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Meteorology and ethnicity as critical factors in HRIPT: Comparing responses between Chinese and Indian ethnicities

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ABSTRACT

Background: Human repeated insult patch test (HRIPT) is regarded as one of the confirmatory test in determining the safety of skin sensitizers. A number of important factors should be considered when conducting and interpreting the results of the HRIPT.
Objective: To investigate for probable critical factors that influence the results of HRIPT with the same protocol in Shanghai and Mumbai.
Methods: Two HRIPTs were carried out in Shanghai and Mumbai in 2011. Six identical products and 1% sodium lauryl sulfate were tested. Two Chinese dermatologists performed the grading in the two cities. Climate conditions of Shanghai and Mumbai were also recorded.
Results: For four lower reaction ratio products, cumulative irritation scores in the induction phase were higher in individuals whose ethnicity was Indian rather than Chinese. Reaction ratio of the same four products was highly correlated to the climatic parameters. The other two higher reaction ratio products and the positive control had no difference between the two ethnicities.
Conclusion: Greater attention ought to be paid to the impact of climate on the results of HRIPT, especially for the mild irritation cosmetics when giving the interpretation. Greater emphasis also needs to be placed on the ethnicity of the subjects.

1. Introduction

Human repeated insult patch test (HRIPT) has been selected as the method in assessing the potential for contact sensitization (Farage et al., 2003; Politano and Api, 2008; David et al., 2003). Although there were naturally some criticisms regarding the ethical implications of HRIPT, myriad of critical factors should be kept in mind when conducting the test and interpreting the results (McNamee et al., 2008). For the most part, there is a high degree of consistency between the results of animal testing and in vitro testing, such as local lymph node assay (LLNA) (Kimber et al., 2001; Tardiff et al., 2003). Therefore, HRIPT is regarded in many countries as a holistic method in evaluating the safety of skin sensitizers (Basketter, 2009).

Conforming to the common protocols used in most HRIPTs, each of the 100–200 volunteers was given 9 × 24-h or 48-h exposures over a 3-week time frame. After a 2-week rest period, a challenge exposure was then taken from both the original and alternate site, again using the same exposure time as induction phase. Given that there are a number of important factors such as vehicle effects, concentration and amount of test materials applied, occlusion type, chemistry, target population, and allergen potency affecting HRIPT, their standardization is crucial when carrying out the test (McNamee et al., 2008). However, there are a couple of factors, namely the endogenous ethnic makeup and climatic conditions, that further influence the response to an irritant (Modjtahedi and Maibach, 2002; Uter et al., 2003; Hegewald et al., 2008a,b). To examine these hypotheses for HRIPT in detail, a two-center HRIPT was executed in Shanghai and Mumbai in 2011.

Using the same protocol, we conducted the test on Oriental and Indian subjects. The findings in critical factors for this confirmatory test are laid out on this paper.

2. Materials and methods

2.1. Test materials

Six different creams were sent by the Johnson & Johnson Worldwide EM Innovation Center. These creams were tested by neat forms and were assessed to be safe based on toxicological, medical,

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clinical and regulatory approvals. Their code numbers were Cream A, Cream B, Cream C, Cream D, Cream E and Cream F. The sponsor had assumed responsibility for the chemical characterization and stability of the test materials.

1% sodium lauryl sulfate (SLS), which had purity greater than 97% and was certified by the supplier (Sigma High Technology Limited Company, Shanghai, China) for its structure and purity, was used as positive control in the induction phase. A blank undosed patch was used as the negative control in the induction phase. An ¢ 8 mm Finn was used in this occlusion patch test.

