Semipermeable Membrane Dressings Can be Used with the Nicotine Transdermal System and Do Not Interfere with Nicotine Absorption

Nobuko Hazeki1, Kazuyuki Kobayashi1, Haruko Shinke1, Masatsugu Yamamoto1, Mitsuhiro Ohta2 and Yoshihiro Nishimura1

Abstract

Objective Adverse skin reactions as a local side effect of nicotine patches sometimes interfere with smoking cessation therapy. We studied the effects of semipermeable membrane dressings (SMD) used under nicotine patches (NP) on nicotine absorption, as assessed according to the urinary cotinine levels, and skin symptoms.

Methods First, the urinary cotinine levels were compared in eight nonsmokers that applied NP over SMD and NP without SMD (Study 1). The urinary cotinine levels were measured using a highly sensitive competitive enzyme immunoassay. Second, 28 subjects undergoing NP therapy for diagnosed nicotine dependence were randomly assigned into two groups in a crossover design to receive NP over SMD and NP without SMD. The urinary cotinine levels and skin symptoms were compared between the two treatment groups. During the follow-up period of 48 weeks, the smoking cessation rate was evaluated (Study 2).

Results No statistical differences were observed in the urinary cotinine levels between the NP over SMD and NP without SMD groups. In Study 2, the skin symptoms improved with the use of SMD in 42.8% (6/14) of the patients and worsened in 28.5% (4/14) of the patients. No serious skin disorders were reported. The subjects followed in Study 2 exhibited smoking cessation rates of 92.8%, 78.5% and 64.2% at 12, 24 and 48 weeks, respectively.

Conclusion The use of NP over SMD is a safe and effective alternative application to NP treatment for preventing the skin symptoms caused by NP without interfering with nicotine absorption.

Key words: nicotine replacement therapy, nicotine patch adverse skin reaction, semipermeable membrane dressings, high-sensitive enzyme immunoassay, urinary cotinine


Introduction

Nicotine patches (NP), such as Nicotinell® TTS® (Transdermal Therapeutic System, Novartis Pharma K.K., Tokyo, Japan), have been widely used in nicotine replacement therapy since 1990 to relieve nicotine withdrawal symptoms. In Japan, some forms of NP have been approved for use as over-the-counter drugs since 2009. While it is important for patients to continue ongoing treatment in order to successfully achieve smoking cessation, local adverse reactions at the patch site have been reported in 10.1% of patients, including erythema, particularly irritation and rubor, in 6.9% of patients and itching in 5.8% of patients [from the package insert (2012) of Nicotinell® TTS®]. Although such reactions are not necessarily severe, they can disturb the continuous use of therapy needed to achieve smoking cessation. Local semipermeable membrane dressings (SMD), such as Tegaderm™ (3M Health Care Ltd., Tokyo, Japan), a medical dressing that is widely used to cover and protect wounds...
and catheter sites, consists of a thin polyurethane membrane coated with a layer of acrylic adhesive, thus suggesting that small molecules, such as nicotine, may permeate the layer into the skin. We hypothesized that SMD exhibit the characteristic feature of being permeable for small molecules and that the use of SMD could block the direct effects of NP on the skin while maintaining nicotine absorption through the semipermeable membrane, resulting in an improved rate of successful smoking cessation. Our aim was to investigate whether the use of SMD under NP interferes with nicotine absorption by measuring the level of urinary cotinine. Nicotine is metabolized into cotinine in the liver following absorption from smoking via alveoli into the circulation. Cotinine is excreted into the urine following glucuronic acid conjugation. Nicotine has a half-life of approximately two hours, while cotinine has a longer half-life of 30 hours. Therefore, the urinary cotinine level can be measured to objectively evaluate the degree of habitual exposure to smoking (1-3).

**Materials and Methods**

We conducted two studies. Study 1 was designed to determine whether SMD decrease the absorption levels of nicotine in healthy nonsmokers using a single application of NP. We measured the urinary cotinine levels to assess nicotine absorption. Study 2 was a randomized crossover study of patients diagnosed with nicotine dependence. The primary outcome was the nicotine absorption level under regular clinical use of NP over SMD compared to the conventional use of NP. The secondary outcomes were the degree of skin irritation and rate of successful smoking cessation. The studies were conducted with the approval of the Ethics Committees of Kobe University. Written informed consent was obtained from all study subjects.

