbed

A concurrent study was performed to estimate the amount of nicotine lost from the edges of the system during wearing. Twelve healthy male volunteers wore two modified NTS systems, one on either side of the chest for 24 h. A slightly larger polyester membrane, of proven impermeability to nicotine, was placed over the NTS adhesive surface to prevent absorption of nicotine from NTS into the body and to minimize nicotine loss and subsequent absorption of nicotine from the edges. After a 24 h application, the systems were removed and assayed for nicotine. The amount of nicotine lost from NTS during 24 h of wearing was calculated as the difference in nicotine content of unworn systems and worn systems.

Demographic variables

The following parameters were calculated and then examined as possible sources of inter-subject variability in nicotine clearance. Age (years), height (cm), and body weight (kg) were obtained from the medical history. Body surface area (SA, cm^2) was calculated as $71.84 \cdot Weight^{0.425} \cdot Height^{0.725}$ [12]. Lean body mass (LBM, kg) was calculated from $2.04 \cdot 10^{-3} \cdot Height^2$ [13]; and from TBW/0.732 [13], where total body water (TBW), in litres, was given by $2.447 - (0.09516 \cdot Age) + (0.1074 \cdot Height) + (0.3362 \cdot Weight)$ [14]. Body mass index (BMI, kg m^{-2}) was calculated from $Weight/Height^{-2}$ and ideal body weight (IBW, kg) from $48.18 + (Height - 150) \cdot 1.0737$. Clearance was regressed against the various demographic variables using a linear model.

Adverse effects

All subjects were asked to complete a questionnaire every 4 h during Day 1, when i.v. nicotine-d2 and NTS were administered simultaneously. The application site was examined at 24 h following NTS removal for topical reactions.

Results

Nicotine kinetics

Plasma nicotine was detectable in only 1 subject before application of the first NTS on Day 1. The mean pharmacokinetic parameters of nicotine following i.v. infusion and NTS application are shown in Table 1. Figure 1 shows the mean plasma nicotine concentrations following Day 1 and Day 7 NTS applications.

NTS single application and i.v. infusion

Plasma concentrations of unlabelled nicotine reached a mean peak of 14.4 ng ml^{-1} 6 h after NTS application on Day 1. They then declined slightly over the following 2 h, remained relatively constant (10.2 to 12.7 ng ml^{-1}) for the rest of the treatment period, and declined after NTS removal with a mean apparent half-life of 2.8 h (Figure 1). Plasma nicotine-d2 concentrations rose sharply after the start of infusion, gradually increased to 15.0 ng ml^{-1} by the end of the 24 h infusion, and then declined to 0.2 ng ml^{-1} 12 h after the infusion ended, with a half-life of 2.0 h (Table 1, Figure 1).

NTS multiple applications

After four consecutive NTS applications, the mean plasma nicotine concentration before the fifth NTS application on Day 7 was 9.4 ng ml^{-1}. Nicotine concentrations increased to 19.2 ng ml^{-1} 4 h after application on Day 7, declined gradually from 16.4 to 8.8 ng ml^{-1} in the 6 to 24 h after application, and declined after

Table 1 Mean (± s.d.) nicotine and cotinine pharmacokinetic parameters following i.v. infusion and NTS

	Nicotine			*Cotinine*		
	Intravenous Day 1 Single dose	*NTS Day 1 Single dose*	*NTS Day 7 Multiple dose*	*Intravenous Day 1 Single dose*	*NTS Day 1 Single dose*	*NTS Day 7 Multiple dose*
C_{max} (ng ml^{-1})	16.0 (7.4)	18.1 (5.3)	20.4 (6.6)	169.7 (65.0)	166.7 (50.4)	265.6 (73.5)
t_{max} (h)	22.0 (2.0)	6.2 (5.9)	4.7 (5.9)	24.1 (1.0)	23.2 (1.2)	12.3 (10.0)
k (h^{-1})	0.363 (0.062)	0.281 (0.115)	0.245 (0.084)	0.054 (0.015)	0.045 (0.014)	0.049 (0.01)
$t_{½}$ (h)	2.0 (0.4)	2.8 (0.9)	3.23 (1.4)	14.2 (5.5)	17.2 (6.5)	14.8 (3.0)
AUC (0, 24) (ng ml^{-1} h)	263 (75)	252 (62)	300 (112)	1992 (370)	2191 (554)	5266 (1795)
AUC (ng ml^{-1} h)	299 (94)	304 (79)	NA	5132 (1687)	5434 (1315)	NA
C_{av} (ng ml^{-1})	11.0 (3.1)	10.5 (2.6)	12.5 (4.7)	83.0 (15.4)	91.3 (23.1)	219.4 (74.8)
C_{min} (ng ml^{-1})	NA	NA	7.7 (3.3)	NA	NA	199.9 (73)
CL (l h^{-1})[a]	80.3[a] (26.7)					
MRT (h)	6.8 (1.5)					

