

Allergic contact dermatitis to topical drugs— epidemiological risk assessment[†]

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SUMMARY

Purpose Estimation of the population-based relative incidence (RI) of contact sensitization to a set of topical drug allergens (cases/100 000 defined daily doses (DDDs) per year) (1995–2004) and comparison of the RI for drugs with a similar therapeutic scope.

Methods Clinical data regarding the frequency of contact sensitization to important topical drug allergens in Germany were obtained from the Information Network of Departments of Dermatology (IVDK). This was extrapolated to the general population level using the ‘clinical epidemiology and drug utilization research’ (CE-DUR) approach. As denominator of exposure, national prescription data (DDDs of topical drug specialties) provided by the WIdO Research Institute (Bonn) were aggregated per substance.

Results The probable RIs of contact sensitization to topical ‘skin’ corticosteroids ranged from 0.3 (dexamethasone phosphate disodium salt) to 23.3 (amcinonide) cases/100 000 DDDs per year. Concerning topical aminoglycoside antibiotics, the RI of framycetin sulphate was about threefold higher than that of gentamicin sulphate. Regarding topical ophthalmic use, the RI of kanamycin sulphate was higher compared to gentamicin sulphate. Active principles marketed over-the-counter (OTC) had, in general, lower RIs, with the exception of bufexamac, benzocaine, clioquinol and phenylephrine.

Conclusions The population-based risk assessment—quantitatively considering exposure in the RI estimation—revealed a ranking of contact sensitization risk to topical drugs which partly differed from the respective frequencies in the clinical patch test population. Some drugs available OTC carry non-negligible risk, too. The current findings should contribute to differential therapeutic considerations regarding topical drug use. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS—allergic contact dermatitis; topical drugs; relative incidence; clinical epidemiology; drug utilization research; defined daily doses

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INTRODUCTION

Skin exposure to drugs such as antibiotics, anti-mycotics or local anaesthetics may induce contact

sensitization. This in turn, leads to allergic contact dermatitis, an acute inflammatory reaction upon each subsequent contact once contact sensitization has been acquired. In fact, allergic contact dermatitis is the most common adverse reaction to topically applied drugs.¹

Information on contact sensitization to topical drugs is mostly generated from patient-based studies. Often case reports and case series are the first to describe sporadic cases.^{2–4} Observational studies, mostly cross-sectional, yield allergy patch test results offering a

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more adequate estimate of contact sensitization frequency than case reports. In addition, a few studies estimating morbidity on the population level have been carried out for neomycin sulphate and benzocaine^{5–10} and more recently for other six topical drugs¹¹ by extrapolating contact sensitization frequencies of a clinical patch test population.¹² In all these studies, the frequency of sensitization is calculated by relating affected cases to the total number of patients patch tested and usually expressed as a percentage. It would, however, be much more informative if contact sensitization frequency was related to the number of actually exposed persons, or a surrogate thereof, as the sensitization risk is surely not only a property of the therapeutic agent, but also strongly, and trivially, depending on the amount of exposure.

The objective of this study was thus to estimate contact sensitization incidence regarding a set of 33 drug allergens relative to topical exposure to these, considering national prescription data in units of defined daily doses (DDDs) as exposure estimate. Specifically, a comparison of the relative risk for prescription drugs with a similar therapeutic scope was performed.

METHODS

Topical drugs analysed comprised 33 contact allergens of the 'German Contact Dermatitis Research Group' standard and special series patch tested in the Information Network of Departments of Dermatology (IVDK, www.ivdk.org)¹³ between 1995 and 2004. These drugs were available, in the same period, on the German market either as over-the-counter (OTC) or per prescription (Rx) or both. Only drug specialties intended for topical application on the skin and adjacent mucous membranes were considered (Table 1).

For the analysis presented, the relative incidence (RI) (cases/100 000 DDD per year) of contact sensitization to single allergens was calculated by dividing the number of cases in the general German population extrapolated with the 'clinical epidemiology and drug utilization research' (CE-DUR) approach¹² by the average of DDDs of topical drug-containing preparations prescribed in Germany between 1995 and 2004. The single methodological steps are described in the following sections.

