

Frequency and trends of contact allergy to and iatrogenic contact dermatitis caused by topical drugs over a 25-year period

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Summary

Background. Allergic contact dermatitis is the most common adverse reaction caused by topical drugs.

Objectives. To study the demographic characteristics and lesion locations of patients with iatrogenic dermatitis, and to analyse contact allergy to active principles and trends in frequencies over the years.

Patients and methods. Between 1990 and 2014, 14 911 patients were patch tested with the European baseline series. Patients with a presumed iatrogenic cause were often tested with a pharmaceutical series, and, if indicated, with photo-patch tests. Most were also tested with the topical products to which they had been exposed, along with their ingredients.

Results. Eight thousand three hundred and seventy-four (56%) patients tested positively, and 2600 (17.4%, 95%CI: 16.8–18.0%) of all patients suffered from iatrogenic contact dermatitis. The most important primary sites of dermatitis were the legs, face, and hands. The most common sensitizers included topical antibiotics, antiseptics, and corticosteroids. The most frequent baseline allergens in this subgroup were budesonide, neomycin, and benzocaine, although with a decreasing trend over the years. Many other allergens from different pharmacological classes were identified.

Conclusions. With a prevalence of 17.4% of consecutive patients, iatrogenic contact dermatitis is a frequent diagnosis in patients attending a general patch test clinic, involving one-third of the patients with at least one positive reaction.

Key words: age; allergic contact dermatitis; epidemiology; iatrogenic; location; MOAHLEA; sex; topical drugs; topical pharmaceutical products; trends.

Topically applied drugs often cause adverse skin reactions, mostly in terms of irritant and, more often, allergic contact dermatitis. In some cases, the antigen is generated by ultraviolet (UV) radiation, resulting in photo-allergic contact dermatitis. Following contact sensitization to a

drug, reactions resulting from airborne exposure may also occur, and systemic administration may even induce systemic contact dermatitis-type reactions, for example in the case of corticosteroids in aerosols (1).

The incidence of contact-allergic reactions to topical drugs varies geographically, and depends on local prescription and self-medication habits (2), and on the presence of predisposing factors such as high age (3), a damaged skin barrier (4), and/or chronic dermatoses (5). Particular sites at risk are the legs (6), eyes (7), and perianal areas (8). The prevalence in patients tested for contact allergy is estimated to be ~15%, when patients with leg ulcers or other high-risk patients

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are excluded (9). The actual culprit may be the active principle (drug) or the vehicle, including excipients, preservatives, antioxidants, and emulsifiers (10), and also fragrance components (11, 12). The main active pharmacological agents involved are local antibiotics, antiseptics, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, and corticosteroids (2), whereas the most frequent reported actual causes of photo-allergic contact dermatitis are NSAIDs and, previously, the anti-histamines promethazine and derivatives (2), which are used less commonly today. The frequencies of sensitization to specific active principles and trends in frequencies over the years, in particular, have been poorly described (13–17); hence, these aspects are addressed in this study.

Methods

This article describes a retrospective analysis of patch testing in a tertiary referral centre, including ~15 000 patients tested since 1990, with the aims of: (i) evaluating demographic characteristics (age and sex) and locations of the lesions of the patients with iatrogenic contact dermatitis and/or photo-allergic contact dermatitis caused by topical drugs; (ii) describing the frequency of positive reactions to the active principles; and (iii) determining trends in the frequencies of frequently tested allergens over the years. The vehicle components encountered as allergens in topical pharmaceutical products in the population studied have already been reported elsewhere (10), and were therefore not taken into account in this study.

Patient data

This was a retrospective analysis of consecutive patch test data retrieved from, and evaluated with, a patient database developed in-house in the Contact Allergy Unit of the University Hospitals of KU Leuven (18). This database contains socio-demographic variables, medical history, and the results of all contact allergy investigations for patients suspected of having allergic contact dermatitis, or other diseases such as irritant dermatitis or other forms of eczema for which an allergenic cause needed to be excluded. Moreover, for each allergen identified, the respective sensitization sources (causal factors) can be retrieved. During the 25-year period from January 1990 until December 2014, 14 911 patients presenting with an eczematous dermatitis were patch tested.

Patch testing

Fourteen thousand six hundred and seventy-two of the patients were tested with a (modified) European baseline

series (as an example, children are sometimes tested with a few allergens only), and those with a presumed iatrogenic cause were often also tested with a pharmaceutical series (411 patients), or, in cases of a photo-induced reactions, also with photo-patch tests (160 patients). Almost all patients were also tested (or photo-patch tested) with the products to which they had been exposed to, and, whenever possible, also with the ingredients of these products. This is facilitated by the fact that the patient database represents an expert system in which all ingredients of the pharmaceutical products used are directly displayed on the computer screen when the history is taken.

The test substances were obtained from Trolab® Allergens (previously Almirall Hermal GmbH, Reinbeck, Germany; now SmartPractice Europe, Barsbüttel, Germany) and/or Chemotechnique Diagnostics (Vellinge, Sweden), or self-prepared *lege artis* [most often according to the concentrations and vehicles proposed by de Groot (19)], and stored at 4°C. The patch tests were applied on the patient's back with van der Bend® (van der Bend, Brielle, The Netherlands) patch test chambers applied to Micropore® (3M Health Care, Borken, Germany), and later with IQ Ultra Chambers® (Chemotechnique Diagnostics); they were fixed initially with Fixomull® (Beiersdorf, Hamburg, Germany), and later with Mefix® (Mölnlycke Health Care, Göteborg, Sweden). The patch test readings were performed according to the international guidelines of the European Society of Contact Dermatitis (20) at 2, 3 (exceptionally) and 4 days, and often also later (especially in the case of corticosteroids and photo-patch tests). A +, ++ or +++ reaction at either reading was recorded as a positive patch test reaction; an irritant, doubtful or negative response was recorded as a negative (non-allergic) result.

