

Allergic Contact Dermatitis From Topical Drugs: An Overview

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Abstract: Allergic contact dermatitis from topical drugs is frequent and is seen in 10% to 17% of patients patch tested for suspected contact dermatitis. More than 360 drugs have been implicated as contact allergens, of which—generally—antibiotics, corticosteroids, local anesthetics, and nonsteroidal anti-inflammatory drugs are the most frequent culprits. This article provides an overview of allergic contact dermatitis to topical drugs, discussing their prevalence of sensitization, predisposing factors, clinical manifestations (both typical and atypical), the drugs described as allergens, cross-reactivity and coreactivity, and diagnostic procedures.

Topical pharmaceuticals are applied in various forms to the skin (eg, cream, lotion, ointment, solution, foam, and suspension) or to the mucous membranes of the eyes, nose, mouth, vulva, vagina, penis, and anus (eg, eye drops, nose drops, ointment, cream, solution, gargle, suppository, and vaginal suppository) to treat a variety of skin and mucous membrane diseases. Frequently used topical drugs are corticosteroids (CSs), antibiotics, antifungal agents, and anesthetics, either as monotherapy or in combination preparations. The use of topical pharmaceuticals can lead to a variety of local adverse effects including itching, burning, irritant contact dermatitis, sensitization, and allergic contact dermatitis and—far less frequently—phototoxicity, photoallergic contact dermatitis, and immediate-type reactions such as (contact) urticaria or anaphylaxis. Misuse of topical CSs can result in acneiform and rosacea-like eruptions, skin atrophy and striae, and various other local adverse effects. The fact that topical drugs are by definition applied to nonintact or nonhealthy skin, often with a compromised barrier, favors the development of adverse reactions.

Whereas most adverse effects affect the skin or mucous membranes where the topical drugs are applied, systemic adverse effects from transcutaneous or transmucosal absorption may also occur. Such effects from CSs have been well known since soon after their introduction in the beginning of the 1950s. Absorption was facilitated by long-term application to large areas of inflamed skin such as in atopic dermatitis in children. Treatment with salicylic acid-containing topical

drugs led to intoxication (“salicylism”) in many children.¹ Also, drugs applied in the eyes, the nose, or the deeper airways by inhalation are very rapidly absorbed into the bloodstream and may reach levels that are able to induce serious systemic adverse effects.

Contact allergy/allergic contact dermatitis is the adverse effect of topical drugs most frequently observed by dermatologists and reported in the literature and is, together with photocontact allergy, the subject of this article. A full literature review of (photo)contact allergy to topical drugs (and nonactive ingredients therein) by the author was recently published in volume 3 of the book series *Mono-graphs in Contact Allergy*.²

ALLERGIC CONTACT DERMATITIS FROM TOPICAL DRUGS

Prevalence

There is little information on the prevalence of sensitization to (individual) topical drugs in the general population. In a 2008–2011 cross-sectional study, in which a random sample of 3119 individuals from the general population aged 18–74 years from 5 different European countries (Sweden, the Netherlands, Germany, Italy, and Portugal) was patch tested, the prevalence of sensitization to 6 (mixtures of) topical drugs (caine mix, neomycin, quinoline mix, budesonide, hydrocortisone butyrate, and tixocortol pivalate) ranged from 0.2% to 0.4%. The frequencies in men ranged from 0.1% (quinoline mix) to 0.6% (budesonide and hydrocortisone butyrate) and in women from 0.2% (quinoline mix) to 0.6% (caine mix).³ It should be realized that the results were read only once, at day 3. Because reactions to neomycin and the CSs often start after day 3, it is quite certain that a number of sensitizations have gone unnoticed.

In patients patch tested by dermatologists for suspected contact dermatitis, the prevalence of allergic contact dermatitis to 1 or more topical drugs is estimated to approximate 15%.^{2,4} However, the

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prevalence in individual countries, regions, and hospitals may be heavily influenced by local and regional prescribing and self-medication habits (over-the-counter [OTC] products),^{5,6} and the availability of products containing drugs that may be prone to cause allergic contact dermatitis such as neomycin, bacitracin, benzocaine, dibucaine, bufexamac, or ketoprofen (photocontact and contact allergy). Other crucial factors are the interest of the investigator in this specific topic, whether the patients' contact materials are patch tested, routine testing of an extended baseline series or targeted additional testing (medicament series), patch testing techniques (when reactions are not read at days 6 to 10, many cases of neomycin and CS allergy may be missed),^{4,7-9} test concentration and vehicle used for patch testing CSs,¹⁰ the profile of the hospital (general, academic, and specialized centers), patient population (elderly people, leg ulcer patients), and the selection of patients for patch testing (liberal vs strongly selected).⁵ Because of all these varying parameters, the prevalence rates of iatrogenic sensitization probably range from 10% in some hospitals to 17% or somewhat higher in tertiary referral centers specializing in medicament allergies.

The screening series of the North American Contact Dermatitis Group (NACDG) and the European baseline series both contain a number of topical drugs. Data on the frequency of positive patch test reactions to these from 2008 on are shown in Table 1. In the United States, very high rates of sensitization (generally >7%) are observed to bacitracin and neomycin. In Europe, bacitracin is not an allergen of any importance, and rates for neomycin are comparatively low (mean for the studies reviewed, unadjusted for sample size: 1.1%). It is thought that, in the United States, the use of triple-antibiotic topical

products, which are readily available as OTC preparations, and their application in high-risk patients (such as those with leg ulcers, stasis dermatitis, otitis externa, and anogenital dermatitis) are mainly responsible for the high sensitization rate to neomycin and bacitracin, which very frequently coreact from their combined presence.^{11,12} In Europe, neomycin products are not available as OTC drugs and are not broadly prescribed by physicians, resulting in low prevalence rates of sensitization. That the availability is a crucial factor also shows from a study in Canada, where the rate of neomycin sensitization steeply dropped from 7.4% before 2009 to 1.7% in the period 2009–2013, after the availability of OTC and prescription neomycin products apparently had been strongly limited in that country.¹³

In the United States, of the other drugs tested in the screening series, only benzocaine and tixocortol pivalate have positive scores consistently over 1% (benzocaine) and 2% (tixocortol pivalate) after 2008. In Europe, scores for these 2 drugs average some 1%. The frequency of positive reactions to budesonide, on the other hand, is somewhat higher in Europe, at least with the 0.01% test concentration. The recent replacement of benzocaine by the caine mix III (containing benzocaine 5%, dibucaine [cinchocaine] 2.5%, and tetracaine 2.5%) in the European baseline series¹⁴ will have the advantage of detecting more cases of contact allergy to local anesthetics, especially to dibucaine.²

The influence of time and place (among other parameters) on the variability of sensitization to topical drugs is obvious from investigations into contact allergy to (1 or more) CSs. Whereas low rates were found in Spain¹⁵⁻¹⁷ and some other countries such as Portugal,¹⁷ frequencies of 4% to 5% of patients attending patch test

TABLE 1. Frequencies of Sensitization to Drugs in the North American Contact Dermatitis Group Screening Series and the European Baseline Series*

Hapten	United States, Canada ^{26-32†}			Europe ^{33-36†}		
	Range, %	Median, %	Mean, %‡	Range, %	Median, %	Mean, %‡
Bacitracin	6.4–8.3	7.4	7.3	NT		
Benzocaine	1.4–2.1	1.5	1.6	0.6–1.8	0.9	1.05
Budesonide						
0.1%	0.7–0.9	0.8	0.8	0.4–0.8	0.4	0.5
0.01%	0.6	0.6	0.6	0.6–2.8	1.2	1.2
Caine mix III	NT			0.5–4.1	1.25	1.6
Clobetasol propionate	0.1–0.8	0.25	0.3	NT		
Desoximetasone	0.1–0.2	0.2	0.15	NT		
Hydrocortisone butyrate	0.1–0.9	0.3	0.4	NT		
Lidocaine	0.3–1.8	0.8	0.8	NT		
Neomycin	1.7–10.3§	8.6	7.8	0.4–2.9	0.75	1.1
Tixocortol pivalate						
0.1%	2.4	2.4	2.4	0.3–1.2	0.75	0.8
1%	1.8–2.3	2.1	2.1	0.9–1.0	0.95	0.95

*In the last 10–12 years.

