Comparison of Nicotine Pharmacokinetics in Healthy Japanese Male Smokers Following Application of the Transdermal Nicotine Patch and Cigarette Smoking

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Transdermal nicotine patch (TNP) contains approximately 16.6 and 24.9 mg of nicotine per 20 and 30 cm² (TNP-20 and TNP-30). The aims of the study are to investigate linearity of nicotine pharmacokinetics after single application of different strengths of TNP and to directly compare plasma nicotine concentrations with those during cigarette smoking. Twelve healthy Japanese male smokers were randomly allocated to 1 of 2 cohorts consisting of 6 subjects each. Cohort 1 subjects received 1 sheet of TNP-20 (TNP-20×1) in period 1, and 2 sheets of TNP-20 (TNP-20×2) in period 3. Cohort 2 subjects were received 1 sheet of TNP-30 (TNP-30×1) in period 2, and smoked a total of 12 cigarettes at 1 h intervals in period 4. Each TNP was applied to the upper arm for 16 h. After TNP-20×1 or TNP-20×2 treatment in cohort 1, the amount of nicotine delivered from TNP (Dose) was proportional to surface area of TNP. Cmax and AUC of nicotine increased with the surface area (Dose), and t max, t 1/2, C/LF and percentage of dose excreted in urine were almost the same between both treatments. These suggest the linear pharmacokinetics of nicotine in proportion to the surface area and Dose following single application of TNP in identical subjects. In cohort 2, the plasma nicotine concentrations after TNP-30×1 treatment were approximately half those just before each smoking.

Key words nicotine; transdermal; pharmacokinetics; cigarette smoking; linearity

Nicotine is the main alkaloid found in tobacco, and is responsible for its addictive potential. Inhalation of nicotine in smoke is considered the most dependence-producing form of drug administration because of rapidly established concentrations in brain and blood. Nicotine replacement therapy (NRT) is the mainstay of treatment for smoking cessation and delivers nicotine to the blood circulation. NRT is available in different forms (gum, transdermal patch, nasal spray, inhaler and sublingual tablet), and has been shown to relieve withdrawal symptoms and to double abstinence rates compared to placebo. There is no evidence favoring the efficacy of one formulation of NRT over another. Most NRT forms deliver nicotine more slowly than smoking, and the increase in nicotine blood levels is more gradual. Transdermal patches are excellent options for NRT due to the convenience of once-daily treatment.

The pharmacokinetics of nicotine has been extensively studied, and nicotine is known to be mainly metabolized to cotinine by CYP2A6. Nicotine is suitable for transdermal therapy because it is volatile, highly lipid soluble, and permeates the skin easily. Transdermal patches can deliver nicotine directly to systemic circulation through the intact skin, thus avoiding hepatic first-pass metabolism. The transdermal nicotine patch (TNP), containing approximately 16.6 and 24.9 mg of nicotine per 20 and 30 cm² thin multilayer film laminate patch (TNP-20 and TNP-30), is designed to deliver about 10 and 15 mg of nicotine in 16 h of application (31 μg/cm²/h). We investigated the linearity of nicotine pharmacokinetics and safety after single application of different strengths of TNP (1 sheet of TNP-20, 2 sheets of TNP-20, and 1 sheet of TNP-30) and directly compared the plasma nicotine concentrations after application of 1 sheet of TNP-30 with those during controlled cigarette smoking.

MATERIALS AND METHODS

Subjects Twelve healthy Japanese male smokers were enrolled following the provision of written informed consent. All subjects were required to be aged 20 to 50 years, have a weight within the limits of [(height−100)×0.9 ±20%], have a supine systolic blood pressure of 100 to 139 mmHg, a diastolic blood pressure of ≤84 mmHg and a pulse rate of 50 to 99 bpm, and have smoked ≤15 cigarettes a day. Volunteers were excluded if they had evidence of history of drug allergies at screening, had received any treatment or donated blood within the 2 months, or had participated in a clinical pharmacology study within 4 months prior to the start of the study. Subjects with an expired air carbon monoxide level above 10 ppm before each treatment were excluded.