Study design

Those patients for whom 'iatrogenic' had been indicated as the sensitization source for their dermatitis and who presented with a positive patch test reaction to at least one active principle and/or topical medicament were taken into account in this study. Patients without an 'iatrogenic' sensitization source were allocated to the 'non-iatrogenic' group. To study the significance of differences in the characteristics and lesion locations between iatrogenic and non-iatrogenic patients, the data were presented in 2 × 2 contingency tables and analysed with the chi-square test in a Microsoft Excel® spreadsheet. To counteract the problem of multiple comparisons, the Bonferroni correction was used, meaning that individual *p*-values of <0.002 were considered to be statistically significant ($\alpha = 0.05$ adjusted for 25 comparisons) (21).

Table 1. MOAHLFA in the total population (n = 14 911), patients with iatrogenic dermatitis with/without other causal factors (n = 2600), patients with iatrogenic dermatitis without cosmetic dermatitis (n = 1831), patients with iatrogenic dermatitis only (n = 843), and the non-iatrogenic group (n = 12 311)

	Total population (n = 14 911) (%)	Iatrogenic dermatitis with/without other causal factors (n = 2600) (%)	Iatrogenic dermatitis without cosmetic dermatitis (n = 1831) (%)	Iatrogenic dermatitis only (n = 843) (%)	Non-iatrogenic group (n = 12 311) (%)
M	33.9	31.6	35.2	40.5	34.4
O	16.4	9.5	9.2	4.5	17.9
A	22.2	18.8	17.7	15.8	22.9
H	37.9	29.4	28.4	19.2	39.7
L	3.5	13.2	14.6	18.5	1.4
F	35.2	31.3	27.8	26.8	36.0
A	49.3	61.8	61.4	68.0	46.7

M, men; O, occupational; A, atopic history; H, hand eczema; L, leg ulcer/stasis dermatitis; F, facial dermatitis; A, age ≥ 40 years.

Moreover, all active pharmaceutical principles that had produced positive reactions in the total patient population were analysed; for each test substance, the number of positive test results and the total number of patch tests performed were stratified for age (< 40 years versus ≥ 40 years) and sex. When > 100 cases were analysed, frequencies of sensitization (as percentage of the patients tested) were calculated as crude proportions, and standardization was performed on the basis of the two age groups and a distribution of 40% men and 60% women (22). Given the large study population, a normal approximation to the binomial distribution could be used to calculate the confidence interval (CI). Five 5-year periods, namely 1990–1994, 1995–1999, 2000–2004, 2005–2009, and 2010–2014, were compared in terms of heterogeneity by use of the chi-square test, with a p -value of < 0.05 considered to be statistically significant. In order to determine trends in frequencies over the years, linear regression was used (Table 2). The study was approved by the ethical research committee in Leuven.

Results

Patient data

Among the 14 911 patients tested, 5059 (34%) were men and 9852 (66%) were women. The MOAHLFA indices are

given in Table 1 for the total population (n = 14 911), the patients with iatrogenic dermatitis and eventually also other causal factors, such as occupation, cosmetics, and 'textiles and accessories' (including jewellery, shoes, and gloves) (n = 2600), the patients with iatrogenic but without cosmetic dermatitis (for example, some topical anti-septics can also be used as preservatives in cosmetics, such as chlorhexidine) (n = 1831), the patients with iatrogenic dermatitis only (n = 843), and the non-iatrogenic group (n = 12 311). Eight thousand three hundred and seventy-four (56%) of 14 911 patients, that is, 2258 men (27%) and 6116 women (73%) showed a positive reaction to at least one of the substances tested.

'Textile and accessories' turned out to be the most important sensitization source (25.9%), followed by cosmetics (19.4%) and pharmaceutical products (17.4%). The importance of iatrogenic allergies has considerably decreased over the years as compared with cosmetic dermatitis (Table 2 and Fig. 1).

Two hundred and thirty-six (9.1%) of the 2600 iatrogenic dermatitis patients were also diagnosed with occupational dermatitis, 771 (29.8%) with 'textiles and accessories', and 763 (29.4%) with cosmetic dermatitis. The 2600 patients suffering from iatrogenic dermatitis represent a prevalence of 17.4 (95%CI: 16.8–18.0%), considering all patients who attended the Contact Allergy Unit (2600/14 911), meaning 31.0%, or approximately

Table 2. Trends in the main sensitization sources over the years (n = 14 911)

Causal factor	Total (n = 14 911), n (%)	1990–1994 (n = 3228), n (%)	1995–1999 (n = 3368), n (%)	2000–2004 (n = 3177), n (%)	2005–2009 (n = 2638), n (%)	2010–2014 (n = 2560), n (%)	R	p
Textile and accessories	3870 (25.9)	878 (27.2)	874 (25.9)	837 (26.9)	661 (25.1)	620 (24.2)	–0.6	0.01
Iatrogenic	2600 (17.4)	700 (21.7)	583 (17.3)	547 (17.6)	430 (16.3)	340 (13.3)	–0.7	< 0.0001
Cosmetics	2893 (19.4)	500 (15.5)	565 (16.8)	608 (19.5)	576 (21.8)	644 (25.1)	0.7	< 0.0001

R, correlation coefficient of correlation between prevalence and time period; p, p-value of chi-square test for the comparison between 1990–1994 and 2010–2014; statistically significant differences (after alpha adjustment) are in bold ($p < 0.002$).

