

Louise Arup Fischer Neergaard

Dose-response relationships in contact allergy and studies on single and repeated exposures – perspectives for prevention

Summary

Allergic contact dermatitis is an inflammatory skin disease triggered by direct skin contact with skin sensitizers in the home environment and/or at the work place. It is a prevalent disease that may have consequences for both the individual and society by requiring treatment and sick-leave and in some cases affecting ability to work. Allergic contact dermatitis is a preventable disease, as reducing or avoiding exposures to the allergens in question will reduce the incidence of individuals becoming sensitized as well as morbidity among those who have already become sensitized.

Experimental data from already sensitized persons can be used to determine safe levels of allergen exposure. Two main methods exist by which data can be generated about thresholds for contact allergic reactions. One is the patch test, which is an easy test to perform. The other is the repeated open application test (ROAT), which is time consuming but mimics some real life exposure situations. A link between the two test methods could be a valuable tool for use in preventive strategies. The aim of this thesis was to study the dose-response relationship for allergens with different physico-chemical properties in order to:

- examine if a relationship exists between the patch test and the ROAT results using both the dose per application of allergen and the total applied dose.
- examine if this relationship is independent of physico-chemical characteristics of the allergen.
- suggest a model for conversion of data from patch tests to ROATs.

Experimental studies were performed with three different allergens using identical methodology. A metal (nickel), a preservative (methylidibromo glutaronitrile, MDBGN) and a fragrance ingredient (hydroxyisohexyl 3-cyclohexene carboxaldehyde, HICC) was used. Test subjects were groups of eczema patients with contact allergy to one of the chosen allergens. A control group of individuals without allergies was included. A serial dilution patch test and ROAT was performed on the same allergic individuals simultaneously. Dose-response curves were drawn and the response to the different doses in the two test methods was compared statistically.

It was a consistent finding for all three allergens that more patients reacted to the allergen, measured as dose per application, when applied repeatedly (ROAT) as compared with the single, occluded exposure in the patch test. This means that a person can be reactive at a repeated open application in spite of a negative finding in the patch test to that dose. This is especially relevant in the context of testing with patients' own (cosmetic) products. When the doses applied everyday was added up in the ROAT to an accumulated one-week, two-week and three-week dose, it was found that in the nickel and MDBGN studies the dose-

response for the patch test and the dose-response for the accumulated doses in the ROAT was approximately the same.

In the HICC study the response to the accumulated ROAT dose was lower than the response to the corresponding dose in the patch test. An explanation of this could be evaporation of HICC from the skin, resulting in a lower accumulated dose over time in the open test, compared with the occluded test.

Based on the two studies with the non-volatile compounds (nickel and MDBGN) it was possible to develop an equation that characterized the relationship between the patch test and the ROAT; the results for the volatile substance HICC were probably influenced by evaporation. The knowledge of this relationship can be used as a tool when risk assessment is based on human elicitation patch test studies and thus as basis for preventive strategies.

In conclusion

- Allergic individuals react to lower doses (μg allergen/cm²/application) in the ROAT than in the patch test.
- The relationship between the two test methods was probably dependent on the physico-chemical characteristics of the allergen.
- A model for conversion of patch test dose-response into ROAT dose-response was suggested for non-volatile compounds.

Investigation of the accumulation of allergen in the skin upon repeated exposure, the immunological response to repeated exposure and the evaporation of volatile compounds from the skin would be interesting as future research subjects.