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REVIEW

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Systemic allergic dermatitis (systemic contact dermatitis) from pharmaceutical drugs: A review

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Abstract

The literature on systemic allergic dermatitis (SAD; also known as systemic contact dermatitis) is reviewed. Both topical drugs (from absorption through mucosae or skin) and systemic drugs (oral, parenteral, rectal) may be responsible for the disorder. The topical route appears to be rare with 41 culprit topical drugs found to cause SAD in 95 patients. Most reactions are caused by budesonide (especially from inhalation), bufexamac, and dibucaine. SAD from systemic drugs is infrequent with 95 culprit drugs found to cause SAD in 240 patients. The drugs most frequently implicated are mitomycin C, methylprednisolone (salt, ester), and hydrocortisone (salt). The largest group of culprit drugs consisted of corticosteroids (19%), being responsible for >30% of the reactions, of which nearly 40% were not caused by therapeutic drugs, but by drug provocation tests. The most frequent manifestations of SAD from drugs are eczematous eruptions (scattered, widespread, generalized, worsening, reactivation), maculopapular eruptions, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE [baboon syndrome]) and widespread erythema or erythroderma. Therapeutic systemic drugs hardly ever cause reactivation of previously positive patch tests and infrequently of previous allergic contact dermatitis. The pathophysiology of SAD has received very little attention. Explanations for the rarity of SAD are suggested.

KEYWORDS
baboon syndrome, budesonide, drugs, eczematous eruption, maculopapular eruption, mitomycin C, pharmaceuticals, SDRIFE, systemic allergic dermatitis, systemic contact dermatitis, symmetrical drug-related intertriginous and flexural exanthema

1 | INTRODUCTION

Systemic allergic dermatitis (SAD; commonly known as systemic contact dermatitis) is a condition that occurs when an individual sensitized to an allergen (hapten) from contact with the skin, mucosa, or both, is exposed to that same allergen or a cross-reacting molecule through a systemic (haematogenous) route. Systemic exposure may occur from transcutaneous, transmucosal, oral, intravenous, intramuscular, intra-articular, subcutaneous, intralesional, intravesical, and inhalational routes as well as implants.[1,2] Possible manifestations of SAD are shown in Table 1 and include reactivation of previous eczema and positive patch tests, acrovesicular (dyshidrotic) dermatitis, various drug eruptions, including dermatitis/eczema, maculopapular eruption, urticaria, erythema multiforme-like reactions, photoallergic dermatitis, and, sometimes, systemic symptoms. The main groups of allergens involved in SAD are metals (notably mercury and nickel), plant products, for example, in herbal teas and in foods including Myroxylon pereirae resin (balsam of Peru) and its constituents used as spices and flavorings, and pharmaceutical drugs. The pathophysiology of SAD, apart from (although highly likely to) being mediated by delayed-type hypersensitivity, is incompletely understood and an explanation for the diverse clinical manifestations is lacking.[1,2,5-15]

This review focuses on drugs, both topical and systemic, as causes of SAD and is based on the data collected during the writing of two

books on delayed-type hypersensitivity to drugs in the author's *Monographs in Contact Allergy* series,[4,16] and on the texts therein. For this review all issues of *Contact Dermatitis*, dating back to the first issue in 1975 and of *Dermatitis/American Journal of Contact Dermatitis* dating back to the first issue in 1990, were manually searched. The references of the relevant articles were screened as were the references of any article found through the reference search, until all relevant information had been retrieved. Data were found in PubMed using several search terms including "systemic allergic dermatitis", "systemic contact dermatitis", alone and in combination with "pharmaceutical" or "drug". Much relevant information was found while searching for data for the other subjects of the books (using multiple, unrelated search terms). The aims were to identify the nature of the drugs that have caused SAD, to assess their clinical manifestations, and to provide an extensive bibliography of the available relevant literature (very early literature regarding penicillins, sulfonamides, and opium alkaloids was excluded). The prerequisite for being considered a case of SAD and being included in this review was that sensitization to the culprit drug or a cross-reacting chemical prior to the event was either proven or very likely.

2 | SYSTEMIC ALLERGIC DERMATITIS FROM TOPICAL DRUGS

Systemic allergic dermatitis from topical drugs results from cutaneous or mucosal absorption of a chemical to which the patient has previously become sensitized. Sensitization may also be the result of cross-reactivity to a related chemical that had previously induced contact allergy. The mucosae, to which drugs may be applied and from permucosal absorption enter the circulation resulting in systemic exposure, are those of the mouth (oral spray, lozenges), airways (drugs for inhalation), conjunctivae (eye drops), genitals (notably the vagina, vaginal tablets), and anus. Suppositories are regarded here as systemic drugs, as the bulk of the drug is released in the rectum.

TABLE 1 Symptoms and signs of systemic allergic dermatitis[1-12]

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 (acrovesicular dermatitis, dyshidrotic eczema)
Drug eruptions
Eczematous eruption (scattered, widespread, generalized)
Maculopapular eruption
Erythroderma, widespread erythema
Urticaria/angioedema (delayed)
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE/ baboon syndrome)[a]
Erythema multiforme(-like eruption)
Purpura
Photosensitivity/photoallergic dermatitis
Vasculitis(-like lesions)
Acute generalized exanthematous pustulosis
Systemic symptoms: fever, malaise, nausea, vomiting, diarrhoea, headache, arthralgia, (rarely) syncope

[a]For convenience sake, SDRIFE and baboon syndrome are used as synonyms in this article (realizing that some authors will disagree)

Cases of SAD from topically applied drugs are summarized in Table 2. The author found 41 culprit drugs causing SAD in 95 patients. The number of reactions shown in Table 2 (n = 104) exceeds the number of patients, as some individuals had more than one manifestation and are shown twice (eg, a systemic reaction to the topically applied drug and later also to the patch test).

In 51 cases (49.0%), the culprit drugs had been applied to the mucosae: airways (inhalation) 19, vagina 12, nose 9, eyes five, mouth four, urethra one and the middle ear one. In 35 cases (33.7%), the drugs had been applied to the skin: intact skin 11, patch tests 10, damaged skin eight, transdermal tests five, and a repeated open application test one. Contact of the culprit drugs, presumably, with both skin and mucosa (anal/perianal) was reported in 16 cases (15.4%) and two patients had developed SAD from drugs present in root canal fillings. The most frequent culprit drugs were budesonide (23 reactions), bufexamac (17 reactions), dibucaine (eight reactions), chloramphenicol (four reactions), diltiazem, tetracaine, acetarsone (historical allergen) and neomycin (three reactions each), together causing over 60% of all cases of SAD to topical drugs. Twenty-four topical drugs (59%) caused only one case of SAD each.

The nature of the causative drugs often mirrored their applications and indications. Budesonide, for example, the most frequently used corticosteroid for asthma, was responsible for 15 of 16 cases of SAD caused by inhalation (the 16th case was caused by albuterol [salbutamol] and three were the result of inadvertent occupational inhalation). Budesonide also caused six of the nine cases with nasal application, while the remaining three were caused by two other corticosteroids and phenylephrine.