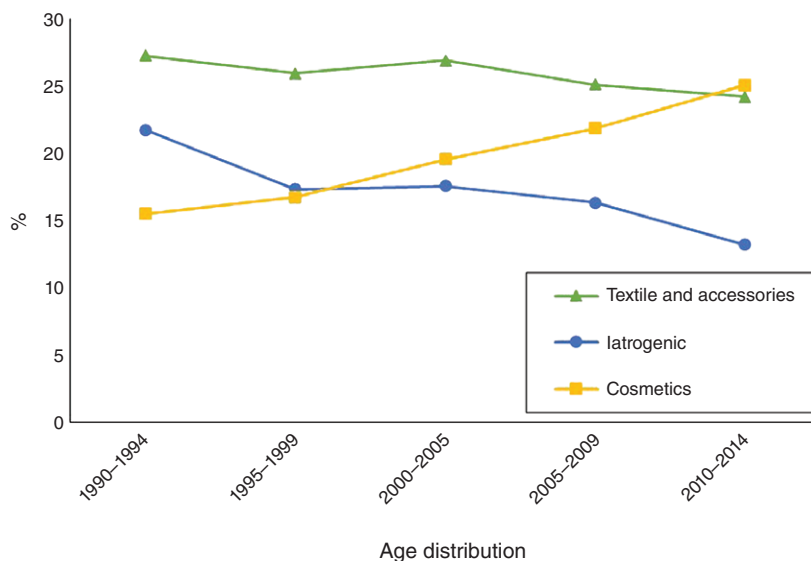


Fig. 1. Trends in the main sensitization sources over the years.

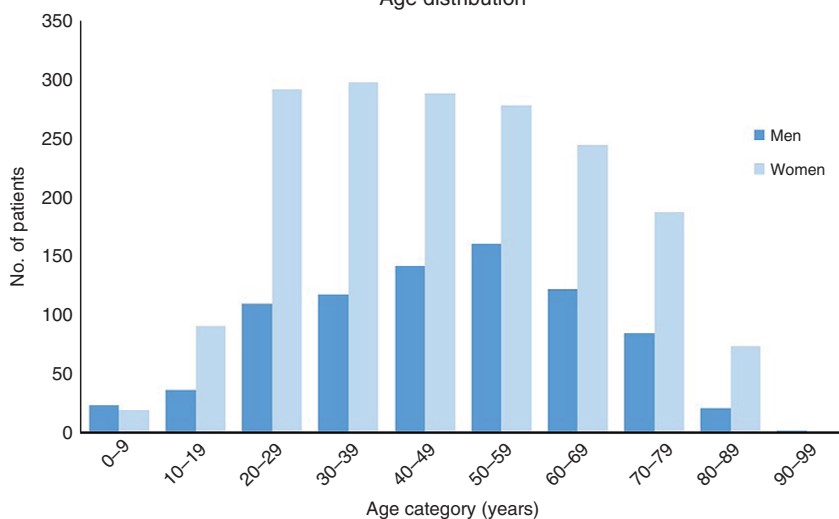


Fig. 2. Age distribution of the patients with iatrogenic dermatitis, with or without other causal factors ($n = 2600$, mean age = 47).

1 in 3, of those who presented with at least one positive reaction on patch testing ($n = 8374$), 822 of them (31.6%) being men and 1778 (68.4%) women. Among the 2600 patients, 2489 (95.9%) presented with relevant positive patch test reactions, and 402 (15.5%) also suffered from irritant contact dermatitis, most often occupation-related. Of those with iatrogenic dermatitis only, 788 (93.4%) suffered from allergic contact dermatitis, and 126 (14.9%) from irritant contact dermatitis; some had both diagnoses.

The mean age of the iatrogenic group was 47 years, for both men and women, and the mean age of the non-iatrogenic group was 40 years (Fig. 2). Eight hundred and sixty-five of the patients with iatrogenic dermatitis (33.4%) had a personal history of atopy (551 of these also a family history), of whom 488 had atopic eczema, that is, 18.8% of all patients with iatrogenic contact dermatitis.

Three hundred and forty-two (13.2%) of the iatrogenic patients suffered from leg ulcers/stasis dermatitis, indicating that 66% of 516 such patients presented with dermatitis caused by topically applied pharmaceutical products.

The most important primary locations of eczema in the iatrogenic group were the legs (734 patients; 28.3%), face (607; 23.4%), and hands (561; 21.6%), as compared with the hands (4002; 32.5%), face (3541; 28.8%) and eyelids (2415; 16.2%) in the non-iatrogenic group. Some of the patients presented with several primary lesion locations. The results of comparison between the groups are given in Table 3 and shown in Fig. 3; a p -value of <0.002 indicates a statistically significant difference. Quite similar results were obtained for comparisons with the 'iatrogenic without cosmetic dermatitis' group; hence, these are not included in Table 3.

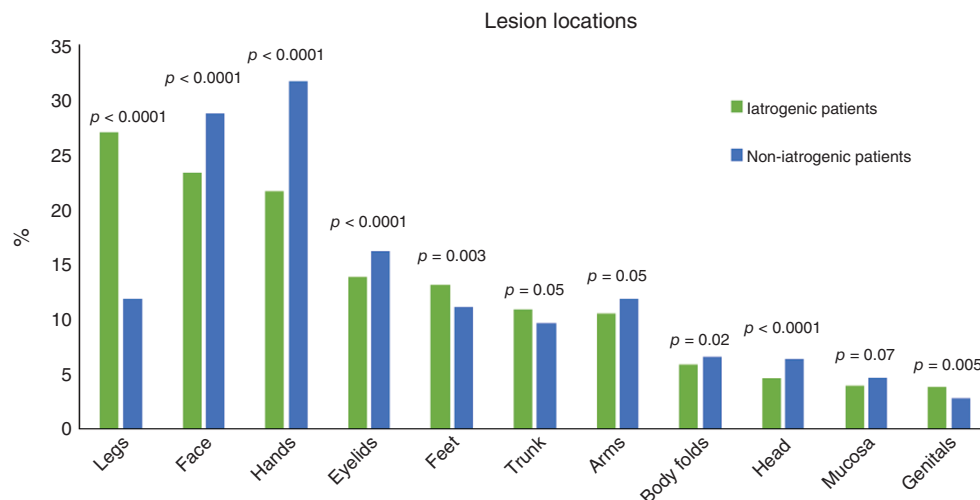


Fig. 3. Lesion locations in the iatrogenic and non-iatrogenic groups.