[a]determined by non-compartmental methods.
NA = not applicable.

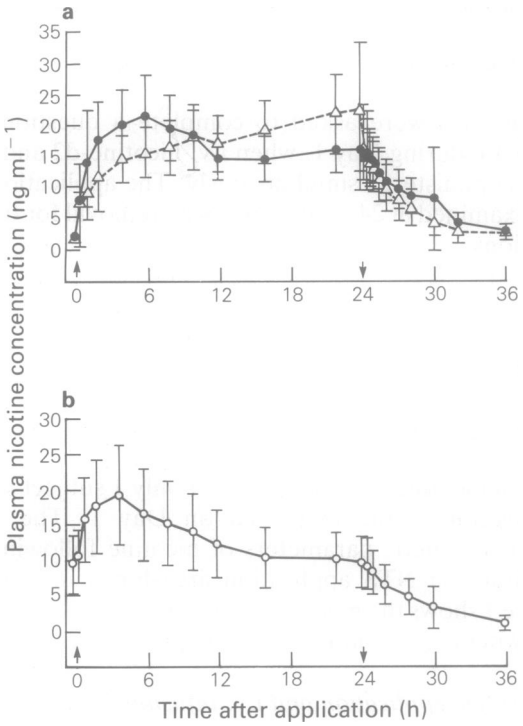

Figure 1 Mean (s.d.) plasma nicotine concentrations following a) i.v. infusion (△) and single application of NTS (Day 1 ●) and b) multiple application of NTS (Day 7). ↑ = NTS applied and start of infusion, ↓ = NTS removed and end of infusion.

NTS removal with a mean half-life of 3.2 h (Table 1, Figure 1).

As expected, the mean nicotine steady-state C_{max}, C_{av} and AUC (0, 24) values were slightly higher following multiple NTS applications (Day 7) than after single application, and t_{max} was shorter (Table 1). The mean Day 7:Day 1 nicotine concentration ratio was 1.16 (Table 2).

The pharmacokinetics of nicotine appeared linear and did not change significantly following multiple applications of NTS, as the mean ratio of Day 7 AUC (0, 24): Day 1 AUC for nicotine (0.97) was not significantly different from 1.00 (P = 0.596) and the 90% confidence interval of the mean ratio (0.87, 1.07) was within 13% of the Day 1 mean AUC value (Table 2).

Intravenous infusion

There was good agreement between the expected nicotine-d2 concentration in the infusion solution (30.8 μg ml^{-1}) and mean observed concentration measured by GC-MS (30.6 μg ml^{-1}) and GC (31.3 μg ml^{-1}), validating the use of the nominal infusion rate (0.2 μg min^{-1} kg^{-1}) for estimating clearance.