**Study subjects and nicotine patch application in Study 1**

In Study 1, eight healthy nonsmokers were recruited. Nicotinell® TTS® 10 (17.5 mg nicotine/24 h) was directly applied to the skin ("NP without SMD") for 24 hours. After a minimum of three days as a washout period, another Nicotinell® TTS® 10 was applied over SMD (Tegaderm™, "NP over SMD"). Urine samples were collected 24 hours after each application and stored frozen at -20°C.

**Randomized crossover study in Study 2**

In Study 2, for a randomized crossover study, we recruited 28 subjects diagnosed with nicotine dependence at the smoking cessation clinic at Kobe University hospital between April, 2008 and March, 2010. In the initiation of smoking cessation therapy with a good indication for Nicotinell® TTS® 30 (52.5 mg nicotine/24 hours), the subjects were randomly assigned into two groups using the sealed envelope method. Group A received Nicotinell® TTS® 30 over SMD for the initial two-week period in the four-week study, while Group B received SMD for the final two weeks (Fig. 1).

All subjects were instructed to use NP every day and refrain from smoking. The subjects made four follow-up visits to the hospital (at two, four, eight and 12 weeks from the beginning of the study) for regular consultations regarding smoking cessation, regardless of their success in achieving smoking cessation. On every follow-up visit, cessation was assessed via interview as well as exhaled carbon monoxide (CO)-oximetry testing (Micro III smokerlyzer, Bedfront Scientific Ltd., Rochester, UK) for biochemical verification of smoking cessation. Subjects who did not follow the protocol in terms of the usage of NP and SMD were excluded from the study. Achieved or sustained smoking cessation was evaluated at four, 12, 24 and 48 weeks from the beginning of the study. At 24 and 48 weeks, we telephoned the subjects for an evaluation if they did not have a visit. Successful smoking cessation was defined as the subject declaring that he/she had quit smoking for more than one month and biochemically verified based on an expiratory CO concentration lower than 10 ppm.

**Assessment of adverse skin reactions**

All subjects were asked to grade their skin symptoms every day for four weeks. The skin was examined for severe adverse effects on every follow-up visit. The grade of each reaction was scored. Erythema was scored as follows: no reaction, 0; erythema, 1; erythema with edema, 2; bulla, 3. Itching was scored as follows: no reaction, 0; mild, 1; moderate, 2; severe, 3. The highest grade was recorded in the symptom diary at the beginning, middle and late period of each of the treatment conditions for two weeks. Urine samples were collected two and four weeks after the beginning of the study.

**Measurement of the urinary cotinine levels**

The urine samples were stored at -20°C until the cotinine levels were measured using a highly sensitive competitive enzyme immunoassay (1). 96-well plates were coated with...
3.8 μg/mL of cotinine-3 antibodies for two hours. The cotinine-3 antibodies were created from a rabbit immunized with antigen, cotinine-3-thyroglobulin. The plates were blocked with a buffer solution (0.05 M Tris-HCl, 0.2 M NaCl, 0.01 M CaCl2, pH 7.4, 0.1% Triton) that contained 1% bovine serum albumin. Following the addition of 5 μL of the urine samples and 100 μL of horseradish peroxidase (HRP)-labeled cotinine, the mixture was incubated at room temperature for one hour. After washing the wells, the enzyme activity of HRP was measured using the peroxidase substrate, tetramethylbenzidine and H2O2. Phosphoric acid was then added to the wells to stop the enzyme reaction. The enzyme activity was detected at 450 nm using a microplate photometer. The range of the cotinine concentration in the assay was between 0.03 and 30 ng/mL. The urinary cotinine level in nonsmokers is below 4 ng/mL (1).

**Statistics**

We analyzed the data with the Mann-Whitney U test or Fisher’s exact test for patient characteristics and the Wilcoxon signed-rank test for the urinary cotinine levels using the SPSS software program version 18.0 (IBM, Armonk, USA). The results are shown as the mean ± SD. For all statistical analyses, a p value of less than 0.05 was considered to indicate a significant difference.