†Plus various other studies presented in De Groot.²

‡Unadjusted for sample size.

§The low percentage of 1.7 was observed in Western Canada in the period 2009–2013; before that, the percentage had still been 7.4; this dramatic decrease of sensitization to neomycin was likely the result of reduced availability of OTC and prescription neomycin products in Canada.¹³

NT, not tested in the baseline/screening series; OTC, over-the-counter.

TABLE 2. Factors Predisposing to Sensitization, or Often Involved in Medicament Allergy

Strong intrinsic sensitizing potential of applied drugs
Application to damaged skin
Application to inflamed skin (notably stasis dermatitis, leg ulcers ^{40–42})
Penetration enhancing factors:
Irritant materials in the topical preparation (eg, propylene glycol)
Use of occlusive dressing
Application to large body folds
Transdermal therapeutic systems
Application to specific anatomic locations (penis, vulva, ⁴³ anus/perianal region, conjunctivae, ear canal)
Long-term treatment (chronic dermatitis) ⁴⁴
Advanced age ^{45,46}

clinics have been reported from the United Kingdom,^{18–20} the United States,²¹ Belgium,²² Finland,²³ and Hungary.²⁴ Even higher frequencies have been found in the United Kingdom (6%¹⁰), Belgium (6.4%¹⁷), and in one—very small—group of Polish consecutive patients tested (7.4%²⁵).

Predisposing Factors

Topical drugs are virtually always used on diseased (often inflamed) or nonintact (wounds, burns, leg ulcers) skin or mucous membranes, often with a damaged or insufficiently functioning skin barrier. This

facilitates penetration and access to the antigen-presenting cells (Langerhans cells, dendritic cells). The presence of inflammation in the skin treated with the topical pharmaceutical (stasis dermatitis, leg ulcer, dermatitis, skin infections) activates the innate immune system, which may favor the presentation of the chemical to the immune system and subsequently the sensitization of T cells.³⁷ Predisposing factors for sensitization to topical drugs are summarized in Table 2.^{4,7,38,39} The most notable of these is treatment of leg ulcers and/or stasis dermatitis. In epidemiological studies, these patients often have very high prevalence rates of positive patch test reactions with multisensitization to active drugs, nonactive ingredients of topical drugs (lanolin alcohol, propylene glycol, and fragrances), and unrelated allergens.^{40–42}

Clinical Manifestations

Spectrum of Allergic Reactions

Reported clinical manifestations of allergic contact dermatitis from topical drugs are summarized in Table 3. In its classic form, it presents as acute itchy dermatitis with erythema, edema, papules, and sometimes with vesicles and exudation (Fig. 1). Subacute forms with papules and scaling also occur (Fig. 2). Often, the dermatitis stays limited to the site of application. However, spreading of the dermatitis to other locations and sometimes generalization are far from rare, especially with strong sensitizers (eg, bupivacaine) or in the case of sensitization to topical pharmaceuticals applied to leg ulcers or

TABLE 3. The Spectrum of Clinical Manifestations of Allergic Contact Dermatitis From Topical Drugs

Common clinical manifestations
Acute or subacute allergic contact dermatitis limited to the site(s) of application (rare with CSs ⁴⁷)
Dermatitis spreading to other (nonapplication) sites or generalization
Therapy resistance of treated dermatosis (CSs, allergy to other drugs in combination preparations with CSs)
Worsening of the treated dermatosis (eczema, skin infection)
Special and atypical forms of contact dermatitis
Allergic contact dermatitis “by proxy” (connubial contact dermatitis, consort contact dermatitis) ^{48–51} (Table 4)
Erythema multiforme–like allergic contact dermatitis/urticarial papular and plaque eruption ^{52,53} (Table 4)
Ectopic dermatitis ^{54,55}
Pustular contact dermatitis (Table 4)
AGEP-like allergic contact dermatitis ⁵⁶
Other atypical forms of allergic contact dermatitis (Table 5)
Allergic reactions of the mucous membranes of the eyes, nose, mouth, and airways (inhalation)
Allergic reactions to eye drops: itching, burning, tearing, red eyes, conjunctivitis, conjunctival injection, erythema and edema of the eyelids, periorbital dermatitis, and systemic contact dermatitis
Allergic reactions to nose drops or nasal spray: nasal itching, dryness, burning, nasal congestion, worsening of rhinitis, dysphagia, edema of the tongue, lips, and face, dermatitis on the nose, upper lip, and face, and systemic contact dermatitis
Allergic reactions from inhalation: stomatitis, perioral eczema, oropharyngeal pruritus, dryness, mouth erythema and edema, dry cough, dysphonia, dysphagia, odynophagia, dyspnea, wheezing, and systemic contact dermatitis
Other manifestations of allergic contact dermatitis
Photoallergic contact dermatitis: eczema limited to light-exposed areas (photocontact allergy) or secondary spread to light-exposed areas (photoaugmented contact allergy)
Occupational allergic contact dermatitis (rare with topical drugs) ⁴⁸
Systemic contact dermatitis

ACD, allergic contact dermatitis; CSs, corticosteroids.

Adapted from De Groot.²

stasis dermatitis (Fig. 3). Spreading may occur from accidental contact, transmission through clothing or hands, and as a manifestation of systemic contact dermatitis, caused by absorption of the culprit drug.

The clinical presentation of allergic contact dermatitis to CSs is often neither specific nor spectacular, which is because of the anti-inflammatory properties of CSs, which suppress the eczematous reactions at the same time as inducing them.^{57,58} Acute weeping dermatitis is not to be expected.⁵⁸ Allergy to CSs should be suspected when skin diseases such as eczema and psoriasis respond poorly or not at all to CS treatment,^{18,59} become worse during therapy, or reoccur rapidly after withdrawal of the CS. Allergic contact dermatitis caused by CSs may also present as chronic eczema, which is often more pronounced at the periphery of the treated zone, which is called the edge effect.¹⁸ Because there is frequently a long delay before the diagnosis of contact allergy is suspected, prolonged use of the CSs has often occurred, which can lead to “classic” adverse effects, such as cutaneous atrophy, rosacea, and perioral or perinasal dermatitis dominating the clinical presentation.^{4,7}

Special and Atypical Forms of Allergic Contact Dermatitis

There are various special and atypical forms and manifestations of allergic contact dermatitis (Table 3). Well known are erythema multiforme-like eruptions. These are not well defined and are usually based on the morphological interpretation of the investigator. However, besides the occasional target-like lesions, the morphology (with urticarial papules and plaques), clinical course, and history of erythema multiforme-like eruptions of contact allergy are not



Figure 1. Purplish erythematous allergic contact dermatitis from ketoprofen; note the gross swelling of the upper leg and the “kissing dermatitis” on the inner side of the left leg.

