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A pharmacokinetic crossover study to compare the absorption characteristics of three transdermal nicotine patches

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Abstract

We compared the pharmacokinetic profiles of the highest marketed doses of three different patch systems using a crossover study design. Specifically, each of the 25 subjects was assigned to receive the Pharmacia-Upjohn (McNeil) 15-mg, 16-h patch, the Novartis 21-mg, 24-h patch, and the Alza (SmithKline Beecham) 21-mg, 24-h patch. Subjects used each patch for 3 consecutive days, applying a new patch each morning. Plasma nicotine concentrations were measured 15 times during the first 24-h period and at 48, 48.5, 49.5, and 51 h following initial patch application. Measures of total nicotine absorbed (AUC), maximum plasma nicotine concentration (C_{max}) and minimum plasma nicotine concentration (C_{min}), were higher for the 21-mg, 24-h patches than for the 15-mg, 16-h patch during both the first day of dosing and during the modeled steady-state period (48–72 h after initial application). Within the 21-mg, 24-h patch systems, the Alza patch produced significantly higher AUC and C_{max} values during acute dosing and during steady state, but there was no difference between C_{min} values. The time to reach C_{max} (T_{max}) was fastest for the Alza patch system; the Pharmacia-Upjohn patch produced a faster T_{max} than the Novartis patch. These results indicate that there are significant differences between the pharmacokinetics of the currently marketed patch systems, which may be important for effective relief of withdrawal symptoms and cigarette craving.

Keywords: Nicotine; Transdermal; Kinetics; Bioavailability; Cigarette smoking; Smoking cessation

1. Introduction

Several forms of nicotine replacement therapy produce overall similar beneficial results of approximately twofold increases in cessation rate compared to persons receiving placebo [9]. Nonetheless, it is plausible that differences in the amount and pattern of nicotine delivery from patches may confer clinical advantages and disadvantages to individual patch users as cigarette users also vary in the amount and pattern of nicotine obtained from smoking. For example, heavily dependent smokers reliably smoke immediately upon awakening in the morning and attain higher overall nicotine blood levels during the day [5]. Furthermore, the effects of nicotine vary as a function of the speed and amount of nicotine administered. For example, at the extreme condition of the cigarette, small amounts of nicotine are very rapidly absorbed, producing a cascade of electrophysiologic, cardiovascular, and neurohormonal effects [8,14]. Similarly, across three brands of oral snuff with similar nicotine content, but varying pH, the peak plasma nicotine concentrations, and several behavioral effects were directly related to the pH, and, hence, speed of nicotine absorption [6]

Several reviews have reported on the pharmacokinetics of the four patch systems [1,4,7,8,10]. These reviews report differences between the systems in terms of both amount of nicotine delivered, as well as rate of delivery; however, the data reported were taken from studies of individual systems. Because these studies used different subject groups and

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protocols, inferences about the differences between the systems is limited. The current study compared the pharmacokinetic profiles of currently marketed patch systems, using a double-blind, incomplete block study design. The three patch systems studied are manufactured by Pharmacia-Upjohn, Novartis, and Alza. Although other patch systems have been marketed, we selected these three on the basis that they appeared to be the three primary patch types of global utilization and appeared to represent diverse patch types.

2. Methods

2.1. Subjects

An Institutional Review Board approved the study, and all subjects provided written informed consent. Of the 25 subjects (nine females) who completed the study, two were Asians, two were blacks, 20 were whites, and one was Hispanic. The mean age of the subjects was 25.8 years (S.D. = 7.3) and the mean weight was 73.3 kg (S.D. = 12.5)

Inclusion criteria consisted of the following: smokers who smoked at least 10 cigarettes per day and had a plasma cotinine level of at least 100 ng/ml at baseline; between 19 and 55 years of age; and shown to be generally in good health according to medical history, physical examination by a physician, and routine laboratory analysis. All subjects were screened for abuse of drugs, and were not permitted to have used over-the-counter medications within 72 h, prescription medications within 14 days, or hepatic enzyme altering agents within 30 days prior to study initiation.

Subjects were housed under controlled conditions starting at least 24 h prior to drug administration and remained on the study unit for 51 h. For each subject, a washout interval of at least 4 days separated drug administration between application of the different types of patches. No smoking was allowed while subjects were housed on the residential unit (CO verified). Alcohol, caffeine, and xanthine-containing beverages were not permitted during the confinement period of the study. On pharmacokinetic sampling days (patch days 1 and 3), subjects fasted at least 9 h prior to, and 2.25 h following patch application. Water and confectionery chewing gum were allowed ad libitum. The same menu and meal schedules were administered uniformly for all subjects and for all treatments and were timed in a manner to prevent interference with drug administration. Alcohol-, caffeine-, and xanthine-containing beverages were restricted during the confinement period of the study.