**Results**

**Urinary cotinine levels and skin findings following a single application in the healthy group**

In Study 1, no significant differences were observed in the urinary cotinine levels between the NP without SMD and NP over SMD groups of healthy subjects (p=0.44) (Fig. 2). None of the eight subjects experienced skin reactions, and no severe systemic symptoms or skin reactions were reported, indicating that the materials could be used in the following study.

**Comparison of the urinary cotinine levels between the NP without SMD and NP over SMD groups among the subjects with nicotine dependence**

Similar to that observed in Study 1, no significant differences were seen in the urinary cotinine levels between the subjects treated with NP without SMD and NP over SMD in

---

**Table 1. The Reasons of Subject Drop-out in Study 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>the reason of drop-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>change in medication</td>
</tr>
<tr>
<td>A</td>
<td>skin reactions</td>
</tr>
<tr>
<td>A</td>
<td>smoking for the first 2 week only</td>
</tr>
<tr>
<td>A</td>
<td>dose down</td>
</tr>
<tr>
<td>A</td>
<td>skin reactions</td>
</tr>
<tr>
<td>A</td>
<td>smoking</td>
</tr>
<tr>
<td>A</td>
<td>no urine</td>
</tr>
<tr>
<td>A</td>
<td>smoking, stopped visiting</td>
</tr>
<tr>
<td>B</td>
<td>dose down</td>
</tr>
<tr>
<td>B</td>
<td>smoking, stopped visiting</td>
</tr>
<tr>
<td>B</td>
<td>smoking for the first 2 week only</td>
</tr>
<tr>
<td>B</td>
<td>no urine</td>
</tr>
<tr>
<td>B</td>
<td>smoking, stopped visiting</td>
</tr>
</tbody>
</table>
either Group A (p=0.17) or Group B (p=0.12) (Fig. 3).

**Adverse skin reactions in the NP without SMD and NP over SMD groups**

A total of eight and seven subjects complained of skin symptoms of erythema and/or itching in the NP without SMD and NP over SMD treatment groups, respectively. The skin symptoms improved with SMD treatment in 42.8% (6/14) of the patients and worsened in 28.5% (4/14) of the patients. Improvements in erythema were seen in six patients (Group A, 2, 3, 5; Group B, 9, 10, 14), and itching was relieved in two patients (Group A, 3; Group B, 10). Conversely, cases in which exacerbated skin symptoms were observed with the application of SMD included four cases of exacerbated itching and one case of exacerbated erythema. Of the four patients with exacerbated itching (Group A, 2, 6; Group B, 9, 11), three had mild itching (Group A, 2, 6; Group B, 9) and one had moderate itching (Group B, 11). In this subject, the itching worsened from mild to moderate from the middle to late periods in the third and fourth weeks. Exacerbated erythema caused by SMD was observed in one patient (Group A, 6). The erythema remained at approximately Grade 1, and no erythema was observed following the direct application of NP. No severe systemic symptoms or skin reactions were reported (Table 3).

**The rate of smoking cessation in Study 2**

The rate of smoking cessation was 92.8% in the enrolled subjects 12 weeks after the beginning of the study. Subject 4 (Group A) failed to achieve cessation at 12 weeks. The rate of successful smoking cessation was 78.5% (11/14) at 24 weeks and 64.2% (9/14) at 48 weeks (Fig. 4).

**Discussion**

We clarified that SMD do not interfere with nicotine absorption from NP in healthy nonsmokers and patients with nicotine dependence. To assess the serum nicotine levels, we measured the urinary cotinine levels using a highly sensitive competitive enzyme immunoassay (EIA). This is an effective measurement method with a high correlation with other methods, such as gas chromatography/mass spectrometry (GC/MS) and high performance liquid chromatography (HPLC) (1-3). EIA can be performed at lower cost and in a
shorter time and can be used to analyze large numbers of samples. EIA can also be utilized in clinical settings to assess surrogate markers of smoking and the effects of nicotine drugs, such as NP. Hence, clinicians should carefully interpret the data obtained with immunoassay systems because the cross-reactivity for each immunoassay system differs (2). The antibodies may cross-react with compounds other than the measured nicotine metabolites (1, 2).