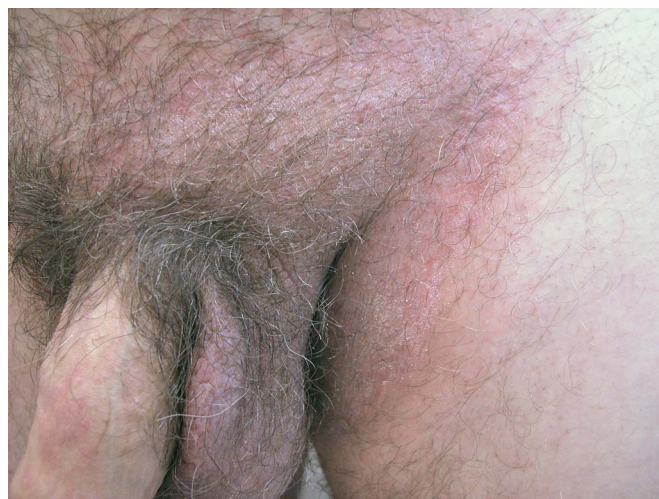


Figure 2. Subacute erythematous and scaly allergic contact dermatitis from miconazole in antifungal cream.

characteristic of classical erythema multiforme. They also lack the histopathology of “real” erythema multiforme. Some authors therefore prefer the term “urticarial papular and plaque eruptions.” The exact mechanism is unknown, but allergic immune complexes are thought to play a role.⁵³ Topical drugs that have caused erythema multiforme-like allergic contact dermatitis are shown in Table 4.

In “connubial” allergic contact dermatitis, also termed consort contact dermatitis and more recently allergic contact dermatitis “by proxy,” the culprit drug causing allergic contact dermatitis is not used by the patient himself or herself but by a partner, child, parent, sibling, or someone else in the patient’s close personal environment (Table 4). Ectopic dermatitis is dermatitis located only at a part of the body distant from the application site, which has been observed with tioconazole in nail lacquer⁵⁵ and with CSs.

Some eruptions of allergic contact dermatitis show pustules, or the clinical picture is even dominated by them (pustular contact dermatitis). Rarely, the allergic contact dermatitis resembles an eruption, which is usually caused by systemic drugs (acute generalized exanthematous pustulosis [AGEP]). Fever, however, a frequent sign of AGEP, is absent.⁶⁰ The culprit products for these and other atypical forms of allergic contact dermatitis are shown in Tables 4 and 5.

Allergic Reactions to the Mucous Membranes of the Eyes, Nose, Mouth, and Airways (Inhalation)

Another route of sensitization is through the mucosae, notably from CSs used as spray in the nasal cavity for allergic or nonallergic rhinitis (especially budesonide and tixocortol pivalate), as inhalation therapy in the pulmonary tract for the treatment of asthma (budesonide), in eye drops for allergic conjunctivitis,⁶¹ and in the mouth for aphthous stomatitis or lichen oris.⁶² Although these treatments are used extensively, sensitization is relatively infrequent; sensitization from therapy on the oral mucosa is rare.²

Application of nose drops or nasal spray may *inter alia* cause nasal itching, dryness, burning, nasal congestion, worsening of rhinitis,

dysphagia, edema of the tongue, lips and face, dermatitis on the nose, upper lip, and face, and systemic contact dermatitis.^{63–66} Local allergic adverse effects of inhaled CSs include stomatitis, perioral eczema, oropharyngeal pruritus, dryness, mouth erythema and edema, dry cough, dysphonia, dysphagia, odynophagia (pain when swallowing), dyspnea, and wheezing.^{67–69} Symptoms often start early in the treatment (after several days) and may develop hours after inhalation.⁶⁷ Allergic reactions to eye drops may manifest as itching, burning, tearing, red eyes, conjunctivitis, conjunctival injection, erythema and edema of the eyelids, and periorbital dermatitis (Fig. 4). Drugs that have caused contact allergic reactions from application to the eyes are shown in Table 6.

Systemic absorption of topical drugs (notably CSs) through the nasal, pulmonary, or ophthalmic mucosae may result in systemic contact dermatitis.

Other Manifestations of Allergic Contact Dermatitis

Photoallergic contact dermatitis to topical drugs, formerly frequent with phenothiazines, is currently rare with the notable exception of

TABLE 4. Atypical Presentations of Allergic Contact Dermatitis

Erythema multiforme–like ACD	Phenylbutazone	Miconazole
Amlexanox	Povidone-iodine	Nifuratel
Bufexamac	Proflavine	Procaine
Clioquinol	Promethazine	Resorcinol
Econazole ⁵³	Pyrrolnitrin	Pustular contact dermatitis (PCD) and AGEF
Fluorouracil	Scopolamine ⁵³	Benzocaine (AGEF)
Furazolidone ⁵³	Sulfanilamide	Bufexamac (AGEF)
Glycol salicylate	Sulfonamide ⁵³	Dibucaine (AGEF)
Idoxuridine	Tocopherol	Fluorouracil (PCD)
Ketoprofen	Tocopheryl acetate	Minoxidil (PCD)
Lincomycin	Connubial allergic contact dermatitis	Nitrofurazone (AGEF, PCD)
Mafenide	Benzoyl peroxide	
Mechlorethamine ⁵³	Bufexamac	
Mephensin	Clotrimazole	
Neomycin	Diphenhydramine	
Nifuroxime ⁵³	Ketoprofen (also photoallergic)	
Nitroglycerin		
Permethrin ⁵³		

ACD, allergic contact dermatitis; AGEF, acute generalized exanthematous pustulosis. Adapted from De Groot.²



Figure 3. Allergic contact dermatitis from Hirudoid cream applied to superficial leg ulcers; in this case, there was only some spreading of the dermatitis to the skin proximal of the application site.

some nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen, piroxicam, diclofenac, and benzydamine. Photoallergic contact dermatitis mainly presents as acute eczema or exaggerated sunburn in areas of drug application that are also exposed to sunlight or artificial UV light (sunbed, solarium), sparing naturally shaded areas such as the body folds and skin covered by dense hair, and is absent on skin protected by cloths or other personal objects including jewelry or a wrist watch.⁴ Topical drugs that have caused photocontact allergy are shown in Table 7.

Occupational allergic contact dermatitis, which is well known in health care professionals and workers in the pharmaceutical industry with systemic drugs, is rare with topical drugs, although seen occasionally with CSs. Topical drugs that have caused occupational sensitization or occupational allergic contact dermatitis are shown in Table 7.

Systemic contact dermatitis, its manifestations, and topical drugs that have caused it are discussed in the section Systemic Contact Dermatitis.

Systemic Contact Dermatitis

Systemic contact dermatitis (also termed systemic allergic contact dermatitis, systemic allergic dermatitis) is a condition that occurs when an individual sensitized to a contact allergen is exposed to that same allergen or a cross-reacting molecule through a systemic route. Systemic exposure to allergens can include transcutaneous, transmucosal, oral, intravenous, intramuscular, and inhalational routes, as well as implants.^{67,68,74–80} Possible manifestations are shown in Table 8 and include reactivation of previous eczema and positive patch test reactions, acrovesicular dermatitis, systemic symptoms, and various drug exanthemas including maculopapular

TABLE 5. Miscellaneous Forms of Atypical Allergic Contact Dermatitis

3-(Aminomethyl)pyridyl salicylate	Airborne allergic contact dermatitis
Benzocaine	Orodynia
Benzoyl peroxide	Purpuric contact dermatitis (probably irritant)
Benzydamine	Lymphomatoid photocontact dermatitis; airborne allergic contact dermatitis
Budesonide	Edema of the lips and face mimicking type I allergy
Bufexamac	Generalized rash resembling the baboon syndrome; pigmented purpuric dermatosis
Clindamycin	Rosacea-like rash; allergic contact dermatitis mimicking a "retinoid flare"
Hydrocortisone butyrate	Allergic contact dermatitis mimicking papular rosacea ⁷⁰
Ketoprofen	Leukomelanoderma after photoallergic contact dermatitis
Lidocaine	Fixed drug eruption (from lidocaine suppository)
Mephensin	Purpuric contact dermatitis
Minoxidil	Psoriasiform dermatitis; pigmented contact dermatitis; persisting pseudolymphoma-like patch test reactions
Neomycin	Lichenoid allergic contact dermatitis
Phenylbutazone	Purpuric contact dermatitis
Prednicarbate	Allergic contact dermatitis presenting as lupus erythematosus ⁷¹ ; edema of the lips and face mimicking type I allergy ^{72,73}
Proflavine	Pigmented contact dermatitis
Sulfiram	Toxic epidermal necrolysis-like allergic contact dermatitis

Adapted from De Groot.²

rashes, urticaria, erythema multiforme, and vasculitis. Such reactions are most frequently caused by drugs given orally or parenterally. However, topical drugs absorbed through the skin or the



Figure 4. Acute allergic contact dermatitis from phenylephrine used in the left eye with erythema, gross edema, and some vesicles of the eyelids and surrounding skin, expanding to the nose.