The causative drugs in cases with application to the anogenital area were topical anaesthetics in 10 of 16 cases (dibucaine in six) and bufexamac (these non-steroidal anti-inflammatory drugs [NSAIDS] are assumed to relieve pain, itch, and inflammation) in four cases.

Table 3 shows the clinical manifestations of SAD from topical drugs with dermatitis/eczema (n = 34, 32.7%), SDRIFE/baboon syndrome (n = 12, 11.5%), maculopapular eruptions (n = 10, 9.6%), and erythematous skin reactions (with or without oedema) (n = 9, 8.7%) being the most frequent eruptions. Only one patient had fever, other systemic manifestations were not observed. In most cases where the culprit drugs had been applied to the skin, dermatitis first started at the site of application (including patch tests), followed by eruptions elsewhere. In the cases of SAD from inhalation, local allergic reactions of the mucosae were infrequent.

When comparing manifestations from applications to the categories skin, mucosae, and (peri)anally (including application to anal fissures), it was found that eight of 12 cases of SDRIFE have been caused by application to the (peri)anal area, that four of the five cases

TABLE 2 Topical drugs that have caused systemic allergic dermatitis

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
Acetarsone	1	Pessary	Acetarsone	Extensive erythematous vesicular eruption	17
	1	Pessary	Acetarsone	Generalized dermatitis	18
	1	Pessary	Neoarsphenamine	Generalized erythema, eyelid oedema	19
Albuterol (salbutamol)	1	Inhalation	Albuterol	Eczematous lesions on the arms and legs	20
Ampicillin	1	Middle ear	Unknown	SDRIFE/baboon syndrome	21
Bacitracin	1	Root canal filling	Bacitracin	Exacerbation of previous dermatitis	22
Benzydamine	1	Oral mucosa	Benzydamine	Exacerbation of previous photodermatitis (positive photopatch test),	23
Budesonide	4	Inhalation	Budesonide	Reactivation of previously positive patch tests	24,25
	4	Inhalation	Budesonide	Maculopapular exanthema	24,26,27
	2	Inhalation	Budesonide	Urticaria	28,29
	2	Inhalation	Budesonide	Eczematous eruption	30,31
	1	Inhalation	Budesonide	Flare-up of previous dermatitis	24
	1	Inhalation	Budesonide	Generalized skin eruption	32
	1	Inhalation	Budesonide	EM-like dermatitis on the face and arms	33
	2	Nasal mucosa	Budesonide	Eczematous eruptions	34,35
	1	Nasal mucosa	Budesonide	Generalized exanthema	36
	1	Nasal mucosa	Budesonide	Pruritic erythematous papular eruption	37
	1	Nasal mucosa	Budesonide	Erythema and oedema of the face and neck	38
	1	Nasal mucosa	Budesonide	Maculopapular eruption on the arms	39
	1	Patch test	Budesonide	Macular erythema of the trunk	40
	1	Patch test	Budesonide	Erythema, oedema, itching face, neck, chest	38
Bufexamac	4	Skin	Bufexamac	Erythema multiforme -like dermatitis with urticarial papules and plaques	41
	4	Skin	Bufexamac	Dermatitis with erythema, oedema, vesicles	42,43
	1	Skin	Bufexamac	Acute generalized exanthematous pustulosis	44
	1	Abraded skin	Bufexamac	Facial oedema and widespread polymorphic eruption	43
	1	(Peri)anal	Bufexamac	Generalized non-palpable purpura	45
	1	(Peri)anal	Bufexamac	SDRIFE/baboon syndrome	46
	1	(Peri)anal	Bufexamac	Dermatitis of the trunk, face, neck, and wrists	47
	1	(Peri)anal	Bufexamac	Erythema multiforme-like eruption; localizations suggest baboon syndrome	48
	1	Vulva	Bufexamac	Erythema and oedema face, trunk, limbs	43
	2	Patch test	Bufexamac	Flare-up of previous eruption/dermatitis	47,48
Buprenorphine	1	TD patch	Buprenorphine	Recurrent generalized eczema	49
	1	TD patch	Buprenorphine	Erythema and transient oedema on the face, eczematous lesions on the eyelids	49
Carbarsone	1	Pessary	Carbarsone	Generalized eczematous eruption	50
Chloramphenicol	1	Leg ulcer	Chloramphenicol	Generalized papular and nodular eruption	51
	1	Leg ulcer	Chloramphenicol	Erythema, oedema and vesicles on the legs, hips, and arms	52

(Continues)

TABLE 2 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
	1	Conjunctiva	Chloramphenicol	Generalized maculopapular exanthema	53
	1	Patch test	Chloramphenicol	Recurrence of previous allergic conjunctivitis	54
Chlorquinaldol	1	Vaginal ovule	Clioquinol	Eczema on abdomen and thorax	55
Clioquinol	1	Vulvovaginal	Clioquinol	Widespread dermatitis, especially flexural	56,57[a]
Dibucaine	4	(Peri)anal	Dibucaine	SDRIFE/baboon syndrome	58-61
	1	(Peri)anal	Dibucaine	Maculopapular eruption	62
	1	(Peri)anal	Dibucaine	Acute generalized exanthematous pustulosis	63
	1	Oral mucosa	Dibucaine	Photoallergic dermatitis	64
	1	Patch test	Dibucaine	SDRIFE/baboon syndrome	65
Diltiazem	1	Anal fissure	Diltiazem	Generalized papular rash	66
	1	Anal fissure	Diltiazem	SDRIFE/baboon syndrome	58
	1	Anal fissure	Diltiazem	Maculopapular eruption	67[a]
Dorzolamide	1	Conjunctiva	Dorzolamide	Patchy "fixed" dermatitis-like lesions abdomen	68
	1	ROAT	Dorzolamide	Recurrence of previous eczema	68
Ephedrine	1	Nasal mucosa	Ephedrine	Maculopapular eruption	69
Eucaine	1	(Peri)anal	Eucaine	Widespread dermatitis	70
Gentamicin	1	Burn ulcer	Gentamicin	Itchy eczema on the scalp, limbs, and hands	71
	1	Patch test	Gentamicin	Generalized eczematous dermatitis	71
Hydrocortisone aceponate	1	Skin	Hydrocortisone aceponate	Eczema on the backs of the legs, mainly the popliteal fossae	72
Hydroxychloroquine	1	Inhalation	Hydroxychloroquine[b]	Fever, generalized erythema	73
Iodoquinol	1	Vaginal tablet	?	*Possibly* SAD	74
Lidocaine	1	(Peri)anal	Lidocaine	Widespread eczema	75
Mesna	1	Inhalation[c]	Mesna[b]	Exacerbation of current dermatitis	76
Methyl aminolevulinate	1	Skin	Methyl aminolevulinate	Generalized eruption with multiple erythematous and oedematous papules and plaques	77
Methylphenidate	1	TD patch	Methylphenidate	Generalized itchy burning red lesions	78
	1	Patch test	Methylphenidate	Itchy burning red lesions on the entire back	78
Neomycin	1	Conjunctiva	Neomycin	Eczema in the axillae, on the arms and legs	79
	1	Patch test	Neomycin	Flare-up previous allergic contact dermatitis	80
	1	Root canal filling	Neomycin	Exacerbation of previous dermatitis	22
Nicotine	1	TD patch	Nicotine	Eczematous lesions at previous sites of transdermal patches + papulovesicular rash	81
Nifuroxime	1	Vaginal ovule	Nifuroxime	Widespread dermatitis (uncertain case)	82
	1	Vaginal ovule	Nifuroxime	Widespread urticaria (uncertain case)	83
Nylidrin (buphenine)	1	Patch test	Nylidrin	Reappearance of previous dermatitis	84
Nystatin	1	Vaginal ovule	Nystatin	Widespread erythematous papular eruption	85
Oxyphenbutazone	1	Leg ulcer	Oxyphenbutazone	Dermatitis of the face and neck, eyelid oedema	86
Phenylephrine	1	(Peri)anal	Phenylephrine	Widespread eczema	75
	1	Conjunctiva	Phenylephrine	Periocular dermatitis spreading to the face, neck, and chest	87