This study was conducted at the Medical Co. LTA, Kyushu Clinical Pharmacology Research Clinic (Fukuoka, Japan) in compliance with good clinical practice and the Declaration of Helsinki. The Institutional Review Board of the Medical Co. LTA provided formal approval for the study.

Study Design This was a single-blind (with respect to the subject and investigator who examined the application sites for local irritation), 4-period, dose-escalating study using 2 subject cohorts. Twelve subjects were randomly allocated to 1 of 2 cohorts consisting of 6 subjects each. Each TNP (Nicorette® patch, Pfizer Health AB, Helsingborg, Sweden) was applied to the upper arm for 16 h (between 8:00 am and 0:00 am). Placebo for TNP was also applied to the upper part of the other arm. Each subject in cohort 1 received 1 sheet of TNP-20 (TNP-20×1) in period 1, and 2 sheets of...
TNP-20 (TNP-20×2) in period 3. Cohort 2 subjects were received 1 sheet of TNP-30 (TNP-30×1) in period 2, and smoked a total of 12 cigarettes at 1 h intervals in period 4 (between 8:00 am and 7:00 pm). The subjects smoked the cigarettes containing approximately 1 mg of nicotine in the main stream of smoke in a usual manner to the length of about 5 cm for 3 to 5 min. Treatment periods in each cohort were separated by a 1-week washout period. The subjects stayed at the clinic from 36 h before TNP application to 8 h after removal in periods 1 to 3, and from 14 h before first smoking to 13 h after final smoking in period 4. In periods 1 to 3, subjects visited the clinic at 32 h after TNP removal to take a safety examination.

The subjects had to abstain from smoking during their stay at the clinic except the treatment in period 4. Standardized breakfast, lunch and dinner were provided approximately at 7:30 am, 0:30 pm and 7:00 pm (6:30 pm in period 4), respectively. Consumption of caffeine-containing beverages was prohibited throughout the stay at the clinic.

**Pharmacokinetic Sampling** Blood samples (7 ml) were collected immediately before TNP application (pre-dose) and at 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 17, 20, 23 and 24 h after each application in periods 1 to 3, as well as immediately before first 1st, 4th, 7th, 10th and 12th smoking, at 5 min after the start of 1st, 4th, 7th, 10th and 12th smoking and at 0.5, 1, 2, 4 and 12 h after the start of 12th smoking in period 4. Samples were centrifuged and the plasma was stored at −20°C.

Urine samples were collected from pre-dose, 0—4, 4—8, 8—12, 12—16 and 16—24 h after application in periods 1 to 3. Samples within a collection period were well mixed, their volumes were measured, and an aliquot was stored at −20°C.

**Drug Assay** Plasma nicotine concentrations were determined by a modification of the GC method of Feyerabend et al.10 and plasma cotinine concentrations and urinary nicotine and cotinine concentrations were analyzed using modifications of the HPLC methods of Pacifi ci et al.11 and Rustemeier et al.12 at the JCL Bioassay Corporation, Nishiwaki Laboratory (Hyogo, Japan). Plasma and urine samples were previously spiked with internal standards, which were 1methyl-anabasine for plasma nicotine assay and N-ethylnorcotinine for the other assays. The lower limit of quantification (LLQ) was 1 ng/ml for plasma nicotine assay, 5 ng/ml for plasma cotinine assay, and 20 ng/ml for urinary nicotine and cotinine assay, respectively.

For the plasma nicotine assay, 1 ml of plasma sample, 1 ml of 5 M NaOH and 3 ml of diethyl ether were added to each tube, and the tubes were shaken for 20 min and then centrifuged at 3000 rpm for 5 min. After transferring the diethyl ether layer to another test tube, 0.1 ml of 2 M HCl was added for back-extraction. The tube was shaken for 10 min and centrifuged, and then the organic layer was removed and discarded. To the remaining aqueous layer, 1 ml of 5 M NaOH and 50 μl of heptane/diethyl ether (1/1, v/v) were added, and the tube was shaken for 15 min and centrifuged. Then, 4 ml of the supernatant was injected onto the GC system. Chromatography was performed at 145°C on an Ultra Alloy UA-1 capillary column (30 m×0.53 mm, Frontier Lab) with flame thermionic detector (FTD-9, Shimadzu) using helium as the carrier gas.