TABLE 6. Drugs That Have Caused Allergic Contact Dermatitis in Eye Drops or Other Ophthalmic Pharmaceuticals

Aceclidine	Dorzolamide	Pilocarpine
Acetylcysteine	Echothiophate	Pirenexine
Acyclovir	Ephedrine	Polymyxin B
Alcaftadine	Epinephrine	Povidone-iodine
Aminocaproic acid	Framycetin	Prednisolone acetate
Amlexanox	Gentamicin	Prednisolone pivalate
Antazoline	Homatropine	Proparacaine
Apraclonidine	Hydrocortisone acetate	Rifamycin
Atropine	Hydrocortisone sodium phosphate	Ripasudil
Azidamfenicol	Idoxuridine	Rubidium iodide
Azithromycin	Interferon beta	Scopolamine
Befunolol	Ketorolac tromethamine	Sparglumic acid
Betamethasone valerate	Ketotifen fumarate	Sulfacetamide
Betaxolol	Latanoprost	Tetracaine
Bibrocathol	Levobunolol	Tetrahydrozoline
Bimatoprost	Levocabastine	Thioctic acid
Brimonidine	Methylprednisolone acetate	Timolol
Carteolol	Metipranolol	Tobramycin
Chloramphenicol	Metoprolol	Tolazoline
Chlorpheniramine	Mitomycin C	Travoprost
Colistimethate	Neomycin	Tretinoin
Cromoglicic acid	Nitrofurazone	Triamcinolone acetonide
Cyclopentolate	Oxybuprocaine	Trifluridine
Dexamethasone sodium phosphate	Oxytetracycline	Tromethamine
Dibekacin	Penicillamine	Tropicamide
Diclofenac	Pheniramine	Vancomycin
Dipivefrin	Phenylephrine	

Adapted from De Groot.²

mucosae may also induce such reactions. Well-known causes are the vasodilator diltiazem used for anal fissure and the topical anesthetic dibucaine, which are absorbed through the anal mucosa and the inflamed perianal skin. Resorption of budesonide in inhalation preparations has resulted in systemic contact dermatitis manifesting as swelling of the eyelids, urticaria, general pruritus, maculopapular exanthemas, flare-up of previous dermatitis, and flare-up of previous positive patch test reactions.^{67,68,79–81}

The most characteristic manifestation of systemic contact dermatitis is the so-called baboon syndrome.^{82–85} It presents as diffuse pink or dark violet erythema of the buttocks and inner thighs (Fig. 5), like an inverted triangle or V-shaped, resembling the red bottom of a baboon, often accompanied by dermatitis in the axillae and sometimes other body folds.⁷⁷ A similar eruption can be caused by systemic drugs, notably antibiotics, without previous sensitization.⁶⁸ For this variant of what was previously also called the baboon syndrome, in 2004, the alternative term “symmetric drug-related intertriginous and flexural exanthema (SDRIFE)” was coined.⁸⁶ One of the considerations of the authors was that the term “baboon syndrome” was ethically incorrect and possibly offensive (in my opinion, baboons are more likely proud of than offended by

TABLE 7. Topical Drugs That Have Caused Photoallergic Contact Dermatitis or Occupational Contact Dermatitis

Photoallergic Contact Dermatitis	Occupational Allergic Contact Dermatitis
Aceclofenac	Benzylamine
Benzocaine	Budesonide
Benzylamine	Chloramphenicol
Coal tar	Coal tar
Chlorproethazine	Diclofenac
Dexketoprofen	Enilconazole
Dibucaine	Ethacridine lactate
Diclofenac	Gentamicin (in bone cement)
Dioxopromethazine	Homatropine
Etofenamate	Hydrocortisone
Fepradinol	Ichthammol
Flufenamic acid	Methyl aminolevulinate
Hexamidine diisethionate	Minoxidil
Indomethacin	Neomycin
Isothipendyl	Phenylephrine
Ketoprofen (and persistent light reaction)	Piroxicam
Methoxsalen	Povidone-iodine
Methyl aminolevulinate	Proflavine
Minoxidil	Proparacaine
Piketoprofen	Tetracaine
Pilocarpine	Thiocolchicoside
Piroxicam	Tocopherol
Promethazine (and persistent light reaction)	Tropicamide
Pyrithione zinc	Virginiamycin
Sulfanilamide	Thiocolchicoside
Suprofen	
Thiabendazole	

Adapted from De Groot.²

referring to their distinctive red behind). Unfortunately, previous sensitization was excluded by the authors introducing this term,⁸⁶ so the baboon syndrome is mostly treated as a separate entity for cases with prior sensitization. Therefore, the term remains in general use,⁶⁸ although some authors treat these names as synonyms,⁴ and it seems to be accepted practice in *Contact Dermatitis*.⁸⁷ Because not all patients with this eruption have the classic red bottom of the baboon, we suggest that the term “symmetric drug-related intertriginous and flexural exanthema (SDRIFE)” is also used for cases *with* previous sensitization.

Topical drugs (including in rectal and vaginal suppositories) that have caused systemic allergic contact dermatitis from systemic absorption through the mucous membranes and skin are shown in Table 9.

THE ALLERGENS

The Allergens

The nature of the allergens in topical pharmaceuticals diagnosed depends *inter alia* on when and where the studies were performed.

TABLE 8. Symptoms and Signs of Systemic Contact Dermatitis From Topical Drugs

Reactivation of previous allergic contact dermatitis
Reactivation of previous positive patch test
Worsening of existing eczema
Vesicular dermatitis of the palms of the hands, sides of the fingers, and soles of the feet, with or without erythema
Drug eruptions
Generalized eczema
Maculopapular exanthema
Urticaria
Baboon syndrome
Erythema multiforme
Purpura
Vasculitis
AGEP
Systemic symptoms: fever, malaise, nausea, vomiting, diarrhea, headache, arthralgia, and (rarely) syncope

Adapted from De Groot.²

AGEP, acute generalized exanthematous pustulosis.

