

Occupational allergic contact dermatitis from systemic drugs

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Abstract

Background: Health-care workers (HCWs) and professionals working in the pharmaceutical industry are at risk of developing occupational allergic contact dermatitis (OACD) from systemic drugs (or drug intermediates).

Objectives: To study demographic characteristics and identify systemic drugs responsible for OACD in patients investigated for contact allergy during the period 2001–2019.

Methods: In the study period, 9780 patients were patch tested with the European baseline series, sometimes with additional series, and other relevant potential allergens. All patients with a positive patch-test reaction to systemic medication exposed to at work were included for further analysis.

Results: Of 1248 HCWs examined in our clinic, 201 suffered from OACD. In 26 (13%) dermatitis was caused by skin contact with a systemic drug: 19 nurses, five chemists working in the pharmaceutical industry, one physician, and one veterinarian. In total, 45 positive patch-test reactions to 20 different systemic drugs were found, with tetrazepam ($n = 11$), ranitidine hydrochloride ($n = 5$), and zolpidem ($n = 4$) being the most frequent. Three pharmaceutical chemists were sensitized to a drug intermediate. The lesions were mostly localized on the hands, but often also on the face, as airborne dermatitis.

Conclusion: As much as 13% of OACD in HCWs, diagnosed in our tertiary referral center, was attributable to systemic drugs, most frequently in nurses.

KEYWORDS

airborne, allergic contact dermatitis, drug intermediates, drugs, occupational, patch testing, prodrugs, systemic medication

1 | INTRODUCTION

Allergic contact dermatitis (ACD) is often occupation-induced, that is, occupational allergic contact dermatitis (OACD). Health-care workers (HCWs), but also workers in the pharmaceutical industry, who may also react to drug intermediates, are at risk.^{1,2} The lesions most commonly occur at the site of contact, which is generally the hands³; however, airborne reactions from powdered drugs, droplets, or vapors are not uncommon,⁴ and even generalized reactions may develop due to inhalation or transcutaneous absorption.⁵

This study aims to identify the causal drugs responsible for OACD in HCW during the period 2001–2019, as follow-up from a study

published by Gielen and Goossens regarding patients observed between 1978 and April 2001,⁶ presently also including employees in the pharmaceutical industry.

2 | METHODS

Data were retrospectively collected from a patient database developed in-house at the Contact Allergy Unit of the Dermatology Department of the University Hospitals Leuven.⁷ From April 2001 to April 2019, 9780 patients presenting with eczema were consecutively patch tested. For all patients with OACD in the pharmaceutical industry or health-care sector (including physicians, nurses, dentists,

physiotherapists, pharmacists, medical pedicures, and veterinarians), information including age, consultation date, gender, occupation, and localization of symptoms was collected in an Excel data sheet (Microsoft Office 2016, Microsoft, Redmond, Washington), along with the nature of the drug allergens and the patch test results. A χ^2 test was performed to evaluate the significance of differences in patient characteristics between the study group and the total patient population observed during this period, with a *P*-value < .05 considered statistically significant.

Besides the European baseline series, patch tests were performed with additional test series and other relevant potential allergens, including the drugs (or chemical intermediates) the patients had been exposed to at work, and sometimes also with potential cross-reacting substances. The test materials were obtained from Trolab Allergens (previously Almirall Hermal, Reinbeck, Germany; now SmartPractice Europe, Barsbüttel, Germany) and/or Chemotechnique Diagnostics (Vellinge, Sweden), or self-prepared according to the concentrations and vehicles proposed by de Groot,⁸ and stored at 4°C. Patch-test chambers (Van Der Bend, Brielle, The Netherlands), later on IQ Ultra Chambers (Chemotechnique Diagnostics), and more recently AllergEAZE Skin Patch test chambers (SmartPractice Europe) were applied on the back using Micropore (3M Health Care, Borken, Germany), and fixed with Mefix (Mölnlycke Health Care, Göteborg, Sweden). At day (D) 2 and D4, and sometimes later, the readings were performed according to ESCD guidelines.⁹ All patients with one (or more) positive allergic reaction (+, ++, or +++) to systemic drugs (or intermediates) were included in our overview. The study was approved by the Ethical Committee of the University Hospitals Leuven.