2.2. Protocol

The study followed a randomized, incomplete, block study design. All subjects were assigned to receive treatment in random sequence to four test products, Pharmacia-Upjohn 4-mg gum (Nicorette), the Pharmacia-Upjohn 15-mg patch, the Novartis 21-mg patch, and the Alza 21-mg patch. Subjects within each patch condition were further randomized to wear the patch for either 16 or 24 h daily for the 3-day patch treatment phase. In this report, we focus on the kinetics of patch regimens as marketed and approved by the Food and Drug Administration and do not report the findings from nicotine gum or nonmarketed regimens. Specifically, the Pharmacia-Upjohn patch is approved for 16-h use and the Novartis and Alza patches are approved for 24-h use. (Note: The Alza patch labeling also allows for 16-h use, but the primary indication is for 24-h use.)

During patch treatment, patches were applied daily on 3 consecutive patch study days. Transdermal patches were

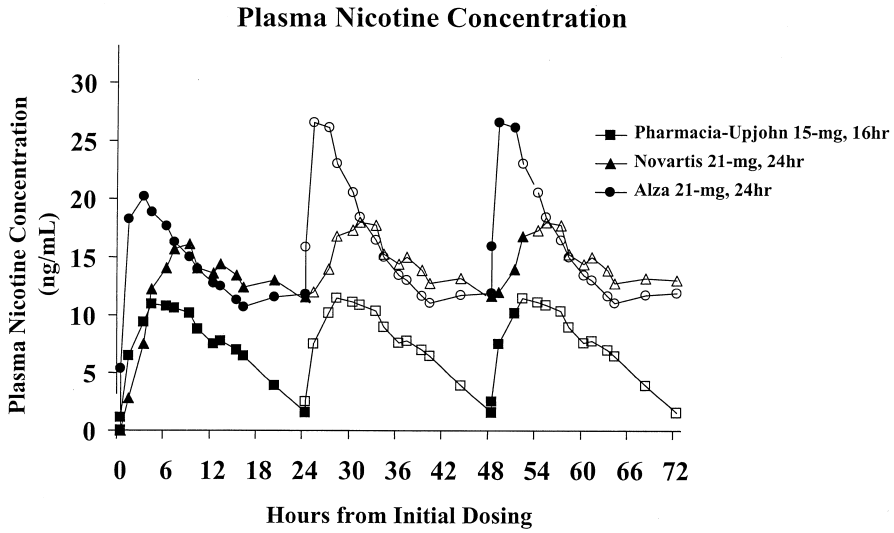

Fig. 1. Mean nicotine plasma concentrations during exposure to three different transdermal nicotine systems. Data points from 0 to 24 h are actual nicotine plasma concentrations (filled points). Data points from 24 to 72 h are nicotine plasma concentrations generated using the method of superposition (unfilled points).

Table 1
Pharmacokinetic profiles of the three patches studied from 0 to 24 h

Parameter	Pharmacia-Upjohn 15 mg (16 h)	Novartis 21 mg (24 h)	Alza 21 mg (24 h)
AUC_{0-24} (ng/ml h)	165 (54)	290[a] (108)	328[a,b] (144)
C_{max} (ng/ml)	11.9 (3.83)	17.6[a] (6.39)	21.9[a,b] (8.86)
C_{min} (ng/ml)	1.52 (0.95)	13.00[a] (5.76)	11.8[a] (5.64)
T_{max} (h)	6.5 (2.7)	10.0[a] (3.7)	3.8[a,b] (2.7)

Values shown are baseline adjusted means excluding outliers and (standard errors).
[a] Significantly different from Pharmacia-Upjohn ($P<.05$).
[b] Significantly different from Novartis ($P<.05$).

applied at the same time each morning to nonhairy, clean, dry sites on the upper arm, and applications sites were alternated (e.g., left, right, left) on study days 1, 2, and 3. Following each patch application, blood samples (7 ml) were drawn 0, 0.5, 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 13.5, 15, 16, 20, 24, 48, 48.5, 49.5, and 51 h after initial application. Efforts were made to draw samples from the arm contralateral to the patch application site. When new patch application time coincided with blood collection, the blood sample was drawn just prior to patch application.

2.3. Plasma analysis

All blood samples were stored in an ice bath for a maximum of 60 min prior to centrifugation. Plasma samples were then separated by centrifugation (2500 rpm for 15 min at 4°C) and stored in aliquots at −20°C until assay. Plasma samples were assayed for both nicotine and cotinine using a validated LC/MS/MS method by Harris Laboratories Analytic Services (Lincoln, NE). The range of quantification for nicotine and cotinine was 1–50 and 10–500 ng/ml, respectively.

2.4. Data analysis and statistics

Nicotine data were adjusted for baseline values because some individuals had residual nicotine from smoking in their blood prior to application of the patches. These baseline-adjusted concentrations were calculated by subtracting the baseline value using reverse superimposition (i.e., subtracting the amount of baseline nicotine that would be left at each time point, taking into account the amount of baseline nicotine that would have been eliminated at that time point). The following parameters were then determined for each subject and treatment: total nicotine absorbed (AUC_{0-24}; area under the plasma concentration curve), maximum plasma nicotine concentration (C_{max}), minimum plasma nicotine concentration (C_{min}), and the time taken to reach the C_{max} (T_{max}).