Formerly, the topical use of penicillin, sulfonamides, and promethazine caused a large number of (photo)sensitizations, but they are unimportant now. Neomycin and bacitracin were very common sensitizers in the 1950s and 1960s in Finland from their combined presence in a very popular OTC antibacterial product,^{88,89} but since stricter regulations were enforced, their prevalence of sensitization has dropped considerably. In fact, in the European Union, thanks to legislation, bacitracin, and to a lesser degree neomycin, is not an important sensitizer anymore. However, in the United States, where such OTC pharmaceuticals are still readily available, these antibiotics both belong to the top 6 of common sensitizers after nickel, methyl(chloro)isothiazolonone, fragrances (fragrance mix I and *Myroxylon pereirae* resin), and formaldehyde, with currently some 7% positive reactions in patients routinely tested by the members of the NACDG.²⁶

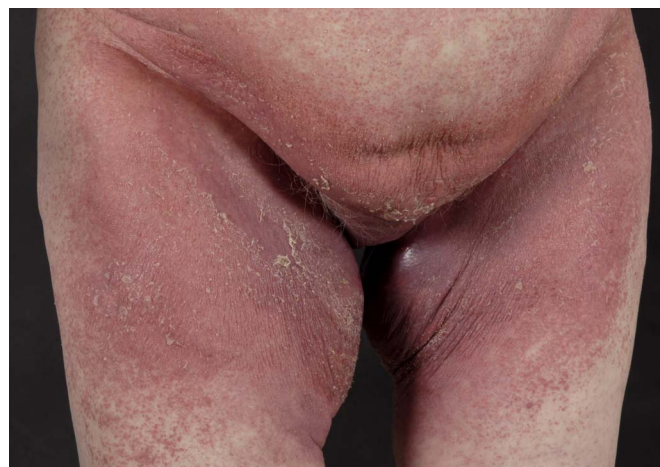


Figure 5. Baboon syndrome from the use of an ointment for hemorrhoids and contact allergy to its components dibucaine and framycetin.

Since the mid-1980s, NSAIDs such as ketoprofen have caused many cases of photoallergic contact dermatitis (and in lesser numbers allergic contact dermatitis) in some countries, notably in Italy, France, Japan, and Belgium, where these products are widely used, but also in Sweden, Croatia, and Spain. Bufenamac caused so many cases of contact allergic reactions in Germany and Austria that the drug was withdrawn by the European Medicines Agency in April 2010.⁹⁰ Several drug allergens have been reported mainly or exclusively from Japan (eg, prednisolone valerate acetate), presumably because they are or were used in that country (on a large scale) only.

Currently, the most important groups of sensitizers in topical drugs are—depending on the countries—antibiotics, CSs, topical anesthetics, and NSAIDs. It should be realized that, with the exception of the NSAIDs, their most important allergenic representatives (neomycin, bacitracin, and benzocaine) or markers of sensitization (caine mix III, budesonide, and tixocortol pivalate) are present in some or most routine series, thus identifying sensitization to them, whereas other (important) drug allergens may be missed when suspected pharmaceutical products or appropriate additional series are not patch tested.

In many cases, the culprit in a topical medicament causing allergic contact dermatitis is the active principle, but the reactions may also be caused by nonactive ingredients⁹¹ such as ethylenediamine, lanolin alcohol, propylene glycol, fragrances or essential oils, or parabens and other preservatives (thimerosal and benzalkonium chloride in eye drops). Contact allergy to transdermal therapeutic systems may result from the active drug or from a nonactive ingredient, for example, present in the adhesive material (Fig. 6).

The author has found 369 topical drugs that have caused contact allergy/allergic contact dermatitis.² These are shown in Supplemental Tables 1–13 (<http://links.lww.com/DER/A55>) and include antibiotics (Supplemental Table 1); CSs (Supplemental Table 2);

anti-infective agents (Supplemental Table 3); antifungal, antiviral, and antiparasitic drugs (Supplemental Table 4); antihistamines (Supplemental Table 5); local (topical) anesthetics (Supplemental Table 6); NSAIDs (Supplemental Table 7); drugs used in the treatment of eczema, acne, and psoriasis and antineoplastic and immunosuppressive drugs (Supplemental Table 8); antiglaucoma drugs and ophthalmological drugs other than for glaucoma (Supplemental Table 9); sex hormones, vitamins, and muscle relaxants (Supplemental Table 10); therapeutic agents for the nose, mouth, and airways (Supplemental Table 11); drugs used in transdermal therapeutic systems (Supplemental Table 12); and miscellaneous therapeutic agents (Supplemental Table 13). Topical drugs that have caused photocontact allergy/photoallergic contact dermatitis can be found in Table 7.

Corticosteroids

Corticosteroids that have caused contact allergy/allergic contact dermatitis are shown in Supplemental Table 2. The CSs that most frequently cause allergic reactions belong to the hydrocortisone–prednisolone–tixocortol pivalate group (Table 10, group 1). These are (mostly) not halogenated and do not have a methyl group at the C₁₆ position of the CS molecule. Far less allergenic are CSs that are halogenated and have a methyl group at the C₁₆ position. To this group (Table 10, group 3) belong *inter alia* betamethasone (esters), dexamethasone (esters), clobetasol propionate, clobetasone butyrate, desoximetasone, flumethasone pivalate, fluocortolone esters, and mometasone furoate.^{4,7}

CROSS-REACTIONS AND COREACTIONS

Corticosteroids

Multiple reactions to CSs are frequent, mostly from cross-reactivity.^{18,51} The allergens are probably not the CSs themselves, but a byproduct from their skin metabolism. The principal metabolites steroid glyoxals or 21-dehydrocorticosteroids (aldehydes) are the most probable haptens.^{4,7,93} Based on the results of patch testing, molecular modeling, and previous work,^{94–98} CSs have been divided into 3 groups (Table 10). Group 1 consists of non-C₁₆-methylsubstituted and (mostly) nonhalogenated molecules, which include hydrocortisone, prednisolone and their derivatives, and tixocortol pivalate. Group 2 consists of (mostly) halogenated molecules with a C₁₆/C₁₇ *cis*-ketal or diol structure. Group 3 consists of halogenated and C₁₆-methylsubstituted molecules and includes betamethasone and dexamethasone and their derivatives.

C₁₆-methyl substitution and halogenation seem to reduce the allergenicity of CS molecules.⁹³ Indeed, by far most allergic reactions are caused by the CSs in group 1, whereas the molecules in group 3 rarely sensitize. As to the cross-reaction pattern, patients sensitized from 1 or more CSs in group 1 often cross-react with other chemicals in group 1. However, another cross-reactivity profile is that patients may be sensitized to steroids in group 1 with cross-reactions not only in group 1 but also in group 2, group 3,

TABLE 9. Topical Drugs That Have Caused Systemic Contact Dermatitis

Acetarsone	Diltiazem	Nifuroxime
Amlexanox	Dimethindene	Nylidrin
Bacitracin	Dorzolamide	Nystatin
Benzylamine (systemic photocontact dermatitis)	Ephedrine	Oxyphenbutazone
Budesonide	Estradiol	Phenylbutazone
Bufenamac	Eucaïne	Phenylephrine
Buprenorphine	Framycetin	Piperazine
Carbarson	Gentamicin	Prednisolone
Chloral hydrate	Hydrocortisone	acetate
Chloramphenicol	aceponate	Promestriene
Chlorquinaldol	Iodine	Pyrazinobutazone
Clioquinol	Iodoquinol	Sisomicin
Clonidine	Lidocaine	Stannous fluoride
Dibucaine (contact and photocontact dermatitis)	Methyl aminolevulinate	Testosterone
	Methylphenidate	Tetracaine
	Neomycin	Triamcinolone
	Nicotine	acetanide
		Trimebutine

Adapted from De Groot.²



Figure 6. Multiple patches of allergic contact dermatitis from a component of the adhesive in rivastigmine transdermal therapeutic system; the number of patches indicates that the dermatitis remains visible for at least 2 weeks.

or both. The classification presented in Table 10 cannot explain all observed cross-reactions and often does not accurately predict cross-reactivity.^{99–101} Therefore, patients with positive patch test reactions to tixocortol pivalate and/or budesonide and/or hydrocortisone butyrate in the baseline/screening series and/or to CSs used by them should also be tested with other CSs to determine the cross-reactivity pattern and to establish which CSs can safely be used for continued treatment. Cross-reactivity can sometimes also be observed to endogenous steroidal sex hormones and derivatives including progesterone, 17- α -hydroxyprogesterone, and testosterone.^{4,7,102–105}

