

Original article

Anaphylaxis and toxic epidermal necrolysis or Stevens–Johnson syndrome after nonmucosal topical drug application: fact or fiction?

Background: Drug-induced anaphylaxis and toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS) represent severe immediate and delayed-type adverse drug reactions (ADRs), respectively. Occurrence of such reactions after topical drug application has only rarely been reported. Hence, we compiled a large number of such cases which we systematically analyzed.

Methods: All such cases contained in the ADR database of the competent pharmacovigilance authority in Germany and cases reported in literature were identified, evaluated and analyzed with regard to potential risk factors. Since the application of drugs to mucous membranes facilitates their entry to the systemic circulation only cases occurring after non-mucosal topical drug application were considered.

Results: After evaluation 28 anaphylaxis database cases and 48 anaphylaxis literature cases remained for analysis. Application to skin wounds or to skin with impaired barrier function was identified as a risk factor in 10/28 (36%) of the database cases and in 42/48 (88%) of the literature cases. In 9/28 database cases (32%), anaphylaxis was induced by drugs used for their hyperemizing effect and, in 8/28 cases (29%) by antibiotics or antiseptics. In the literature cases, anaphylaxis was induced by antibiotics or antiseptics in 35/48 cases (73%). Only one SJS database case and one TEN literature case remained after case evaluation.

Conclusion: Anaphylaxis does occur after non-mucosal topical drug administration. Application of drugs to skin wounds or to skin with impaired barrier function may pose a risk factor for its occurrence. TEN or SJS following non-mucosal topical drug application seems to be extremely rare.

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Anaphylaxis and toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS) represent severe immediate-type and severe delayed-type hypersensitivity reactions to drugs, respectively. They are well-known adverse drug reactions (ADRs) associated with *systemic* drug application. Following *topical* drug application, cutaneous allergic skin reactions, e.g. contact dermatitis, have also long been recognized as ADRs. However, drug induced anaphylaxis following topical drug application has been only rarely (1–7), and the occurrence of TEN or SJS associated with topical drug application has even less rarely been described (8–12). A systematic analysis of such cases is, thus, mainly hampered by the limited number of reports. To overcome this problem, we performed a research in a large ADR database and, in addition, compiled all such cases described in literature. Because the application of drugs to mucous membranes facilitates their entry to the systemic circulation, we

restricted our investigation to drug-induced anaphylaxis and SJS or TEN occurring after nonmucosal topical drug application.

Material and methods

Database

In Germany, numerous cases of suspected serious ADRs are reported spontaneously to the competent authority, the Federal Institute for Drugs and Medical Devices (BfArM). These spontaneous reports arise from physicians and pharmacists who are obliged by their professional conduct code to report suspected serious ADRs. Another considerable amount of reported cases received by the BfArM stems from the pharmaceutical industry which is obliged to report, upon receipt, all serious ADRs associated with the application of their drugs. Hence, the BfArM has covered the whole country regarding the report of ADRs. All these cases are stored in the BfArM's ADR database. Data

concerning the suspected ADRs and the drugs involved are coded using the MedDRA terminology and the Anatomical Therapeutic Chemical (ATC) classification system, respectively.

Identification of anaphylaxis and toxic epidermal necrolysis/Stevens–Johnson syndrome cases in the database

All cases registered between 1 January 1989 and 31 October 2006, which were coded with the MedDRA terms anaphylactic/anaphylactoid shock and anaphylactic/anaphylactoid reaction (preferred terms include the low-level term anaphylaxis) or SJS (Stevens–Johnson syndrome) or TEN (toxic epidermal necrolysis) (both were preferred terms) and in which the drug administration route was described as topical, auricular or cutaneous, were identified in the database. In a second phase, all the cases identified were assessed with regard to the causal relationship with the incriminated drug. For brevity, these cases are addressed as anaphylaxis or SJS/TEN database cases in the following text.

Case evaluation

After identification, cases were evaluated in order to ensure that only those cases were considered which described (i) a nonmucosal drug application and (ii) a causal relationship of the drug application and the observed ADR (i.e. anaphylaxis, TEN, SJS), which was assessed at least as possible based on criteria as used by the WHO drug monitoring centre (13). The categories employed for causality assessment were certain, probable, possible, uncertain and unclassifiable. Cases in which the reported symptoms were not allergic in nature but originated from other conditions (e.g. hypovolemic or cardiogenic shock) were excluded.

