

Compound allergy

An overview

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This review defines the term "compound allergy" in the context of new findings, and discusses evidence that allergenic reaction products have been identified. Material was gathered by searching Index Medicus and the Science Citation Index, and reviewing several standard texts. Issues regarding the validity of patch test results are addressed and we introduce the term "pseudocompound allergy" to cover cases of false-negative patch tests. We present new theories regarding the mechanisms by which new allergens are formed and a means of classification.

Key words: compound allergy; allergic contact dermatitis; pseudocompound allergy; patch test; essential allergen; allergenic reaction; synergistic allergy. © Munksgaard, 1997.

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Definition

Compound allergy is an allergic contact dermatitis in which a preparation is believed to be allergenic on patch testing, whilst its individual ingredients show a negative patch test result. Some or all of those ingredients must have interacted to form a new allergen (Table 1).

Introduction

Compound allergies, first suggested in an allergy to a cosmetic by Calnan (1), are usually identified in allergic reactions to cosmetics or pharmaceutical preparations (Table 2). The ingredients of these allergenic compounds are often supplied by the manufacturers for patch testing. In cases of conventional allergic contact dermatitis, the ingredients of a product known to be allergenic are patch tested individually to identify the allergen(s).

The patient may then be advised to avoid products containing that allergen to avoid further exacerbations of their dermatitis. In the case of compound allergy, however, no ingredient is found to be an allergen on patch testing. The dermatologist can only conclude, after carefully patch testing the

Table 1. Definition of compound allergy

Patch test	Result
entire product	+
irritant controls (at least 20)	-
individual ingredients	-
new chemical formed in mixture	+

Table 2. Compound allergens

1. Proven compound allergens^{a)}

Hirudoid® cream (6, 9)
Daktarin® cream (3)
cutting oil (4)
ethylantraquinone (5)
Elics® eyedrops (10)

Possible compound allergens^{b)}

Zovirax® cream (11)
Spectroban® 15 lotion (9, 11)
patch testing marker (8)
Aureomycin® cream (9)
Ultracool® (9)
Boots E45® (9)
Colgate® toothpaste (9)
Haelan® cream (9)
cosmetic foundation cream (1)
Sepso® (12)
budonide (13)
Steri-lette® (14)

^{a)} Products contain identifiable new allergens or known allergenic combinations of ingredients

^{b)} New allergen not identified or sought.

ingredients, that there must be a new product formed within the preparation which is causing the allergy. The patient is none the wiser and can only be advised to avoid that particular product. A more depressing scenario would be the case of an allergic contact dermatitis of unknown etiology, in which case some unknown substances may have interacted to form an unknown allergen which would be almost impossible to identify.

With such implications for the patients' quality of life, the concept of compound allergy must be fully explored and its importance in clinical practice established. Evidence that the constituents of a preparation can interact to form a new allergen is discussed here. Several researchers provide strong evidence that a combination of ingredients is required to produce an allergen, and teams have isolated allergenic reaction products. In addition, the debate regarding the validity of the entire concept of compound allergy is addressed and theories regarding possible mechanisms are presented.

Diagnosis

The clinical features of a compound allergy are those of allergic contact dermatitis.

Diagnosis of a compound allergy requires the fulfillment of certain criteria:

- the reaction must be allergic and not irritant
- the patch tests for the constituents of the preparation must be negative
- the whole preparation must give a positive reaction on patch testing
- all the ingredients must be known and tested
- vehicle dependent contact allergy (2) must be excluded (the correct vehicle must be used and the individual ingredients must be present in sufficient concentration to produce a reaction).

Can an Interaction Produce an Allergen?

