

Crossreactions In Contact Dermatitis

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Introduction

Allergic contact dermatitis is a classic delayed hypersensitivity-type reaction. By definition, this type-IV immunologic reaction is a prototypic T-cell-mediated cutaneous inflammatory response that mediated by antigen-specific T lymphocytes. Physiopathologic mechanisms of allergic contact dermatitis are complex. During the induction phase, when a substance—the sensitizing agent—that is of low mol wt and by itself nonimmunogenic (referred to as a “hapten”) is applied to the skin, it binds covalently to skin macromolecules to form a hapten-carrier complex that finally acts as an immunogen (antigen). This causes proliferation of T cells bearing antigen-specific receptors on their surface (1–3).

During the subsequent elicitation stage—resulting in contact dermatitis reaction—the factors that control recognition of the immunogen molecule by the T-cell receptors are primarily the chemical nature of the triggering agent and the compatibility of its spatial geometry with that of the receptors on the surface of intradermal T cells. These receptor molecules are highly sensitive to the volume and shape of hapten-carrier determinants. Therefore, the triggering agent must have a similar size and spatial geometry to be recognized by the corresponding receptor. Thus, a substance containing a chemical group that is similar to that of the sensitizing agent may also elicit a contact dermatitis reaction, if its spatial geometry sufficiently resembles that of the triggering agent. In this case, we have a crossreaction, also referred to as a crossallergy. However, we insist that the term “crossallergy” be restricted to well-defined cases that can be identified as being true crossreactions.

A true crossallergy between a sensitizer A and a triggering agent B can occur in various ways:

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1. A and B are chemically and structurally similar haptens.
2. A is metabolized to a hapten that is similar to B.
3. B is metabolized to a hapten that is similar to A.
4. A and B are metabolized to similar haptens.

Crossallergies are sometimes not recognized because of the diversity of allergenic exposures and the different names (synonyms) that a molecule may have. As one example, mercaptobenzothiazole, which is used as an accelerator in the rubber industry, is also contained in anti-freeze, anticorrosive agents, detergents, and fungicides, and can be present under a variety of names such as MBT, 2-Benzathiazaethiol, Captax, Dermacid, Mertax, Thiotax, Nocceler M, and Rotax. Another example is Thiuram. The most common sources leading to the development of sensitivity are rubber gloves and shoes. However, thiuram is also used in agricultural products such as disinfectants, germicides, insecticides, as well as cosmetics, soaps, and shampoos. Administration of disulfiram (Antabuse), a thiuram derivative used in the treatment of alcoholics, may cause also a generalized systemic contact dermatitis in thiuram-sensitive patients (4,5).

Certain other apparent crossallergies are probably not true cross-reactions. When the presumably crossreacting substance is contained in a mixture that also happens to contain the sensitizer, the reaction is most likely directed at the original sensitizer and not to a chemically different substance. For example, a patch test reaction to cinnamic acid in a patient who also reacts to balsam of Peru when tested with the fragrance mix patch test battery is probably due to a cinnamic compound present in balsam of Peru rather than to a true crossreaction between the two substances. Another category of false crossallergy is concomitant multiple sensitizations, otherwise known as polysensitization. For example, it is not unusual to encounter an individual who has been exposed to a number of different substances and who has developed sensitization to two or more that are apparently unrelated. This could be owing to the fact that the metabolism of one of these substances has produced a metabolite similar in structure to the original sensitizing substance (*see example 3 above*).

Clinically, contact dermatitis normally develops 24–48 h after re-exposure of the sensitive individual to the allergen. Typically, the lesion is an eczematous dermatitis that is limited to the area of the skin exposed to the allergen. The distribution of the lesion(s) often helps in identifying the sensitizer: a classic example is dermatitis on the eyelids caused by exposure to nail polish (toluene sulfonamide).

There is an extensive literature on crossreactions that produce contact dermatitis, especially those involving drugs. Here we will review some examples that may be of particular interest to non-dermatologists.

Antibiotics

The penicillins are the antibiotics that most frequently induce contact sensitivity. This is an important occupational dermatitis affecting nurses and people working in the pharmaceutical industry. There are reports of simultaneous allergy to penicillin and cephalosporin, presumably owing to the presence of the β -lactam ring, the common antigenic nucleus in these two substances. However, in some other cases, the contact allergy is caused only by a third generation cephalosporin without any reaction to penicillin or to first- or second-generation cephalosporins (6–8).