The urinary cotinine levels did not differ between the studies, suggesting that SMD can be used with NP for nicotine replacement therapy without affecting nicotine absorption. In Study 2, the urinary cotinine levels had a tendency to decrease over time, being slightly lower in the second two weeks than in the initial two weeks in both Groups A and B, although the differences were not statistically significant. This observation may be influenced by the effects of environmental passive smoking, which decreased over time due to the patients having to avoid smoky places.

Subject 4 (Group A) had a low urine cotinine level of 2.4 ng/mL, suggesting a problem with the regular use of NP. Eventually, subject 4 admitted to resuming smoking again at 12 weeks, when the regular consultations for smoking cessation ended. This failure case may ironically support the importance of regular use of the medication in smoking cessation therapy. In such cases, monitoring parameters such as the urinary cotinine level may be useful for ensuring adherence to NP treatment in the clinical setting.

It has been reported that 5-7.1% of patients drop out of smoking cessation therapy due to adverse skin reactions to nicotine patches (4), indicating the importance of preventing such adverse skin reactions. Adverse skin reactions from this patch medication include nonallergic irritation responses, such as nonallergic reactions that occur directly after application, as well as delayed allergic reactions (4-6). Nonallergic reactions reportedly occur in more than 40-50% of patients (7-9) and can be induced by increased moisture due to occlusion by perspiration, microorganisms such as bacteria and fungi located between the skin and patch and the stimulation of inflammatory responses by adhesives in the patch. Erythema is another nonallergic response caused by the topical vasodilative effects of nicotine in some cases (4-6). Allergic reactions are classified as type III or type IV allergies induced by sensitivities to nicotine, the matrix and adhesives in NP (4-6). Such allergic reactions are reported in 1.6-3.3% of patients (4, 7, 8, 10). In the present study, the skin symptoms improved with SMD treatment in 42.8% (6/14) of the patients and worsened in 28.5% (4/14) of the patients. Skin symptoms were reported not only in the subjects treated with NP without SMD, but also those treated with NP over SMD. The subjects whose symptoms worsened by NP over SMD exhibited little symptoms following the application of NP without SMD, while the use of NP over SMD benefited other patients who originally had symptoms after receiving NP without SMD. These findings suggest that SMD treatment prevents skin symptoms caused by NP and may be a preventive option to optimize smoking cessation therapy in cases of skin reactions induced by NP.

SMD has been reported to not obstruct thermoregulation; however, the material seals skin secretions, resulting in a high level of humidity on the skin (11). Therefore, substances causative for skin symptoms may stay on the sealed skin under moist conditions and consequently cause inflammation due to immune cell infiltration and/or occlusion of the perspiratory glands. These responses, which can be induced by any patch medications, depend on the patient’s susceptibility, including the skin barrier function, skin secretion and immune responses. Our results also indicate the heterogeneity of responses to patch medications. Although we did not investigate such mechanisms in our study settings, further research on this issue would make these medications safer and easier to use.

The limitations of this study include the small sample size due to patient withdrawal before the comparison of the primary outcome (urinary cotinine measurement). We established stringent criteria for the analysis in the crossover study setting. It was necessary to maintain consistent therapy medications and doses for comparison in the crossover setting. Consequently, the subjects were required to continue the smoking cessation therapy during NP treatment, since those who smoke could not use NP due to the risk of toxic nicotine concentrations. Some of the subjects who dropped out complained of skin symptoms; however, most of these patients continued smoking cessation therapy using other approaches. On the other hand, more than 90% of the 14 followed study subjects were successful in maintaining smoking cessation at 12 weeks, suggesting that the SMD treatment did not disturb the treatment goals.

Conclusion

The use of NP over SMD is a safe and effective alternative application to NP treatment for preventing the skin symptoms caused by NP without interfering with nicotine absorption.

The authors state that they have no Conflict of Interest (COI).

References


© 2013 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html