Table 3. Primary lesion locations in the iatrogenic and non-iatrogenic groups

Location	Iatrogenic group (n = 2600)		Non-iatrogenic group (n = 12 311)	
	No. of patients	%	No. of patients	%
Legs	734	28.3	1457	11.8
Face	607	23.4	3541	28.8
Hands	561	21.6	4002	32.5
Eyelids	362	13.9	2415	16.2
Feet	341	13.1	1368	11.1
Trunk	282	10.9	1185	9.6
Arms	272	10.5	1457	11.8
Body folds	151	5.8	879	7.1
Head	119	4.6	785	6.4
Mucosa	102	3.9	583	4.7
Genitals/ perianal	100	3.9	347	2.8



Fig. 4. Illustration of a patient reacting to local anaesthetics, namely lidocaine and mepivacaine (amides), oxybuprocaine (ester), and budesonide (corticosteroid allergy marker).

Patch test results

The active principles yielding positive patch test reactions are shown in Table 4 (allergens from the baseline series are in bold). Several patients also reacted simultaneously to multiple topical drugs; Fig. 4 shows a patient reacting to several local anaesthetics and also to budesonide. However, several positive test reactions resulted from cross-reactivity, such as in the case of benzocaine cross-reacting with *p*-phenylenediamine (PPD), and corticosteroids, and also aminoglycoside antibiotics cross-reacting mutually. The corticosteroids cross-reacting with the markers in the baseline series (tixocortol pivalate, budesonide, and, in Belgium, also

hydrocortisone-17-butyrate), such as methylprednisolone aceponate and prednicarbate, have been extensively studied previously (23, 24), and therefore were deliberately omitted from Table 4. Moreover, some of them (e.g. prednicarbate and mazipredone) are not even commercialized in Belgium. Cross-reactions observed with aminoglycosides, local anaesthetics, sulfonamides, etc. will be discussed in a future article.

In addition, 247 (of 854 tested, i.e. 28.9%) patients reacted to their own pharmaceutical product(s) used. For ketoprofen, 90 of 98 (91.8%) patients suffered from photo-allergic contact dermatitis, and 8 were diagnosed with allergic contact dermatitis. In 5 of these

Table 4. Patch test results with active principles of topically applied pharmaceutical products (total population, n = 14 911)

Allergen	Concentration and vehicle	W<40		W≥40		M<40		M≥40		Total		Crude prevalence (%)	Standardized prevalence (%)	95%CI
		Positive PT result	PT	Positive PT result	PT	Positive PT result	PT	Positive PT result	PT	Total PT result	Total PT			
Antibiotics														
Neomycin	20% pet.	48	4920	134	4725	15	2424	72	2509	269	14578	1.8	1.8	1.6–2.0
Sulfanilamide	5% pet.	35	93	55	123	20	59	51	118	161	393	41.0	40.1	35.3–44.9
Chloramphenicol	5% pet.	15	118	37	384	1	46	19	189	72	737	9.8	9.1	7.0–11.2
Benzoyl peroxide	1% pet.	34	517	20	584	14	493	4	374	72	1968	3.7	3.8	3.0–4.6
Tobramycin	20% pet.	8	44	32	90	5	15	18	37	63	186	33.9	27.1	20.7–33.5
Nitrofurazon	20% pet.	5	62	27	307	3	30	17	152	52	551	9.4	9.3	6.9–11.7
Gentamicin	3% pet.	13	62	23	111	3	25	11	59	50	257	19.5	18.6	13.8–23.4
Clioquinol	1% pet.	5	3297	30	3583	2	1581	12	1909	49	10370	0.5	0.4	0.3–0.5
Fusidic acid	2% pet.	6	275	23	358	7	176	6	226	42	1035	4.1	3.9	2.7–5.1
Frmycetin	20% pet.	3	13	18	30	1	7	9	21	31	71	–	–	–
Virginiamycin	5% pet.	1	50	9	193	2	23	7	91	19	357	5.3	5.3	3.0–7.6
Polymyxin B sulfate	3% pet.	5	153	10	243	0	52	2	89	17	537	3.2	2.7	1.3–4.1
Bacitracin	20% pet.	2	69	7	262	1	26	2	135	12	492	2.4	2.7	1.3–4.1
Oxytetracycline hydrochloride	3% pet.	4	152	1	217	0	51	2	75	7	495	1.4	1.5	0.4–2.6
Erythromycin	5% pet.	1	68	1	62	0	29	3	35	5	194	2.6	2.6	0.4–4.8
Clindamycin	10% pet.	2	20	1	16	–	–	1	7	4	43	–	–	–
Silver sulfadiazine	10% pet.	0	60	2	163	0	35	1	77	3	335	0.9	0.6	0–1.4
Mupirocin	10% pet.	1	47	0	65	0	39	2	37	3	188	1.6	1.7	0–3.5
Rifamycin	5% pet.	0	17	1	6	0	10	0	14	1	47	–	–	–
Gramicidin	5% pet.	1	88	0	112	0	61	0	82	1	343	0.3	0.3	0–0.9
Anthistamines														
Diphenhydramine	1–5% pet.	2	44	1	73	0	15	6	45	9	177	5.1	4.4	1.4–7.4
Clemizole	1% pet.	0	–	2	16	–	–	1	15	3	31	–	–	–
Tripeleannamine	1% pet.	0	0	0	0	0	0	1	1	1	1	–	–	–
Methyldiphenhydramine	1% pet.	0	3	1	6	0	2	0	4	1	15	–	–	–
Dimetindene	5% pet.	0	29	1	35	0	9	0	10	1	83	–	–	–
Dexchlorfeniramine	5% pet.	1	1	0	3	0	0	0	0	1	4	–	–	–
Antmycotics														
Miconazole	1% eth.	4	281	9	289	3	225	5	216	21	1011	2.1	2.1	1.2–3.0
Nystatin	2% pet.	5	134	2	166	2	74	5	115	14	489	2.9	2.9	1.4–4.4
Econazole nitrate	1% pet.	1	37	2	39	2	45	4	43	9	164	5.5	5.1	1.7–8.5
Isoconazole	2% pet.	1	48	3	36	2	33	2	31	8	148	5.4	5.6	1.9–9.3
Chlorquinaldol	3% pet.	0	–	4	11	2	2	1	1	7	14	–	–	–
Clotrimazole	2% pet.	1	52	1	60	–	–	2	55	4	167	2.4	1.8	0–3.8
Ketoconazole	2% pet.	1	59	0	76	0	61	1	80	2	276	0.7	0.8	0–1.9
Dichlorophene	1% pet.	0	5	0	3	0	49	1	38	1	95	–	–	–

