Full Paper

Skin Tests of a Novel Nicotine Patch, PHK-301p, in Healthy Male Volunteers: Phase I, Placebo-Controlled Study

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Abstract. Major local adverse reactions in the nicotine patches are skin reactions. To assess the skin reaction of PHK-301p, a newly developed nicotine patch, we conducted a phase I study that consisted of 2 parts: a skin irritation test (48-h closed patch test) and a photosensitivity test (24-h closed patch test + Ultraviolet A irradiation). Twenty healthy men were treated with PHK-301p and placebo. Both preparations were punched out to a circle of 6-mm diameter and were applied simultaneously to each participant. Skin irritation and photosensitivity were assessed by a physician who was kept unaware of the treatment. In the skin irritation test, moderate and mild erythemas were observed in each participant 72 h after application (24 h after removal) for PHK-301p. Mild erythema was observed in one participant 49 h after application (1 h after removal) for placebo. The skin irritation index, which was calculated based on the skin reactions of participants, was 7.5 for PHK-301p and 2.5 for placebo. In the photosensitivity test, one participant had mild erythema ($\pm$) approximately 25 and 72 h after application of PHK-301p. No solar urticaria was observed. From these results, we concluded that PHK-301p is an acceptable product as a nicotine patch.

Keywords: nicotine replacement therapy, patch test, smoking cessation, nicotine patch, skin reaction

Introduction

Nicotine replacement therapy (NRT) is a therapy that alleviates nicotine withdrawal symptoms and helps a person quit smoking by supplying nicotine by means other than smoking. The results of meta-analysis based on more than 100 randomized, controlled trials have shown that NRT increases the odds of quitting smoking approximately 1.5- to 2-fold (1), and the smoking cessation guidelines of the U.S. Department of Health and Human Services highly recommend NRT (2). Various formulations such as gum, patches, nasal sprays, and inhalers are already available as over-the-counter

drugs in the United States and Europe for NRT. Each preparation has its characteristics, but their efficacies are similar (1).

Smokers can choose the formulation suitable for their needs. For example, nicotine gum, which is already available in Japan, is superior in that the frequency and amount of its usage can be adjusted according to the needs, but this formulation is not suitable for a person who has an injury to their teeth or jaw and cannot continue chewing. On the other hand, a patch (transdermal preparation) is superior in that it is easy to use and it is possible to maintain a steady blood concentration with once daily application. Hence, adding an alternative method leads the users to better compliance.

Pfizer developed a new nicotine patch, PHK-301p, as

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an over-the-counter drug. There are 3 sizes of PHK-301p: 10, 20, and 30 cm², which contain about 8, 17, and 25 mg of nicotine, respectively. They are designed to release approximately 60% of the contained nicotine over 16 h. PHK-301p has been approved and marketed in 14 Western countries by 1993, and its safety and efficacy are well established. In Japan, a phase I study in healthy adult smokers was conducted in December 1993 (3). Although itching and redness around the patch were seen in this study, all were mild and none were considered clinically meaningful. However, this single-dose study was designed to assess the pharmacokinetics of PHK-301p, not designed to fully clarify the adverse skin reaction.

Previous studies that assessed the safety of nicotine patches have reported that the major local adverse drug reactions are skin reactions, including skin irritation (4–6). To assess precisely the skin reactions to PHK-301p, we conducted a phase I study that consisted of 2 parts: a skin irritation test and a photosensitivity test. Based on past experience and previous reports evaluating similar preparations (7, 8), we considered that these tests were optimum to observe the skin reaction to PHK-301p.

Materials and Methods

Study design

This study was conducted from March 17 to April 2, 1997, at the Kyushu Clinical Pharmacology Research Clinic. The purpose of the study was to investigate the safety of PHK-301p in healthy men, and the study consisted of two parts: a skin irritation test (48-h closed patch test) and a photosensitivity test (24-h closed patch test + Ultraviolet A (UVA) irradiation). We compared the safety of PHK-301p with placebo by applying these preparations simultaneously to each participant. The study protocol was reviewed and approved by the ethical review board of the institution before the study.

