

# Reactions of non-immunologic contact urticaria on scalp, face, and back

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**Background:** This study compared the reactivity of scalp, face, and back to nonimmunologic contact urticants (NICU) to ascertain relative responsiveness.

**Methods:** Model urticants, benzoic acid (BA) and hexyl nicotinate (HN) with 3 concentrations of each were applied to marked skin of 10 bald males during 6 weeks. One urticant was applied to one side of nasolabial fold, back, and scalp and the other applied to the contralateral side. Reactivity was assessed by visual scores (VS) and biophysical instruments. Subjects ranked skin sensation with a 10-point visual analogue scale.

**Results:** With 0.25% HN application, upper back VS significantly ( $p < 0.05$ ) exceeded scalp and back VS also showed significantly ( $p < 0.05$ ) stronger reaction than face at 60 min post-application; however, at 2.5% BA site, VS of face exhibited significantly ( $p < 0.05$ ) higher than back at 15 min post-application but with 0.625% BA site, VS of back was sig-

nificantly ( $p < 0.05$ ) higher than face. The  $a^*$  value was significantly ( $p < 0.05$ ) higher on back than scalp with 0.625% BA treatment.

**Conclusion:** Thus symptoms and measurements vary among sites. Differences may be related to solubility related percutaneous penetration. We encourage investigation into this relatively neglected but clinically important arena, to help explain difference in consumer/patient acceptance of topical formulations.

**Key words:** benzoic acid – bioengineering – hexyl nicotinate – irritant contact dermatitis – regional variation – skin sensation – squamometry – transepidermal water loss – visual analog scale

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NON-IMMUNOLOGIC CONTACT urticaria (NICU) is an immediate contact reaction and occurs without prior sensitization. Numerous compounds, such as foods, preservatives, fragrances, plant and animal products, metals, and miscellaneous, have caused NICU (1). The symptoms vary according to the site of exposure, concentration, vehicle, mode of exposure, and the substance itself. More than half of the individuals react with local erythema and edema to these substances within 45 min of application if the concentration is sufficiently high. Furthermore, NICU is often accompanied by itching, burning, and stinging sensations, common cause of consumer complaint for face and scalp products (1,2).

NICU on the face has been investigated with subjective and objective approaches (3–6). The scalp is a target of topical products drugs and cosmetics. For instance, shampoos may contain potential urticants. However, due to the scalp's structure and functions (7–9), scalp may hide

classical irritation morphology (erythema and edema), but sensory (burn, sting, and itch) irritation on scalp is readily judged. To our knowledge, NICU scalp studies have not been published. In particular, data comparing reactions to urticants between scalp and back and face appear lacking.

This study compared the reactivity of different sites (scalp, face, and back) to two model urticants, benzoic acid (BA – water soluble) and hexyl nicotinate (HN – lipid soluble). NICU reactions on the challenged sites were assessed by clinical signs and bioengineering instruments.

## Materials and Methods

### Subjects

Ten bald men (eight Caucasians and two Asians; mean age  $53 \pm 7$  years) were recruited from the San Francisco bay area community and were screened by the investigators. Subjects were healthy with fair skin without obvious skin

disease or known history of atopic dermatitis. This study protocol and informed consent form was approved by the Committee on Human Research at University of California San Francisco.

#### *Test materials*

Benzoic acid (BA) (Fisher Scientific, Fair Lawn, NJ, USA) and hexyl nicotinate (HN) (Sigma Chemical Co., St. Louis, MO, USA) were purchased commercially. Three concentrations of each chemical (BA at 0.625%, 1.25%, and 2.5% and HN at 0.25%, 0.5%, and 1%, respectively) were prepared in isopropyl alcohol (IA) (LabChem, Inc, Pittsburgh, PA, USA).