Aminoglycosides

In patients sensitized to neomycin, the percentage of cross-reactions to other aminoglycoside antibiotics is high: to paromomycin and butirosin¹⁰⁶ approximately 90%, to framycetin 70%, to ribostamycin 70%,¹⁰⁷ to tobramycin and kanamycin 60%, to gentamicin 50%, to amikacin 30%,¹⁰⁸ and to sisomicin¹⁰⁹ 20%.² However, streptomycin cross-reacts (or coreacts more likely) in only approximately 4% of the patients.^{2,107,109} A high degree of coreactivity between framycetin and neomycin can be expected, as framycetin consists mostly of neomycin B, which is also the main constituent of neomycin. However, neomycin B is not the only sensitizer in either framycetin or neomycin, as a considerable number of patients allergic to neomycin do not react to framycetin and vice versa.^{110,111}

The cross-sensitivity pattern in patients primarily sensitized to other aminoglycosides has not been well investigated. Primary

sensitization to gentamicin may infrequently be accompanied by cross-sensitization to neomycin.¹¹² There are also indications that patients primarily sensitized to tobramycin in eye drops or ear drops often do not cross-react to neomycin.^{2,113}

Local Anesthetics

Local anesthetics are divided into 2 groups: PABA (*p*-aminobenzoic acid) esters (benzocaine, butamben, oxybuprocaine, procaine, and tetracaine) and amide compounds (articaine, bupivacaine, dibucaine, lidocaine, mepivacaine, prilocaine, and ropivacaine). The amides are further divided into 2 subgroups: aminoacylamides (all but dibucaine) and aminoalkylamides (dibucaine).¹¹⁴ The esters have strong allergenic potential and may cross-react to other PABA-derived local anesthetics and to other nonanesthetic para-compounds such as *p*-phenylenediamine and other hair dyes, sulfonamides, and certain azo dyes. The amide-type local anesthetics also cross-react (especially with primary lidocaine sensitization) but less frequently and inconsistently and not with articaine or dibucaine. Cross-reactivity between esters and amides does not occur, because their breakdown products differ.²

Coreactions

Patients sensitized to bacitracin very often coreact to neomycin and vice versa. In an older publication, for example, all 99 patients with positive bacitracin patch tests also reacted to neomycin.⁸⁸ Conversely,

TABLE 10. Corticosteroid Classification Based on Cross-Reaction Pattern

Group 1	Group 2	Group 3
No C ₁₆ -methyl substitution	C ₁₆ /C ₁₇ <i>cis</i> -ketal or diol structure	C ₁₆ -methyl substitution
No halogenation (in most)	Halogenation	Halogenation
Budesonide (S-isomer)	Amcinonide	Alclometasone dipropionate*
Cloprednol†	Budesonide, <i>R</i> isomer‡	Beclomethasone dipropionate
Cortisone acetate	Ciclesonide	Betamethasone
Dichlorisone acetate†	Desonide§	Betamethasone dipropionate
Difluprednate†	Fluclorolone acetonide	Betamethasone sodium phosphate
Fludrocortisone acetate†	Flumoxonidell	Betamethasone 17-valerate
Fluorometholone†	Flunisolide	Clobetasol propionate
Fluprednisolone acetate†	Fluocinonide	Clobetasone butyrate
Hydrocortisone	Fluocinonide acetonide	Cortivazol
Hydrocortisone aceponate	Halcinonide	Desoximetasone
Hydrocortisone acetate	Triamcinolone acetonide	Dexamethasone
Hydrocortisone-17-butyrate	Triamcinolone benetonidell	Dexamethasone acetate
Hydrocortisone-21-butyrate	Triamcinolone diacetate	Dexamethasone sodium phosphate
Hydrocortisone hemisuccinate	Triamcinolone hexacetonide	Diflorasone diacetate
Isoflupredone acetate†		Diflucortolone valerate
Mazipredone		Flumethasone pivalate
Medrysone		Fluocortin butyl
Methylprednisolone aceponate		Fluocortolone
Methylprednisolone acetate		Fluocortolone caproate
Methylprednisolone hemisuccinate		Fluocortolone pivalate
Prednicarbate		Fluprednidene acetate
Prednisolone		Fluticasone propionate
Prednisolone caproate		Halometasone
Prednisolone hemisuccinate		Meprednisone§
Prednisolone pivalate		Mometasone furoate
Prednisolone sodium metazoate		
Prednisone		
Tixocortol pivalate		
Triamcinolone†		

*Unexpectedly in group 3, as alclometasone dipropionate often coreacts with group 1.

†Halogenated.

‡Also included in group 2, as it may in exceptional cases cross react with the acetonides.

§No halogen substitution.

||Not used in pharmaceuticals.

Adapted from Baeck and Goossen.⁷

66% to 88% of patients with positive reactions to neomycin coreact to bacitracin.^{115,116} This is not the result of cross-sensitization (dissimilar chemical structures) but is caused by the fact that neomycin and bacitracin are often contained in 1 product, leading to concomitant sensitization. In an American study of 16 patients with positive patch test reactions to lidocaine, 10 coreacted to neomycin and 9 to bacitracin. In the United States, topical pharmaceuticals containing lidocaine as well as neomycin and bacitracin are available.¹¹⁶

Patients sensitized to topical drugs, especially individuals who have become allergic from treatment of leg ulcers and/or stasis dermatitis and patients reacting to CSs, do not infrequently have coreactions to multiple allergens such as preservatives and nonactive ingredients, for example, lanolin alcohol, propylene glycol, sorbitan sesquioleate, parabens, and fragrances. Patients allergic to CSs are

sometimes also sensitized to other drugs such as antibiotics or antimycotic drugs.^{2,4,7,39,51} These coreactivities are the result of successive or concomitant sensitization by their presence in the same or other pharmaceuticals or from other sources.

DIAGNOSTIC PROCEDURES

Patch Testing in Patients With Suspected Contact Allergy to Topical Drugs

When allergic contact dermatitis to 1 or more topical drugs is suspected (eg, development of dermatitis, unexpected exacerbation of a dermatosis during treatment or, in the case of CSs, unresponsiveness of the treated skin disorder), the first step is to patch test

the baseline/screening series and all topical pharmaceutical products (previously) used by the patient. Most of these can be tested “as is,” but some may produce irritant reactions, for example, povidone-iodine solution, permethrin cream, and pharmaceuticals containing dithranol, calcipotriol, tretinoin, and 5-fluorouracil. The NACDG screening series includes topical drugs such as neomycin, bacitracin, tocopherol (vitamin E, not “officially” a topical drug, but frequently used as such, also by physicians), benzocaine, lidocaine, and the CSs budesonide, tixocortol pivalate, hydrocortisone butyrate, clobetasol propionate, and desoximetasone; base ingredients include lanolin alcohol, parabens, ethylenediamine, propylene glycol, and various fragrances and essential oils.²⁶ The American Contact Dermatitis Society core allergen series includes all of these except desoximetasone; in addition, it contains triamcinolone and pramoxine as drugs and benzyl alcohol and cetearyl alcohol as base ingredients.¹¹⁷ The European baseline series contains several topical drugs such as neomycin, the caine mix III (benzocaine, dibucaine, and tetracaine), budesonide, and tixocortol pivalate. In addition, it screens for some nonactive ingredients that may be the allergenic culprit in topical medicaments such as parabens, lanolin alcohol, and fragrances.¹⁴

In a number of cases, the final diagnosis can be made on the basis of the tests results of the routine series plus positive reactions to the patient's own product(s) and knowledge of their contents. The “markers” for CS allergy budesonide, tixocortol pivalate, and—to a lesser degree—hydrocortisone butyrate will detect a large portion of all CS allergies¹¹⁸ but at the same time fail to detect many.¹⁵ Additional testing with a “medicament series” or a “CS series,” either at the first or a second test session, may be advisable to detect additional unrelated drug allergens (eg, used by the patient in the past), cross-reacting chemicals (local anesthetics, aminoglycoside antibiotics, and CSs), but also to find suitable alternatives that are negative on patch testing. Approximately 125 drugs are available for patch testing from the major suppliers of patch test materials, of which nearly 95 are (also) used as topical drugs (Table 11).