Table 4. continued

Allergen	Concentration and vehicle	W<40		W≥40		M<40		M≥40		Total		Crude prevalence (%)	Standardized prevalence (%)	95% CI
		Positive PT result	PT	Positive PT result	PT	Positive PT result	PT	Positive PT result	PT	Positive PT result	PT			
Antiparasitics														
Metronidazole	1% pet.	0	63	3	105	1	13	0	28	4	209	1.9	2.4	0.3–4.5
Crotamiton	5% pet.	0	1	1	4	0	1	0	2	1	8	–	–	–
Antiseptics														
Iodine	0.5% eth.	24	305	98	589	14	157	60	395	196	1446	13.6	12.2	11.1–13.3
Merbromine	2% aq.	19	85	41	298	8	35	20	135	88	553	15.9	18.4	15.2–21.6
Chloramine	0.5% aq.	11	164	51	384	4	68	18	212	84	828	10.1	8.9	7.0–10.8
Cetrimide	0.05% eth.	10	33	32	134	10	28	31	87	83	282	29.4	30.5	25.1–35.9
Povidone iodine	2% aq.	5	171	27	288	1	81	27	235	60	775	7.7	6.2	5.5–7.9
Chlorhexidine digluconate	0.5% eth.	7	1413	10	1549	9	268	12	486	38	3716	1.0	1.5	1.1–1.9
Benzalkonium chloride	0.1% eth.	9	218	12	331	7	86	7	154	35	789	4.4	4.9	3.4–6.4
Isopropanol 99%	'as is'	9	697	14	654	1	224	10	375	34	1950	1.7	1.7	1.1–2.3
Chloroxylenol	0.5–1% pet.	7	398	11	427	–	–	2	130	20	955	2.1	1.6	0.8–2.4
Eosin	50% pet.	2	113	7	221	1	45	7	127	17	506	3.4	3.0	1.5–4.5
Hexamidine	0.15% eth.	4	457	6	531	2	41	4	145	16	1174	1.4	2.1	1.3–2.9
Sodium hypochlorite	10% aq.	0	77	1	76	1	26	1	38	3	217	1.4	1.7	0–3.4
Oxychinolin	10% pet.	0	2	2	6	0	1	0	2	2	11	–	–	–
Mepylcaine	5% pet.	1	12	0	35	1	4	0	18	2	69	–	–	–
Oxychinolin sulfate	10% pet.	0	18	0	40	0	7	1	20	1	85	–	–	–
Antivirals														
Tromantadine	2% pet.	2	13	3	21	0	1	1	2	6	37	–	–	–
Acyclovir	10% pet.	2	33	3	40	0	10	0	15	5	98	–	–	–
Brivudine (BVDU)	5% pet.	1	1	0	0	0	0	0	0	1	1	–	–	–
β-Blockers														
Timolol	5% aq.	0	0	2	27	0	2	2	19	4	48	–	–	–
Metipranolol	5% aq.	0	0	2	9	0	0	1	4	3	13	–	–	–
Carteolol	5% aq.	0	1	1	13	0	1	1	11	2	26	–	–	–
Betaxolol hydrochloride	5% aq.	0	0	1	2	0	1	0	0	1	3	–	–	–
Corticosteroids														
Budesonide^a		70	4779	142	4642	18	2310	44	2461	274	14 192	1.9	1.9	1.7–2.1
Tixocortol pivalate	0.1% pet.	59	4919	119	4724	22	2426	38	2513	238	14 582	1.6	1.6	1.4–1.8
Hydrocortisone-17-butyrate	0.1% eth.	38	4071	86	4092	6	1967	21	2181	151	12 311	1.2	1.2	1.0–1.4
Local anaesthetics														
Benzocaine	5% pet.	71	4886	95	4726	37	2378	64	2513	267	14 503	1.8	1.9	1.7–2.1
Lidocaine	5% pet.	0	78	12	165	0	36	7	66	19	345	5.5	4.3	2.2–6.4
Cinchocaine	5% pet.	1	32	7	72	1	19	4	46	13	169	7.7	6.6	2.9–10.3
Pilocaine hydrochloride	5% pet.	0	22	1	48	0	9	2	21	3	100	3.0	2.5	0–5.6
Oxybuprocaine hydrochloride	5% pet.	1	18	1	49	0	5	1	21	3	93	–	–	–