#### *Procedure*

In a randomized manner, 20  $\mu$ L of one testing chemical (the lowest concentration) was applied to one side (area is approximately at 0.78 cm<sup>2</sup>) of nasolabial fold, back, and scalp whereas another chemical (the lowest concentration) was applied to the opposite side of nasolabial fold, back, and scalp. NICU reactions were assessed by visual scores and biophysical instruments at baseline, 15, 30, and 60 min post-application. In addition, subjects ranked the skin sensation with a 10-points scale for each of burning, stinging, and itching at 15, 30, and 60 min post-application. Each round was completed in one session, followed by a 2-week rest period for the second round (with medium concentrations of each chemical) and the third round (with the highest concentrations).

#### *Visual scores (VS)*

VS assessment was performed by one investigator, according to previous rating scale (10) with modifications: 0 = no redness; 1 = barely spotty redness; 2 = weak spotty redness, but without edema; 3 = diffuse erythema covering the large area of dorsal side of hands with minimal edema; 4 = erythema with moderate edema; 5 = erythema with strong edema; 6 = erythema with severe edema or palpable infiltration.

#### *Visual analog scale (VAS)*

A 10-point visual analog scale (VAS) ranging from 0 to 10 cm was assessed for each sensation

(11). For example itching sensation, on this scale '0' was defined as 'no itch sensation' and '10' as 'the worst itch you ever felt.'

#### *Biophysical measurements*

Erythema was quantified by skin color reflectance measurements using a colorimeter (Chroma Meter CR 300, Minolta, Osaka, Japan, and Aca-derm Inc., Menlo Park, CA, USA). The a\* value represents the color spectrum from total green to pure red and correlates closely with erythema (12,13). Standard guidelines and measuring principles have been published in detail (14).

Skin blood flow volume (BFV) was measured with a laser Doppler Flowmeter (MBF3D; Moor Instruments, Axminster, England) to observe the blood flux on skin test sites. Details and standard guidelines for use were utilized (12,15,16). The values of BFV were expressed as arbitrary units (a.u.).

All measurements were conducted in a room with daily ranges of relative humidity (RH) from 60  $\pm$  10% and temperature from 17  $\pm$  3°C. These values (RH and °C) were recorded during the experimental period. Each subject rested at least 30 min for acclimation before measurements.

#### *Statistical analysis*

Statistical analysis was performed utilizing a computer program SigmaPlot 11.0<sup>®</sup> (Systat Software Inc., San Jose, CA, USA). For non-parametric data, such as VS and VAS were analyzed by Friedman Repeated Measures ANOVA on Ranks. If there was a significant difference, all pairwise multiple comparison procedures were further analyzed with the Holm-Sidak method. For parametric data, such as values of a\* values and BFV on the differences were analyzed by One-Way Repeated Measures ANOVA. If there was a significant difference, all pairwise multiple comparison procedures were further analyzed with the Turkey Test. Statistical significance was accepted at  $P < 0.05$ .

## **Results**

#### *Visual scores (VS)*

With 0.25% HN treatment, the upper back VS significantly ( $P < 0.05$ ) exceeded the scalp at all time points (15, 30, and 60 min) post-application (Fig. 1a-c) and the back VS also showed