For the plasma cotinine assay, 0.5 ml of plasma sample spiked with 0.4 ml of 0.5 M NaOH was loaded on the solid-phase extraction cartridge (Extrelut 1, Merck), which was initially preconditioned by 5 ml of dichloromethane. After 30 min the analytes were eluted with 5 ml of dichloromethane. The eluate was evaporated to dryness under a stream of nitrogen, and the residue was reconstituted with 200 μl of mobile phase. Then, 40 μl of the sample was injected onto the HPLC system. Chromatography was performed at 40°C on a μBondapak C18 125A column (10 μm, 300×3.9 mm, Waters) at a flow rate of 1.0 ml/min. The mobile phase consisted of water/methanol/0.1 M sodium acetate/acetaminite (670/245/65/20, v/v, pH 4.3). The analytes were monitored by UV detection with 261 nm.

For the urinary nicotine and cotinine assay, 0.1 ml of urine sample, 60 μl of 4 M acetic acid buffer (pH 4.7), 30 μl of 1.5 M potassium cyanide solution, 30 μl of 0.4 M sodium p-toluene-sulfonchloramide solution and 100 μl of 0.05 M 1,3-diethylthiobarbituric acid solution (acetone/water=1/1, v/v) were admixed and shaken. After 5 min for chemical reaction, 40 μl of the sample was injected onto the HPLC system. Chromatography was performed at 25°C on a Nova-Pak C18 60A column (4 μm, 150×3.9 mm, Waters) at a flow rate of 0.8 ml/min. The mobile phase consisted of water/methanol (3.5/5.5, v/v), which contained 20 mM heptane sulfonate. The analytes were monitored at 532 nm.

Residual content of nicotine in recovered TNP was analyzed using a modification of the method of Kochak et al.13 In brief, the nicotine in TNP was extracted by shaking in a flask containing 50 ml of n-heptane and then mixed with 100 ml of 25 mM HCl for back-extraction. The HCl phase obtained was diluted and an aliquot was monitored by UV detection with 254 nm.

In these assay methods, calibration standards demonstrated acceptable linearity (r>0.999). The accuracy of the method was demonstrated by comparing the measured concentration with their theoretical values to be ±20%, expressed as a percentage of deviation from theoretical values. The precisions were <5%, expressed as a percentage coefficient of variation.

**Pharmacokinetic Analysis** The pharmacokinetic analysis of nicotine concentrations was performed by non-compartamental method using the computer program WinNonlin Professional (version 3.1). The concentrations below LLQ were treated as missing. The maximum value of all the observed plasma concentrations in each subject (Cmax) and the first time to Cmax(tmax) were taken directly from the recorded plasma concentration–time data. The tmax in smoking period is the time from the start of 1st smoking to Cmax. The apparent terminal phase half-life (t1/2) was calculated as ln2/k2, where k2 was the terminal phase rate constant, which was estimated by linear regression of the log concentration versus time profile. The area under the plasma concentration–time curve from time 0 to infinity (AUC) was calculated as AUC(0–∞)(Cmax/t1/2), where C0 was the concentration at the last measurable time (t), and AUC was the area under the plasma concentration–time curve from time 0 to the time (t) by the linear trapezoidal method. The amount of nicotine delivered from each TNP (Dose) was determined from the initial content and residual content in each recovered TNP. The transdermal clearance (CL/F) was calculated as Dose/AUC. Dose-normalized Cmax and AUC were also calculated by dividing by Dose. The percentage of the dose excreted in the urine up
to 24 h after application \([\text{Ae}_{24} \text{ }(\%)]\) was calculated as \(\Sigma (\text{concentration} \times \text{volume})/\text{Dose}\), where summation \((\Sigma)\) was over the urine collection intervals.

**Safety Assessment** The investigator recorded all observed or volunteered adverse events. Application sites were examined for local irritation pre-dose, immediately and at 1, 8 and 32 h after TNP removal in periods 1 to 3 by the blinded investigator. Laboratory safety tests including urinalysis, haematology and clinical chemistry, blood pressure, pulse rate, body temperature and 12-lead electrocardiogram (ECG) measurements were performed at screening, throughout the stay at the clinic and at follow-up (7 d after final treatment).