CE-DUR estimate of morbidity

The numerator of the RI, that is, the number of newly diagnosed contact sensitization cases per year on the

general population level, was estimated using the CE-DUR approach, as reported in a previous analysis of eight topical drug allergens published in this journal.¹¹ Briefly, the CE-DUR approach is a combination of methods of the Clinical Epidemiology and Drug Utilization Research. It is used to extrapolate the frequency of specific contact sensitizations from clinical patients to the general population. For this purpose two data sources are used:

- i) Patch test results of patients attending the IVDK dermatological departments. The IVDK patients represent approximately 2–3% of all patients patch tested in Germany. Characteristics such as gender, age, disease pattern or suspected causal exposure and the frequency of positive patch tests are considered to be largely representative of all German patients patch tested^{11,12} and
- ii) sales of patch test material in Germany, the latter representing a starting point for the estimation of the number of persons 'eligible' for testing at the population level because of a suspected contact sensitization.

The original sales figures are corrected for several factors (e.g. discarded test material, previous tests, see Reference¹²), yielding three different scenarios offering a corridor for the estimation of morbidity. The most conservative scenario yields estimates which are lower than those from the medium scenario by a factor of 0.58 whereas the most extreme scenario yields incidence estimates roughly 2.4-fold higher than the estimates from the medium scenario. The frequencies of positive reactions to individual allergens obtained from the German IVDK centres are related to the corrected sales data to arrive at gross estimates of the absolute number of contact sensitization cases to single allergens according to the three scenarios in Germany.¹²

Drug prescriptions database

Prescription data were provided by the WiDO Research Institute ('Wissenschaftliches Institut der Ortskrankenkassen', Bonn, Germany). The database comprises information on medical prescription of drugs dispensed at the ambulatory level to the individuals covered by the statutory health insurance,¹⁴ accounting for approximately 86% of the total German population in the period of analysis.¹⁵ These data are published yearly in the 'Arzneiverordnungs-Report'.¹⁶

In the database, drug specialties were classified according to the German Anatomical Therapeutic Chemical (ATC) classification system and the DDD methodology.¹⁴ This methodology is based on that of

Table 1. Topical drug specialties available at the German market (1995–2004)—patch test preparations, status (Rx and OTC) and anatomical site of topical application (ATC classification)

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Pet. = petrolatum; aq. = aqueous solution.

D, dermatologicals; S, sensory organs; R, respiratory system; G, genito urinary system and sex hormones; C, cardiovascular system ('antihemorrhoidals for topical use').

the World Health Organization (WHO)¹⁷ which has been extended and applied by the WiDO, in cooperation with the WHO, to the specialties available on the German market not covered by the international standards. In particular, the DDD assignment has been extended in Germany to drugs for topical application on the skin ('dermatologicals' ATC code D) and on adjacent mucous membranes, for example 'ophthalmologicals' and 'antihemorrhoidals for topical use' ATC coded S01 and C05, respectively. The methodology of the German ATC-classification, the DDD-assignment and the ATC-index with DDDs are published yearly.¹⁴ Relevant DDD assignments are shown in Table 2.¹⁴

Exposure to selected topical drugs

In the WiDO database prescription information was identified both by brand specialties and (possibly aggregated, in case of several similar specialties) by one ATC code. Four possibilities of identifying the relevant prescription (exposure) data had to be considered:

- i) Active ingredient in mono preparation: direct identification *via* ATC codes.
- ii) Active ingredient in a combination, as the one 'major' component identified by the ATC coding: direct identification *via* ATC codes. In both cases 'i' and 'ii', prescription data (as DDD) were supplied aggregated per ATC code by WiDO.
- iii) Active ingredient in a combination, but as 'minor' component not identifiable by the ATC coding: all drug specialties potentially falling in these categories were manually scanned using the 'Rote Liste'.¹⁸ Respective ATC codes were matched to brand specialties by WiDO and the prescriptions aggregated per active ingredient delivered.
- iv) Active ingredient possibly in combinations not specifically identifying any ingredient on the substance level: as 'iii'.

The denominator of exposure for each single topical drug comprised the sum of the DDDs of all topical specialties including mono and combinations without respect to the site of topical application. As an exception, data for the drug allergens of the ophthalmic series were examined separately, because in this case only it was possible to relate site-specific morbidity (the drug allergens patch tested in the ophthalmic series in the IVDK centres) to site-specific exposure data (prescriptions of ophthalmic specialties).