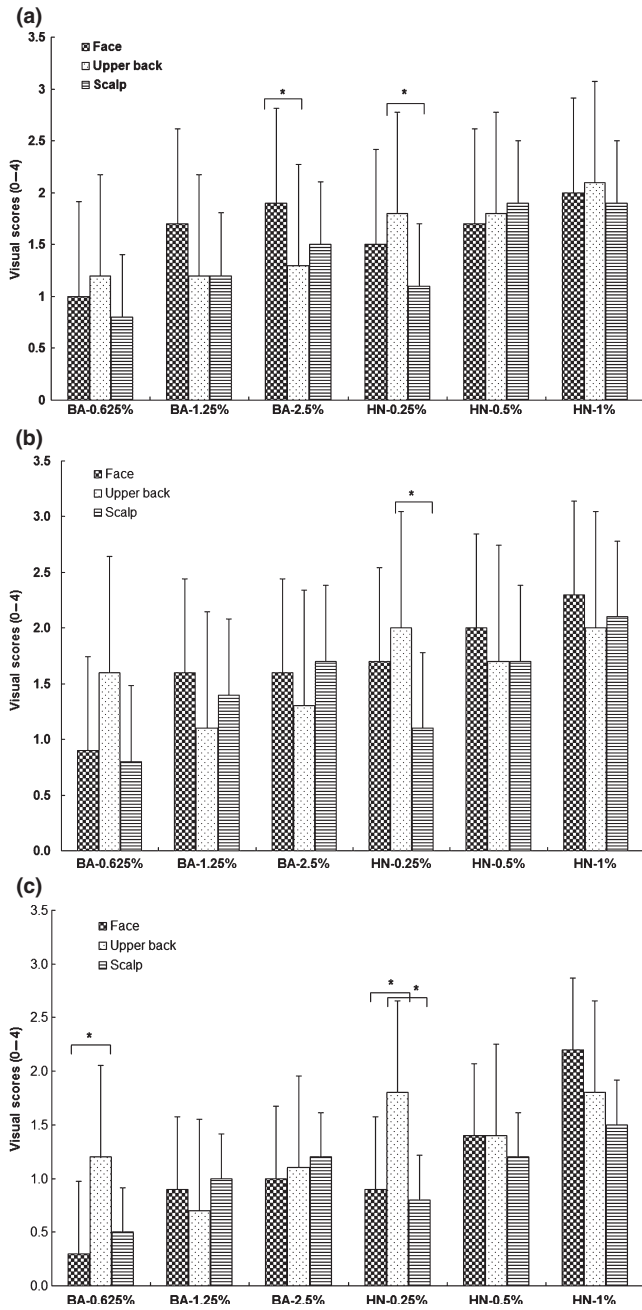


Fig. 1. (a-c) VS results between scalp, face, and upper back at 15, 30, and 60 min post-treatment with two urticants. \* $P < 0.05$ . With 0.25% HN treatment, the upper back VS significantly ( $P < 0.05$ ) exceeded the scalp at all time points (15, 30, and 60 min) post-application (Fig. 1a-c) and the back VS also showed significantly ( $P < 0.05$ ) stronger reaction than the face at 60 min post-application (Fig. 1c); however, at 2.5% BA treated site, the VS of face exhibited significantly ( $P < 0.05$ ) higher than the back at 15 min post-application (Fig. 1a), but with 0.625% BA treated site, the VS of back was significantly ( $P < 0.05$ ) higher than the face at 60 min post-application (Fig. 1c).

significantly ( $P < 0.05$ ) stronger reaction than the face at 60 min post-application (Fig. 1c); however, at 2.5% BA treated site, the VS of face