The mean clearance (CL) of nicotine determined by noncompartmental methods (80.3 l h^{-1}) was in good agreement with that determined by compartmental methods (72.1 l h^{-1}). As 5–10% of total clearance of nicotine occurs renally [15], nonrenal clearance was

Table 2 Comparisons of nicotine and cotinine-to-nicotine AUC ratios

	Nicotine AUC ratios for NTS		*Cotinine:Nicotine AUC ratios*		
	Drug concentration ratio[a]	*Linearity ratio*[b]	*Intravenous*	*NTS Single dose*[c]	*NTS Multiple dose*[d]
Mean	1.16	0.97	17.41	18.60	18.13
s.d.	0.25	0.21	3.10	5.21	3.24
		P = 0.596		P = 0.215	P = 0.607
		C.I.[e] = 0.87 to 1.07		P = 0.353	

[a]AUC (0, 24) day 7 MD:AUC (0, 24) day 1 s.d.
[b]AUC (0, 24) day 7 MD:AUC day 1 s.d.
[c]AUC cotinine day 1:AUC nicotine day 1.
[d]AUC (0, 24) cotinine day 7:AUC (0, 24) nicotine day 7.
[e]C.I. 90% Confidence interval of the mean.

estimated to be 65 l h^{-1}. Based on a hepatic blood flow of 90 l h^{-1}, the maximum hepatic extraction ratio of nicotine was estimated as 0.72, assuming nicotine is only metabolized in the liver.

Observed and predicted (using linear kinetics) plasma nicotine concentrations over the 24 h infusion were comparable and without consistent deviations, as were the mean infusion rates (0.2 μg min^{-1} kg^{-1}) estimated using deconvolution and target value. This suggests that nicotine disposition was invariant throughout the 24 h infusion.

Nicotine absorption from NTS

The nicotine absorption data following NTS application are summarized in Table 3. Figure 2 shows the cumulative *in vitro* and *in vivo* release of nicotine following NTS application for 24 h.

The mean nicotine content of unworn systems and the mean residual nicotine content of worn systems were 105.05 mg and 74.46 mg, respectively. Thus, the mean amount of nicotine released from each system during the 24 h application was 30.6 mg (CV = 15.7%) and did not appear to change with multiple applications. Based on nicotine release *in vitro* from NTS over 24 h, MIT_{TTS} was calculated as 7.67 h. Based on the MAT value of 4.3, the mean absorption half-life was calculated as approximately 3.0 h.

The residual amount of nicotine in the skin after 24 h of application, was estimated to be 1.9 mg, which is the difference between the calculated mean total amount of nicotine absorbed (20.9 mg) and the amount absorbed by the end of the 24 h application (19.0 mg). The difference between the 24 h curves for the *in vitro* and *in vivo* amounts of nicotine released (Figure 2) represents the amount of nicotine present in the skin and the amount lost due to evaporation.

The amount of nicotine absorbed from NTS calculated by either noncompartmental methods (22.7 mg for Day 1 and 21.6 mg for Day 7) or the Loo-Riegelman [11] method (20.9 mg) differed from the mean amount released *in vivo* (30.6 mg) by approximately 10 mg (Table 3). This difference represents the amount of nicotine on the site of application lost by evaporation or skin metabolism. Only trace amounts of nicotine were measured in skin swabs taken from NTS application sites (mean 0.045 mg; s.d. 0.027). Therefore, neither residual nicotine on the application site nor skin metabolism of nicotine are likely explanations for this discrepancy. From the second study, the estimate of the mean amount of nicotine lost from the edges (not absorbed) of the NTS system during the 24 h application period was 9.2 mg. The sum of the mean amount of nicotine absorbed (20.9 mg) and the mean amount lost other than by absorption (9.2 mg) approximated the amount released (30.6 mg). Therefore, of the mean amount released, 68% was absorbed, and the remainder was lost.

Table 3 Mean nicotine absorption parameters following NTS application for 24 h (s.d.) (n = 13)

	Day 1 Single dose	*Day 7 Multiple dose*
Amount absorbed (mg)	22.7 (4.1)[a] 20.9[b]*	21.6[a] (4.3)
MIT (h)	7.69[a]	
MAT (h)	4.3 (1.1)[a]	
ka (h^{-1})	2.97 (0.77)[a]	

*90% confidence interval: 18.6 to 23.2.
[a]estimated by noncompartmental method (moment analysis).
[b]estimated by Loo-Riegelman method [11].