Table 4. continued

Allergen	Concentration and vehicle	W<40		W≥40		M<40		M≥40		Total		Crude prevalence (%)	Standardized prevalence (%)	95%CI
		PT	Positive PT result	PT	Positive PT result	PT	Positive PT result	PT	Positive PT result	PT	Positive PT result			
Mydriatics														
Phenylephrine	1% aq.	1	10	6	26	0	6	1	11	8	53	–	–	–
Atropine	1% aq.	0	10	1	18	1	5	4	10	6	43	–	–	–
Homatropine	1% aq.	0	2	1	6	1	1	2	3	4	12	–	–	–
Tropicamide	1% pet.	0	0	0	5	1	1	0	2	1	8	–	–	–
Dipivefrine	1% aq.	0	1	1	3	0	0	0	0	1	4	–	–	–
NSAIDs														
Ketoprofen ^b	1% pet.	37	103	35	104	14	36	12	51	98	294	35.4	33.4	28.0–38.8
Etofenamate ^b	2% pet.	25	102	23	108	14	38	8	47	70	295	24.1	24.5	19.6–29.4
Bufexamac	5% pet.	5	30	9	29	1	9	2	16	17	84	–	–	–
Methyl nicotinate	2% pet.	5	25	4	23	1	8	2	10	12	66	–	–	–
Diclofenac	5% pet.	1	109	2	125	0	40	0	62	3	336	0.9	0.8	0–1.8
Phenylbutazone	1% pet.	1	2	1	4	0	0	0	1	2	7	–	–	–
Niflumic acid	3–5% pet.	0	16	0	4	2	4	0	4	2	28	–	–	–
Buprenorphine ^d	TTS 35 µg/h	0	0	1	3	0	0	1	3	2	6	–	–	–
Indomethacin	2% pet.	1	10	0	17	0	7	0	10	1	44	–	–	–
Antipsoriatics														
Coal tar	5% pet.	5	79	7	91	1	68	2	71	15	309	4.9	5.1	2.6–7.6
Calcipotriol	2 µg/g eth.	1	24	3	65	2	25	0	25	6	139	4.3	4.2	0.9–7.5
Ichthyl	5% pet.	2	88	1	116	0	40	0	65	3	309	1.0	0.9	0–2.0
Others														
Minoxidil	2% eth.	6	17	13	35	1	3	2	7	22	62	–	–	–
Mephesisin	5% pet.	2	23	5	14	2	8	1	10	10	55	–	–	–
Nitroglycerin	1% pet.	0	0	3	6	0	0	1	3	4	9	–	–	–
Fluorouracil	5% pet.	0	1	1	6	0	0	3	9	4	16	–	–	–
Troloxerutin	2% pet.	0	0	1	2	0	0	1	4	2	6	–	–	–
Resorcinol	2% pet.	0	433	0	565	0	67	1	93	1	1158	0.1	0.2	0–0.5
Methyl-aminolevulinate hydrochloride	16% cream	0	0	0	0	0	0	1	1	1	1	–	–	–

CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; PT, patch test; TTS, transdermal therapeutic system; W<40, women aged <40 years; W≥40, women aged ≥40 years; M<40, men aged <40 years; M≥40, men aged ≥40 years.

The allergens from the baseline series are in bold.

Herbal medicines not taken into account.

^aTested as quinoline mix 6% pet. before 1995.

^bTested at 0.002% eth. between 1990 and 1994, and then switched to 0.1% pet. from 1994 until 1999, and to 0.01% pet. from 1999 onwards.

^cAlso photosensitization.

^dTTS 'as is'.

8 patients, the reaction was stronger after UV exposure, which is referred to as 'photo-aggravation'. For etofenamate, 38 patients already reacted without UV exposure; of these, 10 had photo-aggravation, and 32 of 70 were photo-allergic. Forty-five patients reacted to both etofenamate and ketoprofen. The positive reactions to the different pharmacological categories are shown in Table 5. This represents a high number of patch tested subjects, particularly with regard to antibiotics and corticosteroids, among which neomycin and clioquinol, and budesonide and tixocortol pivalate, respectively, are routinely tested.

The most frequent reactions were to antibiotics, antiseptics, and corticosteroids. Among the non-categorized drugs were minoxidil, which is used for hair loss ($n = 22$), mephensin, which is a muscle relaxant ($n = 10$), nitroglycerin in topical transdermal systems for the treatment of angina pectoris ($n = 4$), the cytostatic agent fluorouracil ($n = 4$), troxerutin, which is a capillary stabilizing agent for varicose veins ($n = 2$), resorcinol, which is used for the treatment of warts ($n = 1$), and methylaminolevulinate, which is used for the treatment of actinic keratosis ($n = 1$).

Trends over the years

Positive patch test reactions obtained with the active principles in the European baseline series over the years, standardized for sex and age, are given in Table 6. The numbers of positive patch test reactions per time period to some other interesting allergens are summarized in Table 7.

Discussion

Prevalence, age, and sex

Among the population of 14 911 patients tested between 1990 and 2014, those with at least one positive patch test reaction represented 56%, a reflection of our department being a tertiary referral centre, meaning that many patients were prediagnosed with, or highly suspected of having, allergic contact dermatitis. Women were sensitized significantly more often than men (62.06% of all women versus 44.61% of all men had at least one positive patch test reaction; $p < 0.0001$). Despite regulatory interventions in Europe for nickel in jewellery and metal clothing accessories (25), and for chromate in leather (footwear) (26, 27), 'textiles and accessories' remain the main causes of dermatitis, albeit with a recent slight overall decrease. Interestingly, contact allergy to pharmaceutical products shows a decreasing trend over the years,

Table 5. Positive reactions to the different pharmacological categories ($n = 14\,911$)

Drug group	Positive PT result	PT	Crude prevalence (%)	Standardized prevalence (95%CI) (%)
Antibiotics	933	33 177	2.8	2.7 (2.5–2.9)
Antiseptics	679	13 356	5.1	5.1 (4.7–5.5)
Corticosteroids	663	41 085	1.6	1.6 (1.5–1.7)
Local anaesthetics	305	15 210	2.0	2.0 (1.8–2.2)
NSAIDs	207	1160	17.8	18.0 (15.7–20.3)
Antimycotics	66	2364	2.8	2.7 (2.0–3.4)
Others	44	1307	3.4	3.9 (2.9–4.9)
Antipsoriatics	24	757	3.2	3.2 (1.9–4.5)
Mydriatics	20	120	16.7	16.0 (9.4–24.6)
Antihistamines	16	311	5.1	4.4 (2.1–6.7)
Antivirals	12	136	8.8	7.3 (2.9–11.7)
β -Blockers	10	90	11.1	5.9 (1.0–10.8)
Antiparasitics	5	217	2.3	2.5 (0.4–4.6)

CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; PT, patch test.

in contrast to cosmetic dermatitis, which has become increasingly important. Several factors may account for the latter: mandatory labelling and subsequent better identification of the allergenic culprits, the growth in the cosmetic industry, the influence of fashion trends, and the impact of the preservatives methylchloroisothiazolinone and methylisothiazolinone, in particular (28); moreover, our specific interest in cosmetic dermatitis also plays a role.

