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ORIGINAL RESEARCH ARTICLE

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis: Are Drug Dictionaries Correctly Informing Physicians Regarding the Risk?

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Abstract

Background Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are severe drug reactions associated with high mortality and multiple incapacitating sequelae. In the past 20 years, two large multinational case control studies, published in 1995 and 2008, had identified different degrees of drug association with SJS/TEN: 'strongly associated', 'associated', 'suspected' and 'not suspected' medications.

Objective The aim of this study was to check the adequacy of mention of risk of SJS/TEN in the drug dictionaries most widely used by physicians in five European countries.

Study Design In each country one expert investigator looked at the most widely used drug dictionary (2009 edition) for mentions of risk of SJS/TEN. This was done for a predefined list of medications with a different degree of risk. The presence and clarity or absence of warning was compared with available evidence provided by published results from case–control studies.

Setting The five countries participating in the RegiSCAR group: Austria, France, Germany, The Netherlands and the UK.

Results A total of 3,268 drug descriptions of medications for systemic use were analysed, including all brands of 14 'strongly associated' drugs, 5 'associated' drugs and 12 widely used drugs with no established association. Discrepancies were found by country, and between descriptions for different brands of the same generic. Among 522 descriptions of 14 'strongly associated' drugs, only 5 did not mention the risk. For the 1,013 descriptions of 'associated' drugs, 3 % did not mention the risk. One-third of 'not suspected' drugs contained a specific or less specific warning (e.g. bullous cutaneous eruption). Warnings for 'strongly associated' medications were often as imprecise as those for 'not suspected' drugs.

Conclusion Information on the risk of SJS/TEN in drug dictionaries needs improvement to enhance the quality of advice given by general physicians and to raise the understanding of risk by patients.

For the RegiSCAR Study Group.

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1 Introduction

Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are severe cutaneous adverse reactions, mostly associated with drug intake [1, 2]. Although rare [3], these reactions are a public health concern because of the high mortality rate and associated incapacitating sequelae [2, 4, 5].

The delivery of marketing authorization of a medicine by regulatory agencies is accompanied by the release of an official Summary of Product Characteristics (SPC) or a drug description, which details all information necessary for appropriate prescriptions by physicians. Within the SPC and patient information leaflet, a section is devoted to adverse effects.

Information contained in the SPCs is more usually transmitted to physicians through drug dictionaries, which are in daily clinical use. Most physicians do not consult original SPCs even if they are accessible through the Internet.

Patients rely on their physician to provide medications that are effective and as safe as possible. They also require information on expected benefits and possible risks. Therefore, it is essential to ensure that the information provided by drug dictionaries reflects best available evidence.

Quantitative evaluation of medication efficacy and common adverse effects is achieved in premarketing trials. SJS/TEN are so uncommon that a risk is rarely suspected in phase III studies and is usually identified by pharmacovigilance activity once the drug has been marketed, requiring an update of the SPC. For drugs that are frequently used, spontaneous reports may lead to spurious associations, and for very rare diseases such as SJS/TEN, it is generally agreed that case–control studies are the best available means to quantify the risks [6].

Two multinational case–control studies evaluated the risk of SJS/TEN in relation to medication use. The first SCAR (Severe Cutaneous Adverse Reactions) study was conducted from 1989 to 1995, with results on 372 cases and 1,720 controls published in 1995 [7]. The second EuroSCAR (European SCAR) was conducted from 1997 to 2001, with results on 379 cases and 1,505 controls published in 2008 [8]. Before publication, the results of both studies had been presented to several medical meetings and to pharmacovigilance officers. One important result of these studies is that 12 'strongly associated' (also called 'high risk' in these previous studies) medications are responsible for one-half of all cases [8, 9].

The present study aims to evaluate the quality of information delivered to prescribing physicians by drug dictionaries on epidermal necrolysis risk (either SJS or TEN). This was done by comparing, on a large sample of medications, the mention of a risk in the dictionaries to the best evidence on magnitude of risk, as provided by the two existing case–control studies (SCAR and EuroSCAR).

2 Material and Methods

SCAR and EuroSCAR studies have highlighted different classes of drugs based on their odds ratio of inducing SJS/TEN [9]: 'strongly associated drugs', 'associated drugs', 'suspected drugs', 'not suspected drugs' and drugs with an 'unknown risk'.

In each country the most commonly used drug dictionary (2009 edition) was chosen by a national expert investigator: Arzneimittelinformation MedEval GmbH® in Austria [10], Vidal® in France [11], Rote Liste® in Germany [12], Farmacotherapeutisch Kompas® in The Netherlands [13] and the British National Formulary® in the UK [14].