**Statistical Analysis** In cohort 1, Dose, log-transformed \(C_{\text{max}}\), log-transformed \(AUC\) and \(CL/F\) were assessed for significant differences between TNP-20×1 (period 1) and TNP-20×2 (period 3) treatments using the paired \(t\) test. Prior to analysis, Dose, \(C_{\text{max}}\) and \(AUC\) values after TNP-20×2 treatment were divided by 2 to investigate the linearity. \(C_{\text{max}}\) and \(AUC\) divided by Dose were also subjected to the same statistical analyses.

RESULTS

**Demographics** All subjects who were enrolled completed the study. Demographic data were similar between cohort 1 and cohort 2 subjects. The means (ranges) of age, height and weight were 22.0 (20—24) years, 169.5 (165.0—180.0) cm and 58.5 (53.5—63.5) kg for cohort 1, and 22.0 (21—23) years, 169.4 (165.0—175.4) cm and 56.3 (54.0—61.0) kg for cohort 2. All subjects had been smoking 16 to 25 cigarettes per day except 1 subject in cohort 1 (more than 25 cigarettes per day). All subjects presented the expired air carbon monoxide level less than 10 ppm before each treatment, indicating abstinence from smoking.

**Pharmacokinetics** Mean plasma concentration profiles and pharmacokinetic parameters of nicotine are shown in Fig. 1 and Table 1, respectively. The pharmacokinetic analysis of cotinine concentrations was not performed because high concentrations were observed in the samples taken immediately before treatment.

In all TNP treatment groups, mean plasma concentrations of nicotine increased gradually and reached a broad peak at 8 to 12 h after application (Fig. 1). After removal of TNP, the plasma concentrations exhibited a transient maintenance, which dissipated within 1 h and then declined with a mean \(t_{1/2}\) of approximately 4 to 5 h (Table 1).

In cohort 1, the plasma concentrations after application of TNP-20×2 were approximately 2 times higher than those of TNP-20×1. Dose, \(C_{\text{max}}\) and \(AUC\) increased in proportion to the surface area of TNP-20×1 (20 cm²) and TNP-20×2 (40 cm²).

Table 1. Comparison of Nicotine Pharmacokinetic Parameters after Single Application of the Transdermal Nicotine Patch (TNP) and Cigarette Smoking (12 Cigarettes at 1 h Intervals) in Healthy Japanese Male Smokers (\(n=6\)/Each Treatment)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(AUC) (ng · h/ml)</th>
<th>(C_{\text{max}}) (ng/ml)</th>
<th>(t_{\text{max}}) (h)</th>
<th>(t_{1/2}) (h)</th>
<th>Dose (mg)</th>
<th>(CL/F) (1/min)</th>
<th>(\text{Ae}_{24}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNP-20×1</td>
<td>Mean(^{a})</td>
<td>155.13 (17.12)</td>
<td>9.15 (1.01)</td>
<td>13.3</td>
<td>3.76</td>
<td>9.1</td>
<td>1.00</td>
</tr>
<tr>
<td>(20 cm²)</td>
<td>S.D.</td>
<td>±29.51 (3.27)</td>
<td>±1.79 (0.21)</td>
<td>±3.4</td>
<td>±0.61</td>
<td>±0.6</td>
<td>±0.17</td>
</tr>
<tr>
<td>TNP-20×2</td>
<td>Mean(^{a})</td>
<td>280.96 (15.59)</td>
<td>17.25 (0.96)</td>
<td>8.2</td>
<td>4.09</td>
<td>18.1</td>
<td>1.08</td>
</tr>
<tr>
<td>(40 cm²)</td>
<td>S.D.</td>
<td>±31.08 (2.10)</td>
<td>±1.60 (0.11)</td>
<td>±5.2</td>
<td>±1.03</td>
<td>±1.0</td>
<td>±0.14</td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNP-30×1</td>
<td>Mean(^{a})</td>
<td>412.27 (32.58)</td>
<td>20.58 (1.62)</td>
<td>8.5</td>
<td>5.09</td>
<td>12.9</td>
<td>0.63</td>
</tr>
<tr>
<td>(30 cm²)</td>
<td>S.D.</td>
<td>±192.99 (16.65)</td>
<td>±7.82 (0.67)</td>
<td>±4.8</td>
<td>±1.60</td>
<td>±0.9</td>
<td>±0.28</td>
</tr>
<tr>
<td>Smoking</td>
<td>Mean(^{a})</td>
<td>NC</td>
<td>47.55</td>
<td>9.1</td>
<td>4.95</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td></td>
<td>S.D.</td>
<td>±21.24</td>
<td>±3.1</td>
<td>±1.42</td>
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</tr>
</tbody>
</table>