The 2600 patients suffering from iatrogenic dermatitis represent a prevalence of 17.4% (95%CI: 16.8–18.0%), considering all patients who attended the Contact Allergy Unit. This is in accordance with the estimate of 15% as a realistic figure to be expected in a contact dermatitis clinic (9). The majority of the iatrogenic patients (including those with other causal factors) were women (68.4%); however, this did not differ significantly from the proportion of women in the non-iatrogenic group (65.6%) ($p = 0.006$). The mean age of the iatrogenic patients was 47 years, and that of the non-iatrogenic group was 40 years. Simultaneously, the percentage of patients aged > 40 years was higher in the iatrogenic group ($p < 0.0001$). The higher frequency of iatrogenic dermatitis indicates greater exposure because of increased use, and increased penetration of topical agents with age (3). When cosmetics as causal factors were excluded, the proportion of men increased; also, fewer patients with facial dermatitis were observed. Among the patients with iatrogenic dermatitis only, significantly less hand dermatitis and a lower proportion of occupational contact dermatitis were noted.

Table 6. Sex-adjusted and age-adjusted prevalence rates (%) of positive patch test reactions to the active principles from the baseline series over the years

Allergen	1990–94 (n = 3228)	1995–1999 (n = 3368)	2000–2004 (n = 3177)	2005–2009 (n = 2638)	2010–2014 (n = 2560)	Overall (95%CI)	R	p
Neomycin	3.2	2.1	2.6	1.3	0.7	2.0 (1.8–2.2)	–0.9	< 0.0001
Benzocaine	2.3	2.2	1.6	1.7	1.3	1.8 (1.6–2.0)	–0.9	0.004
Tixocortol pivalate	1.7	2.1	1.7	1.3	1.1	1.6 (1.4–1.8)	–0.8	0.003
Budesonide	3.3	1.9	1.8	1.1	1.3	1.9 (1.7–2.1)	–0.9	< 0.0001
Clioquinol/quinoline mix	0.5	0.0	0.5	0.3	0.1	0.3 (0.2–0.4)	–0.3	0.02

CI, confidence interval; R, correlation coefficient of correlation between prevalence and time period; p, p-value of chi-square test for the comparison between 1990–1994 and 2010–2014; statistically significant differences are in bold ($p < 0.05$).

Atopy

Among the iatrogenic group, 18.1% suffered from personal atopic eczema. Even though such patients are often exposed to multiple topical agents, this proportion was, surprisingly, significantly lower ($p < 0.0001$) than the proportion of patients with a personal atopy within the total population attending the contact allergy unit (22.2%) and the non-iatrogenic group (22.9%). In the group of patients with iatrogenic dermatitis only, this proportion was even lower (15.8%).

Lesion location

The most important primary lesion locations in the iatrogenic group (Fig. 3) were the legs (28.3%), and 13.2% presented with stasis dermatitis, a leg ulcer, or both. This percentage increased to 18.5% in those with iatrogenic dermatitis only. A higher proportion of leg dermatitis, accompanied by a high proportion of older patients, has often been found to be linked to a high prevalence of contact sensitization to topical medicaments. Also, patients with stasis dermatitis are at high risk (6, 14), which can be explained by local inflammation, an impaired skin barrier, and the use of occlusive bandages favouring skin penetration, together with the use of multiple topical medicaments and dressings. The last of these were not taken into account in this study, but were recently found to account for 19% of the reactions in chronic leg ulcer patients (29). The perianal region, which is another location at risk (8), was not significantly more involved in this study. Isothiazolinones in cosmetic wet wipes became a more frequent cause in recent years.

The allergens

The most common sensitizers included topical antibiotics (prevalence 2.7%, 95%CI: 2.5–2.9%), antiseptics (prevalence 5.1%, 95%CI: 4.7–5.5%), and corticosteroids (prevalence 1.6%, 95%CI: 1.5–1.7%) (Table 5). We identified neomycin as the most common topical

antibiotic (overall prevalence 1.8%, 95%CI: 1.6–2.0%), with the majority of positive patch test reactions occurring only at the second reading. Neomycin belongs to the group of structurally similar aminoglycoside antibiotics, which accounts for its high rate of cross-reactivity with framycetin and paromomycin, in particular (30). However, trends in sensitization (Table 6) have decreased significantly over the years: in Belgium, commercialized products in association with corticosteroids have been withdrawn from the market, and neomycin is now available by prescription only. Comparable results were found in Germany, with an overall prevalence of 2.2% (95%CI: 2.1–2.3%). The frequency of reactions to clioquinol is far below 1% (0.4%, 95%CI: 0.3–0.5%) of the positive reactions in routinely tested dermatitis patients, and it is not a common exposure anymore (31); hence, its inclusion in the baseline series is questioned, as already mentioned by the European Surveillance System on Contact Allergy (16).

Sulfanilamide ($n = 161$), an agent that can potentially cross-react with PPD, turned out to be the second most frequent contact allergen among the tested topical antibiotics (overall prevalence 40.1%, 95%CI: 35.3–44.9%); however, it was mostly tested when PPD had already given a positive reaction. Luckily, its use has been almost eliminated; in Belgium, only one topical pharmaceutical product containing it is still on the market. Other, newer topical antibiotics, such as mupirocin and fusidic acid, need to be considered as potential allergens as well (Table 7).