Participants

The participants were recruited from those who were registered in the institute as candidates of phase I studies. The inclusion criteria were: healthy Japanese men between 20 and 45 years of age; body weight within $\pm 30\%$ of $(\text{height} - 100) \times 0.9$; supine systolic blood pressure of 100 to 139 mmHg and supine diastolic blood pressure ≤ 84 mmHg; and pulse rate of 50 to 99 beats/min. The exclusion criteria were as follows: a history of drug allergy, donated or received blood within 2 months before the study, participation into any phase I study of a new drug within 4 months before the study, a history of drug addiction or alcoholism, and those

whose enrollment into the study was considered to be inappropriate by the investigator. All participants gave written informed consent. The participants took part in the study by visiting the institute.

In this study, we used 2 preparations (PHK-301p and placebo). PHK-301p is a 30-cm² patch that contains approximately 25 mg of nicotine, and 15 mg of the nicotine is designed to release over 16 h. The composition of placebo is the same as that of PHK-301p with the exception that placebo did not contain nicotine. PHK-301p and placebo looked similar and were indistinguishable. A 6-mm diameter circle was punched out from both preparations and used in each patch test. A circle of PHK-301p contains 0.23 mg of nicotine, and the total dose of nicotine was 0.46 mg in each participant.

Study treatment

We conducted the skin irritation test and the photosensitivity test simultaneously by applying the preparations to the upper back of each participant. A combination of PHK-301p and placebo was applied on the left side for a skin irritation test, and the other combination was on the right side for a photosensitivity test. As a consequence, 4 patches were applied to each participant. Four sites of the upper back were numbered, and the site of each preparation was determined using the circuit method (a method in which the sequence of the preparations was generalized before the study and was assigned according to the participant number). Each combination of PHK-301p and placebo was fixed with a Finn Chamber (9).

Concomitant use of the other drugs was not allowed during the study. Bathing was prohibited for 72 h after application. Intense exercise with sweating was prohibited during the study. Participants were also instructed to avoid touching the application site. The study was to be discontinued if the participant required it or if the investigator deemed necessary for medical reasons.

Outcome measurement

In the skin irritation test, PHK-301p and placebo were applied for 48 h, and skin reactions were assessed 1 and 24 h after removing the Finn Chamber according to the criteria (Table 1) of the patch test study group (8). "Total score" was calculated by summing up each participant's higher score between the 2 assessments (1 and 24 h after removing). A skin irritation index was calculated using the formula "skin irritation index = (total score) / (number of participants) $\times$ 100" based on the scores yielded by the assessment. A skin irritation index was classified according to the criteria for irritation caused by medicines for external application (8). In

Table 1. Japanese criteria for patch test

Condition	Assessment	Score
No reaction	–	0
Mild erythema	±	0.5
Erythema	+	1
Erythema and edema	++	2
Erythema and edema with papular rash or vesicles	+++	3
Bulla	++++	4

Table 2. Photosensitivity test criteria

Condition	Assessment	Score
Lack of reaction or reaction comparable to non-irradiated site	–	0
Slightly pronounced compared with non-irradiated site	±	0.5
Clearly pronounced compared with non-irradiated site	+	1
Reaction two ranks more pronounced using domestic criteria compared with non-irradiated site	++	2
Reaction three ranks more pronounced using domestic criteria compared with non-irradiated site	+++	3

this classification, a safe, acceptable, and mildly irritating product was defined as a skin irritation index of 5.0 or lower, 15.0 or lower, and above 15.0, respectively.

