

Appendix E

APPENDIX E

Summary of Contact Urticaria (by Howard I. Maibach, MD)

Contact Urticaria (Immediate Type Hypersensitivity and Dermatitis)

Howard I. Maibach, MD

FDA Document (3)

Jerry S. Roth, President of Hill Dermaceuticals, Inc., requested that I summarize the dermatotoxicologic knowledge of contact urticaria to a chemical and contrast this with oral exposure.

The contact urticaria syndrome, presumably an ancient evolutionary development, codified approximately 25 years ago includes immunologic (ICU – immunologic contact urticaria) and NICU (non-immunologic contact urticaria).¹

In ICU, skin exposure can produce, in a dose and individual sensitivity-related manner, a spectrum from burn, sting, and itch, to wheal (urticaria) and erythema, as well as, with higher dose and greater individual sensitivity, extracutaneous organ manifestations, including allergic rhinitis, allergic conjunctivitis, angioedema, anaphylactoid response, and anaphylaxis.

The original publication referred to ICU to the insect repellent N-diethyl-m-toluamide (DEET). Subsequently, latex protein ICU has been the most frequently diagnosed etiology.

In all instances, the eliciting exposure can either be via the skin, or mucous membrane. (See below regarding exposure). The response is typically transient – developing in minutes and lasting less than several hours.

The algorithm for the diagnosis of contact urticaria includes:

1. Exposure history
2. Appropriate morphology (erythema and wheal)
3. Extracutaneous signs and symptoms, such as: allergic rhinitis, allergic conjunctivitis, angioedema, asthma, and anaphylaxis

Skin Testing

Skin testing (Dermal Route) consists of application to either normal skin, most prototypically on the forearm, or slightly damaged skin.^{2,3} There is significant regional variation so that testing on the forearm may be negative, but on the face positive⁴.

If the open test (non-invasive) is negative, the next step is a prick test – with appropriate virgin controls to ascertain the correct non-irritating concentration. Controls are not required for the open test – for in this instance, positive means contact urticaria and the only next step is differentiating between immunologic contact urticaria (ICU) such as with latex protein, and non-immunologic contact urticaria (NICU). A typical example of the latter would be cinnamic aldehyde and dimethylsulfoxide (DMSO).

Some contact urticants, of an immunologic nature (ICUs) elicit by oral and mucosal, as well as dermal exposure. A prototypical example of this consists of latex protein – skin or mucous membrane exposure, elicited by ingesting certain foods such as kiwi.

Taken together, the studies listed by Drs. Steve Taylor⁵ and John Yunginger⁶ in the briefing document, describe the dermatotoxicologic, dermatoimmunologic, and immunochemical investigations of the refined (proprietary) Hill Dermaceuticals' peanut oil, certified by batch to contain less than 2.5 ppm has been negative in prick and patch tests and has not led to reported immediate reactions.. The aforementioned studies, as well as those by Dr. BJ O'Hourihane,⁷ Dr. Amy Paller,⁸ Dr. Steven J. Simonte,⁹ Dr. C. Loza,¹⁰ Drs. Boch and Atkins,¹¹ and Drs. Sampson and Ho,¹² which were also referenced in the briefing package, included prick and patch testing.

Delayed Reactions

When the contact urticaria syndrome codification was proposed¹, it was believed to be immunologically straightforward (IgE mediated) and only of immediate onset.

Subsequent experience has demonstrated that repetitive exposures to certain immunologic contact urticants (a prototypical example being latex protein and certain foods) may lead to dermatitis. The original descriptions are those of Hjorth and Maibach³. In this clinical example, the patient had immediate sensitivity (positive immediate test(s) such as open testing and/or prick test) which lead to dermatitis. This has not been reported with the proprietary peanut oil (Ref) or with any other refined peanut oil. The pathophysiology involved in immediate type hypersensitivity (contact urticaria) producing (in minutes) dermatitis remains sub judice.

A more complete documentation of the literature on the Contact Urticaria Syndrome is found in Amin et. al.¹³

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