Each dictionary was analysed for the presence and clarity of the mention of a risk of inducing SJS/TEN. A mention of SJS or TEN, or both, was considered as a clear warning. Mention of 'blistering skin reactions' or 'exfoliation' was considered as a partial warning.

In each country the analysis was done for: (i) all brands of 14 'strongly associated' drugs (allopurinol, carbamazepine, lamotrigine, nevirapine, phenobarbital, phenytoin, sulfamethoxazole, sulfasalazine, sulfadiazine, sulfafurazole, sulfadoxine, meloxicam, piroxicam and tenoxicam); (ii) all brands of five 'associated' drugs chosen for being widely used and existing with numerous brand names (amoxicillin, ciprofloxacin, clarithromycin, diclofenac and doxycycline); and (iii) all brands of 12 widely used drugs with no established risk, also called 'not suspected' according to the SCAR study classification [aspirin (acetylsalicylic acid), atenolol, captopril, digitoxin, digoxin, fenofibrate, furosemide, hydrochlorothiazide, isosorbide, levothyroxine, nifedipine and spironolactone].

Since published results of the case–control studies only concerned systemic administration, topical and local administrations (e.g. eyedrops, etc.) were not evaluated.

3 Results

A total of 3,268 drug descriptions of systemic medications were analysed in the five participating European countries (Table 1).

Discrepancies were found by country, and between descriptions for different brands of an individual generic.

Of the 522 descriptions for 14 'strongly associated' ('high risk') drugs, all but 5 (99 %) mentioned the risk of epidermal necrolysis (Table 2). The exceptions were one French brand of phenytoin, and four brands of allopurinol in Austria.

Among these 14 'strongly associated' medications, only 2 (lamotrigine and nevirapine) had a strong and clear warning, and only in the French dictionary: a black box on the notice and the drug description with a warning

Table 1 Number of drug descriptions (systemic administration) evaluated in each European country for selected medications within different categories of risk of inducing Stevens–Johnson syndrome/toxic epidermal necrolysis

Category of risk	Austria	France	Germany	Netherlands	UK	Total
Strongly associated	131	28	105	217	41	522
Associated	251	28	250	458	26	1,013
Not suspected	553	111	538	420	111	1,733
Total	935	167	893	1,095	178	3,268

Table 2 Number of drug descriptions (systemic administration) with mention of the risk of inducing Stevens–Johnson syndrome/toxic epidermal necrolysis

	Specific mention	Partial mention[a]	No mention	Total evaluated
Strongly associated	517	0	5	522
Associated	933	48	32	1,013
Not suspected	396	184	1,153	1,733

[a] For example, 'severe bullous skin disease', 'bullous skin disease', 'bullous exanthema' 'exfoliative dermatitis', etc.

indicating the rare but severe cutaneous adverse reaction that may occur with this treatment, and an advice to stop the drug and consult the treating physician if a cutaneous eruption develops.

Of the 1,013 descriptions analysed for 5 drugs 'associated' with SJS/TEN, 933 (92 %) mentioned specifically the SJS/TEN risk, and 48 (5 %) had some partial warning, while for 32 (3 %) a mention was absent (Table 2). As evidenced in Table 3, the rather elevated overall percentage of a mention corresponded to a mixture by medication and by country of mention or absence of mention for all brands. For three of the five medications, the risk was not mentioned in one country (UK for amoxicillin and ciprofloxacin) or two countries (France and only partially in The Netherlands for doxycycline).

For the 12 'not suspected' drugs evaluated, 23 % of 1,733 dictionary descriptions contained a specific warning, using the words SJS, TEN or both, and 11 % included non-specific caution, such as 'bullous cutaneous eruptions' (Table 4). Only 4 of the 12 'not suspected' medications had no mention of SJS/TEN as a possible adverse effect in any of the dictionaries. For the eight others there were strong inconsistencies by country and by brand. As an example, for captopril a risk was never mentioned in The Netherlands and the UK, always mentioned in France and Germany, and mentioned in 76 % of brands in Austria.

The results according to each country and class of association to SJS/TEN are summarized in Fig. 1 and detailed in Appendix 1 (see Online Resource 1).

Figure 1 suggests some possible heterogeneity of results across countries for all categories of risk. Because of varying numbers of drug formulations by country, the figure was built on the mean of rough percentages of mentions for each drug in each risk category.

4 Discussion

This study has documented a partial correlation only between the mention of a risk of SJS/TEN in drug dictionaries used in five European countries and the magnitude of the risk as evaluated by two large case–control studies previously conducted in Europe. Not only did a few brands of 'strongly associated' medications not mention the risk, but one-third of 1,733 'not suspected' medications were cited as carrying a risk of SJS/TEN (specific warning for 23 %, partial for 11 %). The overall 'sensitivity' of a mention of SJS/TEN for drugs associated with a risk is high (95–99 %), but there is poor 'specificity', with reactions being cited in drugs possessing no documented evidence for risk.