Most of the reports identified as SJS or TEN in the database had either been submitted by or contained the assessment of an independent expert panel of the German registry for severe skin reactions (14). This assessment was dedicated to the causal relationship with the incriminated drug and the correctness of diagnosis. Cases of SJS or TEN were included in the analysis only when the following conditions were met: (i) the causal relationship with the topically applied drug was considered at least as possible, (ii) no other drugs had been administered systemically (e.g. oral or intravenous) for which a causal relationship with the induction of the SJS or TEN could have a higher probability and (iii) the diagnosis of TEN or SJS could be considered at least as possible.

Search for cases published in literature

A literature search was performed in the databases Embase, Medline and Durban Drug File using the search terms 'topical (cutaneous) drug administration and anaphylactic/anaphylactoid reaction/shock, anaphylaxis, Stevens–Johnson syndrome, toxic epidermal necrolysis, Lyell's syndrome'. The data lock point of the literature search was 31 October 2006. Only articles written in English or German were considered. Publications reporting about topical mucosal drug application or application on wounds during surgery were excluded. In publications reporting on more than one patient, only patients with nonmucosal drug application were considered. Publications informing about anaphylaxis or SJS or TEN cases associated with skin tests were excluded because drug application was not within a therapeutic but a diagnostic approach.

For all publications, the causal relationship of drug application and observed reaction was *per se* considered at least possible.

All cases reporting anaphylactic/anaphylactoid reaction/shock and anaphylaxis were considered without prior assessment of the correctness of the diagnosis. This approach was taken because anaphylaxis is considered an umbrella term (15) and its exact definition may vary in different countries and in the more remote literature. In addition, not all publication provided complete information to assess the correctness of the diagnosis. In analogy, no assessment of the correctness of the diagnosis of SJS or TEN in the cases published in literature was performed. For brevity, the cases identified in the literature are referred to as anaphylaxis or SJS/TEN literature cases in the following text.

With regard to the additional presentation of the figures in percentages, it should be noted that as a result of rounding of, the sum may not exactly total 100%.

Results

Anaphylaxis cases identified in the database

Fifty-four spontaneous reports of anaphylaxis associated with topical drug application were identified in the database. Among these, 26 were excluded because the application was not topical, or the causal relationship with the drug was assessed as unlikely or not assessable, or the described ADRs were not compatible with an allergic or even anaphylactic reaction, or it was a double reporting (one case).

Hence, 28 cases (15 female, 13 male) remained for analysis, which reported about a total of 27 patients, as two cases reported about the same female patient who experienced a second reaction one year after the first report. The mean age in the cases, where age was provided, was 38 years (no information in one case, information not readable in another case). In 9/28 cases (32%), drugs or combinations of drugs used for their hyperemizing effect were incriminated. Anaphylaxis was associated with the use of antibiotics for local use in 4/28 cases (14%), and with the use of antiseptics in 4/28 cases (14%). Table 1 provides an overview of the substances reported in the 28 anaphylaxis database cases.

Drug allergy to the particular drug or to other drugs was known in 3/28 cases (11%). In one case of anaphylaxis following topical diclofenac administration, it was stated that hypersensitivity to diclofenac was already known. In another case of framycetin-induced anaphylaxis, sensitization to neomycin was known before. In one case of anaphylaxis induced by an unguentum containing hyperemizing substances, a penicillin allergy was known. In another 3/28 cases (11%), atopy was reported.

In 8/28 cases (29%), the drug was applied to skin wounds (ulcus cruris $n = 4$; infected clavus $n = 1$; knee wound $n = 1$; wound location not specified $n = 2$), in two cases (7%) to skin with impaired barrier function (face, head), and in one case (4%) to intact skin (upper arm). In the remaining 17/28 cases (61%), no information on skin status or that the skin barrier function was impaired was provided (see Table 2).

Table 1. Description of the 28 substances reported to have induced anaphylaxis in the 28 database cases

