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Assessment of the Risk of Fragrance Allergy in the General Population

Challenges and Methodological Issues

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Abstract

There are still unanswered questions about the safety of fragrances. In this conference paper, fragrance allergy will be considered in the context of a wider discussion concerning the prevalence and causes of contact dermatitis.

No criteria for a reliable diagnosis of 'contact dermatitis' are available. International recommendations and standardization for the patch test method exist; however, the question of whether agents that are positive are causally linked to contact dermatitis remains fraught with uncertainties concerning false-positive rates and clinical relevance. Most of the discussion concerning prevalence or incidence variations of allergic contact dermatitis to fragrances concentrate on the frequency of positive patch tests in clinical series, i.e. 'floating numerators'.

Risk assessment requires that data from different sources are integrated and compared. Therefore, both a 'sentinel surveillance' system and more refined epidemiological studies in well defined populations are needed to reliably assess risks associated with fragrance exposure.

'Fragrances' are volatilized chemical compounds, generally at a very low concentration, which humans and other animals perceive by the sense of olfaction as a pleasant odour. The term 'perfume' (from the Latin 'per fumum', meaning through smoke, with reference to the distillation procedures used to extract fragrances from herbs, spices, etc.) is employed to indicate all those products that are characterized by mixtures of individual fragrance ingredients in combination with fixatives and solvents, used to give the human body, objects and living spaces a pleasant smell. Fragrances, similar to those found in perfumes, may be added to scented shampoos, scented deodorants and several other products, according to social and cultural factors. As with any other chemical substance, adverse reactions can follow repeated contacts with fragrances, ranging from a slight headache to anaphylactic shock. Most of the discussion dealing with the safety of fragrances concentrates on allergic contact dermatitis. In this conference paper, fragrance allergy will be considered in the context of a wider discussion concerning the prevalence and causes of contact dermatitis. Because the use of fragrances is widespread, any increase in risk of adverse reactions raises public health concern. Several relevant regulations concerning the use of fragrances in commercial products are contained within the European Union Cosmetics Directive 76/768/EEC (14), which has been amended more than 50 times.[1]

1. Frequency of Contact Dermatitis

The term 'contact dermatitis' identifies a skin reaction resulting from exposure to allergens (aller-

gic contact dermatitis) or irritants (irritant contact dermatitis). Photoallergic and phototoxic dermatitis occurs when the allergen or irritant is activated by sunlight. Many clinical variants of allergic contact dermatitis have been identified, the most common one being the eczematous pattern, characterized by a localized itchy skin rash, which usually appears 24–72 hours after exposure to the allergen in the sensitized person, frequently accompanied by blisters. Eczematous allergic contact dermatitis is a type IV delayed hypersensitivity reaction, sustained by T lymphocytes and immunoregulatory cytokines. Contact allergens are usually soluble haptens with low-molecular weight. They induce a response through association with epidermal proteins forming hapten-protein conjugates.

There are few, truly epidemiological studies of contact dermatitis in the general population and selected occupational groups.[2-4] Case definition varies from one study to another and few attempts have been made to distinguish between allergic and irritant contact dermatitis. In spite of the many limitations of the available studies, it can be estimated that contact dermatitis is a common disease involving 5–10% of the general population at any given timepoint. The risk is increased in selected occupational categories and could be as high as 40% among nurses. Clearly, any factor contributing to an increased rate of these reactions should be considered with great care, and efforts should be taken to decrease the overall risk.

One established means of documenting sensitization to topical allergens *in vivo* is the 'patch test' procedure. This involves the application, through properly developed supports, such as aluminium chambers, of tiny quantities of allergens diluted in suitable vehicles, such as petrolatum, to the skin. They are kept in place for at least 48 hours and a first reading is usually made at 72 hours by noting the appearance of a local reaction at the site of application. Sensitization does not necessarily translate into clinical symptoms. In clinical series based on patients referred to patch test clinics, the so-called 'patch test population', nickel sulfate, thimerosal, colophony, formaldehyde and fragrance mix, are among the most frequently reported allergens.[4]

2. Contact Allergy due to Fragrances

Most of the discussion concerning prevalence or incidence variations of allergy to fragrances concentrates on data obtained from the above-mentioned patch test populations. Since no reference can usually be made to an underlying at-risk population, these data can be considered as 'floating numerators', and can hardly be used to assess true prevalence or incidence rates either in the reference population or in patients with eczema.

It should be noted that fragrance allergy is usually first screened for by using a limited number of allergens combined together in the so-called 'fragrance-mix'. This mix is composed of only eight ingredients deemed to be representative of about 5000 recognized fragrance ingredients. A number of studies have assessed the correlation between positive reactions to fragrance-mix and to individual components. Overall, the data suggest that positive reactions to the fragrance-mix do not necessarily guarantee that one or more of its components will give reactions in subsequent or concomitant patch tests.