TABLE 2 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
Prednisolone acetate	1	Nasal mucosa	Prednisolone or other corticosteroid	Maculopapular eruption	88
Promestriene	1	Vaginal ovule	Unknown	Eczema on abdomen and thorax	55
Sevoflurane	1	Inhalation	Sevoflurane[b]	SDRIFE/baboon syndrome	89
Sisomicin	1	Conjunctiva	Gentamicin	Very small reddish papules over the chest and one popliteal fossa; erythema periorbital right	90
Stannous fluoride	1	Oral mucosa	Tin	Perianal itching and mild flexural dermatitis in the elbow folds, axillae, and groin (resembling the baboon syndrome)	91
	1	Oral mucosa	Tin	Recurrent (idiopathic) urticaria	92
Testosterone	1	TD patch	Testosterone	Generalized dermatitis	93
Tetracaine	2	(Peri)anal	Tetracaine	SDRIFE/baboon syndrome	94,95
	1	Urethra	Tetracaine	Dermatitis in the groin area	96
Triamcinolone acetonide	1	Nasal mucosa	Budesonide	Acneiform facial rash; flexural eczema	97[a]
Trimebutine	1	(Peri)anal	Trimebutine	Delayed urticaria	98

Abbreviations: EM, erythema multiforme; ROAT, repeated open application test; Route, route of administration; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; Sensitizat., sensitization; TD, transdermal.
[a]Systemic allergic dermatitis highly likely, but patch tests were not performed or negative.
[b]Occupational sensitization.
[c]Drug provocation test.

of urticaria were the result of a drug applied to mucosae (the fifth case to the perianal area), and that five of six cases of exacerbation of previous dermatitis were the result of positive patch tests.

3 | SYSTEMIC ALLERGIC DERMATITIS FROM SYSTEMIC DRUGS

Systemic allergic dermatitis from systemic drugs results from oral, parenteral (injections) or rectal (suppositories, enemas) administration of a chemical to which the patient has previously become sensitized from topical administration to the skin or mucosae. Sensitization may also be the result of cross-reactivity to a related chemical that has previously induced contact allergy.[1-12,99] In most cases, the sensitization is caused by topical therapeutical administration of the drug, but has in some cases resulted from occupational contact with bacampicillin, deflazacort, heroin, piperazine, nitrofurazone, propacetamol, pyridoxine, ranitidine, and thiamine (Table 4).

Cases of SAD from systemically administered drugs are summarized in Table 4. The author found 95 culprit drugs causing SAD in 240 patients. The number of reactions shown in Table 4 (n = 279) exceeds the number of patients, as some individuals had different manifestations or were orally challenged with several corticosteroids.

The route of administration of the culprit drugs was oral in 192 of the 279 cases (68.8%) (of which 70 [36.5%] were drug provocation tests), intravesical in 31 (11.1%) (29 from mitomycin C), intravenous in 21 (7.5%), intra-articular in 13 (4.7%), intramuscular in nine (3.2%), rectal (suppositories) in six (2.2%) and "other" in seven cases (2.5%). The drugs most frequently implicated are shown in Table 5, with the most common being mitomycin C (n = 29, 10.4%), methylprednisolone (salt, ester) (n = 21, 7.5%), and hydrocortisone (salt) (n = 20, 7.2%). The largest group of drugs consisted of corticosteroids (n = 18, 19%) with 85 SAD reactions (30.5%), 33 of which (39%) were not caused by therapeutically administered drugs, but by drug provocation tests. Of the 20 reactions to hydrocortisone (salt), for example, 16 (80%) were not caused by the drugs used

TABLE 3 Clinical manifestations of systemic allergic dermatitis caused by topical drugs

Clinical manifestations	Number of cases (%)
Dermatitis/eczema (de novo, worsening, limited or generalized)	34 (32.7)
SDRIFE/baboon syndrome	12 (11.5)
Maculopapular eruption	10 (9.6)
Erythematous eruption (+/− oedema)	9 (8.7)
Reactivation of previous dermatitis	7 (6.7)
Erythema multiforme-like dermatitis	6 (5.8)
Urticaria	5 (4.8)
Reactivation of previous positive patch tests	4 (3.8)
Papular eruption	4 (3.8)
Acute generalized exanthematous pustulosis	2 (1.9)
Photoallergic dermatitis	2 (1.9)
Other reactions	9 (8.7)

TABLE 4 Systemically administered drugs that have caused systemic allergic dermatitis