Neomycin is the topical antibiotic most widely used in North America and Europe. For example, in France, more than 30 preparations used by dermatologists, ophthalmologists, and ENT specialists contain neomycin, and it is frequently combined with others antibacterial agents and/or corticosteroids (4,5).

Cross-sensitivity has been reported to occur among other antibiotics belonging to the aminoglycoside family, including gentamycin, kanamycin, streptomycin, pectinomycin, tobramycin, paromomycin, and butyrosin.

Antimycotic Agents

Introduced in 1969, imidazole derivatives have become the most widely used antifungal agents in medicine. The first report of contact dermatitis to imidazole appeared in 1974. The imidazole derivatives most frequently reported to be allergenic are miconazole, econazole, tioconazole, and isoconazole. Crossreactions are frequent but not constant (about 50%) (9–12). Using patch tests, Doooms-Coossens et al. (28) found a statistically significant association between miconazole, econazole and isoconazole, sulconazole, miconazole, and econazole, and also between isoconazole and tioconazole (Table 1). The common structure between tioconazole and isoconazole, 2(2,4-dichlorophenyl)-ethyl imidazole, would appear to be the antigenic determinant, but other cross-sensitizations cannot be totally explained by the chemical structure of the imidazole derivatives. This fact means that more stereochemical studies are necessary to understand these cross-sensitizations (13–16).

Benzocaine

Benzocaine is a local anesthetic that is incorporated into a myriad of topical agents marketed for relief of pain and itching. Benzocaine is also a member of the benzoic acid group. For this reason, benzocaine can exhibit crossreactivity to other benzoic acid derivatives, such as the esters of *p*-aminobenzoic acid, *m*-aminobenzoic acid, or benzoic acid

Table 1
Local Anesthetics that Crossreact with Benzocaine

Common name	Synonyms
<i>p</i> -Aminobenzoic acid esters	
Benzocaine	Americaine Anesthesin Anesthane
Procaine	Novocaine
Tetracaine	Pontocaine
Butacaine	Butelline
<i>m</i> -Aminobenzoic acid esters	
Metabuthamine	Unacaine
Proparacaine	Alcaine
Benzoic acid esters	
Amylocaine	Stovaine
Metabutozycaine	Primacaine

Table 2
Local Anesthetics
that Do Not React with Benzocaine

Chemical	Common name
Lignocaine or lidocaine	Xylocaine Xylestesine Pressicaine Xylonor Pradicaine Ziacaine Spartocaine
Mepivacaine	Scandicaine Carbocaine
Prilocaine	Citanest
Bupivacaine	Marcaine
Etidocaine	Duranest
Peracaine	Peracaine Nupercaine
Articaine	Alphacaine

esters (Table 1) (4,5). In addition to crossreactivity within the benzoic acid-derivative groups, patients who are sensitized to benzocaine may develop allergic reactions with procainamide, sulfonamides, *p*-aminosalicylic acid (PAS), *p*-phenylenediamine hydrochloride, hydrochlorothiazide diuretics, sulfonylurea oral hypoglycemics, and azo dyes. On the other hand, persons sensitive to benzocaine usually tolerate chemically unrelated local anesthetics agents such as anilide or amide derivatives with no allergic manifestations (Table 2) (17–19).

Table 3
Classification of Clinical
Crossreactions Between Topical
Corticosteroids^a

Group A
Hydrocortisone
Tixocortol pivalate
Prednisolone
Prednisone
Methylprednisolone
Meprednisone
Group B
Triamcinolone acetonide
Amcinonide
Budesonide
Desonide
Group C
Betamethasone
Dexamethasone
Group D
Hydrocortisone-17-butyrate
Clobetasone-17-butyrate
Prednicarbate
Betamethasone-17-valerate
Alclometasone-17-propionate

^aData from ref. 21.