3 | RESULTS

3.1 | Patient data

Of 9780 patients who visited the department (6564 women and 3216 men), of whom 5473 (56%) had at least one positive patch test, 1248 (13%) were HCW or employees in the pharmaceutical industry. A total of 201 (16%) were diagnosed with OACD, with the proportion of women (*n* = 151, 75%) being significantly higher than the share of men when compared with the total population (*P* = .02). Their occupations were the following: 104 nurses (52%), 53 chemists working in the pharmaceutical industry (26%), 17 physicians (8%), 11 dentists (5%), 11 physiotherapists (5%), four community pharmacists (2%), and one veterinarian (0.5%).

In 26 of 201 (ie, 13%), systemic drugs, or in a few cases chemical intermediates patients were exposed to at work, were the cause of their OACD. Other work-related sensitizing culprits in HCW concerned (rubber) gloves, metallic objects (nickel), cosmetics, and (ingredients of) topical pharmaceutical products, including antiseptics and disinfectants, which will not be further discussed here.

The main characteristics of the 26 patients with OACD from drugs are given in Table 1. Nine (35%) patients were men and 17 (65%) were women. Nineteen were working as nurses, five as pharmaceutical

chemists, one as a physician, and one as a veterinarian. The age ranged from 24 to 63 years, and the mean age was 41 years, 40 for men and 41 for women. Symptoms were most commonly located on the hands (*n* = 15), followed by the face (*n* = 10) and/or eyelids (*n* = 10), arms (*n* = 6), neck (both *n* = 4), and cleavage, ears, and legs (each *n* = 2). Several patients presented with lesions at multiple locations.

3.2 | Patch-test results

In total, 43 positive patch tests to systemic drugs, including three to a drug intermediate, were observed, and 20 different allergens could be identified, as shown in Tables 1 and 2, which also lists the number of tests performed with each component, budesonide being the most frequently tested as it is present in the baseline series.

Benzodiazepines (15 of 45 positive patch tests), particularly tetrazepam (*n* = 11); ranitidine hydrochloride (*n* = 5); zolpidem (*n* = 4); and corticosteroids, such as budesonide (*n* = 3), were the most frequent culprits.

Six patients (Table 1) showed positive patch tests to different drugs from the same medication class, that is, corticosteroids (cases 3, 17, and 19) and benzodiazepines (cases 12, 13, and 18). Allergens to which the patients had not been exposed to at work are indicated (as footnote a), probably indicating cross-reactivity. As shown in Figure 1, the majority of patients were diagnosed between 2008 and 2011, after which the prevalence of patients with OACD from drugs visiting the department decreased.

4 | DISCUSSION

4.1 | Patients

With regard to demographic data, comparable results were obtained in a previous study,⁶ in which 33 patients with an average age of 38 had been included during a 23-year period, compared with 26 patients with an average age of 41 in this 18-year study period. Women were more frequently involved, possibly explained by a larger number working in the health-care sector,¹⁰ particularly nurses, which is in agreement with the literature.¹¹ As they are daily exposed to irritants, their skin barrier is more likely to be damaged, facilitating sensitization¹²; most lesions were indeed located on the hands. However, vapor or dusts formed by crushing tablets for patients with dysphagia also caused OACD on air-exposed body parts (Figure 2).¹³ Similar findings have been reported for nurses and care takers assisting patients in using aerosols.^{14,15}

Of the four community pharmacists with OACD diagnosed between 2001 and 2019, none had OACD from systemic drugs, whereas in the former study between 1978 and 2001,⁶ two had been reported. Chemists working in the pharmaceutical industry are said to be at higher risk, as they are involved in manufacturing or laboratory processes.¹⁶ Therefore, the pharmaceutical industry was also taken into account in this study, and indeed, five chemists could be diagnosed with OACD due to contact with drugs or chemical intermediates. Interestingly, four of them presented with lesions on the face, because of airborne exposure, or unintentional transmission of

TABLE 1 Characteristics of patients with OACD from drugs and positive patch-test reactions