Class of substance or indication for use	Number of cases per substance	Total per class of substance
Antibiotics for local use	Framycetin + lidocaine <i>n</i> = 3 neomycin + bacitracin <i>n</i> = 1	4
Antiseptics	Polyvinylpyrrolidone <i>n</i> = 1 Mercurochrome <i>n</i> = 1 Benzyl alcohol + ethanol + propanol <i>n</i> = 1 Chlorhexidine digluconate <i>n</i> = 1	4
Antiphlogistics	Diclofenac <i>n</i> = 1	1
Venous insufficiency	Arnica + heparin + conker <i>n</i> = 1	1
Seborrheic dermatitis	Ammonium bituminosulfonate <i>n</i> = 1 Cocostilipidacid-mono-isopropylamide + glykolidstearate <i>n</i> = 1	2
Facial skin care	Mares milk <i>n</i> = 1	1
Bee venom/rheumatic arthritis	Bee venom <i>n</i> = 3	3
Sexual steroids	Estradiol <i>n</i> = 1	1
Anticoagulant	Heparin natrium <i>n</i> = 1	1
Nicotinerge substance	Nicotine <i>n</i> = 1	1
Hyperemizing agent	Combination: histamine hydrochloride + glycol salicylate + methyl nicotinate <i>n</i> = 6 Nonivamide + nicoboxil <i>n</i> = 1 Capsaicin + hydroxyethyl salicylate + benzyl nicotinate <i>n</i> = 1 Camphor + methyl nicotinate <i>n</i> = 1	9
Total	<i>n</i> = 28	<i>n</i> = 28

Table 2. Classification of the status of the skin in the 28 anaphylaxis database cases

Status of the skin	Total number of patients
Wounds	<i>n</i> = 8
Impaired skin barrier function	<i>n</i> = 2
Intact skin	<i>n</i> = 1
No information on skin status or no information that skin barrier function was impaired	<i>n</i> = 17
Total	<i>n</i> = 28

In 12 of the 28 cases (43%), various skin tests for immediate [prick-, scratch test (*n* = 10)] and delayed-type hypersensitivity [patch-test (*n* = 2)] were performed with incriminated substances. Positive reactions were observed in 10/12 (83%) and negative in 2/12 (17%) cases (one prick and one patch test).

Cases of toxic epidermal necrolysis or Stevens–Johnson syndrome identified in the database

The search in the BfArM database retrieved 49 cases of SJS or TEN associated with topical drug application. Among these 49 cases, 18 cases were excluded because they did not represent SJS or TEN [localized bullous contact dermatitis (*n* = 6), erythema exudativum multiforme (*n* = 10)], or the diagnosis was considered unlikely (*n* = 2). Of the remaining 31 cases, 27 were

excluded because the causal relationship with the drug administered topically was considered unlikely or other drugs had been administered systemically (e.g. oral or intravenous), which had a higher probability for the causal relationship with the induction of SJS or TEN than the drug which was applied topically. Three of the remaining four cases were excluded because the drug was applied to mucous membranes. Hence, one case of a SJS remained. This case reported that a 21-year-old male, who had been treated for bronchopneumonia with clindamycin tablets, acetylcystein tablets and an unguentum which contained eucalyptus oil, pine-needle oil and menthol, developed SJS. The causal relationship between the drugs administered and the occurrence of SJS was considered by the expert panel as possible for all three drugs.

Anaphylaxis cases reported in literature

Fifty-seven articles were identified in literature. Of these, 13 publications were excluded because they reported either administration of the drug on mucous membranes or application on wounds during surgery, or since it became obvious for other reasons that the drug administration could not be described as nonmucosal topical. In one publication (16), three of the four cases reported were excluded for these reasons. One publication was excluded because it reported anaphylaxis associated with skin tests (17). The remaining 43 publications reported on 48 patients (cases) and 48 incriminated drugs. None of these literature cases had been submitted as a spontaneous ADR report to the BfArM.

Among 48 patients, there were 25 female (52%) and 23 male (48%). Mean age was 39 years. In 23/48 cases (48%), the incriminated drugs were antibiotics for local use, and in 12/48 cases (25%) they were antiseptics. Table 3 provides an overview of drugs most often reported among the 48 drugs.

In 24/48 patients (50%), the drugs were applied to skin lesions/wounds (e.g. disinfection or lavage of wounds); in 18/48 patients (38%), the drugs were applied to skin with impaired barrier function (stasis dermatitis, psoriasis, atopic dermatitis); and in 6/48 patients (13%), the drugs were applied to intact skin or no information on impaired skin barrier function was provided in the publications (see Table 4). One publication reported about an anaphylactic shock after intradermal injection of the mitogen phytohemagglutinin (48).

In 35/48 patients (73%), various skin tests with incriminated substances were performed, which were reported to give positive reactions in all cases (at least one skin test was positive in cases where different skin tests were performed). Among the remaining 13/48 patients, one patient refused skin tests (3), and in one case (6), a Prausnitz–Küstner test was performed which gave a positive result. No information on skin tests was provided for the remaining 11/48 cases (23%).