In addition, when a mention was present the wording of the drug dictionary entries did not differ between the 'strongly associated' drugs and 'not suspected' drugs.

Our study suffered from several limitations. It did not evaluate the full content of the drug dictionaries but was limited to a sample that included all medications for which a strong SJS/TEN risk had been demonstrated and two samples of medications of frequent use: one group of five drugs with a modest but definite SJS/TEN risk and a further group of 12 drugs with no reported association. Since there are no published data on the risk of inducing SJS/TEN for topical (e.g. cream, plaster, etc.) and local (e.g. eyedrops, ophthalmic ointment, etc.) medications, no comparison could be made for drug descriptions of non-systemic administration. Only drug descriptions of systemic brands were analysed. The number of notices evaluated was large enough (a total of 3,268) to make it unlikely that the percentages observed would be very different in a larger analysis of the same dictionaries.

We did not explore whether the discrepancies observed in drug dictionaries were also found in each SPC, and varied with the type of marketing authorization (national versus centralized) or with the links between editors of the dictionaries, regulatory agencies or pharmaceutical companies. For example, the German Rote Liste is an industry-owned compendium of some companies that may not reflect the entire market of medicinal products. This is different than the British National Formulary.

There was also a strong heterogeneity in the number of drug descriptions evaluated across the five countries. This depended on large variations in the number of generics marketed in each country, but also on different policies on

Table 3 Percentages of brand names (systemic administration) containing a specific or partial warning by country for five drugs that were shown to be significantly 'associated' with a moderate risk of Stevens–Johnson Syndrome/toxic epidermal necrolysis

	Austria	France	Germany	Netherlands	UK
Amoxicillin	97	100	96	100	0
Ciprofloxacin	98	100	100	100	0
Clarithromycin	78	100	100	100	100
Diclofenac	99 (3 % partial)	100	100	100	100
Doxycycline	76	0	100 (87 % partial)	100 (100 % partial)	100

Table 4 Percentage of brand names (systemic administration) containing a specific or partial warning by country for 12 drugs for which 'no evidence of association' to a risk of Stevens–Johnson syndrome/toxic epidermal necrolysis was found by case–control studies

	Austria	France	Germany	Netherlands	UK
Aspirin (acetylsalicylic acid)	3	0	100 (92 % partial)	51	0
Atenolol	85	0	13 (13 % partial)	37	0
Captopril	76	100	100	0	0
Digitoxin	0	0	0	NA	0
Fenofibrate	0	0	0	NA	100
Furosemide	73 (66 % partial)	100 (100 % partial)	9 (9 % partial)	100	0
Hydrochlorothiazide	70 (1 % partial)	80	17 (2 % partial)	56 (21 % partial)	0
Insulin	0	0	0	0	0
Isosorbide	13	0	100 (75 % partial)	0	0
Levothyroxine	0	0	0	0	0
Nifedipine	0	0	100 (100 % partial)	0	0
Spironolactone	38 (38 % partial)	0	4 (4 % partial)	0	0

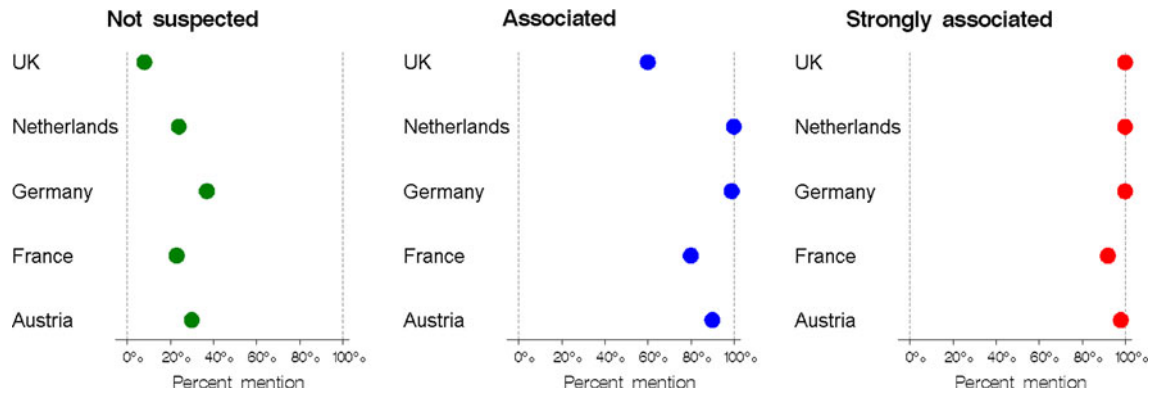

Fig. 1 Percentages of a mention (clear or partial) of Stevens–Johnson syndrome/toxic epidermal necrolysis risk by country for each class of risk

generics: some dictionaries included a notice for each marketed medication, when others only listed generic medications, with the reader being directed to the original brand name for the notice with obviously no room for heterogeneity.