Patient number	Occupation	Sex	Year of diagnosis	Location of lesions	Drugs	Patch-test reading	
						D2	D4
1	Physician	F	2002	Hands, eyes	Propacetamol HCl	+	++
2	Veterinary	M	2011	Hands, arms, face	Penicillin	+	+
3	Nurse	F	2001	Face, eyes	Budesonide	NR	+++
					Amcinonide ^a	NR	+
					Hydrocortisone	NR	+
4	Nurse	F	2002	Hands	Propacetamol HCl	—	+
					Cephazolin	—	+
5	Nurse	F	2002	Hands	Ranitidine HCl	+	++
6 ^b	Nurse	M	2003	Hands, arms, eyes	Tetrazepam	+	+
7 ^b	Nurse	F	2005	Hands	Tetrazepam	+++	+++
8 ^b	Nurse	M	2005	Hands	Ranitidine HCl	+++	+++
9	Nurse	F	2007	Face	Tetrazepam	+	++
					Valproate	—	+
					Atorvastatin	—	+
10 ^b	Nurse	F	2008	Eyes	Tetrazepam	++	++
11 ^b	Nurse	F	2008	Face	Tetrazepam	+	+
12 ^b	Nurse	M	2008 2009	Hands, eyes, neck, ears	Zolpidem	—	+++
					Lorazepam	++	++
					Tetrazepam	++	+++
					Alprazolam (2009)	+	+++
					Trazodone (2009)	+	+
13 ^b	Nurse	F	2009	Eyes, hands, arms, face	Lorazepam	?+	+
					Tetrazepam	+	++
14 ^b	Nurse	F	2009	Eyes	Tetrazepam	+	++
15 ^b	Nurse	F	2009	Face, neck	Tetrazepam	++	++
					Zolpidem	+	++
					Risperidone	+	+
16 ^b	Nurse	F	2009	Hands, arms, legs, ears	Tetrazepam	++	++
					Zolpidem	+	+
					Ranitidine HCl	+	++
17	Nurse	M	2010	Hands	Budesonide	—	++
					Amcinonide ^a	—	++
					Desonide ^a	—	+
					Mazipredone ^a	—	+
					Ranitidine HCl	+	++
18 ^c	Nurse	F	2011 2012	Hands, arms Face, eyes (2012)	Lorazepam	+	+
					Bromazepam ^a	+	+
					Diazepam ^a	+	+
					Alprazolam ^a	+	+
					Tetrazepam	+	++
					Zolpidem	+	+
					Trazodone	+	+
					Captopril	—	+++
					Aldactazine (2012)	+	+++
19	Nurse	F	2011	Face	Budesonide	+	+
					Methylprednisolone aceponate ^a	+	+
					Alclometasone ^a	+	+
					Prednicarbate ^a	+	+
					Difluprednate ^a	+	+
					Hydrocortisone-17-butyrate ^a	+	+
20	Nurse	F	2011	Hands	Hydrocortisone aceponate ^a	+	+
					Ranitidine HCl	?+	+

(Continues)

TABLE 1 (Continued)

Patient number	Occupation	Sex	Year of diagnosis	Location of lesions	Drugs	Patch-test reading	
						D2	D4
21	Nurse	F	2014	Neck, eyes, cleavage	Aldactazine	+	++
22	Chemist	M	2001	Face	6-Chloro-2-chloromethyl 4-phenyl-quinazoline-3-oxide	+	NR
23	Chemist	M	2003	Hands, eyes	Quinine sulphate	—	+
24	Chemist	M	2004	Hands, arms, legs	Fluoro dihydro-oxiranyl-benzopyran	+	+
25	Chemist	M	2008	Face	Fluoro dihydro-oxiranyl-benzopyran	+	++
26	Chemist	F	2009	Face, cleavage	Tylosin	+	+

Abbreviations: D, day; F, female; HCl, hydrochloride; M, male; NR, not read; OACD, occupational allergic contact dermatitis.

^aCross reaction.

^bPreviously published by Vander Hulst et al¹⁸ but with additional positive patch tests for patient 12 in 2009.

^cPreviously published by Swinnen et al¹⁷ but with additional positive patch test obtained in 2012.

TABLE 2 Drugs responsible for OACD in HCW and employees in the pharmaceutical industry, number of positive reactions, and total number of tests performed with each component

	Allergen	Test concentration and vehicle	Number of positive reactions	Number of cases tested
1	Tetrazepam	10% pet. ^a	11	68
2	Ranitidine HCl	10% pet. ^a	5	149
3	Zolpidem	10% pet. ^a	4	34
4	Lorazepam	10% pet. ^a	3	33
5	Budesonide	0.01% pet.	3	9496
6	Aldactazine (altizide/spironolactone)	10% pet. ^a	2	5
7	Fluoro dihydro-oxiranyl-benzopyran	10% pet. ^a	2	2
8	Trazodone	10% pet. ^a	2	28
9	Propacetamol HCl	aq. ("as is")	2	35
10	Alprazolam	10% pet. ^a	1	28
11	Atorvastatin	10% pet. ^a	1	1
12	Captopril	10% pet. ^a	1	27
13	Cefazolin	10% pet. ^a	1	34
14	6-Chloro-2-chloromethyl 4-phenyl-quinazoline-3-oxide	10% pet. ^a	1	1
15	Hydrocortisone	1% alc. ^a	1	60
16	Penicillin G, potassium salt	10% pet.	1	59
17	Quinine sulfate	1% pet.	1	5
18	Risperidone	10% pet. ^a	1	3
19	Tylosin	10% pet. ^a	1	16
20	Valproate	10% pet. ^a	1	1
	Total		45	

Abbreviations: HCl: hydrochloride; pet.; petrolatum; aq.: aqua; alc.: alcohol.