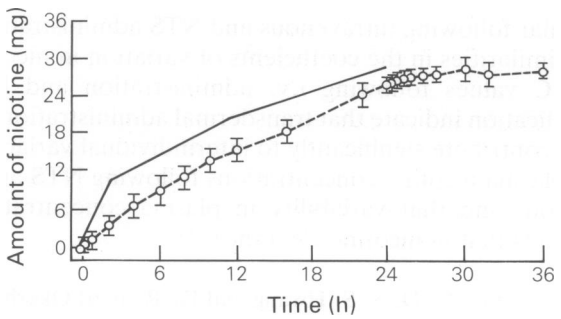

Figure 2 Cumulative amounts (± s.d.) of nicotine released (*in vitro*, —) and absorbed (*in vivo*, ○) following NTS application for 24 h.

Variability in nicotine kinetics and relation to demographic variables

The coefficient of variation of nicotine CL following i.v. infusion was 33%. The CVs of NTS nicotine Day 1 AUC and Day 7 AUC (0, 24) values were 26% and 37% respectively. The similar magnitude of the CV values for the i.v. treatment and NTS suggest that neither the dosage form nor the transdermal absorption process contributed significantly to variability in plasma nicotine concentrations. Significant ($P < 0.05$) positive linear relationships were found between nicotine CL and lean body mass, height, ideal body weight, and body surface area. When the relationship of each variable to CL variability was examined separately, lean body mass was found to account for most of the variability ($r^2 = 0.62$).

Pharmacokinetics of cotinine

As expected, plasma cotinine-d2 (deuterium labelled cotinine) concentrations were not detected in all subjects before the start of nicotine-d2 infusion. However, plasma concentrations of unlabeled cotinine (mean 42.7 ng ml^{-1}) were detected in all subjects as the 48 h prestudy abstinence period and the relatively long elimination half-life of cotinine did not allow for sufficient clearance of cotinine from plasma. The mean pharmacokinetic parameters of cotinine are summarized in Table 1.

Figure 3 shows the mean plasma cotinine concentrations following nicotine-d2 i.v. infusion, NTS application on Day 1 and after NTS application on Day 7. Plasma cotinine-d2 concentrations reached a mean of 13.0 ng ml^{-1} 2 h after the start of infusion, then increased gradually to 164 ng ml^{-1} at the end of the 24 h infusion, and declined to 81 ng ml^{-1} 12 h later, with a mean half-life value of 14 h (Table 1).

Following NTS application on Day 1, mean plasma cotinine concentrations increased gradually to 160 ng ml^{-1} at 24 h after application and declined to 87 ng ml^{-1} 12 h after system removal with a mean apparent half-life value of 17 h (Figure 2, Table 1). As expected, the

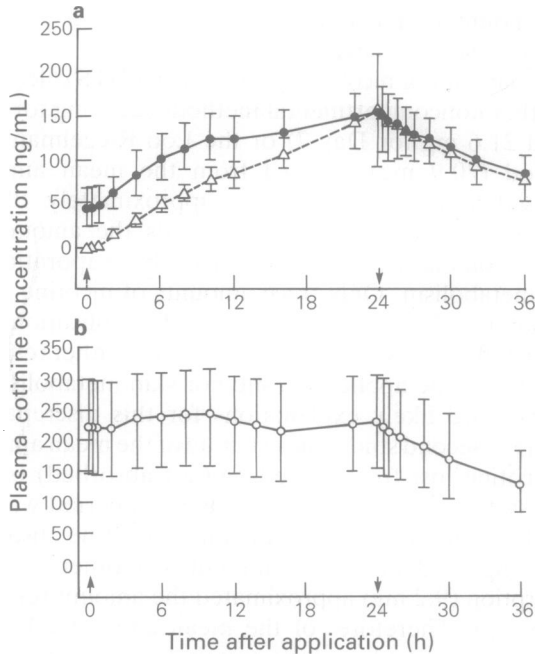

Figure 3 Mean (± s.d.) plasma cotinine concentrations following a) i.v. infusion (△) and NTS 1.5 (Day 1, ●) and b) NTS 1.5 (Day 7). ↑ = NTS applied and start of infusion, ↓ = NTS removed and end of infusion.