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
Acyclovir	1	Oral	Acyclovir	Urticaria	100
	1	Intravenous	Acyclovir	Urticaria	101
	1	Oral	Acyclovir	Maculopapular eruption and eczema	102
	1	Oral	Acyclovir	Eczema	102
	1	Oral	Acyclovir	Generalized symmetrical exanthem	103
Alprenolol	1	Oral	Alprenolol	Widespread dermatitis	104
Aminophylline[a]	2	Intravenous	Ethylenediamine	SDRIFE/baboon syndrome	105,106
	2	Oral	Ethylenediamine	Lichenoid eruption	107
	1	Intravenous	Ethylenediamine	Generalized dermatitis	108
	1	Intramuscular	Ethylenediamine	Erythroderma	108
	1	Oral	Ethylenediamine	Erythematous eruption	109
	1	Oral	Ethylenediamine	Exfoliative erythroderma	110
	1	Oral	Ethylenediamine	Maculopapular eruption	111
	1	Intravenous[b]	Ethylenediamine	Maculopapular eruption	111
	1	Suppository	Ethylenediamine	Exfoliative erythroderma	112
	1	Suppository	Ethylenediamine	Generalized eruption of erythematous papules	113
Amlexanox	1	Oral	Amlexanox	Erythema multiforme-like eruption	114
Amoxicillin	1	Oral	Topical penicillin	SDRIFE/baboon syndrome	115[c]
Bacampicillin	1	Oral[b]	Bacampicillin[d]	Hand eczema, relapse of positive patch test, stomach pain, diarrhoea	116
Betamethasone	2	Oral	Betamethasone/other CSs	SDRIFE/baboon syndrome	117,118[b]
	1	Oral	Hydrocortisone	Facial erythema	119
	1	Oral	Triamcinolone acetonide	Generalized papular dermatitis	97
Betamethasone acetate	1	Intralesional[b]	Hydrocortisone	Facial erythema	119
Betamethasone dipropionate	1	Intramuscular	Unknown corticosteroid(s)	Maculopapular exanthema + flare-up	120
	1	Intra-articular	Unknown corticosteroid(s)	Generalized eczema, flare-up of previous eczema	120
	1	Intramuscular	Unknown corticosteroid(s)	Unknown exanthema	120
Betamethasone sodium phosphate	1	Intralesional[b]	Hydrocortisone	Facial erythema	119
	1	Intramuscular	Unknown corticosteroid(s)	Maculopapular exanthema + flare-up	120
	1	Intra-articular	Unknown corticosteroid(s)	Generalized eczema, flare-up of previous eczema	120
	1	Intramuscular	Unknown corticosteroid(s)	Unknown exanthema	120
Carbutamide	7	Oral[b]	Sulfanilamide	Relapse of dermatitis and previous patch test	121[c]
Cefalexin	1	Oral	Cefalexin	Generalized itching, erythema, scaling	122
Chloral hydrate	2	Oral & oral[b]	Chloral hydrate	"Eruption"	123
Chloramphenicol	1	Intramuscular	Chloramphenicol	Edematous and exudative reaction of the face	54
Chlorpheniramine	2	"Injection"	Dexchlorpheniramine	Generalized dermatitis	124
Chlorpromazine	2	Oral	Promethazine	Exacerbation of previous dermatitis	125
	1	Oral	Chlorpromazine	Oedema of the hands, arms and face, vertigo, tendency to fainting	125
Chlorpropamide	1	Oral[b]	Sulfanilamide	Relapse of dermatitis and patch test	121[c]
Chlorquinaldol				See under Clioquinol	
Clioquinol	6	Oral[b]	Clioquinol	Flare-up of original dermatitis (n = 5); scattered papules (n = 2); localized itching (n = 2), generalized papular dermatitis (n = 1); some patients were sensitized to clioquinol, others to	126

TABLE 4 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
				chlorquinaldol; some were orally challenged with one drug, some with the other; these were treated as one group, no differentiating data were provided	
	2	Oral	Clioquinol	Generalized dermatitis	127,128
	1	Oral	Clioquinol	Flare-up of previous dermatitis	129[c]
Clonidine	1	Oral[b]	Clonidine	Flare-up of previous dermatitis	130
	1	Oral[b]	Clonidine	Maculopapular eruption	130
Cloprednol	1	Oral[b]	Unknown corticosteroid(s)	SDRIFE/baboon syndrome	118
Codeine[e]	?		Codeine or other opium alkaloids	Various manifestations of systemic allergic dermatitis	131-136
Cyanocobalamin	1	Oral	Cobalt	Widespread nummular and hand dermatitis	137
Deflazacort	1	Oral	Three other CSs	Maculopapular eruption	138
	1	Oral	Unknown corticosteroid(s)	Erythematous plaques with pustules	139
	1	Oral	Deflazacort[d]	SDRIFE/baboon syndrome with fever, nausea, vomiting, and hypotension	140
	1	Oral[b]	8 other corticosteroids	Pruritic rash on the forearms and chest	141[c]
	1	Oral	Betamethasone valerate	Dermatitis on the arms and legs	142
Dexamethasone	1	Oral[b]	Unknown corticosteroid(s)	Maculopapular exanthema	143
	1	Oral[b]	Unknown corticosteroid(s)	SDRIFE/baboon syndrome	118[c]
Dexamethasone disodium phosphate	1	Oral	3 other corticosteroids	Maculopapular eruption	138
Dexketoprofen[f]	1	Oral	Ketoprofen	Systemic photoallergic dermatitis	144
Dimethindene	1	Oral	Dimethindene	Maculopapular and vesicular rash	145
Dimethyl sulfoxide	1	Intravesical	Dimethyl sulfoxide	Erythematous micropapular eruption	146
Diphenhydramine	1	Oral	Diphenhydramine	Generalized dermatitis	147
	1	Oral	Diphenhydramine	Systemic photoallergic dermatitis (uncertain)	148
	1	Oral	Diphenhydramine	Unknown exanthema	149
Disulfiram	1	Oral	Disulfiram (rubber)	Erythematous scaly rash, fever, vomiting	150
	1	Oral	Disulfiram (implant)	Dyshidrotic eczema, nummular eczema	151
	1	Oral	Disulfiram (rubber)	Generalized dermatitis	152
	1	Oral	Disulfiram (implant)	Erythema and oedema of the face, widespread erythematous, oedematous and vesicular patches and an urticarial plaque around the operation scar of a previous disulfiram implant (removed because it was "inflamed")	151,153
	1	Oral	Disulfiram (rubber)	Erythematous and vesicular dermatitis	154
	1	Oral	Disulfiram (rubber)	Violent reaction with widespread skin rash	155
	1	Oral	Disulfiram (implant)	Generalized dermatitis	156
	1	Oral	Disulfiram (rubber)	Oedema of the feet + vesicular rash face, arms, and dorsal feet	157
Doxepin	1	Oral	Doxepin	Extensive scaly patches and plaques	158
Ephedrine	3	Oral	Ephedrine	Generalized erythema	159,160
Epirubicin	1	Intravesical	Mitomycin C (uncertain)	Widespread dermatitis (uncertain case)	161
Erythromycin	1	Oral	Erythromycin	Generalized dermatitis	162,163
Estradiol	1	Oral	Estradiol	Systemic pruritic rash	164
	2	Oral	Estradiol	Maculopapular eruptions	165
Estradiol derivative	1	Oral	Estradiol	Generalized eczema	166
Famciclovir	1	Oral[b]	Acyclovir	Erythematous dermatitis	100[c]
	1	Oral[b]	Acyclovir	Pruriginous rash	102[c]
	1	Oral[b]	Acyclovir	Itchy erythematous patches	103[c]
Fenofibrate[f]	2	Oral	Ketoprofen	Systemic photoallergic dermatitis	167,168

(Continues)