In the photosensitivity test, PHK-301p and placebo were applied for 24 h and skin reactions were assessed 1 h after removing the Finn Chamber. Afterwards, they were subjected to long-wavelength (UVA) irradiation for (3 Joules/cm²). Ten FL20S-BLB/DMR (Toshiba Medical Supply Co., Ltd., Tokyo) attached to a DERMARY M-DMR-80 (Toshiba Medical Supply Co., Ltd.) were used for optical irradiation. The presence or absence of solar urticaria was assessed 30 min after optical irradiation, and thereafter, the site was covered with a Finn Chamber for an additional 22.5 h. Photosensitivity after treatments were compared with those on the non-irradiated side (left side, 48-h closed patch test) at 1 and 24 h after removal of the Finn Chamber and assessed according to the evaluation criteria for photo-patch tests (Table 2) (8).

All skin reactions were assessed by a physician who was kept unaware of the preparation sequence. The investigator generated the preparation sequence, and the other physicians and co-workers applied and removed the preparations. The assessor did not apply nor remove

the preparations during the study and was never told the preparation sequence. A photograph of the application site was taken before application and at the time of assessment.

To address adverse events, participants were instructed to report symptoms in a pre-defined form. Vital signs (blood pressure, pulse rate, and respiratory rate) and laboratory tests were performed before and 4 days after application. The investigator recorded the results for each participant in a case report form and confirmed that there were no discrepancies in the documented symptoms, physiological examination results, and laboratory findings. In addition, the investigator kept track of any new symptoms and objective findings by means of observations and interviews. The interviews were conducted in a way that allowed for objective evaluation.

Statistical consideration

The sample size of 20 was determined as the minimum number to confirm skin irritation with adequate precision. The frequency of signs and symptoms observed during the study and the number of participants who experienced them were tabulated. All demographic data were given as the mean and standard deviation.

Results

Twenty men were enrolled in the study, and all participants completed the study without protocol deviation. All data obtained from these participants were used in the analysis. The mean (standard deviation) age was 21.4 (1.42) years; height, 168.7 (4.40) cm; body weight, 56.7 (5.65) kg; degree of obesity, –8.1% (9.28%).

In the skin irritation test, one participant had mild erythema (±) and the other participant had erythema (+) 72 h after application of PHK-301p (24 h after removal), while one participant had mild erythema (±) 49 h after application of placebo (1 h after removal) (Table 3). The skin irritation index was 7.5 for PHK-301p and 2.5 for placebo (Table 4); thus, PHK-301p was classified as an acceptable product.

In the photosensitivity test, one participant had mild erythema (±) approximately 25 and 72 h after application of PHK-301p. No solar urticaria was observed after 30 min of UVA irradiation in either preparation.

No adverse events occurred during the study. No symptoms or signs were observed. Neither clinically meaningful findings nor drug-induced changes were observed in the vital signs. Some laboratory values deviated slightly from the reference values. However, these deviations were within the range of physiological

Table 3. Scores of each subject in 48-h closed patch test

Subject No.	1 h after removal		24 h after removal	
	PHK-301p	Placebo	PHK-301p	Placebo
1	0	0	0	0
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	1	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
9	0	0	0	0
10	0	0	0	0
11	0	0.5	0	0
12	0	0	0	0
13	0	0	0	0
14	0	0	0	0
15	0	0	0	0
16	0	0	0	0
17	0	0	0	0
18	0	0	0	0
19	0	0	0	0
20	0	0	0.5	0

variation, and no clinically meaningful or drug-induced changes were observed.

Discussion

Skin reactivity is a major concern as a local adverse reaction to a nicotine patch. For example, in a pre-approval investigation of a nicotine patch (Nicotine TTS; Novartis Pharma K.K., Tokyo) now available in Japan, a local adverse drug reaction was seen in at least 30% of 747 persons evaluated. The main symptoms of local adverse drug reaction were erythema and itching,

and each accounted for about 20% of the total 560 adverse drug reactions [from package insert (2005) of Nicotinell TTS]. Moreover, results of meta-analyses have indicated the rates of nicotine patch-induced skin irritation differs depending on the study, and the incidence rates ranging up to about 70% (4, 5).