Table 3. Description of the 48 substances reported to have induced anaphylaxis in the 48 literature cases

Class of substance or indication for use	Number of cases per substance	Reference
Antibiotics for local use	Bacitracin <i>n</i> = 5	5, 7, 18–20
	Rifamycin <i>n</i> = 6	2 (2 patients), 16, 21–23
	Neomycin <i>n</i> = 1	24
	Framycetin <i>n</i> = 1	4
	Streptomycin <i>n</i> = 1	25
	Sulfadiazine <i>n</i> = 1	26
	Combinations	
	Bacitracin + neomycin <i>n</i> = 2	6, 27
	Bacitracin + polymyxin <i>n</i> = 5	3, 28–30
	Clioquinol + bacitracin + neomycin <i>n</i> = 1	31
Antibiotics	Total cases: 23	
	Arsenobenzol derivate (Salvarsan®) = 1	32
Antiseptics	Total cases: 1	
	Chlorhexidine <i>n</i> = 10	1, 33–39
	Polyhexanide <i>n</i> = 1	40
	Povidone <i>n</i> = 1	41
Local anaesthetics	Total cases: 12	
	Benzocaine <i>n</i> = 1	42
Cytostatic drugs	Total cases: 1	
	Nitrogen mustard <i>n</i> = 1	43
	Mechlorethamine <i>n</i> = 1	44
Antiphlogistics	Total cases: 2	
	Bufexamac <i>n</i> = 1	45
	Dimethylaminophenyldimethylpyrazolon = 1	46
Insecticide	Total cases: 2	
	Pyrethrin <i>n</i> = 1	47
Mitogen	Total cases: 1	
	Phytohaemagglutinin <i>n</i> = 1	48
Australian tea tree oil	Australian tea tree oil <i>n</i> = 1	49
Thrombin	Total cases: 1	
	Bovine plasma thrombin <i>n</i> = 2	50 (2 patients)
Hair bleaching substance	Total cases: 2	
	Ammonium persulfate <i>n</i> = 1	51
Preservative	Total cases: 1	
	Sodium sulfite (contained in Nizoral® cream) <i>n</i> = 1	52
Total	Total cases: 1 <i>n</i> = 48 cases	<i>n</i> = 43 publications

In 4/48 patients (8%), there was evidence of preexisting sensitization to the particular substance that later induced the reaction (3, 20, 24, 25), and in 1/48 patients (2%) to the different substance (42). In 2/48 patients (4%), a history of asthma was reported (47, 52). In 1/48 patients (2%), a history of seasonal and perennial allergic rhinitis (7), and in 1/48 patients (2%), a history of atopic dermatitis (41) was reported. However, in 10/48 patients (21%), it was stated that there was no history of allergy or atopy [1, 2 (2 patients), 16, 22, 23, 26, 30, 37, 39].

Cases of toxic epidermal necrolysis or Stevens–Johnson syndrome reported in literature

With regard to the occurrence of TEN or SJS following topical drug administration, five articles reporting about five patients were identified (8–12). However, four of the five reports were excluded because the drug was administered to mucous membranes (conjunctivae, intranasal). The fifth article (10) reported about a 67-year-old woman with mycosis fungoides stage IB with plaques who developed SJS following the application of nitrogen mustard (mechlorethamine) to the entire body. Impaired skin barrier with increased resorption because of inflammation may be assumed as an underlying risk factor in this patient.

Discussion

Our investigation showed on a larger scale than single case reports that drug-induced anaphylaxis does occur following nonmucosal topical drug application. In 36% and 88% of the database and literature anaphylaxis cases, respectively, incriminated drugs were applied to skin lesions or skin with impaired barrier function. By this means, the drug may have gained more easy access to the systemic circulation. Although impaired skin barrier was identified as a major risk factor, this was not mentioned or no information on impaired skin barrier function was provided in 61% of spontaneous and 13% of literature anaphylaxis cases. However, it remains unsolved whether the skin barrier was intact in these cases or impaired barrier function was simply not reported.

The high number of anaphylaxis cases after nonmucosal topical drug application stands in contrast to the paucity of data with regard to the induction of TEN or SJS by topical nonmucosal drug application. It may be hypothesized that the threshold concentration of topically applied antigen sufficient to induce the immediate-type reaction anaphylaxis may be lower than the antigen concentration needed to induce the delayed-type reactions TEN or SJS which are thought to be T cell-mediated (14, 53).