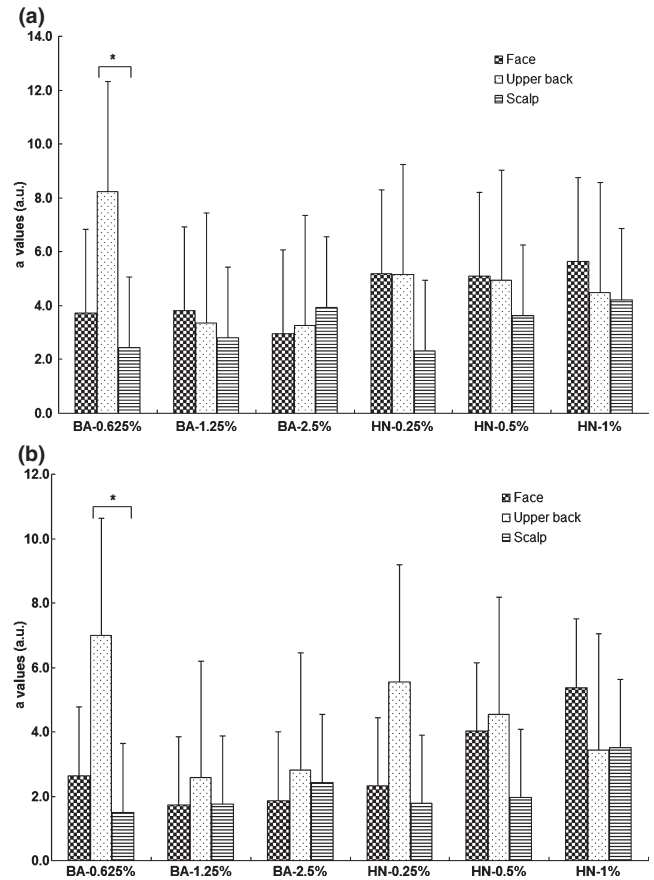


Fig. 2. (a-b)  $a^*$  values between scalp, face, and upper back at 15, 30, and 60 min post-treatment with two urticants. \* $P < 0.05$ . The  $a^*$  value was significantly ( $P < 0.05$ ) higher on the back than the scalp with 0.625% BA treatment at 30 and 60 min post-application.

exhibited significantly ( $P < 0.05$ ) higher than the back at 15 min post-application (Fig. 1a) but with 0.625% BA treated site, the VS of back was significantly ( $P < 0.05$ ) higher than the face at 60 min post-application (Fig. 1c).

#### Visual analog scale (VAS)

Both urticants caused minimal skin sensation. However, VAS data showed no significant difference between sites with both urticants (data not shown).

#### Skin color ( $a^*$ value)

The  $a^*$  value was significantly ( $P < 0.05$ ) higher on the back than the scalp with 0.625% BA treatment at 30 and 60 min post-application (Fig. 2a-b).

Remaining instrumental data showed no significant difference between sites with both urticants (data not shown).

## Discussion

NICU can cause sufficient stinging, itching, and burning, which might deter an individual from using even the most effective of skin care products. Investigations of this biologic arena, especially to objectively assess such sensations, should lead to optimally tolerated skin hair care products.

The mechanisms of NICU has not been fully established, but it might be a direct influence upon dermal vessel walls or a non-antibody-mediated release of histamine, prostaglandins, leukotrienes, substance P, or other inflammatory mediators. Previously, histamine was assumed to be released from mast cells in response to exposure to an eliciting substance. However, evidence suggests that histamine is not the main mediator in NICU; compelling data infers that prostaglandins are one mediator (1).

The selected model urticants (BA and HN) and their concentrations were used here because they have induced NICU on human skin in the experimental settings (3,5,17) and have different solubilities: aqueous/lipid.

The skin of the face, neck, back, and extensor sides of the upper extremities react more readily than other body parts; in particular, the face is considered a preferred site for testing NICU as it is richly vascularized and is also highly permeable owing to a high density of follicular shunts and a relative poor horny layer barrier (17). In contrast, Lammintausta et al. (3) studied subjective (sensory) irritation with lactic acid test on the faces of 74 women; 8 women reacted positively with 'stinging' and/or itching or burning and another 5 women had mild subjective sensations. Their results indicated that the stingers developed significantly more erythema to 0.5% sorbic acid ( $P < 0.05$ ) and to 1% BA ( $P < 0.02$ ). Our NICU results here showed that 2.5% BA caused VS significantly ( $P < 0.05$ ) higher on face than the back at 15 min post-application, but with 0.625% BA treated site, the VS of back was significantly ( $P < 0.05$ ) higher than the face at 60 min post-application. The  $a^*$  value was significantly ( $P < 0.05$ ) higher on the back than the scalp with 0.625% BA treatment at 30 and 60 min post-application.