A few truly epidemiological studies are available concerning the prevalence of fragrance-mix sensitization in the general population.[5,6] These studies suggest that the prevalence of fragrance-mix positive reactions is about 1–3%. A study documented a prevalence of fragrance-mix sensitization among school children (14–15 years of age) of about 1.8% similar to the prevalence observed in the general population as a whole.[5] This observation would suggest that, in the absence of a strong period or cohort effect, fragrance sensitization may be acquired early in life, while clinical manifestations may represent a relatively late event. A study of contact dermatitis and fragrance allergy in the European population was started in 2005 by the European Dermatoepidemiology Network (EDEN), supported by the Research Institute for Fragrance Materials. It is expected that such a study will provide reliable data on the prevalence and clinical

relevance of contact sensitization to fragrances in the European population.[6]

3. Safety Issues and Surveillance Systems

There are similarities between the safety problems encountered with medications and with cosmetics. For example, for both medications and cosmetics, toxicological tests in animals do not *per se* rule out a potential for reactions in humans, and are usually employed as a preliminary screening procedure. The number of subjects exposed to drugs in the pre-marketing phase does not exceed a few thousand individuals, and they may not be fully representative of the final users (children and elderly people may be excluded as are individuals already exposed to other medications or products). So-called 'predictive tests' are envisaged by cosmetic companies as a way to assess the sensitization potential of contact products before commercialization. They are conducted on volunteers by such techniques as the Maximization Test and the Draize Repeat Insult Patch Test procedure. Similar to pre-marketing medication studies, the usual size of predictive tests does not exceed 2000–3000 people. Moreover, predictive tests are usually conducted on volunteers. It is quite plausible that people experiencing skin problems or contact allergy select themselves out of such a sample, according to a phenomenon which, in occupational medicine, is referred to as the 'healthy worker effect'. Predictive patch tests also provide estimates over a limited time span in standardized conditions. The exposure in a real-life situation may show a different pattern. It is quite plausible that predictive tests can only offer a conservative estimate of the sensitization rate in the general population and need to be supplemented by other factual evidence.

For both medications and cosmetics, risk assessment is not a simple process and requires that data from different sources are integrated and compared. In particular, post-marketing surveillance studies are needed to establish safety.[7] A 'sentinel surveillance' system and more refined epidemiological studies in well defined populations may be envisaged for both medications and cosmetics.

Sentinel surveillance systems should be able to raise early signals. They should be distinguished by their practicability, uniformity and rapidity rather than by complete accuracy. Their main purpose is to detect changes in trend or distribution of an adverse event to initiate further investigations.

A well known example of a sentinel surveillance programme is the surveillance of adverse reactions to drugs, which involves the voluntary reporting of adverse reactions observed by physicians and other people (spontaneous surveillance) to a central agency. Because they lack appropriate denominators, these programmes are not usually suited to incidence rate calculation. They are most effective with revealing unusual or rare adverse events. They do not reliably detect adverse reactions that represent an increased risk of an adverse event that occurs commonly in populations not exposed to the drug. This may be the case for contact dermatitis to cosmetics, especially when the diagnosis is based on consumers' complaints.

A well known problem with spontaneous surveillance is under-reporting. The proportion of reactions to drugs that are not reported by physicians may be as high as 90%. An even higher proportion of under-reporting is expected for reactions to cosmetics when reported by consumers in the lack of external sustained stimuli. Compared with consumers' complaints, data from nation-wide networks of dermatological centres, e.g. patch test clinics, seem to offer the advantages of standardized clinical assessment and systematic registration and may better function as a 'sentinel system'.[8] Numbers of well defined cases of contact allergy to specific products rather than vaguely defined sensitization rates should be better reported from such a 'patch test population'. Explicit criteria for testing and reliable criteria for diagnosing allergic contact dermatitis to specific allergens are also required. Warning could be triggered by taking into account estimated exposure rates to specific products in the population, and proportional rates of reactions observed in the patch test population.[9] Evaluation according to anatomi-

cal site, modalities of exposure, pattern of reaction, and disease severity and course can be made.[10]

As is the case for drugs, formal epidemiological studies may be needed to validate signals with reference to the safety of fragrances. The starting point may be represented by the exposure to fragrance-containing products (i.e. the risk factor) or clinical manifestations of contact allergy (i.e. the final event). Fragrance sensitization is an intermediate indicator that may either be considered as a risk factor for clinical manifestations or an event that follows exposure to fragrance-containing products.

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