^aSelf-prepared *lege artis*.

substances from hands to face (ectopic contact dermatitis), suggesting that their hands seemed to be better protected. Of the 17 physicians with OACD, systemic drugs were involved in only one case, possibly because of minor contact with drugs compared with nurses and pharmacists.

4.2 | Allergens

The benzodiazepine tetrazepam was the most frequent sensitizer, observed in 11 cases, having been previously published separately.^{17,18} Its occupational relevance has been extensively studied in

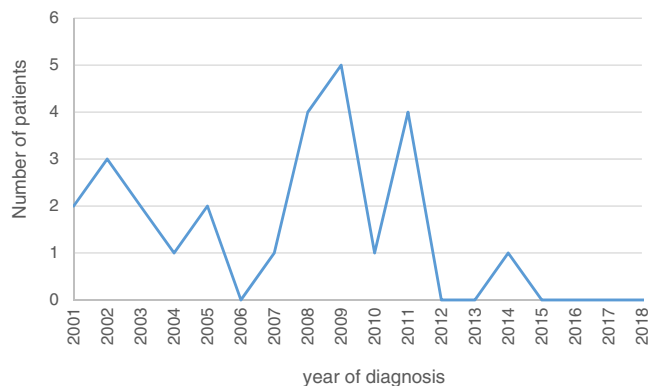


FIGURE 1 Number of patients with occupational allergic contact dermatitis from systemic drugs observed in our department between 2001 and 2019



FIGURE 2 Nurse with airborne contact dermatitis on the neck and cleavage after crushing Aldactazine tablets (Continental Pharma, Puurs, Belgium), a combination of altizide and spironolactone (case 22)

the past.^{19–21} All affected nurses suffered from airborne dermatitis after crushing tablets, five of whom showed multiple positive reactions, with three of them to other benzodiazepines, such as lorazepam. Although nurses often handle several drugs, which may induce concomitant or subsequent sensitization, cross-reactivity is a possibility, particularly because benzodiazepines are metabolized the same way. Furthermore, tetrazepam has been reported as an occupational contact allergen in the pharmaceutical industry as well.²² Its high sensitizing potential and the severe drug eruptions via systemic exposure,²³ in particular, have been the reason for its withdrawal from the market in May 24, 2013²⁴ This probably explains why the last case observed was in 2010. Interestingly, four tetrazepam-allergic nurses concomitantly reacted to zolpidem, a non-benzodiazepine hypnotic drug,¹⁷ which has been previously described as a potential allergen in the pharmaceutical industry and the health-care sector.²⁵

Five positive patch tests were observed to ranitidine hydrochloride, the last case being diagnosed in 2011. In accordance with the literature, nurses used to be more frequently affected,^{6,17} but one article describes six cases from the same pharmaceutical company.²⁶

Antibiotics were the culprits in three cases. In contrast to the previous article,⁶ only one patient, a veterinarian, presented with a positive patch test to penicillin, which used to be a common cause of OACD in nurses in the past; however, in recent years there has been an increasing number of cephalosporin cases,²⁷ and we observed one to cephazolin. Moreover, similar to the case reported by Gielen and Goossens in 2001, tylosin, a macrolide antibiotic used in veterinary medicine, caused OACD in a pharmaceutical industry worker.

Corticosteroids were responsible for OACD in three patients, who all presented with a positive test to budesonide, and one of them also to hydrocortisone, co- and cross-reactions to other corticosteroids, such as amcinonide, as also described in the literature.²⁸ Symptoms were observed on air-exposed areas, as budesonide is an inhalation corticosteroid.

In this study, only two cases of OACD from propacetamol hydrochloride, the prodrug of paracetamol (acetaminophen) for parenteral use, were identified, compared with 10 between 1978 and 2001. Both nurses consulted before 2002, because from then on, the administration method indeed changed to avoid leakage on the skin,²⁹ and from 2006 onward it even is no longer available on the Belgian market (personal communication with our hospital pharmacy and Belgisch Centrum voor Farmacotherapeutische Informatie in May 2019).