The method of superposition was used to simulate plasma profiles at steady state. The actual nicotine plasma concentration time data from 0–24 h was used as the starting data for the simulations. Simulated nicotine plasma concentrations were generated for each subject and treatment from 24 to 72 h by adding the levels on 1 day to the residual of what would have been left from the previous days, as estimated by extrapolation of terminal levels using the elimination half-life. A 3-h half-life of nicotine was used for the method of superposition.

Analysis of variance (ANOVA) was used to compare AUC, C_{max}, C_{min}, and T_{max} values between the three patch systems under modeled steady-state conditions (48–72 h). The ANOVA model included the following factors: sequence, subject within sequence, period, and treatment. Pairwise comparisons between the three patch systems were made using Fisher's Least Significant Difference (LSD) statistic (α=.05, two-tailed).

3. Results

Fig. 1 shows the plasma nicotine concentrations measured during the first 24 h of patch exposure and the steady-state modeled nicotine plasma concentrations over the subsequent 2 days of exposure. Table 1 shows the actual measured pharmacokinetic parameters calculated for the first day of patch administration (0–24 h). Table 2 shows the pharmacokinetic parameters calculated from modeled data during the second and third days of patch administration (48–72 h).

Table 2
Pharmacokinetic profiles of the three patches studied from 48 to 72 h (modeled steady-state data)

Parameter	Pharmacia-Upjohn 15 mg (16 h)	Novartis 21 mg (24 h)	Alza 21 mg (24 h)
AUC_{48-72} (ng/ml h)	161 (52.7)	295[a] (111)	332[a,b] (146)
C_{max} (ng/ml)	12.3 (3.85)	19.5[a] (7.44)	27.8[a,b] (10.90)
C_{min} (ng/ml)	1.53 (0.96)	13.0[a] (5.75)	11.9[a] (5.66)
T_{max} (h)	6.0 (2.8)	8.0[a] (2.2)	2.8[a,b] (2.2)

Values shown are means and (standard errors).
[a] Significantly different from Pharmacia-Upjohn ($P<.05$).
[b] Significantly different from Novartis ($P<.05$).

As shown in Tables 1 and 2, the relative dose of nicotine (AUC) into the bloodstream was higher for both 21-mg, 24-h patches than for the 15-mg, 16-h patch. This finding was significant under both acute dosing (0–24 h) and steady-state (48–72 h) conditions. C_{max} and C_{min} were also significantly higher for both 21-mg, 24-h patches than for the 16-h patch during acute dosing and at steady state. Among the 21-mg, 24-h patches, the Alza patch delivered a higher relative dose of nicotine than the Novartis patch as shown by AUC and C_{max} values; however, C_{min} values were not significantly different between the two 21-mg, 24-h patches. The T_{max} values were lowest for the 21-mg, 24-h Alza patch. T_{max} values were lower for the 15-mg, 16-h Pharmacia-Upjohn patch than for the 21-mg, 24-h Novartis patch.

4. Discussion

The results of this study demonstrated significant differences in nicotine delivery among transdermal patches at the highest marketed dose and approved duration of use (i.e., 16 or 24 h). This is consistent with reviews [1,4,7,8,10] that have been reported on the pharmacokinetics of the four patch systems from studies of individual systems. The data showed that the 21-mg, 24-h patches delivered a higher relative dose of nicotine over the course of the day than the 15-mg, 16-h patch, as reflected by the higher AUC values. The 15-mg, 16-h patch also showed the lowest C_{min}, reflecting the overnight drop in nicotine levels on this regimen. Further, there were differences even among the two 24-h patches, despite their similar labeling (21 mg): among 24-h patches, the Alza patch delivered a higher relative dose of nicotine than the Novartis patch, reached higher C_{max}, and reached them more quickly.

Differences in the amount of nicotine absorbed and the speed of nicotine delivery may be important for effective relief of withdrawal symptoms and cigarette craving. Several studies have shown that symptom relief by nicotine replacement is dose dependent [2,3]. Further, many smokers report their strongest craving soon after waking [13], and morning craving significantly predicts relapse [12]. Thus, the marked differences among patches in nicotine levels seen during the first several hours after waking may translate into differences in symptom relief. Indeed, a recent randomized trial comparing the 16-h Pharmacia-Upjohn patch and the 24-h Alza patch among smokers with morning craving showed lower craving and withdrawal scores throughout the day among smokers who received the 24-h Alza patch [11]. This had been attributed to the ability of the 24-h Alza patch to deliver higher nicotine levels both in the morning and throughout the day.

Further study will be required to determine definitively the overall clinical advantages and disadvantages of the differing profiles of nicotine delivery of the various patches. However, the significant variation in dosing parameters is consistent with the conclusion that the patches are not equivalent to individual users.

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