When a topical drug gives a positive patch test reaction, but the allergenic culprit(s) cannot be established on the basis of positive reactions in the baseline/screening series or additional series tested, all ingredients should be patch tested separately, preferably after having confirmed sensitization by a repeated open application test (ROAT) or reusing the drug and exclusion of irritancy by adequate control testing. The best approach is to contact the supplier or manufacturer and request samples of all ingredients. It is advisable to ask for the pure ingredients or at least include a list of all known ingredients, mentioning the concentration and vehicle suitable for the patch tests, for example, based on the information in *Patch Testing, Fourth Edition*.¹¹⁹ If no (gentle) directions are given to the manufacturer, most likely the materials will be provided in the concentrations as present in the topical formulation, which entails a great risk of false-negative reactions. An easier alternative is to purchase the active ingredient, if available, from 1 of the providers of patch test materials (Table 11) or from a chemical company, but (additional) sensitizations to nonactive ingredients, which are far from rare, will then go unnoticed.¹²⁰

With the exception of budesonide and tixocortol pivalate, which perform well in petrolatum, most CSs can best be tested in alcohol 70% in a concentration of 0.1% to 1%.^{4,7} The lower concentration of 0.1% (and sometimes even lower) may often perform better, as the anti-inflammatory action of the molecule, which suppresses the allergic reaction, is less pronounced. It is very important to test alcohol 70% as a control, because it does not infrequently cause false-positive, irritant, reactions,¹²¹ and occasionally allergic reactions. Intradermal testing with CSs may reveal additional sensitizations not picked up by patch tests, especially in the case of hydrocortisone. However, especially with the stronger CSs, there is a risk of skin atrophy.^{4,7,8} Also, in the case of hydrocortisone, these allergies are almost always picked up by the tixocortol pivalate marker in the baseline series.

Unique for patch testing with CSs is the “edge effect”; at the first reading, there is often infiltration and erythema only on and around the edge of the patch test chamber with a completely clear center. Later, this center becomes eczematous as well.^{18,58,122} Many patch tests to CSs become positive only after days 3 and 4 (because of the anti-inflammatory effect of the molecule), and a reading at days 6 to 10 is imperative to avoid missing late positive reactions.^{4,7-9} Such late developing positive patch test reactions are also frequent with neomycin and other aminoglycosides.

False-Negative Patch Test Reactions

Patch testing with topical drugs may be problematic and may result in false-negative results, for example, in the case of contact allergy to a CS or to an antibiotic or antifungal in a combination preparation with a CS.

In both situations, the anti-inflammatory action of the CS may suppress the inflammatory patch test reaction, resulting in a false-negative reaction. Late developing positive patch test reactions are frequent with CSs, neomycin, and other aminoglycosides. If the patient is not seen for a late reading at days 6 to 10, or not properly instructed to return when visible reactions emerge, these reactions will be missed, resulting in test results incorrectly documented as negative (which is not a “false-negative patch test reaction,” of course).

Patch tests with commercial eye drop preparations containing β -blockers may also—not infrequently—be false-negative.¹²³⁻¹²⁶ The likely explanation is that, whereas the anatomic and physiologic properties of the eyelid skin and conjunctivae are associated with a lower threshold to development of sensitization and allergic contact dermatitis, the low concentration of the allergens (usually 0.25% to 0.5%) in commercial products is insufficient to elicit an allergic reaction in the far thicker skin of the back. When contact allergy is strongly suspected, but patch tests are negative, the following alternative diagnostic methods have been suggested^{127,128}: patch test on adhesive tape-stripped skin,^{124,129} on skin 10 times pricked with a prick-test lancet,¹³⁰ or on scarified skin.¹²⁴ Other possibilities are pretreatment of the test area with 0.5% aqueous sodium lauryl sulfate solution for 24 hours,¹³¹ enlarging the patch test area or to perform intradermal testing.¹³² By far the best method, however, is to patch test

TABLE 11. Topical Drugs Commercially Available for Patch Testing*

Patch Test Allergen (Hapten)	Chemotech	SPCanada	SPEurope
Acyclovir	10.0%		
Alclometasone dipropionate	1.0%		
Amcinonide		0.1%	0.1%
Amylocaine hydrochloride	5.0%		
Atropine sulfate		1% Water	1% Water
Bacitracin	5.0%, 20.0%	20%	20%
Benzocaine	5.0%	5%	5%
Benzoyl peroxide	1.0%	1%	1%
Benzylamine hydrochloride	2.0%	1%, 2%	
Betamethasone dipropionate	1.0%	0.5%	
Betamethasone valerate	1.0%	1%	0.12%
Budesonide	0.01%, 0.1%	0.01%, 0.1%	0.1%
Bufexamac	5.0%	5%	5%
Chloramphenicol	5.0%	2% Alcohol, 5%	5%
Chlorpheniramine maleate		5%	
Chlorquinaldol	5.0%	5%	5%
Chlortetracycline hydrochloride		1%	
Clindamycin phosphate	10.0%		
Clioquinol	5.0%	5%	5%
Clobetasol propionate	1.0%	0.25%, 1%	0.25%, 1%
Clotrimazole		1%	1%
Coal tar	5.0%	5%	5%
Desoximetasone	1.0%	1%	
Dexamethasone		0.5%	
Dexamethasone phosphate		1%	
Dexamethasone sodium phosphate	1.0%		1%
Dexpanthenol		5%	5%
Dibucaine (cinchocaine) hydrochloride	2.5%, 5.0%	2.5%, 5%	5%
Diclofenac sodium salt	1.0%, 5.0%	2.5%, 5%	2.5%
Diltiazem hydrochloride	10.0%		
Diphenhydramine hydrochloride	1.0%		

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TABLE 11. (Continued)

Patch Test Allergen (Hapten)	Chemotech	SPCanada	SPEurope
Econazole nitrate	1.0% Alcohol		
Erythromycin base	10.0%	1%, 2%	2%
Etofenamate	2.0%		
Framycetin sulfate	20.0%	10%	10%
Fusidic acid sodium salt	2.0%	2%	2%
Gentamicin sulfate	20.0%	20%	20%
Hexylresorcinol		0.25%	0.25%
Hydrocortisone		1%	1%
Hydrocortisone acetate	1.0%	1%	
Hydrocortisone butyrate	1.0%	0.1%, 1%, 1% Alcohol	0.1%
Hydroquinone	1.0%	1%	1%
Ibuprofen	5.0%, 10.0%	5%	
Idoxuridine		1%	
Indomethacin		1%	1%
Kanamycin sulfate	10.0%	10%	10%
Ketoprofen	1.0%	2.5%	
Lidocaine hydrochloride	5.0%, 15.0%	15%	15%
Mafenide		10%	10%
Methylprednisolone aceponate	1.0%	0.1% Alcohol	
Metronidazole		1%	1%
Miconazole	1.0% Alcohol		
Mometasone furoate		0.1% Alcohol	
Monobenzone	1.0%	1%	1%
Neomycin sulfate	20.0%	20%	20%
Nitrofurazone	1.0%	1%	1%
Nystatin		2%	2%
Oxytetracycline		3%	3%
Panthenol	5.0%		
Penicillamine		1%	
Phenylbutazone	10.0%	10%	10%
Phenylephrine hydrochloride		10% Water	10% Water
Piketopropfen		1%	
Pilocarpine hydrochloride		1% Water	1%
Piperazine		1%	1%
Piroxicam	1.0%	1%	
Polidocanol		3%	3%
Polymyxin B sulfate	5.0%	3%	3%
Povidone-iodine		10% Water	10%