Several other allergens were identified in HCW, including the angiotensin-converting enzyme inhibitor captopril, only rarely reported in the literature,³⁰ and the psychopharmaceuticals trazodone ($n = 2$) and risperidone ($n = 1$), as previously observed in our center.^{17,18} Interestingly, also two relevant positive reactions to Aldactazine (Continental Pharma, Puurs, Belgium), a combination of altizide and spironolactone, were noted, which was, to our knowledge, not previously reported in an occupational setting (see Figures 2 and 3). The latter also applies to the antiepileptic drug valproate, and the lipid-altering agent atorvastatin, causing one positive patch-test reaction each. Other allergens related exclusively to the pharmaceutical industry employees included the

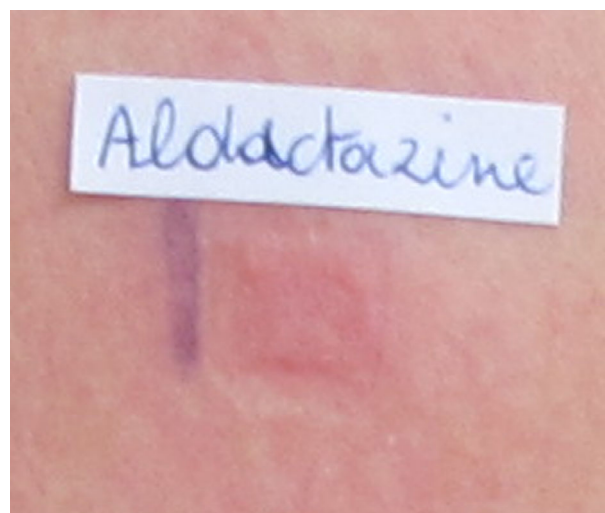


FIGURE 3 Positive patch-test reaction to Aldactazine (Continental Pharma, Puurs, Belgium; +, day 2) in a nurse with airborne contact dermatitis on the eyelids and face (case 19)

antiarrhythmic agent quinine sulfate,³¹ and quinazoline oxide (6-chloro-2-chloromethyl 4-phenyl-quinazoline-3-oxide) in a patient who came in contact with it as a precursor in the production of chlordiazepoxide, a benzodiazepine; only one case seems to be known from the literature.³²

Finally, fluoro dihydro-oxiranyl-benzopyran has, as far as we know, not been reported yet; it is used in the manufacturing of nebivolol, a beta-blocking agent. ACD to this latter drug has previously been reported in a non-occupational setting.³³

Since the knowledge about potential drug allergens has increased and more prevention measures are applied, such as the use of appropriate ventilation systems and more careful handling, including the use of crushing devices, masks, and gloves, less patients with OACD from drugs have been observed during recent years, as illustrated in Figure 1. Tetrazepam, one of the most frequent culprits in nurses, was withdrawn from the market, albeit because of severe systemic drug eruptions, and since OACD cases were indeed no longer observed. Furthermore, beside protective measures in pharmaceutical manufacturing,³⁴ changes in drug administration methods for HCW to avoid skin contact, such as in the case of propacetamol, have proven to be efficient to prevent OACD.

We suggest to proactively ask for all medication handled by HCW or workers in the pharmaceutical industry with hand- and/or airborne dermatitis, especially in those cases where contact dermatitis from gloves and disinfectants has already been excluded. If the patient's history proves unhelpful, it might be useful to test with a drug series, such as the one suggested by Chemotechnique Diagnostics. Other medications can be tested separately as commercialized allergens when available, or with medication brought by the patients and further prepared as stated in the "Methods" section.

4.3 | Limitations

Not all patients were tested with every possible culprit drug they were exposed to, also because these were not always available for patch testing. Moreover, OACD due to systemic drugs is certainly overlooked, attention being more often given to soaps, anti-septics/disinfectants, and gloves as possible causes. Therefore, the results of this retrospective analysis probably underestimate sensitization prevalence.

5 | CONCLUSION

In our tertiary referral center, during the period 2001-2019, 13% of cases of OACD in HCW, mostly nurses, were found to be attributable to systemic drugs belonging to various pharmacological classes. Besides drugs, a few chemical intermediates as culprit allergens were observed in pharmaceutical chemists. Fortunately, a decreasing trend was observed in recent years, stressing the importance of close monitoring, preventive and protecting measures during manufacturing, and changes in the administration methods, all in order to avoid skin contamination.

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CONFLICT OF INTEREST

None to declare.

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