TABLE 4 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
Fluorouracil	1	Intravenous	Fluorouracil	Acute dermatitis with severe neck and head oedema	169
Framycetin	1	Subconjunctival injection	Framycetin	Generalized acute and subacute dermatitis	170
Fusidic acid	1	Oral	Fusidic acid	Generalized micropapular exanthema	171[c]
Gentamicin	1	Intravenous	Gentamicin	Eczematous eruption arms and neck	172
	1	Intravenous[b]	Gentamicin	Generalized eczema	173
	1	Bone cement	Probably neomycin	Dermatitis of legs and arms	174
	1	Intravenous	Neomycin	Severe drug reaction	175
	1	Intravenous	Neomycin	Exfoliative erythroderma	176
Hydrocortisone	1	Oral[b]	Hydrocortisone	Facial erythema	119
	4	Oral[b]	Hydrocortisone	Flare-up positive patch tests (n = 2), indurated papules on the thigh (n = 1), perianal oedema and erythema (n = 1)	177-179
	2	Oral[b]	Prednisolone (ester, salt?)	Maculopapular eruption	6,120
	1	Intravenous	Unknown corticosteroid(s)	Maculopapular eruption	120
	1	Oral[b]	Unknown corticosteroid(s)	SDRIFE/baboon syndrome	118[c]
	1	Intravenous	Prednisolone ester	Rash	180
	1	Oral	Unknown corticosteroid(s)	Generalized erythematous plaque-like lesions	181
	1	Oral[b]	Unknown corticosteroid(s)	Flare-up of positive patch tests	181
	7	Oral[b]	Unknown corticosteroid(s)	Flare-up of previous eczema or positive patch tests (n = 6); widespread erythema or exanthema (n = 2)	182
Hydrocortisone sodium phosphate	1	Intravenous	Hydrocortisone (ester?)	Erythematous rash neck, trunk, and thighs	183
Hydromorphone	1	Subcutaneous	Hydromorphone	Generalized papulovesicular dermatitis	184
Hydroxyprogesterone	1	Oral	Unknown corticosteroid(s)	Itchy papular and vesicular eruption	185
Hydroxyzine	1	Oral	Piperazine[d]	Unknown	186
Ibuprofen	1	Oral	Ibuprofen	Eczematous eruption with nausea and fever	187
Iodoquinol	1	Oral[b]	Clioquinol or iodoquinol	Exacerbation of previous ACD	188
Isoxsuprine	1	Oral	Nylidrin (buphenine)	Generalized dermatitis	84
Ketoconazole	1	Oral	Econazole, miconazole (?)	Generalized eczema	189
	1	Oral	Ketoconazole	SDRIFE/baboon syndrome	190
Ketoprofen	2	Oral	Ketoprofen	Photoallergic dermatitis	191
Methoxsalen	1	Oral	Methoxsalen	Burning, erythema, oedema, vesicles	192
Methylprednisolone	1	Oral[b]	Multiple CSs	Maculopapular exanthema	143
	1	Oral	Unknown corticosteroid(s)	Unspecified exanthema, possibly SDRIFE	118[c]
	1	Oral[b]	Many other CSs	Pruritic rash on the chest	141
	3	Oral[b]	Unknown corticosteroid(s)	Relapse of previous positive patch test or eczema (n = 1), widespread erythema or exanthema (n = 1), facial erythema (n = 1); see also "methylprednisolone, unspecified salt or ester" below (the group contains 4 cases of systemic allergic dermatitis from methylprednisolone *base*)	182
Methylprednisolone acetate	1	Intra-articular;	Hydrocortisone (ester?)	Erythema around the neck	183
Methylprednisolone sodium succinate	1	Intravenous	Hydrocortisone (ester?)	Generalized erythematous rash	183
	1	Intravenous[b]		SDRIFE from provocation with drip infusion	183
	1	Intra-articular	Unknown corticosteroid(s)	Widespread erythema	119
	1	Oral[b]	Unknown corticosteroid(s)	Widespread erythema	119

TABLE 4 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
Methylprednisolone, unspecified salt, or ester	11	3 i.v., 4 oral, 4 Intra-articular;	Unknown corticosteroid(s)	Maculopapular eruption (n = 9), generalized eczema (n = 2), flare-up previous eczema (n = 1)	120
Metronidazole	1	Oral	Metronidazole	Maculopapular rash + flare-up of previous eczema	57
Mitomycin C	13	Intravesical	Mitomycin C	Dermatitis	193-200
	6	Intravesical	Mitomycin C	SDRIFE/baboon syndrome	193,196,201
	4	Intravesical	Mitomycin C	Acrovesicular dermatitis	202,203
	1	Intravesical	Mitomycin C	Maculopapular eruption (also from patch test)	204
	1	Intravesical	Mitomycin C	Urticaria	202
	2	Intravesical	Mitomycin C	Generalized rash	199,205
	1	Intravesical	Mitomycin C	Henoch-Schönlein purpura (also from patch test)	206
	1	Intravesical	Mitomycin C	Fever	197
Mofebutazone	1	Oral	Mofebutazone	Generalized dermatitis	207
Morphine	1	Intravenous	Heroin (diacetylmorphine)[d]	Maculopapular rash with vesicles	208[c]
Neomycin	1	Oral	Neomycin	SDRIFE/baboon syndrome	209
	1	Oral	Neomycin	No data available to the author	210
	10	Oral[b]	Neomycin	Flare-up patch test (n = 6), flare-up previous eczema (n = 5), generalized itching (n = 4), vesicular dermatitis of the palms (n = 3), nausea (n = 3), papular eruption (n = 2), localized itching (n = 2), generalized dermatitis (n = 1), vomiting (n = 1)	126
Nitrofurantoin	1	Oral	Nitrofurazone[d]	Drug rash	211
Norfloxacin	1	Oral	Possibly clioquinol	Papulopustular, erythematous and oedematous lesions abdomen, lumbosacral, thighs; recurrence from positive patch test	212[c]
Nystatin	1	Oral	Nystatin	SDRIFE/baboon syndrome	213
	1	Oral	Nystatin	Generalized eruption	214
	1	Oral (lozenge)	Nystatin	Maculopapular eruption with fever, arthralgia, malaise and diarrhoea	215
Oxyphenbutazone	1	Suppository	Oxyphenbutazone	Dermatitis progressing to erythroderma	216
Phenylbutazone	1	Suppository	Phenylbutazone	Exacerbation of previous eczema with spreading erythema; same case as in piperazine[217] and pyrazinobutazone[217]	217
Piperazine	2	Oral	Ethylenediamine	Morbilliform rash	218,219
	1	Oral	Ethylenediamine	Exfoliative erythroderma	219
	1	Oral[b]	Ethylenediamine	Maculopapular exanthema, shivering, anxiety, and tachycardia	219
	1	Oral	Ethylenediamine	Angioedema eyelids and tongue	220
	1	Oral	Ethylenediamine	Erythroderma, facial oedema, malaise	221
	1	Suppository	Piperazine	Exacerbation of previous eczema with spreading erythema; same case as in phenylbutazone[217] and pyrazinobutazone[217]	217
Prednisolone	1	Oral[b]	Beclomethasone/other CS	Worsening of existing dermatitis	222
	1	Oral	Various other CSs	Malaise, oral enanthema, flexural erythema and maculopapular eruption on the trunk	223
	1	Oral	Hydrocortisone	Worsening of existing dermatitis	224[c]
	1	Oral	5 other corticosteroids	Generalized maculopapular eruption	225
	1	Oral	Unknown corticosteroid(s)	Unspecified exanthema	118
	1	Oral	Hydrocortisone	Generalization of face dermatitis	226

(Continues)