Statistical considerations

To address the precision of the RI estimates, 95% confidence intervals (CIs) were calculated (Formula 1) based on the following assumptions:

- i) The proportion of positive patch test reactions $\hat{p}$ (to a particular topical drug) estimated from the IVDK population is a random variable,
- ii) a is a constant, comprising the sales of patch test material PT (i.e. crude number of persons in the general population eligible for testing) multiplied with correction factors CF (see above) and the prescription data Rx which were generated from a complete data survey,
- iii) Count data such as the proportions of positive patch test reaction $\hat{p}$ among all patients tested n follow a binomial distribution $B(n, p)$, which approximates to a normal distribution given a sufficiently large sample size.

Thus, the 95% CIs can be obtained as follows:^{19,20}

$$CI_{95\%}(RI) = a \cdot \hat{p} \pm Z_{\alpha/2} \cdot a \cdot \sqrt{\widehat{\text{var}}(\hat{p})} \quad (1)$$

$$a = \frac{PT \cdot \text{sales} \cdot CF}{Rx}; \widehat{\text{var}}(\hat{p}) = \frac{\hat{p}(1-\hat{p})}{n}$$

where $Z_{\alpha/2} = 1.96$ is the 100 $(1-\alpha/2)$ percentile of the standard normal distribution for $\alpha = 0.05$.

Table 2. Unit dose (UD) of topical dosage forms taken as basis for the calculation of DDDs for German drug specialties according to manufacturers' recommended daily doses (average manufacturer-DDD)

	ATC code (1st or 3rd level)	UD	Dosage forms
C05	Antihemorrhoidals for topical use	1 unit	Solid, semisolid and liquid preparations
G01	Gynaecological	1 application	
D	Dermatologicals	1 g	Semisolid and liquid preparations
S01	Ophthalmologicals	0.1 g 0.1 ml	Semisolid and liquid preparations for small limited substances
S02	Otologicals		
S03	Ophthalmologicals/otologicals		
R	Respiratory system		

RESULTS

The results of the patient- and population-based (extrapolated) analysis for the 10-year period 1995–2004 are summarized in Table 3, together with the prescription data in terms of DDDs and the RIs of contact sensitization according to the medium scenario, which is considered the most appropriate estimate of incidence.¹² The most important findings are:

- Neomycin was the most important allergen of the standard series in the clinical IVDK population (2.3%). RIs at the population level of the two other standard series allergens, benzocaine and bupivacaine, are difficult to compare, as these (also) available OTC. Hence, exposure is underestimated and the RI thus overestimated. This caveat applies also to other OTC drugs.
- Concerning the drug allergens of the antibiotic series, the ranking of allergens in the general popu-

Table 3. Population-based relative incidence of contact sensitization to topical drugs (1995–2004) obtained from the extrapolation of CS morbidity in clinical patients—IVDK network (numerator) and national prescription data in units of DDDs (denominator) according to the medium scenario

Topical drugs	Clinical data % CS	CS cases	Prescriptions (millions DDDs)*	RI (cases/100 000 DDD-year) (95%CI)	
Standard					
Neomycin sulphate	2.3	21 179	35.7	59.4	(50.8–68.0)
Benzocaine	1.5	14 211	≥3.4	413.9	(340.0–487.8)
Bupivacaine	1.4	11 558	≥15.3	75.7	(61.2–90.2)
Antibiotics					
Bacitracin	1.5	1701	10.2	16.7	(8.1–25.3)
Gentamicin sulphate	2.9	3245	11.2	29.0	(18.2–39.8)
Framycetin sulphate	4.1	4619	5.8	86.2	(60.4–112.0)
Oxytetracycline	0.1	146	9.1	1.6	(0.0–4.5)
Fusidic acid	1.1	1269	17.1	7.4	(3.0–11.8)
Polymyxin B sulphate	1.0	1076	13.2	8.2	(2.6–13.8)
Chloramphenicol	3.3	4040	17.3	23.3	(15.5–31.1)
Antimycotics					
Nystatin	0.4	287	≥30.7	0.9	(0.0–2.2)
Clotrimazole	0.5	574	≥69.8	0.8	(0.1–1.5)
Further topical drugs					
Clotrimazole	1.1	1146	≥1.8	64.5	(23.8–105.2)
Dexpanthenol	1.3	1466	≥243.8	0.6	(0.3–0.9)
Local anaesthetics					
Lidocaine HCl	1.1	256	≥16.6	1.5	(0.0–3.8)
Procaine HCl	1.6	391	≥12.3	3.2	(0.0–6.4)
Polidocanol	1.9	3835	≥52.1	3.1	(1.5–4.7)
Tetracaine HCl	0.9	797	0.7	107.8	(29.3–186.3)
Cinchocaine HCl	1.9	1621	27.7	5.9	(2.9–8.9)
Ophthalmics					
Atropine sulphate	0.3	155	5.7	2.7	(0.0–7.4)
Phenylephrine HCl	1.9	891	≥4.1	21.6	(6.2–37.0)
Pilocarpine HCl	0.4	169	59.6	0.3	(0.0–0.7)
Kanamycin sulphate	2.9	1336	15.4	8.7	(3.7–13.7)
Gentamicin sulphate	3.5	2077	43.3	4.8	(2.5–7.1)
Chloramphenicol	0.9	436	10.4	4.0	(0.0–8.7)
Polymyxin B sulphate	0.7	314	22.7	1.4	(0.0–3.1)
Corticosteroids					
Amcinonide	1.6	1155	4.9	23.6	(8.9–38.3)
Hydrocortisone	0.3	228	≥24.1	0.9	(0.0–2.2)
Triamcinolone acetonide	0.5	392	27.5	1.4	(0.0–2.9)
Clobetasol 17-propionate	0.4	299	21.0	1.4	(0.0–3.2)
Hydrocortisone 17-butyrate	1.5	1062	10.0	10.7	(3.7–17.7)
Betamethasone 17-valerate	0.5	335	60.4	0.6	(0.0–1.2)
Budesonide	2.6	2082	4.8	43.2	(24.4–62.0)
Prednisolone	0.4	320	59.9	0.5	(0.0–1.1)
Dexamethasone 21-phosphate disodium salt	0.4	288	86.1	0.3	(0.0–0.7)

