Specific challenges in the evaluation of irritation and sensitization for transdermal systems: A dermatological appraisal focusing on scoring and application

Walter Wigger-Alberti
Dermal Tolerability of Transdermal Patches

Transdermal Patches
• once daily
• intact skin
• application site is to be rotated daily
• any application site should not be used more than once in 14 days

Irritant Contact Dermatitis by GM White. www.regionalderm.com

HR Na et al. Dement Neurocognitive Disord 2015;14:31-38

Locations of skin adverse events. A: Limited erythema. B: Extended erythema.
Cutaneous Safety Testing Irritation and Sensitization Potential

5 DAYS

SCORE

21 DAYS – 21 APPLICATIONS

SCORE

21 DAYS – 15 APPLICATIONS

Panel size $n = 30-35$
Induction: In the event of any significant response, the patch site is moved to a new naive site adjacent to the original site of application.
HRIPT Interpretation

For example, in the challenge phase if a subject shows scores of:

- 0,1,0,0
- 1,1,1,1
- 2,1,1,0
or similar, these would be indicative of an irritation response

If, for example they show:

- 3,2,2,2
- 1,2,2,3
- 2,2,2,2
or similar, these would be indicative of a sensitization type response

Higher values, and persistence or increase in scores suggest sensitization

McNamee, Api, Basketter et al. Regulatory Toxicology and Pharmacology 52 (2008) 24-34
Challenge Phase Irritant and Allergic Reactions
SCORING
Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)
Dermal response:
0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond test site

Other effects:
A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
F = glazing with fissures
G = film of dried serous exudate covering all or part of the patch site
H = small petechial erosions and/or scabs

A REAPPRAISAL OF THE 21-DAY CUMULATIVE IRRITATION TEST IN MAN

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ABSTRACT

The standard 21-day cumulative irritation test was reexamined to determine if it could be abbreviated in order to lessen costs and delays and simplify operations. The relative scores on 150 cosmetic-type products were compared at 14 and 21 days. In more than 90% of products studied, we found that we would have made the same decision regarding the level of irritation and the relative ranking of the products at either 14 or 21 days. This high correlation between scores at 14 or 21 days justifies using a 14-day test for many products and for product development comparisons.

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The Role of Human Patch Testing in a Product Development Program

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INTRODUCTION

Every dermatologist knows that there is nothing so variable and unpredictable in nature as man's reactivity to his environment. As difficult as it may be for the dermatologist to distinguish allergic responses from primary irritations, it is even more difficult for the manufacturer to make the distinction on the basis of his complaint file. By definition, allergic responses are less the responsibility of the latter, and it is to primary irritation that the following presentation is addressed. These reactions to virtually any topical preparation should be a continuing matter of concern to any responsible manufacturer. Dr. Albert M. Kligman put this problem into perspective in a talk delivered six years ago (1) in which he said:

"Experts are not required to tell us that A is worse than B when A is phenol and B is boric acid. The really practical need is to be able to discriminate among substances which are only mildly active to begin with, and then only for certain persons in certain circumstances. In the modern world of mass production, that is the difference which may decide whether a product is or is not merchandisable. Even if the usual incidence of irritation for a given product is quite low, say, 1 in 10,000 (0.01%), the manufacturer will be harassed by complaints if millions of units are to be sold. He will most certainly alter this product, or replace it with a new one, if he could know beforehand that the incidence would jump to 5 in 10,000. Even if he were prodigal with money, his statisticians would inform him of the futility of safety-

Phase I Cutaneous Safety Testing Irritation Potential
Symptoms of Irritation in Patch Testing with single application

Fig. 1. Kinetics of the development of individual reactions based on the irritation scores. Time points pertain to hours after patch removal. Mean scores for all tested surfactants are shown: red: erythema; blue: oedema; brown: scaling/fissure (error bars were omitted to increase clarity).

Alternatives for Scoring - Irritation

0 = no reaction
1 = minimal (barely perceptible) erythema
2 = mild but well defined erythema only
3 = moderate erythema only OR mild erythema plus edema and/or papules
4 = severe erythema only OR moderate erythema plus edema and/or papules
5 = severe erythema plus edema and/or papules OR any vesicular reaction
6 = bullous reaction or any grade 3 - 5 skin reactions that spread beyond the test field

### Table I. Irritation grading scale for exaggerated irritation patch study

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>No apparent cutaneous involvement</td>
</tr>
<tr>
<td>0.5</td>
<td>Faint, barely perceptible erythema or slight dryness (glazed appearance)</td>
</tr>
<tr>
<td>1.0</td>
<td>Faint but definite erythema, no eruptions or broken skin, or no erythema but definite dryness; may have epidermal fissuring</td>
</tr>
<tr>
<td>1.5</td>
<td>Well-defined erythema or faint erythema with definite dryness; may have epidermal fissuring</td>
</tr>
<tr>
<td>2.0</td>
<td>Moderate erythema; may have few papules or deep fissures, moderate to severe erythema in cracks</td>
</tr>
<tr>
<td>2.5</td>
<td>Moderate erythema with barely perceptible edema or severe erythema not involving significant portion of patch (halo effect around edges); may have few papules or moderate to severe erythema</td>
</tr>
<tr>
<td>3.0</td>
<td>Severe erythema (beet redness); may have generalized papules or moderate to severe erythema with slight edema (edges well defined by raising)</td>
</tr>
<tr>
<td>3.5</td>
<td>Moderate to severe erythema with moderate edema (confined to patch area) or moderate to severe erythema with isolated eschar formations or vesicles</td>
</tr>
<tr>
<td>4.0</td>
<td>Generalized vesicles or eschar formations or moderate to severe erythema and/or edema extending beyond area of patch</td>
</tr>
</tbody>
</table>

### Alternatives for Scoring - Sensitization

Skin irritation score for induction phase

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reaction</td>
<td>0</td>
</tr>
<tr>
<td>Slight uniform or spotty erythema</td>
<td>1</td>
</tr>
<tr>
<td>Sharply demarcated erythema</td>
<td>2</td>
</tr>
<tr>
<td>Severe erythema with infiltrate</td>
<td>3</td>
</tr>
<tr>
<td>Severe erythema with infiltrate and/or epidermal defect</td>
<td>4</td>
</tr>
</tbody>
</table>

Dermal reaction scores of skin sensitization used in Challenge Phase

<table>
<thead>
<tr>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reaction</td>
<td>0</td>
</tr>
<tr>
<td>Erythema, no infiltration</td>
<td>0.5</td>
</tr>
<tr>
<td>Erythema, infiltration, discrete papules</td>
<td>1</td>
</tr>
<tr>
<td>Erythema, infiltration, papules, vesicles</td>
<td>2</td>
</tr>
<tr>
<td>Erythema, infiltration, confluent vesicles</td>
<td>3</td>
</tr>
</tbody>
</table>

APPLICATION
Reaction on Test Plaster
Tape Stripping increases Allergic Reactions

Rotigotine Patch - Sensitization

Induction phase: 9 applications / 3 weeks

Figure 2.2: Skin Reaction during Challenge Phase: Rotigotine 1.125mg
(PPS N=202)
Rotigotine Patch - Irritation

Irritation: 21 applications / 3 weeks
Conclusions

- Recommended score and application scheme is not adequate for TDS
- Score has been developed for topical formulations, in fact cosmetics
- Leading symptom for irritation is an increasing erythema, for allergic reactions additional symptoms such as papules and oedema
- 21-day daily application of TDS causes false positive reactions and includes a higher risk for iatrogenic sensitization
Thank you for your attention

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