\(^{a}\)\(AUC\), area under the plasma concentration–time curve from time 0 to infinity; \(C_{\text{max}}\), maximum value of all the observed plasma concentrations in each subject; \(t_{\text{max}}\), first time to \(C_{\text{max}}\) (in smoking period the time from the start of 1st smoking to \(C_{\text{max}}\)); \(t_{1/2}\), terminal phase half-life; Dose, amount of nicotine delivered from each patch; \(CL/F\), transdermal clearance; \(\text{Ae}_{24}\), percentage of the dose excreted in the urine up to 24 h; NC, not calculated. \(^{a}\)\(AUC\) and \(C_{\text{max}}\) divided by Dose are shown in parentheses.
cm$^2$). There were no statistically significant differences for Dose, $C_{max}$ and AUC between TNP-20×1 and TNP-20×2 treatments when these values after TNP-20×2 treatment were divided by 2 ($p=0.82$, $p=0.40$, $p=0.09$, respectively). No statistically significant difference was also observed in dose-normalized $C_{max}$ ($p=0.40$). Although statistically significant differences were observed in $CL/F$ ($p=0.03$) and dose-normalized AUC ($p=0.04$), mean values of these parameters were similar between TNP-20×1 and TNP-20×2 treatments. There was comparatively high intersubject variability in pharmacokinetic parameters, and the $t_{1/2}$, $CL/F$ and $Ae_{24}$ values were comparable between TNP-20×1 and TNP-20×2 treatments.

On the other hand, the plasma nicotine concentrations after application of TNP-30×1 (30 cm$^2$) in cohort 2 were a little higher than those of TNP-20×2 (40 cm$^2$) in cohort 1. $C_{max}$, AUC and $Ae_{24}$ after TNP-30×1 treatment were higher, and $CL/F$ was lower compared with TNP-20×2 treatment. However, Dose increased in a correlation with the surface area across the 3 TNP treatments.

In cohort 2, the nicotine concentrations were rapidly increased by approximately 10 ng/ml after each cigarette smoking. The concentrations immediately before smoking (trough) or at 5 min after smoking (peak) increased with times of smoking and were almost the same between 10th and 12th smoking. Mean $C_{max}$ and $t_{max}$ values were 47.55 ng/ml and 9.1 h after the start of 1st smoking. The trough concentrations after each smoking were approximately 2 times higher than corresponding values after TNP-30×1 treatment. Mean $t_{1/2}$ value after 12th smoking (4.95 h) was similar to those after TNP treatments.

**Safety** There were no serious adverse events in this study. Two, seven and five treatment-related adverse events were reported in periods 1, 2 and 3, respectively. These all were itching (1, 5 and 3 subjects in periods 1, 2 and 3) or redness (1, 2 and 2 subjects in periods 1, 2 and 3) at the application sites of TNP. One subject in period 2 also reported itching at placebo application site. In period 4, 2 subjects reported treatment-related light-headed feeling at 1st smoking. These symptoms were mild in intensity and disappeared without medical treatment.

In the application site examination for local irritation, erythema was observed in 3, 2 and 6 subjects immediately after TNP removal in periods 1, 2 and 3, respectively. These symptoms disappeared within 1 h, except 2 subjects in period 1 who had mild erythema until 8 h after removal, and were considered not clinical concern. Erythema was also observed at placebo application sites in 2 subjects each of periods 1 and 3. These symptoms were milder in intensity and/or disappeared earlier compared with TNP application sites in the same subjects.