Previous clinical studies of PHK-301p have reported that it produced local adverse drug reactions such as itching, redness, and erythema (3, 10; M. Nakamura et al., unpublished data). In one of these studies, itching was observed in 5 of 6 participants who were applied with one 30-cm² PHK-301p to the upper arm for 16 h (3). Although the rate of local adverse reactions was high, all symptoms were mild and no clinically meaningful reactions were observed. To assess local adverse reactions precisely, we conducted the skin test study. The skin irritation index of PHK-301p was 7.5, classified as an acceptable product, and was lower than that of other product evaluated by a previous study (7). The results show that PHK-301p is an acceptable product as a nicotine patch without clinically meaningful skin irritation or photosensitivity.

Contact skin reactions to nicotine patches are classified into the two types, that is, nonimmunological reaction and allergic reaction (11). Nonimmunological reaction includes irritation induced by occlusion which increases accumulation of humidity, sweat, and microbial overgrowth (11–13); irritation to the delivery system (matrix and adhesive layers) (12); and erythema due to topical vasodilative effect of nicotine (11, 12). Allergic reaction is a type IV or cell-mediated immune reaction to sensitization to nicotine, matrix, or adhesive layers (11, 12). The nonimmunological reaction is usually transient and maximal at the time of patch removal, and allergic reactions are mostly delayed and often worsen after patch removal (11, 12).

In our study, no skin reaction was observed immediately after removal of PHK-301p, and only 2 erythemas ($\pm$ and $+$) were observed 24 h after removal.

Table 4. Results of evaluation of skin irritation

At the time of observation	Preparation	Assessment result						Score total	Skin irritation index
		–	$\pm$	+	++	+++	++++		
49 h after application (1 h after removal)	PHK-301 (n = 20)	20	0	0	0	0	0	0	0
	Placebo (n = 20)	19	1	0	0	0	0	0.5	2.5
72 h after application (24 h after removal)	PHK-301 (n = 20)	18	1	1	0	0	0	1.5	7.5
	Placebo (n = 20)	20	0	0	0	0	0	0	0

We consider that these erythemas were induced by an allergic reaction to nicotine because no late-onset reaction was observed in the placebo treatment. Although nicotine is not a highly reactive chemical substance (12), the majority of allergic reactions reported with nicotine patches is attributed to nicotine (11). Since the minor occurrences of allergic reaction to nicotine are inevitable, varying the site of drug administration is recommended to minimize skin reactions (11). Furthermore, the component of the matrix and the adhesive layers used in PHK-301p may have little influence on skin because only 1 mild erythema was observed in the placebo treatment. A previous study has reported that both immediate and continuous irritant reactions were frequently observed in the placebo treatment (7). Although the formulations of this placebo are not disclosed, we consider that the skin reactions associated with PHK-301p may be milder than those with other products by comparing those data with our present results.

Our study had the following 3 limitations: skin reactions were evaluated with a single application; PHK-301p was applied to the small area (circle of 6 mm diameter); and the sample size was small. First, while the nonimmunological reaction occurs even with a single contact, the likelihood of allergic reaction increases with repeated contact until sensitization. Given the aim of NRT, nicotine patches will be applied every day. Hence, further investigations should be performed to assess the safety of PHK-301p in repeated application. Second, the previous study has used the same size preparation as the commercial product (7), whereas our study used a circle 6 mm in diameter punched out of the PHK-301p preparation. Thus, the skin reactions should be evaluated by using the commercial product. Finally, our study recruited 20 healthy men with normal skin. Previous research has investigated skin reaction in 14 volunteers with a history of adverse skin reactions to a nicotine patch and found that atopy and contact sensitization to standard patch test allergens were identified in 6 participants (12). Therefore, it is necessary to gather data in a large, diverse population that includes persons with sensitive skin. With respect to these, other investigations were conducted (3, 10; M. Nakamura et al., unpublished data).

In conclusion, PHK-301p is an acceptable product for NRT because no clinically meaningful skin irritation, no hypersensitive reaction to light, no clinically meaningful change in the laboratory tests, and no medical examinations were observed. Further study will be warranted to assess the safety of PHK-301p in the real clinical setting.

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