Day 7 mean plasma cotinine concentrations were higher than those on Day 1, ranging from 214 to 244 ng ml^{-1} during the 24 h treatment period (Figure 3).

Mean NTS Day 7 cotinine AUC (0, 24):nicotine AUC (0, 24) and Day 1 cotinine AUC:nicotine AUC ratios were 18.6 and 18.1, respectively, and were not significantly different (Table 2). These NTS ratios also did not differ significantly from the mean cotinine-d2 AUC:nicotine-d2 AUC ratio (17.4) following intravenous administration. The lack of significant differences between these ratios indicates that the extent of nicotine metabolism following single and multiple NTS applications was similar.

Safety and adverse effects

Following 5 consecutive days of NTS application, the most frequently reported systemic side effects were fatigue and nervousness. The incidence of adverse effects was higher following simultaneous administration of intravenous and transdermal nicotine. Nervousness, insomnia, dizziness, anxiety and fatigue were the most frequent complaints.

Mild, transient itching at the application site was the most commonly reported topical effect, occurring in eight subjects after one application and in four subjects after multiple applications. Papules were observed at the skin site in one subject.

Discussion

The once-a-day NTS system used in the present study is designed to deliver a constant amount of nicotine for 24 h. Approximately 68% (20.9 mg) of the mean amount of nicotine released (30.6 mg) from each NTS during the 24 h wearing period was absorbed. An estimated 9.2 mg (30%) was shown by a concurrent study to be lost from the exposed edges of the system, most likely by evaporation, considering the high volatility of nicotine. Only 1.9 mg (10%) of nicotine was estimated to be in the skin. However, nicotine metabolism does not appear to occur in the skin during transdermal absorption, as shown by similarities in cotinine-to-nicotine AUC ratios between i.v. and NTS administration.

The mean absorption half-life (3.0 h) of nicotine from the NTS was similar to the apparent nicotine elimination half-life (2.8 h) and both were significantly longer than the elimination half-life of nicotine following i.v. administration (2.0 h, $P = 0.020$; Table 1). This suggests that plasma nicotine concentrations following NTS application are governed by nicotine absorption, which is determined by the release of nicotine from this NTS.

Although a small degree of nicotine accumulation (16%) occurred with multiple NTS applications, the absorption of nicotine from NTS was not affected by repeated applications since AUC (0, 24) and AUC values for NTS and i.v. were similar (252 *vs* 263 and 304 *vs* 299 ng ml^{-1} h, respectively). In addition, there were no significant changes in the pharmacokinetics of nicotine between single and multiple applications of NTS, as the mean nicotine Day 7 AUC (0, 24): Day 1 AUC ratio (0.97) did not differ significantly from 1.00 and was within 13% of the Day 1 mean AUC value. Thus, kinetics appeared linear. Linear nicotine kinetics after single and multiple transdermal nicotine doses have been reported by other investigators [16, 17] who also found no change in nicotine metabolism following multiple applications of NTS. In addition, since mean cotinine apparent half-lives and k values on Day 3 were similar following NTS removal and discontinuation of intravenous infusion (17.2 and 14.2 h; 0.045 and 0.05 h^{-1}, respectively), this suggests that cotinine elimination was independent of the route of nicotine administration.

The metabolite-to-drug AUC ratio represents the clearance ratio of metabolite formation to metabolite elimination [18]. The cotinine-to-nicotine AUC ratio is considered a valid index of nicotine metabolism because approximately 70% of nicotine is converted to cotinine in the body. Similar cotinine-to-nicotine plasma AUC ratios following intravenous and transdermal administration of nicotine indicate that significant metabolism of nicotine to cotinine does not occur in the skin when nicotine is given transdermally. It is unlikely that the constancy of cotinine-to-nicotine AUC ratios was a result of simultaneous equal increases in both formation and clearance of metabolite, as cotinine half-lives were similar following intravenous and NTS administration.

Similarities in the coefficients of variation in nicotine AUC values following i.v. administration and NTS application indicate that transdermal administration did not contribute significantly to interindividual variability in plasma nicotine concentrations following NTS application, and that variability in plasma concentrations reflects that in nicotine clearance.

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