Benzocaine is now hardly being used in topical local anaesthetic preparations for pruritus ani or haemorrhoids, or in anaesthetic eyedrops or eardrops. It is included in the European baseline series as an indicator for sensitization to 'caines'; however, several authors have suggested the use of a 'caine mix' containing benzocaine, tetracaine, and cinchocaine. Indeed, a significant number of allergic reactions to local anaesthetics are missed if benzocaine alone is used as a screening agent (32). Also in our department, the use of a caine mix may be beneficial: for example, lidocaine and cinchocaine,

Table 7. Number of positive patch test reactions over the number of patch tests performed for sulfanilamide, fusidic acid, ketoprofen and etofenamate over the years

Allergen	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014
Sulfanilamide	56/144	80/121	26/67	31/62	2/20
Fusidic acid	5/29	4/104	10/260	14/340	9/306
Ketoprofen	3/8	6/22	26/43	24/72	39/150
Etofenamate	7/17	11/30	15/39	15/70	22/141

which are amides that are usually considered to be less allergenic, gave positive reactions in 19 of 365 and 13 of 169 tested subjects, respectively.

For the corticosteroid markers of the baseline series, the highest number of positive reactions was found for budesonide (overall prevalence 1.9%, 95%CI: 1.7–2.1%), which is a marker for corticosteroids of group B (24), although it is no longer used as a topical dermatological drug itself, but only in aerosols. However, its prevalence has shown a decreasing trend over the years, and in recent years it has reached the incidence of positive reactions to tixocortol pivalate (overall prevalence 1.6%, 95%CI: 1.4–1.8%), a marker for the molecules of group A. Both were added to the baseline series in 2000 (33), and together they are able to detect 88.5% of corticosteroid-allergic patients (23); hydrocortisone-17-butyrate (group D2) accounts for another 4% of corticosteroid-allergic patients. In our department, all patients with a positive test reaction to one of those three markers, or to a specific corticosteroid used, are tested with an extended corticosteroid series in order to check for cross-sensitivity; the results of this have been extensively discussed in previous publications (23, 24).

Concerning antiseptics, such as quaternary ammonium compounds and iodine, the results have to be interpreted more carefully, as they have irritant properties, and occlusion may cause irritant reactions that could be misdiagnosed as allergic reactions (34). Table 4 shows iodine as a leading cause. Reactions to iodine, however, are particularly difficult to interpret, as in the case of surgical interventions (35), when excess PVP-iodine solution is applied, and the patients are exposed to it for a long time in the operating room; even mixed irritant and allergic reactions are possible (36). Here, we considered only the reactions that we interpreted as allergic, and the irritant reactions often contributed to the diagnosis of irritant dermatitis. Merbromine used to be another common sensitizer, but this organic mercury compound is no longer used in clinical practice, like most other mercurials, because of their toxicological and sensitizing properties (37). Furthermore, 38 positive reactions in 3716 patients tested with chlorhexidine digluconate were observed, and

it is therefore considered to be a relatively rare allergen (standardized prevalence 1.5%, 95%CI: 1.1–1.9%), although some reactions may have been missed. Indeed, Opstrup et al. (38) recently investigated chlorhexidine contact allergy in Denmark, and detected a prevalence of 1.0%; they suggested that chlorhexidine diacetate should also be tested.

In the group of NSAIDs, we found ketoprofen, etofenamate and bufexamac to be the three most frequent allergens in topical pharmaceutical products. Positive patch test reactions to the last of these are no longer seen or are not relevant, as it was withdrawn from the EU market in 2010 by the European Medicines Agency, because of its high sensitizing properties (39). In contrast, reactions to etofenamate and ketoprofen, in particular, still remain a current problem, with severe clinical symptoms and a high number of concomitant reactions (40, 41). This was also shown in the European multicentre photo-patch test study (42). Despite the risk–benefit analysis of ketoprofen by the European Medicines Agency in 2010 leading to prescription use only, and more awareness among the patients, we have still observed 39 cases in the last 5 years. With etofenamate, an increasing number of positive photo-patch test reactions have also been found, often concomitantly with reactions to ketoprofen, for which, beside some cases of simultaneous exposure, no explanation has yet been put forward. Adding NSAIDs to the European photo-patch test series in 2013 (43) certainly also contributed to improved detection. As seen in Table 4, many other active principles in topical drugs were identified as contact allergens. In contrast to more extensive use in the past, and consequently many contact-allergic reactions being reported in France (44), the frequency of sensitization to resorcinol in topical medications (and even hair dye formulations) is very low (45, 46).

Limitations of the study

As the specific iatrogenic contribution in patients suffering from 'iatrogenic dermatitis and other causal factors' cannot be strictly separated, we also included the results for 'iatrogenic without cosmetic dermatitis' and 'iatrogenic dermatitis only'. This was a single-centre

study, but, because of the large sample size and wide time range, it may be considered to be generalizable, providing valuable information on iatrogenic contact dermatitis not only for our unit, but probably also for Belgium. It has to be kept in mind that the study population is selected, as it comprised patients consulting our specialized contact allergy unit, so there might be an overestimation of contact allergy prevalence. Differences in overall sensitization attributable to differences in the sex and age distribution were accounted for by standardization.

Conclusions

In this retrospective study encompassing 14 911 patients attending a tertiary referral patch test clinic over a 25-year period, 17.4% (95%CI: 16.8–18.0%) of patients were found to suffer from iatrogenic contact dermatitis, which mostly arises as a complication of a pre-existing,

often eczematous dermatitis or skin damaged in other ways. We observed decreasing trends for the active principles tested in the baseline series, but frequent positive reactions to various other active pharmaceutical ingredients. This underlines the need for extensive testing with the topical products used, and their ingredients. It also emphasizes the importance of continuous monitoring and regular screening for allergens, especially in the light of pharmacovigilance for new drugs (topical immunomodulators, 'bio-similars', etc.). Moreover, it is important to consider cross-reactivity patterns, a topic that will be discussed in a further article.

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