Several papers provide strong evidence that the ingredients of a preparation must interact with each other for that preparation to become allergenic. Aldridge & Main (3) demonstrated the necessity for particular ingredients of Dakta-cort® (2% miconazole nitrate/1% hydrocortisone) cream to be present together for an allergic response to take place. They report 2 patients in whom a compound allergy to Dakta-cort® was diagnosed on the basis that patch testing the individual constituents of the drug showed negative results, whilst the full preparation was allergenic. Having identified that Dak-tarin® (2% miconazole nitrate) differs from Dakta-cort® only by 2 ingredients, hydrocortisone and ethylenediamine tetraacetate (EDTA), they tested the patients with Daktarin® alone and obtained a

negative patch test result. However, when hydrocortisone and EDTA were added to Daktarin®, an allergic response was seen. Neither hydrocortisone nor EDTA, alone or in combination, together produced a positive reaction. This demonstrates that the combination of the 3 ingredients, i.e. miconazole nitrate, hydrocortisone and EDTA, is required to produce a compound allergy. As alone they are non-allergenic, there must be an interaction between these substances to make them so.

Logically, the next step would be to elucidate the putative reaction product and demonstrate its allergenicity. 3 authors have been able to demonstrate the existence of an allergenic reaction product. Shrank (4) describes a patient with an occupationally related allergic contact dermatitis. The allergenic preparation was an industrial cutting oil, but the ingredients supplied by the manufacturer were not found to be allergenic by patch testing using an appropriate vehicle. A diagnosis of compound allergy was made. As the cutting oil was manufactured in 5 stages, it was possible to determine that the allergen was formed in the first stage, which consisted only of mixing triethanolamine and caprylic acid. This resulted in the formation of triethanolamine caprylate, which is a water-soluble amine soap, believed to be allergenic. This case of compound allergy demonstrates direct evidence of the formation of an allergenic reaction product when non-allergenic ingredients are combined.

High-performance liquid chromatography can be used to extract allergenic derivatives from industrial working solutions (5). 2 patients who patch tested negatively to the ingredients were found to be allergic to TEEQ, a derivative of ethyl-anthraquinone, which had formed in the solution. Of the 30 controls who patch tested negatively, one developed late reactions at 3 weeks, suggesting that TEEQ is strongly allergenic.

Smeenk et al. (6) use a sophisticated process of nuclear magnetic resonance (NMR) and infra-red (IR) spectroscopy to isolate a reaction product and prove its allergenicity, when investigating contact allergy to Hirudoid® cream. This preparation had been previously shown to contain a contact allergen which has been removed by the manufacturers (7). Despite this, patients continued to present with allergic reactions which Smeenk et al. (6) diagnosed as a compound allergy. 2 ingredients, 1,3,5-trihydroxyethyl-hexahydrotriazine (THT) and thymol, had to be present simultaneously for a positive reaction to occur. As a chemical reaction between THT and thymol was thought to be unlikely, patients were patch tested with the combination of the degradation products of THT with thymol. A positive reaction was found when both the degradation products (formaldehyde and ethanolamine)

were present together with thymol. Using NMR and IR spectroscopy, the reaction product was identified (a benzoxazine derivative) and was found to be allergenic when the patients were patch tested. In non-allergic control subjects, the result was negative.

The above studies demonstrate strong evidence that an allergy-inducing reaction product can be found in cases of compound allergy. It has been clearly shown that specific products must be simultaneously present for an allergy to occur. However, Cox et al. (8), despite a comprehensive study of a compound allergy to a skin marker used in patch testing, failed to identify a reaction product by thin layer chromatography or gas liquid chromatography. Despite this, the authors are confident of their diagnosis of compound allergy. One must question where the site of the interaction between the products is. Rather than a chemical reaction in the preparation, it may be within the skin itself, perhaps a result of protein binding, or the reaction may be at the cellular level, perhaps a result of altered antigen processing or T-cell responses.

Compound Allergy and Patch Testing

Current debate on this topic centers on whether there is an interaction within a preparation to form a new allergen, or whether there is merely a deficiency in the patch test. Rietschel (2) argues that the appearance of a compound allergy is due to the vehicle employed in the patch test failing to deliver an adequate concentration of a proposed allergen to the stratum corneum in the lipid phase. As a result, a negative result is obtained. For example, dimethylsulfoxide (DMSO) has been reported to increase the penetration of allergens; patch testing without DMSO may produce erroneously negative results (15). Should the original preparation itself be a better vehicle for the adsorption of the unaltered allergenic molecule than the patch testing vehicle, a negative test would falsely imply that the substance was non-allergenic. This could be taken to indicate that there had been an interaction where there had in fact been none. Rietschel terms this pharmacodynamic phenomenon "vehicle dependent contact allergy". Details of vehicle effects on elicitation of allergic contact dermatitis are provided by Tanglertsampan & Maibach (16). We propose an alternative term, *pseudocompound allergy*, – to cover this and other mechanisms of false-negative patch tests.