(Continued on next page)

TABLE 11. (Continued)

Patch Test Allergen (Hapten)	Chemotech	SPCanada	SPEurope
Pramocaine hydrochloride	2.0%		
Prednicarbate		1% Alcohol	
Prednisolone		1%	1%
Prilocaine hydrochloride	5.0%		
Procaine hydrochloride	1.0%	1%, 2%	1%, 2%
Promethazine hydrochloride	0.1%	2%	
Propranolol hydrochloride		2%	
Resorcinol	1.0%	1%, 2%	2%
Salicylamide		2%	2%
Salicylic acid		5%	
Silver nitrate	1.0% Water	1% Water	1%
Spiramycin base	10.0%		
Streptomycin sulfate		5%	
Sulfanilamide	5.0%	5%	5%
Sulfur, precipitated		10%	
Tetracaine hydrochloride	5.0%	1%	1%
Tetracycline hydrochloride		2%	2%
Tioconazole	1.0%		
Tixocortol pivalate	0.1%, 1.0%	0.1%, 1%	1%
Tobramycin	20.0%	20%	
Tocopherol (vitamin E)	100%	100%	
Tocopheryl acetate	10.0%		
Triamcinolone acetonide	1.0%	0.1%, 1%	1%
Vancomycin hydrochloride	10.0% Water		
Zinc pyrithione (pyrithione zinc)	1.0%	0.1%	
Mixes of haptens†			
Caine mix II	10.0%		
Lidocaine	5.0%		
Dibucaine HCl	2.5%		
Tetracaine HCl	2.5%		
Caine mix III	10.0%		
Benzocaine	5.0%		
Dibucaine HCl	2.5%		
Tetracaine HCl	2.5%		
Caine mix IV	10.0%		
Lidocaine	5.0%		
Amylocaine HCl	2.5%		
Prilocaine HCl	2.5%		

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TABLE 11. (Continued)

Patch Test Allergen (Hapten)	Chemotech	SPCanada	SPEurope
Caine mix V	7.0%		
Benzocaine	5.0%		
Dibucaine HCl	1.0%		
Tetracaine HCl	1.0%		
Caine mix A		7%	
Benzocaine	5%		
Dibucaine HCl	1%		
Tetracaine HCl	1%		
Caine mix C		7%	
Benzocaine	5%		
Dibucaine HCl	1%		
Procaine HCl	1%		
CS mix	2.1%		
Hydrocortisone butyrate	1.0%		
Tixocortol pivalate	1.0%		
Budesonide	0.1%		
CS mix		2.01%	
Hydrocortisone acetate	1%		
Hydrocortisone butyrate	1%		
Budesonide	0.01%		
Oxyquinoline mix		6.0%	
Clioquinol	3%		
Chlorquinaldol	3%		
Quinoline mix	6.0%		
Clioquinol	3.0%		
Chlorquinaldol	3.0%		

*The vehicle for all haptens is petrolatum, unless otherwise indicated.

†Not a drug hapten per se, but a mixture of drugs for diagnostic patch testing.

Chemotech, Chemotechnique Diagnostics (www.chemotechnique.se); CS, corticosteroid; SPCanada: SmartPractice Canada (www.smartpracticecanada.com); SPEurope, SmartPractice Europe (www.smartpracticeeurope.com).Adapted from De Groot.²

HCl, hydrochloride.

the active principle itself at a concentration higher than the one present in the commercial preparation,^{123,125} up to 10% active drug. ROATs are usually negative,^{123,125,133} but provocative use testing may be positive and aid in diagnosis.¹³³ The same problem of false-negative reactions may be encountered with other ophthalmic drugs.

False-Positive Patch Test Reactions

When not properly diluted, some topical drugs, such as povidone-iodine solution, permethrin cream, pharmaceuticals containing dithranol, calcipotriol, tretinoin, 5-fluorouracil, and probably some others, may result in false-positive, irritant patch test reactions. Patients with drug allergies, especially those with leg ulcers, stasis dermatitis or CS allergy, often have multiple positive patch test reactions. This entails a great risk of induction of additional false-positive reactions

TABLE 12. Topical Drugs Present in the European Photopatch Test Baseline and Extended Baseline Series¹³⁵

Baseline Series			Extended Series		
		Drug Type			Drug Type
Benzydamine	2% pet.	NSAID	Dexketoprofen	1% pet.	NSAID
Etofenamate	2% pet.	NSAID	Diclofenac	5% pet.	NSAID, treatment of AK
Ketoprofen	1% pet.	NSAID	Ibuprofen	5% pet.	NSAID
Piroxicam	1% pet.	NSAID	Piketoprofen	1% pet.	NSAID
Promethazine	0.1% pet.	Antihistamine			

AK, actinic keratosis; NSAID, nonsteroidal anti-inflammatory drug; pet, petrolatum.

(excited skin syndrome). Therefore, in all cases with many “positive” patch test reactions, retesting with the haptens to which positive patch test reactions cannot readily be explained, a few at a time, is strongly recommended.

New Allergens and Compound Allergy

When a “new” or rare allergen is found, either the active drug or an excipient, contact allergy should be confirmed by (a combination of) retesting, testing with a dilution series, positive ROAT, and exclusion of irritancy by testing the material in at least 20 unexposed controls. Sometimes, patch testing with a topical drug is positive but with the ingredients negative. This is often reported as “compound allergy”; that is, a new chemical is formed by the interaction of 2 or more ingredients. This is probably a very exceptional situation and has rarely been well documented, for example, in the case of contact allergy to Hirudoid cream.¹³⁴ It is far more likely that the earlier positive patch test to the pharmaceutical had been false-positive or testing with the ingredients false-negative (concentration too low, inadequate vehicle, not all ingredients provided and tested, batch variations).

Photopatch Testing

When photoallergic contact dermatitis is suspected on the basis of patient history and clinical manifestations (allergic contact dermatitis at sites exposed to sunlight or artificial UV radiation), photopatch tests should be performed.^{135,136} Because photoallergic contact dermatitis is relatively infrequent, the practice of photopatch testing is fairly complicated, time-consuming, and laborious, and the yield of positive reactions is usually less than 20%,¹³⁷ few dermatologists in general hospitals or private practice and not all university centers perform this diagnostic procedure. In photopatch testing, 2 sets of allergens are applied for 1 or 2 days, after which 1 set is irradiated with 5 J/cm² of UV-A. Readings are performed immediately after irradiation and 2 or more days thereafter.¹³⁶ Patients may be routinely tested with the European photopatch test baseline series (n = 20) and—either routinely or on indication—with the extended series of photoallergens (n = 15), consisting mostly of UV filters and (topical) drugs, particularly NSAIDs (Table 12).¹³⁵ Apart from the baseline and the extended baseline series, patients' own products or other chemicals to which he or she was exposed to should also be considered for photopatch testing.¹³⁶ Very likely, (many) cases of

photoallergic contact dermatitis go unnoticed, as a result of few centers performing photopatch testing.

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