No changes were considered to be treatment-related, and there were no abnormal changes of clinical concern in blood pressure, pulse rate, body temperature, 12-lead ECG and laboratory safety tests during all periods.

**DISCUSSION**

After treatments of TNP-20×1 and TNP-20×2 in cohort 1, the amount of nicotine delivered from TNP (Dose) was proportional to the surface area of TNP (20 and 40 cm$^2$). The $C_{max}$ and AUC of nicotine increased with the increasing surface area of TNP and Dose, and the $t_{max}$, $t_{1/2}$, $CL/F$ and $Ae_{24}$ values were almost the same between both treatments. These suggest the linear pharmacokinetics of nicotine in proportion to the surface area and Dose following single application of TNP in identical subjects. It has been reported after single application of 3 different doses of other nicotine patches (containing 17.5, 35.0 and 52.5 mg nicotine per 10, 20 and 30 cm$^2$ each), nicotine increased with the surface area of the patch, and the $C_{max}$, AUC and the amount of nicotine excreted in urine were linearly related to the Dose.\(^{14,15}\) The nicotine and cotinine pharmacokinetics at steady state after applications of 3 dosage levels of other nicotine patches (designed to deliver 7, 14 and 21 mg nicotine per 7, 15 and 22 cm$^2$ each) have been also investigated in a crossover study.\(^{16}\)

The AUC, $C_{max}$, minimum plasma concentration ($C_{min}$), average plasma concentration ($C_{avg}$) of nicotine, and total urinary cotinine were proportional to the dose of nicotine released in vitro from the patches. The $t_{max}$, $t_{1/2}$ and renal cotinine clearance were similar for all 3 dosages. After applications of other nicotine patches, the $C_{max}$, $C_{min}$ and amount excreted in urine at steady state for both nicotine and cotinine were proportional to the theoretically delivered dose (designed to deliver 11, 22 and 44 mg nicotine per 3.5, 7 and 7×2 cm$^2$ each),\(^{17,18}\) and the AUC and $C_{max}$ values of nicotine were proportional to the labeled content of the patch (containing 15, 30 and 30×2 mg nicotine per 3.5, 7 and 7×2 cm$^2$ each).\(^{19}\) These patches are designed to deliver nicotine in proportion to the surface area of the system. These results agree well with our data and suggest the linear pharmacokinetics of nicotine delivered from these nicotine patches in proportion to the surface area of the patches (Dose).

On the other hand, the plasma concentrations and exposure of nicotine after TNP-20×2 treatment in cohort 1 were lower than those after TNP-30×1 treatment in cohort 2. Higher intersubject variability in nicotine pharmacokinetics was observed in cohort 2, and 2 subjects showed higher plasma concentration profiles (AUC values in period 2: 556.1, 708.7 ng·h/ml) compared with the other subjects in cohort 2. Nicotine concentrations during cigarette smoking in period 4 of these subjects were also higher ($C_{max}$ values: 78.6, 66.8 ng/ml), and cotinine concentrations were lower than the others in cohort 2. Approximately 70 to 80% of nicotine is metabolized to cotinine and roughly 90% of this conversion is mediated by CYP2A6.\(^{20}\) CYP2A6 shows the genetic polymorphisms, which affect nicotine pharmacokinetics.\(^{21}\) The frequency of CYP2A6 poor metabolizers is below 1% in Caucasians, but up to 20% in East Asians.\(^{22}\) These suggest that one of the possible reasons of higher nicotine exposure in cohort 2 compared with cohort 1 is high intersubject variability in the activity of metabolic enzymes (e.g. CYP2A6).

The percutaneous absorption of a drug delivered by a transdermal delivery system is determined by release of the drug from the device, diffusion across the stratum corneum, partitioning into the viable epidermis, and diffusion into the upper dermis, where the drug is taken up by cutaneous blood vessels.\(^{23}\) It has been reported that systemic exposure after TNP application to the abdomen is statistically significantly lower compared with the upper arm and the back. The most probable explanation for this finding is the regional variation of the skin permeability of nicotine caused by the skin blood.
flow, lipid content and hydration of the stratum corneum, and so on. Therefore, another possibility of non-linear pharmacokinetics across cohort 1 and cohort 2 in our study is inter-subject variability in the skin permeability of nicotine.