*‘≥’ refers to prescription data including OTC specialties.

lation corresponds to that of the IVDK patch test population. Framycetin sulphate was the top allergen, with a significantly higher RI than that of gentamicin sulphate (CIs do not overlap). While fusidic acid and polymyxin B showed similar contact sensitization frequencies and RIs, oxytetracycline occupied the last rank at both clinically and at the population level.

- A comparison of the RIs of the OTC antimycotics carries some uncertainty (see above). At any rate, these can be considered very rare allergens.
- While clioquinol and dexpanthenol had similar contact sensitization frequencies in the IVDK patch test population, the consideration of the volume of prescriptions (in units of DDDs) revealed an extremely low risk regarding dexpanthenol, taking RI overestimation into account (see above).
- Tetracaine was the most important local anaesthetic allergen at the population level, followed by cinchocaine. The OTC local anaesthetics exhibited lower RIs.
- Comparing aminoglycosides from the ophthalmic series, the RI of kanamycin sulphate was higher than that of gentamicin sulphate, reversing the ranking based on clinical data alone.
- Among the corticosteroids, which were all available by prescription only in the study period 1995–2004 (except for hydrocortisone at a concentration $\leq 0.25\%$ ¹⁸) striking differences can be noted between the frequencies of contact sensitization and, in particular, the RIs. Budesonide, which is used as a marker allergen rather than as a typical 'skin corticosteroid' (see discussion), amcinonide and hydrocortisone butyrate are apparently associated with a higher risk than other topical corticosteroids.

DISCUSSION

In this study, an important adverse event associated with the topical application of drugs on the skin or adjacent mucous membranes was assessed, namely, allergic contact dermatitis due to contact sensitization to the active compound(s). To our knowledge, this is the first report relating the incidence of contact sensitization to topically applied drugs to the amount of exposure to these, in order to achieve a more valid risk assessment. Until now, pharmacoepidemiological studies addressing such RIs have focused on adverse event(s) after systemic use only (e.g. Reference²¹).

The extension of the DDD definition to topical drug-containing specialties in Germany¹⁴ has made possible to employ this quantitative measure as

denominator of exposure of the RI of contact sensitization for a set of well-known and still widely prescribed drugs. It should be noted, however, that the DDDs do not necessarily correspond to a certain number of exposed drug users, as might appear desirable: a given DDD may be the product of (multiple) prescription of the drug to a few users, or of single prescriptions (of small quantities) to a higher number of users, yielding something like a 'person time of treatment'. Only in the particular situation of (i) the DDD being in agreement with the prescribed daily doses (PDD), (ii) the drug being used to treat a single (chronic) disease exclusively, therefore (iii) requiring continuous (long-term) drug therapy^{22,23,21} can DDDs be used to calculate a number of persons exposed. While these conditions generally do not hold for topical therapy, one topical drug fulfils these requirements, namely, pilocarpine. This drug is used in Germany exclusively for the continuous treatment of open-angle glaucoma. Thus, assuming continuous application by one person during 1 year, a cumulative annual pilocarpine CS incidence of 103/100 000 persons treated can be derived (medium scenario). However, especially if active compounds with a similar (set of) indication(s) are compared, the use of DDD as an approximate, person-time related exposure estimate appears also valid, as the extent and direction of inevitable exposure misclassification by use of the DDD can be expected to be similar across the different compounds. We expect such similarity also regarding other inevitable sources of exposure misclassification when using prescription data, namely, the proportion of drugs prescribed, but not, or incompletely, used.