The difference in the number of anaphylaxis cases as compared with the number of TEN or SJS cases might have even been higher if an under-reporting of anaphylaxis cases and an over-reporting of SJS or TEN cases are assumed. This could have been the case if physicians may have considered a case of TEN or SJS following nonmucosal topical drug application more exceptional and worthwhile reporting than a case of anaphylaxis. Such a reporting bias would probably apply to both, the database and the literature reports.

Drug-induced anaphylaxis may be because of immune mechanisms (e.g. IgE-dependent) or not (nonallergic anaphylaxis) (15, 54). The latter does not give positive results in skin tests. In the present investigation, skin tests

Table 4. Classification of the status of the skin reported in the 48 anaphylaxis literature cases

Status of the skin	Reference
Wounds/lesions	2, 7, 16, 21–23, 25–31*, 33–37*, 39, 40, 50* (total 21 publications reporting about 24 patients*)
Impaired skin barrier function	2–6, 18–20*, 24, 32, 38, 42–45, 48, 49, 52 (total 18 publications reporting about 18 patients)
Intact skin or no information on impaired skin barrier function provided	1, 36, 41, 46, 47, 51 (total six publications reporting about six patients)
Total	43 publications† reporting about 48 cases

*References (29, 36, 50) refer to two patients, respectively.

†References 2 and 36 report about >1 patient who are listed in different categories.

were performed in 43% of database and 73% of literature anaphylaxis cases, respectively. These tests gave positive results in 83% and 100% of database and literature cases, respectively. This finding suggests that a majority of anaphylaxis cases was immune-mediated, most likely IgE-dependent. This observation is in line with the clinical experience that immune-mediated immediate-type reactions may be induced by lower drug (antigen) concentrations than those required to induce nonimmune-mediated immediate-type reactions. It should be noted, however, that drugs typically associated with the induction of nonimmune-mediated immediate-type reactions (e.g. contrast-media) are mostly not topically applied. Hence, the finding that a majority of anaphylaxis cases was immune-mediated may also reflect the spectrum of drugs applied.

A majority of anaphylaxis literature cases are referred to antibiotics (48%) and antiseptics (25%). Together, these two classes of drugs accounted for 73% of the literature cases. The corresponding figures for the database cases were 14% and 14%. However, it was also noted that anaphylaxis may be induced by a variety of different other substances (see Tables 1 and 3).

With regard to the preponderance of antibiotics and antiseptics, it cannot be concluded that these drugs carry a higher risk of drug-induced anaphylaxis associated with nonmucosal topical drug application than other classes of drugs. This is because of the immanent limitations of spontaneous reports, either directed to the pharmacovigilance authority or published as case reports in literature. Since reporting rates may be different from occurrence rates and the exposure with drugs is unknown, the true

incidence of anaphylaxis associated with antibiotics and antiseptics cannot be calculated, and this holds true also for the other classes of drugs incriminated. For instance, the preponderance of antibiotics and antiseptics among incriminated drugs may simply mirror that they are widely used for topical drug application. Consequently, no comparison with other classes of drugs can be made on the basis of this data.

In 8% of the literature cases and in 7% of the database cases, there was evidence of a preexisting sensitization to the particular substance that later induced the reaction. Hence, one to two in 20 reactions could have been avoided. An underlying atopy was reported in 11% of the database and 8% of the literature cases. This is in accordance with the respective literature that states that atopy is not a recognized risk factor for drug allergy. It may, however, be associated with a more severe course of reaction (54). Female gender was reported in 54% of the database and 52% of the literature cases. This finding fits to published studies on gender distribution in ADRs (54, 55) and drug-induced anaphylaxis, in particular (56), which found a slight preponderance of the female gender.

The anaphylaxis cases were not assessed according to recently published criteria (57) with regard to the correctness of the diagnosis anaphylaxis. This was because of the heterogeneity of the data sources and some of the cases stemmed from remote literature or originated from different countries. However, even if single cases would not allow for the classification of anaphylaxis following application of stringent criteria, say, for lack of appropriate information, these cases at least represented severe immediate-type reactions.

It was noted that the quality of information provided within the literature cases was higher than that of the database cases. This may be explained by the nature of the data. Cases reported in literature have to meet certain conditions concerning the quality of information provided. Thus they are usually more detailed than the spontaneous ADR reports submitted to the pharmacovigilance authority.

In summary, physicians and patients should be aware that anaphylaxis can occur with nonmucosal topical drug application. The risk is probably higher when the substance is applied to skin with impaired barrier function. The evaluation of the patients' history with regard to drug allergies is advisable and may prevent 7–8% of such cases. TEN or SJS following nonmucosal topical drug application seems to be extremely rare.

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