Similarly, a sufficient concentration of the allergen must be used in the patch test, enabling a sufficient dose to penetrate the skin to elicit an allergy. If the concentration used is incorrect, then a false-negative result will be obtained, resulting in the

misdiagnosis of a compound allergy (i.e., pseudocompound allergy). For example, patch testing with neomycin is usually performed at 20% pet., whereas the concentration in many preparations is 0.5%. Patch testing at the lower dose will lead to a false-negative result (17).

However despite these arguments, there is evidence to demonstrate the presence of a new allergen in some cases. The studies reviewed above show the formation of a new reaction product as the compound allergen. Cox et al. (8) refute the suggestion that the compound allergies they report could be the result of a greater absorption of an allergen than their patch test model. They used a dose 12× that in the original preparation and obtained negative patch test results. They believe that it is unlikely that enhanced absorption would result in the delivery of such a high dose, and thus reaffirm the result as negative. Kellett et al. (9) reported 7 cases of compound allergy, despite determining the best vehicle and concentration for patch testing. They employed standard references and their judgment, based on the solubility of the ingredient and its concentration in the medication. Corrazza et al. (13) report a compound allergy to budenoside, in which case they patch tested at 0.026%, 1% and 2% pet. This was on the basis that 0.005% had previously been shown to be sufficient to produce a positive result (18). Therefore, their 1st test dose should have been sufficient to produce a reaction, and yet low enough a dose to avoid immunosuppression of an allergy. However, the patch tests were negative, even at the higher doses. Petrolatum had previously been demonstrated to be a good vehicle for budenoside. (19) so it appears that this compound allergy was diagnosed on solid patch testing data.

In summary, several authors who have been mindful of the problems of patch testing have documented cases of compound allergy. It is unlikely that compound allergy can be explained by erroneous patch testing in these studies.

Confusion in Diagnosis

Irritant or allergic contact dermatitis?

In the correct diagnosis of compound allergy, an irritant contact dermatitis must be excluded. As it is occasionally difficult to distinguish between an irritant and an allergic reaction, it is possible to argue that a compound allergy may be a misdiagnosed irritant contact dermatitis. However, some studies have excluded this explanation either by careful clinical diagnosis or by exposing control subjects to the proposed allergen and looking for an irritant reaction. For example, Cox et al. (8) rule out the possibility of irritant contact derma-

titis from gentian violet dye (used in patch testing as a skin marker), as it is known to produce ulcerative lesions when an irritant, and eczematous lesions when an allergen (20). Also, the combined dye containing the gentian violet had been exposed to thousands of their patch test patients as unwitting controls. None of them had ever shown an irritant reaction. Kellett et al. (9) report 7 cases of compound allergy, testing each of the preparations involved on at least 25 controls. They only found 1 product, a toothpaste, to be irritant in the control group. However, the patient undertook a daily use test for 1 week and the result was a marked perioral allergic reaction, suggesting that in this case the toothpaste was allergenic rather than irritant.

Excited skin syndrome or angry back

It may be argued that the patch tests are positive because the skin is in a state of hyperreactivity termed excited skin syndrome or "angry back" (21). This may lead to strong positive reactions to patch tests of minor irritants or subclinical or weak allergens. Authors who report compound allergy, such as Cox et al. (8) or Kellett et al. (9), have eliminated this as far as possible by repeating the patch tests 2 months later and obtaining another positive result.

Chemical Contaminants and Unknown Ingredients

Another point of contention is whether all the ingredients of a preparation have been patch tested. Although almost all the studies obtained samples of the ingredients used in patch testing from manufacturers, one can argue the possibility that the manufacturers themselves do not know the exact ingredients. To take this matter into consideration, Cox et al. (8), Smeenk et al. (6) and Aldridge & Main (3) made up mixtures of the allergenic preparation in their own pharmacies, to compare the response to the original. All found positive results using the preparation that they had made. Therefore, in these cases, the allergen cannot be an unknown contaminant or ingredient that was not supplied in the manufacturer's data.