Lastly, the prescriptions of all specialties containing one particular compound have been aggregated to arrive at a global denominator of exposure (Table 1), even though the respective specialties are partly used to treat different sites, use different vehicles, package sizes, and partly different concentrations, since all these routes may account for the induction of contact sensitization. Thus, application to wide skin areas, to confined areas such as the hands, or to particular anatomical sites such as the perianal region or the outer ear are all put together. Again, for groups of active principles used for a similar set of indications we believe this will not distort comparisons within such groups. At any rate, as it can often not be determined and is not regularly documented, respectively, which route of topical application (corresponding to any one of the ATC codes) has led to contact sensitization in a patch tested patient, it is deemed necessary that the level of aggregation regarding exposure mirrors the level of aggregation regarding

morbidity—notably with the exception of ‘ophthalmics’.

OTC topical drugs

Some of the drug allergens were available exclusively or partially as OTC drugs in Germany from 1995 to 2004 (Table 1). Therefore, an unknown proportion of these acquired without medical prescription was not recorded by WIdO and can thus not be considered in the denominator of exposure. Consequently, the RIs of these topical drugs represent not more than an upper ceiling of the true RI. This should be kept in mind in the interpretation of the results, namely, when comparing the RIs for a group of similar active principles, which are available only by prescription (Rx) *versus* OTC (also). Even despite the presumptive (severe) overestimation of the RI, these estimates were often quite low for OTC topical drugs, for example for the antimycotics exclusively available OTC as well as for the broadly used dexpanthenol (OTC and Rx). Regarding some other compounds such as bufexamac, benzocaine, clioquinol and phenylephrine, however, the consideration of the contact sensitization prevalence observed clinically alone indicates that these seem to be relevant allergens, even if a proper comparison of the RI is hampered by an unknown amount of exposure misclassification. The unfavourable risk–benefit ratio of bufexamac (high allergenic potential *vs.* disputable efficacy) has been already discussed.^{24,11} The fact that bufexamac is still available OTC in Germany is thus a reason for concern.

Prescription drugs (Rx)

The drug prescription data employed in the current analysis refer to the vast majority of the German population which is covered by the statutory health insurance. Thus, the topical drug exposure concerning persons privately insured (14% on average¹⁵) could not to be addressed. Hence, a certain overestimation of the RI of the single drugs allergens of up to 14% must be expected. Nevertheless, we believe the pattern of exposure to topical drugs between both—private and statutory health systems—did not vary markedly, so that our comparative analysis of RIs should not be biased.

A comparison of the contact sensitization risk in terms of the RI is meaningful only for drugs of the same pharmacologic and therapeutic group, for example the topical antibiotics and corticosteroids, respectively. While generally application to all skin

sites or adjacent mucous membranes was aggregated (see above), it was possible to separately analyse ophthalmic preparations: site-specific morbidity was identified by the fact that patients were specifically patch tested with the ‘ophthalmic’ series, and exposure was restricted to prescriptions of coded ATC ‘S01’ or ‘S03’ (ophthalmics).¹⁷ The most common allergens were kanamycin and gentamicin sulphate. Both aminoglycosides, especially gentamicin, have been shown to be important contact allergens of the periorbital region previously.²⁵ Interestingly, related to actual exposure, the ranking of contact sensitization risk reversed and the RI for kanamycin sulphate was higher than that of gentamicin sulphate (albeit not significantly), in view of the higher exposure to ophthalmic preparations containing this latter drug.

Comparing aminoglycosides of the antibiotics series beyond ophthalmological application, framycetin sulphate had a RI roughly threefold higher than gentamicin sulphate. While this reflects the ranking of the contact sensitization frequencies in the patch test population, the mere consideration of clinical data would yield a crude prevalence ratio of just 1.4, thus considerably underestimating the difference in risk between these two related compounds. Further relevant antibiotic allergens comprised bacitracin, often used in combination with neomycin and polymyxin B, and the old, still widely used, chloramphenicol.