2.2. Subjects

According to the subjects inclusion/exclusion criteria, 113 subjects in Shanghai and 121 subjects in Mumbai were screened for HRIPT participation. Individuals with active or history of psoriasis, active allergic skin responses, or active eczema as determined by the initial paperwork were excluded. In addition, subjects that had been under treatment for any type of cancer within the last 6 months, or used anti-inflammatory drugs, immunosuppressive drugs, or antihistamine medication were also excluded. Participation in any patch tests for irritation or sensitization, known as sensitization to adhesives, within the last 4 weeks or current participation in any clinical testing was not allowed. Individuals with damaged skin in or around the test sites that include sunburn, extremely deep tans, uneven skin tones, tattoos, scars, excessive hair, numerous freckles, or other disfiguration of the test site, or individuals with known allergies to the test articles were not included in the study. In Shanghai, 100 subjects finished the whole study and 13 subjects were rejected due to failure in adhering to the schedule. Among those who finished the study were 13 males and 87 females between the ages of 22 and 63 years. In Mumbai, 99 subjects finished the whole study – 10 males and 89 females between the ages of 18 and 45 years completed the study – and 22 subjects were rejected for the same reason. Each subject had been fully informed of the whole study and had signed a copy of the consent document. The study was conducted in strict accordance to the instructions governed by the Ethics Committee of Johnson & Johnson Worldwide EM Innovation Center.

2.3. Method

The method used was a reworked version of the HRIPT. In the induction phase, subjects were exposed to the products and controls through an occlusion patch test three times every 48 h over a 3-week period. Following a 2-week rest period, a challenge exposure – again using a 48-h occlusion patch – was made on both the original site and an alternate site. For the original site, patches were placed on roughly the same area as the initial patch test. For the alternate site, however, patches were always applied on new areas. The areas were then examined approximately 48 and 96 h after the application. In challenge phase, the SLS was not used. The HRIPT schedule for China and India is shown in Table 1.

Reactions to the test materials were scored using a combination of the grading scales; see below for details.

Induction grading scale

Erythema and elevated responses:

0	No evidence of irritation
1	Minimal erythema, barely noticeable
2	Definite erythema, easily visible; or minimal edema; or minimal papular response
3	Erythema and edema
4	Erythema and edema and minimal papular
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

Effects on superficial layers of the skin:

A	0	Slight glazed appearance
B	1	Marked glazing
C	2	Glazing with peeling and cracking
D	3	Glazing with fissures
E	3	Film of dried serous exudates covering all or portion of the patch site
F	3	Small petechial erosions and/ or scabs

Challenge grading scale

Erythema scale: this scale is used only for grading the degree of erythema (redness).

0	No visible erythema
1	Mild erythema (faint pink to definite pink)
2	Moderate erythema (definite redness)
3	Severe erythema (intense redness)

Shanghai's climate data including air temperature and minimum humidity was provided by the Meteorological Bureau in Shanghai. The climate data in Mumbai was taken from http://www.wunderground.com.

Table 1
Schedule of HRIPT in Mumbai and Shanghai.

		Mumbai	Shanghai
Induction phase	Baseline	May 9, 2011	September 6, 2011
	1	May 11, 2011	September 8, 2011
	2	May 13, 2011	September 10, 2011
	3	May 16, 2011	September 13, 2011
	4	May 18, 2011	September 15, 2011
	5	May 20, 2011	September 17, 2011
	6	May 23, 2011	September 20, 2011
	7	May 25, 2011	September 22, 2011
	8	May 27, 2011	September 24, 2011
	9	May 30, 2011	September 27, 2011
Challenge phase	Baseline	June 13, 2011	October 10, 2011
	48 h	June 15, 2011	October 12, 2011
	96 h	June 17, 2011	October 14, 2011

Note: 1 corresponds to the first induction, 2 refers to the second induction, and so on.

2.4. Evaluators

Two experienced Chinese dermatologists were in charge of the evaluation in Shanghai and Mumbai. They came from the Shanghai Evaluation Institute for Safety and Efficacy of cosmetic approved by the State Food and Drug Administration of China.

2.5. Statistics

The ***SPSS13.0*** software was used in the statistical calculation. Cumulative irritation scores (CIS) were calculated by adding 9 scores in the induction phase. The reaction ratios in induction phase were calculated using this formula:

$$\text{Reaction ratio} = \frac{CIS}{10 \times \text{number of subjects} \times 9} \times 100\%$$