In cohort 2, the plasma nicotine concentrations after application of TNP-30×1 were lower than corresponding values for cigarette smoking, and were approximately half the trough concentrations during smoking of 1 cigarette every hour. A few reports in the literature have directly compared the plasma nicotine concentrations following application of nicotine transdermal patches and cigarette smoking. The \( C_{\text{max}} \) and \( C_{\text{avg}} \) values after the treatment with other nicotine patch (designed to deliver 21 mg per 22 cm\(^2\)) were approximately half those for controlled smoking (30 cigarettes at half-hourly intervals). The plasma concentrations after application of other nicotine patch (containing 52.5 mg nicotine per 30 cm\(^2\)) showed good agreement with the trough concentrations of 1 cigarette every hour. The steady state nicotine concentrations taken at 4 h intervals were similar for a nasal spray and TNP-30 treatments, while those were on average twice as high during cigarette smoking of 16 cigarettes per day. Plasma nicotine concentrations from NRTs (gum, transdermal patch, nasal spray, inhaler and sublingual tablet) tend to be in the range of low-level cigarette smokers. Usually ad libitum use of NRTs results in one-third to two-thirds the concentration of nicotine that is achieved by cigarette smoking. These results suggest that the nicotine concentrations are similar between TNP treatment and available NRTs, and support the clinical efficacy for smoking cessation of once-daily TNP treatment.

Cigarette smoking yielded plasma nicotine concentrations that rise and decline rapidly with each smoking. The rapidity of rise in nicotine levels permits the smoker to titrate the level of nicotine and related effects during smoking and makes smoking the most reinforcing and dependence-producing form of nicotine administration. During application of TNP the plasma nicotine concentrations were maintained at a fairly constant level. Therefore, once-daily TNP treatment probably has a low dependency potential.

In our study the cigarettes containing approximately 1 mg of nicotine in the main stream of smoke were used. The smoker can manipulate the dose of nicotine and nicotine brain levels on a puff-by-puff basis. The intake of nicotine during smoking depends on the puff volume, the depth of inhalation, the extent of dilution with room air, the rate of puffing, and the intensity of puffing. For this reason, the machine-determined nicotine yields of cigarettes (U.S. Federal Trade Commission, FTC yields) cannot be used to estimate the dose of nicotine by a smoker. Nicotine uptake, as measured by urinary cotinine, has been reported to be the same in smokers of regular, light, and ultralight cigarettes. Blood or plasma nicotine concentrations sampled in the afternoon in smokers generally range from 10 to 50 ng/ml. Mean (standard deviation) nicotine concentrations in light (10 to 15 cigarettes per day), moderate (16 to 30 cigarettes per day), and heavy (>30 cigarettes per day) smokers in the afternoon were 13.4 (8.4), 20.6 (7.2), and 23.7 (10.3) ng/ml, respectively. Typical trough concentrations during daily smoking are 10 to 37 ng/ml, and typical peak concentrations range between 19 and 50 ng/ml. The mean increase in nicotine levels that occurs after smoking a single cigarette was 10.9 ng/ml in smokers with no smoking abstinence on the study day. Our nicotine concentration data during smoking were within the range of these values, but close to the upper range. This suggests the presence of the subjects who have low activity of metabolic enzymes in cohort 2 of our study.

Only mild itching, redness and erythema were observed at the application sites of TNP in our study. Regarding other nicotine patches the most common adverse effect is also the transient mild itching, erythema and burning at the application sites. Mild itching and erythema were observed at the application sites after multiple doses of TNP as well.

In conclusion, the linear pharmacokinetics of nicotine in proportion to the surface area (Dose) was observed after single application of TNP in identical subjects. The plasma nicotine concentrations after application of TNP-30×1 were lower compared with cigarette smoking and were approximately half those just before each smoking (12 cigarettes at 1 h intervals) as in the case of other NRTs. Only mild itching, redness and erythema were observed at the application sites. These findings support clinical efficacy and safety for smoking cessation of once-daily TNP treatment.

REFERENCES