The topical corticosteroids included in the patch test series evidently comprise substances of low and high sensitization potency. In this analysis, the highest RIs of budesonide, amcinonide and hydrocortisone butyrate mirrored the highest contact sensitization frequencies in the patients patch tested. However, as these were the least prescribed corticosteroids, the higher allergenic potential of these three corticosteroids is obvious. The better skin penetration of hydrocortisone butyrate, a known factor enhancing the induction of contact sensitization, could explain, at least partially, its higher RI estimates compared to those found for hydrocortisone. Budesonide has a special role: it is used as inhalation spray in the treatment of bronchial asthma and rhinitis and for the intraluminal ‘topical’ treatment of inflammatory conditions of the intestines, but not in any topical preparation for use on the skin (according to ‘Rote Liste’¹⁸). It is patch tested basically as a marker allergen, indicating contact sensitization to antigenetically related corticosteroids, namely, those of the proposed ‘group B’ (acetonides) and some esters of ‘group D2’ (e.g. hydrocortisone-17-valerate or -butyrate).^{26–29} Hence, the seemingly very high RI

for budesonide (Table 3) must be put into perspective: if as denominator of exposure not just the few prescriptions of budesonide nasal sprays originally considered (4.8 million DDDs), but 42.4 million DDDs, the sum of the DDDs of amcinonide, triamcinolone and hydrocortisone butyrate, are used, the RI is reduced to 4.9 (95%CI: 2.8–7.0), according to the medium scenario. However, even if conservatively assuming this higher denominator of exposure, the RI found for this drug is quite high compared to other corticosteroids.

In contrast, the further corticosteroids can be classified as less-sensitizing corticosteroids, as they usually produce very few positive patch test reactions despite their widespread use. Indeed, betamethasone valerate was one of the corticosteroids most often prescribed and still with a low RI, similar to prednisolone or dexamethasone and somewhat lower than that of hydrocortisone (and its acetate form), which was partially available OTC in Germany between 1995 and 2004 (at concentrations $\leq 0.25\%$).¹⁸

New topical corticosteroids, such as mometasone furoate, have not been included in our analysis, because newer drug agents are still protected by patent laws and are thus not yet available as patch test material. This general drawback also affects other substance classes, such as calcineurin inhibitors, or new antibiotics or antimycotics.

CONCLUSION

A valid systematic assessment of contact sensitization risk of topical drug components—in this case, active ingredients—under actual use conditions in humans has been lacking so far. The consideration of just the contact sensitization prevalence observed in clinical (patch test) populations may be quite misleading, as shown in our analysis, because the vastly differing exposure to the various agents is not being taken into account. In this situation, the use of prescription data in terms of DDD offers at least a useful, standardized surrogate of exposure to these agents, despite some inevitable, probably non-differential, misclassification going along with this approach. Moreover, the utilization of three existing set of data—patch test data of the IVDK, sales data of test materials from different manufacturers and prescription information from the WiDO Research Institute renders the approach quite economical. Further studies, which could validate the estimates of the RI of contact sensitization to the different agents in the German population, employing different approaches, are not on the horizon. Hence we believe that the findings of this analysis offer a unique

KEY POINTS

- Allergic contact dermatitis caused by contact sensitization is a relatively common adverse reaction to drugs applied topically on the skin and adjacent mucous membranes. Various drug classes are potential sensitizing agents (allergens), even corticosteroids. For the first time, our analysis related the clinically observed contact sensitization frequency to estimates of exposure to the respective agents in terms of the defined daily dose (DDD).
- The comparison of the relative incidences (RIs, as cases/100 000 DDD-year) of different agents of a similar therapeutic class yielded interesting results. For instance, for ophthalmic use, kanamycin sulphate showed higher RIs compared to gentamicin sulphate.
- Especially taking the (partly severe) exposure underestimation into account, topical drug agents marketed over-the-counter were, in general, rare allergens, suggesting a very low allergenic potency. Exceptions to this comprise bupivacaine, benzocaine, clioquinol and phenylephrine.

body of evidence with regard to the risk of this adverse event associated with different topically applied drugs. This can promote (primary and secondary) prevention of contact sensitization, and serve as additional consideration in the differential therapy of conditions treated with topical drugs.

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