TABLE 4 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
	1	Oral	Prednisolone acetate	Generalized erythema, facial oedema and disseminated papules	227
	2	Oral[b]	Unknown corticosteroid(s)	Exacerbation of previous eczema or positive patch tests (n = 1); widespread erythema or exanthema (n = 1)	182
Prednisone	1	Oral	Probably hydrocortisone	Generalized erythematous dermatitis	228
	1	Oral[b]	Probably hydrocortisone	Generalized dermatitis	228
	1	Oral	Prednisolone acetate	Generalized dermatitis	40
	1	Oral[b]	Unknown corticosteroid(s)	Maculopapular exanthema	143
Pristinamycin	3	Oral	Virginiamycin	Macular erythema, vesicles, fever (n = 1); generalized erythema, facial oedema (n = 1); truncal erythema, fever, headache (n = 1)	229
	1	Oral	Virginiamycin	Delayed urticaria, stupor, vomiting; transient oedema of the eyes and lips from positive patch test with wheals adjacent to the patch	230
	1		Virginiamycin	Acute generalized exanthematous pustulosis	231
	1		Virginiamycin	No data available to the author	232
	3	Oral	Virginiamycin	Eczematous eruptions, possibly the same patients as in[229]	233
Procaine[g]			Procaine/*p*-phenylene diamine/sulfonamides	Recurrence of previous dermatitis, spreading of existing dermatitis, generalized pruritus, oedema of the face, fever	e.g. 234
Promazine[f]	1	Oral	Promethazine	Photoallergic dermatitis	235
Promethazine	?	Oral		No data available (cited in[125])	236
Propacetamol	1	Intravenous	Propacetamol[d]	Maculopapular eruption	237
Pseudoephedrine	1	Oral	Phenylephrine	Erythroderma	238
Pyrazinobutazone	1	Oral	Phenylbutazone	Lesions on the hands and flare-up of previous patch test	239
	1	Suppository	Phenylbutazone and piperazine	Exacerbation of previous eczema with spreading erythema; same case as in piperazine[217] and phenylbutazone[217]	217
Pyridoxine (vitamin B_6)	1	Oral[b]	Pyridoxine[d]	Eczema in sun-exposed areas, reactivation of previous positive patch tests	240
Ranitidine	1	Oral	Ranitidine[d]	Swelling and burning of the lips	237
Ribostamycin	1	Intramuscular	Neomycin	Exfoliative erythroderma	241
Succinylcholine	1	Intravenous	Not mentioned	Eczematous rash (uncertain case)	242
Sulfamethoxazole	1	Oral	Sulfanilamide	Clinical exacerbation	243
	1	Oral	Sulfanilamide	Severe drug eruption	244
Sulfanilamide[g]			Sulfanilamide and other topical sulfonamides or other para-amino chemicals, eg, procaine and *p*-phenylenediamine	Various, including exacerbation of previous eczema, extensive dermatitis, maculopapular drug eruptions, photoallergic eruptions	234,245-248
Sulfathiazole	2	Oral	Sulfathiazole	Exacerbation of previous eczema and extensive erythematous macular eruption	249
Terbinafine	1	Oral	Terbinafine	SDRIFE/baboon syndrome	250[c]
Thiamine (vitamin B_1)	1	Oral[b]	Thiamine[d]	Exacerbation of previous eczema	251
	1	Oral	Thiamine[d]	Exacerbation of previous eczema	252
	1	Intramuscular[b]	Thiamine	Erythematous plaques, micropapular rash	253
	1	Oral[b]	Thiamine	Pruritic erythematous micropapular rash	253
Tiaprofenic acid[f]	1	Oral	Ketoprofen	Photodistributed eruption	254[c]

TABLE 4 (Continued)

Drug	No. of cases	Route	Previous sensitization	Clinical manifestations	Refs.
	2	Oral	Ketoprofen	Photosensitive vesiculobullous eruption	255
Tolbutamide	3	Oral[b]	Sulfanilamide	Relapse of dermatitis and patch test	121[c]
Tramadol	2	Oral	Buprenorphine	Exacerbation of previous eczema, fever	256[c], 257
Triamcinolone	1	Oral[b]	Unknown corticosteroid(s)	Maculopapular eruption	143
	1	Oral[b]	Prednisolone (ester/salt?)	Erythematous rash	6[c]
Triamcinolone acetonide	1	Intra-articular	Unknown corticosteroid(s)	SDRIFE/baboon syndrome	258
	1	Intra-articular	Unknown corticosteroid(s)	Erythema multiforme-like eruption	258
	1	Intra-articular	7 other corticosteroids	Generalized pruritic eruption	141
	1	Intra-articular	Unknown corticosteroid(s)	SDRIFE with bullae resembling bullous pemphigoid	259
	1	Oral	Desoximetasone	Generalized papulovesicular eruption	260
	1	Intramuscular	Clobetasol propionate, betamethasone valerate	Spreading of existing eczema becoming vesicular	222
	1	Oral	Budesonide	Generalization of dermatitis	261
	1	Intra-articular	Unknown corticosteroid(s)	Maculopapular eruption	120[c]
Trimebutine	1	Oral[b]	Trimebutine	Generalized urticaria	98
Valaciclovir	1	Oral	Acyclovir (probably)	Itchy exanthema on the face, trunk, arms, and legs	103
Virginiamycin	1	Oral	Virginiamycin	Bullous eczema on the hands and elbow, facial oedema, pruritus, and generalized erythema	229

Note: Table adapted from De Groot.[16]

Abbreviations: ACD, allergic contact dermatitis; CSs, corticosteroids; EM, erythema multiforme; MP, maculopapular; i.v., intravenous.

[a]Aminophylline = theophylline + ethylenediamine.

[b]Drug provocation test.

[c]Systemic allergic dermatitis highly likely, but patch tests were not performed or were negative.

[d]Occupational sensitization.

[e]Some examples of literature given; data not specified because of difficulties in assessing very early literature. In this literature, (occupational) contact dermatitis and (in some cases) systemic allergic dermatitis to opium alkaloids, including codeine, morphine, apomorphine, and ethylmorphine have been described (eg, refer[131-136]; reviews in refs.[131,133]), the first report dating back to 1882 (cited in ref.[131]). In those days, eczematous dermatitis from opium compounds used externally in the form of lotions, suppositories and other application forms was apparently well known.[133] A more recent review of the subject was provided in 2006.[262] Although occupational sensitization to opium compounds still occurs today, no recent cases of systemic allergic dermatitis to codeine have been found.

[f]Photocross-reaction.

[g]Some examples of literature given; data are not specified because of difficulties in assessing very early literature and because this is largely a historical allergen.

for disease, but from a drug challenge. Likewise, most reactions to neomycin (10/12, 83%), clioquinol (6/9, 67%),[126] and the sulfonylureas[121] were not seen in clinical circumstances but from drug provocation tests in patients selected based on known pre-existing contact allergy to these (or cross-reacting) drugs. Forty-six systemic drugs (48%) caused only one reaction each. The SAD reactions to aminophylline (= theophylline + ethylenediamine) were all based on previous sensitization to ethylenediamine, mostly from the use of a formerly widely used corticosteroid combination cream containing ethylenediamine as a stabilizer.

Table 6 shows the most frequent clinical manifestations with dermatitis/eczema (n = 59, 21.1%), reactivation of previous dermatitis (n = 39, 14.0%), maculopapular eruption (n = 35, 12.5%), reactivation of previous positive patch tests (n = 26, 9.3%), SDRIFE (n = 22, 7.9%), and erythroderma or erythematous eruption (each 17 cases, 6.1%) heading the list.