One may have expected less discrepancies if we had analysed the SPCs instead of the dictionaries. However, we considered it more sensible to evaluate dictionaries that are used daily by prescribers, when SPCs are rarely the direct source of information of general practitioners.

We also looked at dictionaries used in only five European countries and do not know to what extent our findings can be generalized to other countries. In addition, since the structures of the dictionaries analysed were different, our results should not be interpreted as allowing any comparison on the 'quality' of these books.

Whatever the limitations of our study, we demonstrated that mentions on the risk of SJS/TEN were not homogeneous and too often non-adequate in the drug dictionaries widely used in five European countries. We consider it very

important to improve information on this topic because it is an important tool to reduce the burden of these reactions.

The burden is elevated because these reactions are very severe. Based on an incidence of 1.5–2 cases per million inhabitants per year [3] and a short-term mortality rate of 22 % [4], we can estimate that SJS/TEN are responsible for at least 200 deaths each year within the European community.

These reactions remain unpredictable. If studies in the Han Chinese population have demonstrated genetic predisposition with HLA-B*1502 allele for carbamazepine-related cases [15] and with HLA-B*5801 for allopurinol related cases [16], pharmacogenetic studies in Europe did not conclude that there was any genetic link strong enough to allow prevention in European populations [17, 18].

Finally, no specific treatment of proven efficacy is available for SJS/TEN [19]. The management of patients depends on a series of symptomatic measures within specialist centres. Prompt referral to such centres was shown to decrease the risk of dying [5, 19], as was early withdrawal of the medication responsible [20].

Therefore, a reduction in the usage of 'strongly associated' drugs, which account for one-half of all cases [8], an earlier diagnosis resulting in prompt withdrawal of the suspected medication and a more rapid referral to a reference centre are the only measures that can now be implemented to reduce the number of victims.

SJS/TEN are very rare and their early diagnosis is difficult. Improved education of general physicians on these diseases is unlikely to be efficient because most practitioners will never encounter the disease. On the other hand, we hypothesize that an improved system of warnings directed to prescribers and users of the 'strongly associated' drugs may have some practical impact on the magnitude of the risk. First, a 'black-box' warning on patient inserts and drug dictionaries could help to decrease the off-label use of some 'strongly associated' drugs, e.g. allopurinol, carbamazepine and lamotrigine. Second, a clear warning should also inform patients on the risk and encourage cessation of a culprit drug at the earliest sign of symptoms.

We are aware that 'black-box' warnings are not routinely employed by the European Medicines Agency. They have been used by the US FDA and shown to be efficient in some situations by decreasing the misuse of antidepressant drugs among children and adolescents [21] and the misuse of antipsychotics, especially among elderly patients with dementia [22]. Strong warnings were also considered helpful in improving the management of SJS/TEN in relation to nevirapine use for HIV infection. We therefore recommend similar black-box warnings for all brands of 'strongly associated' medications. Conversely, we recommend deletion of the mention of SJS/TEN risk in the absence of evidence, since such mention is confusing and may even reduce the likelihood of spontaneous notification by physicians who may consider it useless to report an effect already mentioned.

5 Conclusions

We evaluated the information on the risks of SJS/TEN present in drug dictionaries commonly used in five European countries. Compared with best-available literature evidence, the information was far from being perfect, with a large heterogeneity by drug and by country. Previous studies have clearly identified the notoriety of drugs causing SJS/TEN but this information has not been reflected accurately in the drug dictionaries. This highlights the difficulties for physicians to assess the real risk of adverse event of the drugs they prescribe and to correctly inform their patients We consider that improvement is needed since adequate warnings on life-threatening adverse effects in these dictionaries (in paper or electronic format) are not only essential for prescribing physicians but also may have an impact on causality assessment in pharmacovigilance studies and on governance and legal issues. We suggest that changes should include a clearer SJS/TEN warning in drug dictionaries and package inserts for the 'strongly associated' drugs and that a comment indicating the magnitude of SJS/TEN risk is universally adopted in all drug dictionaries. There should also be a re-evaluation of the SJS/TEN mentions for the drugs 'not suspected' of inducing SJS/TEN because of the counterproductive effects of 'false positive' warnings.

Evaluating the possible effect of such recommendations will need further studies, especially looking at how often a prescribing physician consults a drug dictionary and to what extent the mention of high- versus low-risk impacts prescribing habits.

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