Corticosteroids

Most corticosteroid-allergic patients react to several types of corticosteroids (20). The existence of crossreactivity is confirmed by the occurrence of allergic reactions to substances to which the patient has never been exposed. Reviewing the observations reported in the literature, Coopman et al. distinguished four crossreacting groups of corticosteroids (Table 3) (21). Lepoittevin et al. (22) proposed a different classification, based on a statistical and structural analysis of these drugs. In their analysis, groups A, B, and D were confirmed as different on the basis of the different shape of their substituents at the C 17 position. They also confirmed that contact allergies caused by tixocortol pivalate and hydrocortisone are definitely associated, and reactions to budesonide are strongly correlated with the reactions to compounds in both the acetonide group (Group B) and the ester group (Group D). More recently, Wilkinson et al. (23–25) reported that patients hypersensitive to topical budesonide are more likely to react to other non-C6- and non-C9-substituted corticosteroids (for example, tixocortol pivalate and hydrocortisone butyrate).

Ethylenediamine Dihydrochloride

Ethylenediamine is a colorless alkaline caustic liquid used in many topical creams, especially in dermatologic preparations. In addition to this pharmacological application, ethylenediamine has numerous uses in industry (4,26,27). Crossreactions between ethylenediamine and similar aliphatic polyamines such as diethylenetriamine, triethylenetetramine, tetraethylenepentamine, diethylenediamine are frequent. It should now be well-known that treatment of ethylenediamine-sensitive asthmatics with aminophyllin is contraindicated, since this drug is a combination of theophylline and ethylenediamine. However, crossreactions between topical ethylenediamine and ethylenediamine-related oral antihistamines such as cyclizine, chlorcyclizine, buclizine, or meclizine seem rare. Finally, there are no reports of crossreactions between ethylenediamine and *p*-phenylenediamine, which is used in permanent hair coloring.

Nonsteroidal Anti-inflammatory Drugs Exclusive of Aspirin

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in rheumatology and orthopedics, and they are also sold over the counter. The first report of allergic contact dermatitis to an NSAID appeared about 20 yr ago (28). The topical NSAIDs may induce allergic contact dermatitis as well as photoallergic and phototoxic contact dermatitis (29–31). In most cases, sensitization is to a single agent. Some authors have reported photoallergic contact dermatitis owing to previous systemic administration of NSAIDs (32–34).

NSAIDs can be divided into several groups, according to their chemical structure (Table 4). Crossreactions occur between drugs in the same group. Those most frequently reported are the propionic acid derivatives, and the pair most frequently involved is ketoprofen and ibuprofen (35–37). There are no reports of crossreactions between drugs of different groups (Table 5).

Textile Dyes

Perhaps textile dye dermatitis illustrates best the wide range of crossreactivities that may occur due to the large number of related substances. Reports of multiple azo dye sensitivities suggest that all of them may be crossreactive (38–41). On the basis of the chemical similarity of the azo dyes, they were classified into the following four groups: aminoazobenzene, Paraphenylenediamine (PPD), benzothiazol-azo-PPD, and thiazolazo-PPD.

In the thiazol-azo-PPD group, Disperse Blue 106 and Disperse Blue 124 are the most frequently reported textile dye sensitizers.

Table 4
Classification of Crossreactions
Between Topical Nonsteroidal
Anti-inflammatory Drugs

Pyrazolone derivative
Phenybutazone
Ixyphenbutazone
Antipyrine
Indomethacin and sulindac
Indomethacin
Benzydamine
Fenamate
Bufexamac
Diclofenac
Etofenamic acid
Propionic acid derivative
Ibuprofen
Ibuproxam
Ketoprofen
Suprofen
Tiaprofenic acid
Oxicam
Piroxicam

Table 5
Crossreacting Topical
Nonsteroidal Anti-inflammatory Drugs

Drug	Crossreacts With
Pyrazolone derivative	
Oxyphenbutazone	Phenybutazone
Propionic acid derivatives	
Ibuprofen	Ibuproxam
Ibuproxam ^a	Ketoprofen ^a
Ketoprofen ^a	Ibupro xam ^a
	Atrosilene gel
	Ibuprofen
	Flurbiprofen
Tiaprofenic acid	Flurbiprofen
Suprofen	Tiaprofemc acid
Piroxicam	Thimerosal

^aMost frequently occurring crossreaction.

Crossreactivity between them is not surprising as they are closely related chemically, their only difference being the presence or absence of an acetate group (42,43). Considering the structure–activity aspect of thiazol-azoyl-PPD derivatives in general, it appears that, on cleavage

at the azo bridge, these dyes can be degraded into a nitro-thiazol derivative and a PPD derivative. Nevertheless, crossreactions between PPD and Disperse Blue dyes are not inevitable.

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