Mitomycin C frequently induced manifestations on the palms of the hands (either desquamation or acrovesicular dermatitis) and SDRIFE. No other relationship between drugs and clinical presentations could be found in patients with SAD from therapeutically administered drugs. However, comparison between the clinical pictures in the provocation group tests (n = 76) and the non-provocation group (the 'clinical' group, n = 203) shows a far higher frequency of reactivation of previous dermatitis in the provocation group (36.8% vs 5.4%) and of reactivation of previous positive patch tests (32.9% vs 0.5%), but a lower frequency of dermatitis/eczema (6.6% provocation group, 26.7% clinical group) (Table 6).

4 | DISCUSSION

4.1 | Topical drugs

With only 95 reported patients showing SAD (proven or likely) caused by 41 different culprit drugs, such reactions appear to be very infrequent. Nearly 60% of these drugs have induced only one case of SAD and over half of all reactions were caused by four topical

TABLE 5 Systemic drugs most frequently implicated in systemic allergic dermatitis

Systemic drug	Cases n (%)	Reactions caused by drug provocation tests n (%)
Mitomycin C	29 (10.4)	–
Methylprednisolone (salt, ester)	21 (7.5)	7 (33)
Hydrocortisone (salt)	20 (7.2)	16 (80)
Aminophylline	12 (4.3)	1 (8)
Betamethasone (salt, ester)	12 (4.3)	2 (17)
Neomycin	12 (4.3)	10 (83)
Triamcinolone (acetonide)	10 (3.6)	–
Clioquinol	9 (3.2)	6 (67)
Prednisolone	9 (3.2)	3 (33)
Pristinamycin	9[a] (3.2)	–
Disulfiram	8 (2.9)	–

[a]Three patients may have been presented twice.

TABLE 6 Most frequent clinical manifestations of systemic allergic dermatitis caused by systemic drugs

Clinical manifestations	All reactions (n = 279) Cases, n (%)	NP reaction (n = 203) Cases, n (%)	Provocation tests (n = 76) Cases, n (%)[a]
Dermatitis/eczema (de novo, worsening, limited or generalized)	59 (21.1)	54 (26.7)	5 (6.6)
Reactivation of previous dermatitis	39 (14.0)	11 (5.4)	28 (36.8)
Maculopapular eruption	35 (12.5)	26 (12.8)	9 (11.8)
Reactivation of previous positive patch tests	26 (9.3)	1 (0.5)	25 (32.9)
SDRIFE/baboon syndrome	22 (7.9)	18 (8.9)	4 (5.3)
Generalized erythema/erythroderma	17 (6.1)	17 (8.4)	–
Erythematous eruption (+/- oedema)	17 (6.1)	8 (3.9)	9 (11.8)
Photoallergic dermatitis	9 (3.2)	9 (4.4)	–
Papular eruption	7 (2.5)	4 (2.0)	3 (3.9)
Urticaria	6 (2.2)	5 (2.5)	1 (1.3)
Acrovesicular dermatitis	6 (2.2)	6 (3.0)	–

Abbreviation: NP reaction, Non-provocation reaction (clinical group); SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.
[a]The number of clinical manifestations exceeds the total number of provocation tests, as 15 patients had both reactivation of patch tests and of previous dermatitis, which were both counted.

pharmaceutical products: budesonide, bufexamac, dibucaine, and chloramphenicol. The rarity may be the result of low concentrations of the drug attained systemically from absorption through the skin and mucosae. In 34 of the 104 cases, the culprit drug had been applied to the skin. However, in only 11 of these cases, the skin had been intact, of which nine were caused by the topical NSAID bufexamac. Most of these cases were reported from Germany and Japan. Bufexamac has caused many cases of sensitization, often with generalized eczematous eruptions. In April 2010, the drug was withdrawn by the European Medicines Agency.[263] Currently, it is not available in New Zealand, Japan, the European Union, the USA or Canada. Various Australian pharmaceutical companies do not produce bufexamac anymore, although it is still available in that country.[42] Therefore, the role of bufexamac in SAD may decrease considerably. In the other cases of SAD with drugs applied to skin, there were penetration-enhancing factors including damaged skin, patch tests, and transdermal tests (occlusion). The same may apply to the many cases (n = 16) of SAD observed after (peri)anal administration of drugs, often for haemorroids, anal eczema, or pruritus ani. Absorption-enhancing factors here are anatomical occlusion, damaged skin (eczema, intertrigo), and application to the anal mucosa.

The absence of a stratum corneum facilitates penetration into and systemic absorption from the mucosae. Indeed, in nearly half of all cases (not including the 16 cases of [peri]anal application), the drugs causing SAD had been applied to mucosae, notably the airways (inhalation, n = 19), vagina (n = 12), and nose (n = 9). The proportionally large number of cases of budesonide causing SAD from inhalation may have three explanations: (a) patients with asthma may frequently also have atopic dermatitis, which is treated with corticosteroids that can sensitize the patient and cross-react to budesonide; (b) patients may be exposed to a high dose of corticosteroids (0.2 mg) 2–4 times daily; and (c) the drug reaches an enormous mucosal surface (upper respiratory airways, lungs), facilitating considerable absorption into the bloodstream.

At the same time, one may wonder why so few cases of SAD from budesonide inhalation have been reported. Various explanations can be considered: (a) in cases of SAD, budesonide is suspected, stopped, and replaced with another non-cross-reacting corticosteroid (beclomethasone, ciclesonide, or fluticasone) or a non-steroid medication, which solves the problem, and no further diagnostic action is taken; (b) underreporting; and (c) the anti-inflammatory effect of budesonide surpasses its hypersensitivity-stimulating inflammatory effect.

The most frequent clinical manifestations of SAD from topical drugs (Table 3) was dermatitis/eczema, followed by SDRIFE, maculopapular eruption, erythematous eruption, and reactivation of previous dermatitis. Remarkably, eight of 12 cases (67%) of SDRIFE were caused by drug application to the (peri)anal area. With regard to the bladder, in patients with SAD from intravesical mitomycin C application, six of 18 (33%) had SDRIFE (Table 4) vs 16 of 250 (6.4%) with SDRIFE in the entire group of SAD (n = 279, minus the mitomycin group of n = 29). Although, in that group, twice as many cases of SDRIFE were caused by orally administered drugs and four by intravenous or intra-articular injection, it may be hypothesized that the

primary presence of sensitizing drugs in the anogenital area and the nearby located bladder may favor SDRIFE as a developing clinical expression of SAD.

In most cases where the culprit drugs of SAD had been applied to the skin, a dermatitis was first noticed at the site of application (including patch tests), followed by eruptions elsewhere. This was assumed (by the authors of the articles or by this reviewer) to be caused by hematogenous spreading of the allergen (hence SAD). However, whether this is correct, or that other mechanisms were also involved, is uncertain. No case of SAD from topical drugs has been found in which the presence and concentration of suspected drugs has been analyzed. Another possible mechanism might be that a fierce localized contact allergic reaction (patch test) or extensive allergic contact dermatitis (eg, from bufexamac) stimulates the production of drug-specific T cells and that the spreading of these T cells through the bloodstream and into the skin elsewhere results in or initiates the clinical manifestations of SAD, rather than the hematogenous spreading of the allergen.