Marrakchi and Maibach (5) utilized HN to induce NICU in human volunteers of two age groups: young subjects (24–34 years) and older volunteers (66–83 years) and defined skin func-

tion and potential age-related differences in various facial areas. The perioral area exhibited the strongest reaction to HN in the young group, where the chin was the most sensitive site in the older group; the forearm was the least responsive in both groups. In the current study, with 0.25% HN treatment, the upper back VS significantly ( $P < 0.05$ ) exceeded the scalp at all time points (15, 30, and 60 min) post-application and the back VS also showed significantly ( $P < 0.05$ ) stronger reaction than the face at 60 min post-application.

Jourdain et al. (6) objectively assessed sensory irritation ethnic variations in facial skin neuro-sensitivity through individual detection thresholds of topically applied capsaicin. Asian women tend to have higher capsaicin detection thresholds than Caucasians, but lower thresholds than Africans. Nevertheless, they concluded that the changes across individuals of different ethnic backgrounds appear minimal. Fujita et al. (2) used a self-assessment questionnaire to measure the sensory irritation in various body regions caused by two model hair-dye bases that contained different amounts of alkali agents without dyes. The occipital region was found as an alternative region of the scalp to test for sensory irritation of the hair-dye bases. In addition, we previously compared the potential irritancy of sodium lauryl sulfate between scalp and arm and back, and results supported that the back is the reasonable region for potential irritation testing of hair care products (18). These studies provided some of clinical relevance information about irritation and sensations.

This study is the first to evaluate the sensitivity of these anatomic regions (scalp, face, and back) to determine which region displays the most intense NICU response to the application of BA and HN. With the lowest concentration of HN (0.25%), back appeared more sensitive than face and scalp, but it did not show the same trend at higher concentrations (i.e., 0.5% and 1%). BA data were varied. However, our results did not provide a simple answer to which site was the most NICU sensitive. Presumably, all three areas are appropriate sites for testing the NICU of NA and BA, and the severity of reaction might be different due to the anatomic percutaneous penetration pathways differences. An escalated application mass at each concentration would aid in identifying subtle differences. Previously,

Kligman (19) stated that the nature of the immediate reaction depended on the concentration: wheals were induced with the highest tested concentration, erythema with a five-fold dilution, and pruritus alone with a 25-fold dilution. However, in the current study, both urticants caused minimal skin sensation and conceivably higher urticant concentration might be more discriminating. Though the VAS data were small and varied these observations may help explain some aspects of the cutaneous intolerance in skin/hair care products. Standard clinical dogma suggests that face is more reactive than most body sites; examples have been summarized by Marrakchi (5,17). However, this study fails to support this widely accepted hypothesis. Perhaps men differ from women in this regard – or there may be multiple not yet disclosed reasons.

In conclusions, the skin reactions to urticants vary among the sites, but objective differences are small. Percutaneous penetration studies might help explain these observations, as these anatomic sites might have different diffusion pathways (20,21). Taken together, the discriminating (positive findings) suggested that: (i) both urticants caused minimal skin sensation

but there is no significant difference between sites with both urticants; (ii) 2.5% BA caused VS significantly higher on face than the back at 15 min post-application, but with 0.625% BA treated site, the VS of back was significantly higher than the face at 60 min post-application. The  $a^*$  value was significantly higher on the back than the scalp with 0.625% BA treatment at 30 min and 60 min post-application; (iii) with 0.25% HN treatment, the upper back VS significantly exceeded the scalp at all time points (15, 30, and 60 min) post-application and the back VS also showed significantly stronger reaction than the face at 60 min post-application. We cannot generate a simple hypotheses based on this data and encourage investigation into this relatively neglected, but clinically important arena, to help explain difference in consumer/patient acceptance of topical formulations applied to these anatomic sites. Further study should be suggested to help clarify some clinical and biologic points characterizing NICU and to discriminate between scalp and face and back. Refined dermatopharmacokinetic methods that aid in separating diffusion pathways may help explain the differences noted here.

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