Bacterial Contamination

Cox et al. (8) ruled out the possibility of bacterial contamination causing a false-positive result. They performed microbiological investigations to detect bacterial and fungal colonization of the original marker solution, and were also able to produce an allergenic response to a mixture that they had freshly made.

Theories

The authors above have shown the need for particular ingredients to be simultaneously present, demonstrated the formation of allergenic reaction products, ruled out accidental contamination and reproduced the allergic reaction with their own pharmacy's preparations. It seems that these are indeed cases of compound allergy, the mechanisms of which must now be considered.

Site of the reaction

The first matter to consider is the site of the allergen-producing reaction (*allergenic reaction*). In the 2 studies above in which the compound allergen has been identified, the site of the reaction has been within the preparation. Therefore, a *chemical allergenic reaction* has occurred, which is distinct from a *biological allergenic reaction*. That is to say that in the former there is no biological involvement from the patient, whilst in the latter there may theoretically be.

Chemical allergenic reactions

These may be subdivided into 2 broad categories. Firstly, we will consider reactions in which the formation of an allergen is the inevitable result of the ingredients being included in the mixture, forming *essential allergens*. This is distinct from a 2nd scenario in which environmental conditions dictate whether or not the allergen is formed. For example, a cosmetic may be left lying in direct sunlight for a long period of time. This avoidable event may have catalyzed the formation of an *incidental allergen*.

The presence of an essential allergen in a product leads to the exposure of all its users to that allergen. It is impossible to predict what proportion of the exposed population will suffer an allergic reaction: perhaps only a small group of people will be affected, as their immunological constitution favors a T-cell response to that molecule. On the other hand, many may be sensitized following chronic exposure. The implications of this on product licensing may be profound, forcing manufacturers to change the ingredients of their product.

However, if a particular environmental situation resulted in the formation of an incidental allergen, it may be possible for a patient to continue to use that product, whilst observing reasonable storage instructions. For example, products may need to be refrigerated or have a finite shelf-life. In an occupational setting, changing the way certain chemicals are stored or handled may allow a patient to keep his or her job.

Biological allergenic reactions

It may be that the allergen is produced metabolically rather than as the result of an external chemical reaction. In this scenario, human metabolic processes theoretically combine the ingredients of a preparation to form a molecule which stimulates T-lymphocytic activity. A variety of mechanisms may act singly or in combination to bring this process about. For example, the ingredients of a product may undergo a conformational change if bound to proteins or inorganic molecules such as phosphates or calcium ions. This conformational change may serve to catalyze an allergen-producing reaction between the necessary molecules. Alternatively, enzymes may catalyze a reaction by cleaving the molecules, allowing them to bind more favorably with each other than their parent molecules.

Cellular processes may also be implicated in the formation of an allergen. Within the antigen-presenting cells themselves, there may be interaction between molecules, either before they are expressed on the cell surface, or even at the cell surface. Whatever the process may be, the compound allergen is presented to a T-lymphocyte, which is stimulated to differentiate, resulting in an allergic response.

Conclusion

Previous work has shown patients to be allergic to a new reaction product formed within a preparation to which they are allergic. Meanwhile, other studies have demonstrated the need for reaction ingredients to be present together before the preparation can be allergenic. However, difficulties in diagnosing a compound allergy do exist. In each individual case presenting as a compound allergen, the issue of dosing and vehicle selection remains a gray area, which researchers must overcome. Each individual constituent must be patch tested in all possible combinations in order to determine which ingredients are reacting together. Further, the reaction product should be identified, if possible. If it cannot be found, a compound allergy may still be diagnosed as the allergen may be made within the skin itself. In future, adding these products to epidermal cultures may help to identify newly formed chemicals.

Several authors have provided valuable insights into the issue of compound allergy, opening new avenues of investigation. Contact dermatitis is a prominent problem, and, as more compound allergens undoubtedly remain to be reported, much investigation is necessary.

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