4.2 | Systemic drugs

With 240 reported patients showing SAD (proven or likely) caused by 95 different culprit drugs, such reactions appear to be infrequent. Ten drugs together (Table 5) account for >50% of all SAD reactions, whereas nearly 50% of the 95 culprit drugs have induced only one case of SAD each. Mitomycin C, an antineoplastic antibiotic used to treat superficial bladder cancer with intravesical instillations, was the most frequent culprit drug with 29 reactions, >10% of all SAD cases. This drug probably has a strong sensitizing capacity: skin eruptions may be observed in up to 8.5% of patients treated.[264] The skin manifestations usually first develop after five to eight instillations. During earlier treatment sessions, the patients become sensitized to mitomycin C from contact with the vesicular mucosa. The bladder wall contains antigen-presenting cells, making induction of sensitization in the bladder possible, which is now generally regarded as the usual route of sensitization to mitomycin C.[16,198] Once sensitized, each following treatment will result in SAD from resorption of mitomycin C through the mucosa into the bloodstream, usually worsening and with a shorter time interval with each session. The most common cutaneous reaction is found on the palms of the hands and sometimes the soles of the feet, which may be either desquamation or vesicular dermatitis (acrovesicular/dyshidrotic eczema). This reaction is often combined with dermatitis of the genitals, sometimes accompanied by erythema of the buttocks, groin, and abdomen, consistent with the clinical picture of SDRIFE. Sensitization to mitomycin C is also frequent in patients without skin reactions.[198] In these asymptomatic patients, with continued treatment hypersensitivity probably builds up and at one point results in an allergic cutaneous reaction.[198] Many cases of allergic reactions were reported in the 1980s and 1990s, with the largest series of six patients reported by the author in 1991.[196] After 2009, no new reports of SAD to mitomycin appear to have been reported, which is probably caused by the fact that these reactions are now well known and reports are not accepted for publication anymore. The drug is, however, still used for bladder cancer.

Methylprednisolone (salt, ester) (7.5%) and hydrocortisone (salt) (7.2%) were the second and third most frequent culprit drugs. Indeed, the corticosteroids were the largest group, comprising 18 of the 95 drugs (19%), and 85 of the 279 SAD reactions (30.5%). This does not come as a surprise, as the prerequisite for the development of SAD from systemic drugs is previous sensitization from topical application. Corticosteroids are the most widely used topical pharmaceuticals; they frequently cause contact sensitization and cross-reactivity among them is widespread.[3,4,265,266] In addition, recent experimental research into SAD with systemic drugs and drug provocation has focused on corticosteroids, because (1) so many patients with corticosteroid allergy are "available" and (2) they rarely cause serious side effects with short-term exposure. Indeed, of the 85 corticosteroid SAD reactions, 33 (39%) were not caused by therapeutically administered drugs but resulted from drug provocation tests, including 80% of all reactions to hydrocortisone (salt). In the entire group of 279 SAD reactions, 76 (27.2%) were in response to drug provocation tests.

In the list of most frequent clinical manifestations (Table 6), there are high rankings for reactivation of previous dermatitis (rank 2; n = 39, 14.0%), and reactivation of previous positive patch tests (rank 4; n = 26, 9.3%). The author noticed that the majority (28/39 reactivation of previous dermatitis; 25/26 reactivation of a previous positive patch test) were the result of drug provocation tests. Many of these have been performed in two somewhat older studies (1969 and 1981) with neomycin and hydroxyquinolines (clioquinol/chlorquinaldol) in patients previously shown to have been sensitized to these drugs[126] and with anti-diabetic sulfonylureas (carbutamide, tolbutamide, chlorpropamide) in patients previously sensitized to the related sulfanilamide.[121] This resulted in high percentages of reactivation of previous dermatitis (36.8%) and of previous positive patch tests (32.9%) in the provocation group vs 5.4% resp. 0.5% in the other ("clinical") group.

That so many patch tests and previous dermatitis reactivations were observed in these studies[121,126] can easily be explained by the following: (a) all patients were selected on the basis of previous allergic contact dermatitis and previous positive patch tests; (b) the oral provocation tests were performed soon after the dermatitis had resolved or even during the phase of resolution, probably leaving memory T cells in the dermis and epidermis;[267] (c) because of the presence of these T cells, SAD, if elicited, will preferentially start in the areas of previous dermatitis and patch tests; (d) because the start doses of oral provocation were relatively low (neomycin and hydroxyquinolines are poorly absorbed from the intestinal tract) and the oral administrations were stopped as soon as dermatitis/patch tests reappeared, the risk of sudden extensive or generalized dermatitis or other eruptions was minimized, which enabled any reappearance of dermatitis/patch tests to be easily recognized; (e) oral provocation tests were considered positive when flare-up of original dermatitis or of patch test reactions were observed (i.e. the primary end point).

In the clinical group, reactivation of positive patch tests was rare (only one reaction) and reactivation of previous dermatitis infrequent. Possible explanations include: (a) patch tests may previously not have been performed (in which cases the patch tests were performed after the event and the required, previous sensitization was assumed based on a history of topical exposure and eczematous reactions); (b) patch tests may have been performed a considerable time before, leaving the site less susceptible to reactivation; (c) previous sensitization may not have resulted in clinical dermatitis when exposure was stopped before elicitation of allergic contact dermatitis; (d) previous allergic dermatitis may have been mild and short-lived from prompt interruption of topical therapy, leaving it less susceptible to reactivation; (e) many patients with mild reappearance of patch test and/or dermatitis will not be seen by a dermatologist in time for the phenomena to be recognized; (f) many patients who are seen by a dermatologist with an emergency appointment have widespread or even generalized dermatitis or another exanthema, which may mask any reappearance of previous patch test or dermatitis.

The question remains why SAD is so infrequent, or at least infrequently reported, considering the high frequency of such reactions – albeit in ideal circumstances – in studies with provocation tests.[121,126] Indeed, whereas some case series of six patients (mitomycin C[196]) and 14 (corticosteroids[120] with SAD have been reported, most authors have presented only one or two cases. Explanations may be similar to those with SAD from topical drugs (see above): underdiagnosing, underreporting (mitomycin C) and, in the case of corticosteroids, the suppression of SAD manifestations by their anti-inflammatory actions. However, there are additional plausible reasons. Strong topical sensitizers that are also available for systemic administration, such as penicillins and sulfonamides (which must have caused many cases of SAD in the 1930s and 1940s), are not used anymore, or at least, not in many parts of the world (bufexamac, promethazine [photosensitizer]). Topical drugs that may cause contact allergy relatively frequently, such as benzocaine, bacitracin, dibucaine, neomycin, framycetin, and tetracaine, are not or hardly used in systemic formulations. Finally, whereas the topical use of corticosteroids is widespread and sensitization fairly frequent, the systemic use of these pharmaceuticals is rather limited because of their long-term serious side effects. Yet, in a university hospital in Leuven, Belgium, specializing in allergy to drugs and cosmetics, in a group of 315 patients with established contact allergy to one or more corticosteroids, 45 (14%) had been previously exposed to systemic corticosteroids and 14 (4.5%) developed SAD.[120] That these patients were observed in a period of 18.5 years[268] and in a specialized tertiary referral center would seem to underscore the infrequent occurrence of SAD, at least to corticosteroids.

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Research data are not shared

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