

Epidemiological study of severe cutaneous adverse drug reactions in a city district of China

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Summary

Background. An epidemiological study of severe cutaneous adverse drug reactions (SCADRs) in China has not been reported.

Aims. To estimate the incidence of SCADRs in a city district of China.

Methods. A retrospective study was performed in Peking University Third Hospital, the only hospital in Haidian district, Beijing with a dermatology ward. The medical records of inpatients with SCADRs from January 1994 to December 2002 were studied.

Results. The prevalence rates for overall SCADRs, Stevens–Johnson syndrome (SJS), exfoliative dermatitis (ED), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) among hospitalized patients were 0.32, 0.15, 0.10, 0.04 and 0.07 per thousand, respectively. The risk of SCADRs from systemic drugs among hospitalized patients was 0.03/1000 (0.02/1000 for SJS, and 0.01/1000 for ED and DRESS). The reported incidence of SCADRs in Haidian district was not less than 1.8 per million person-years. The reported incidence of ED, SJS, TEN and DRESS in Haidian district was not less than 0.6, 0.8, 0.05 and 0.4 per million person-years, respectively. The most common underlying disorders were infection, pain-related diseases and epilepsy. Antibiotics were the most common offending drugs followed by anticonvulsants and traditional Chinese medicines (TCM).

Conclusions. These results confirm the relatively low incidence of SCADRs in China. Antibiotics, anticonvulsants and TCM are the most common causative drugs.

Introduction

Severe cutaneous adverse drug reactions (SCADRs), such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are life-threatening adverse drug reactions (ADRs) and have been intensively studied.^{1–8} Hypersensitivity syndrome, also called drug reaction with eosinophilia and systemic symptoms (DRESS), is a new type of ADR and also considered a SCADR.² The reported incidence is about 1–3 per

million person-years for SJS and 0.4–1.4 per million person-years for TEN.^{2–5,9}

China is the largest developing country in the world. With the improvement in living conditions and increase in life expectancy, China has become a large consumer of pharmaceutical drugs. To our knowledge, however, an epidemiological study of SCADRs in China has not been reported. Although in recent years, the Chinese government has issued similar laws and regulations to those of the US Food and Drugs Administration requiring manufacturers, healthcare professionals and consumers to report ADRs, many ADRs may not be reported accordingly. It was reported that in 2005, the annual ADR reports in China were less than 60 per million people and that most of the reports were from healthcare professionals, with very few from pharmaceutical companies.¹⁰ A study on the knowledge of ADR reporting in China among healthcare professionals

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showed that they had little knowledge of the basic ADR-reporting process. The main reasons for under-reporting were related to factors on the reporting process. Most healthcare professionals did not know the address of related centres and how to obtain the forms.¹¹

In China, drug-induced exfoliative dermatitis (ED) is also considered a SCADR. DRESS, however, is still new to many Chinese doctors and is not usually diagnosed. Because of the huge population in China, and the potential for a large number of SCADRs, we deemed it necessary to study the epidemiology of SCADRs in China.

In this investigation, a retrospective analysis of all hospital cases of SCADRs in our hospital during the years 1994–2002 was conducted. The aims of this study were to: (i) estimate the incidence of SCADRs in China; (ii) analyse the characteristics of patients with SCADRs; (iii) evaluate the underlying disease justifying the use of medications and identify the causative drugs for SCADRs, and (iv) discuss the preventability of SCADRs.

Subjects and methods

Patients

All patients were from Peking University Third Hospital, the biggest hospital in Haidian district, Beijing from January 1994 to December 2002. This hospital is a 1000-bed teaching hospital and is the only hospital in Haidian district with a dermatology ward.

Methods

A retrospective study was performed. The medical records of all patients with SCADRs were collected and analysed. Inclusion criteria were: SCADRs responsible for hospitalization and SCADRs developed during hospitalization.

Definition of ADR and identification of causative drugs. An ADR was diagnosed according to the World Health Organization definition. This includes any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy.¹²

The causative drugs for SCADRs were identified according the following criteria¹³: (i) previous experience of SCADRs on a given drug, (ii) time of events (reactions occurred less than 2 months after the use of suspected drug), (iii) other possibilities excluded, and (iv) de-challenge (a reaction is unlikely to be drug-related if

improvement occurs without removal of the suspected drug). If in any patient several drugs came under suspicion, all of them were considered.¹³

Definition of SCADRs and diagnostic criteria. In this study, SCADRs included TEN, SJS, ED and DRESS. To diagnose SCADRs, the skin condition had first to be defined as an ADR. Specific types of SCADRs were diagnosed according to standard textbooks and literature.^{2–5,13}

TEN was diagnosed according to the following criteria: (i) bullae or erosions covering 30% or more of the body surface or involving three separate anatomical regions; (ii) bullae developing on an erythematous base; (iii) lesions occurring on non-sun-exposed skin; (iv) peeling of areas of skin larger than 300 mm²; (v) frequent involvement of mucous membranes; (vi) appearance of tenderness within 48 h of the onset of the rash; (vii) positive Nikolski sign; (viii) fever; and (ix) histology compatible with drug-induced TEN.

SJS was diagnosed according to the following criteria: (i) atypical target-like lesions; (ii) positive Nikolski sign; (iii) involvement of at least two mucous membranes; (iv) fever; and (v) histology compatible with SJS. Based on our definition, some SJS–TEN overlap may be included in this group.¹³

ED was diagnosed based on: (i) generalized erythema and swelling (oedema) involving 90% or more of the skin surface; (ii) oozing, resulting in clothes and dressings sticking to the skin and an unpleasant smell; (iii) scaling 2–6 days after the onset of erythema, as fine flakes or large sheets; and (iv) histology compatible with drug-induced ED.

DRESS was diagnosed based on the clinical presentation of: (i) fever; (ii) extensive skin rash lasting 5 days or more; (iii) internal organ inflammation (liver, kidney, muscle, lung, brain and heart); (iv) lymphadenopathy; and (v) haematological abnormalities (hypereosinophilia or presence of atypical lymphocytes).

Statistical analysis. Incidence rates were calculated from the data collected in our hospital. Data were tabulated on a Microsoft Excel spreadsheet, and statistical analysis performed using the χ^2 test.

The proportion of hospitalization due to SCADRs among hospitalized patients was calculated by dividing the number of admissions due to SCADRs by the total admissions during the study period. The risk of SCADRs in hospitalized patients was calculated by: number of newly developed SCADRs in hospitalized patients divided by the total number of hospitalized non-SCADRs patients during the study time. The prevalence rates of SCADRs among hospitalized patients were calculated by

dividing the total number of SCADRs in the hospital during the study period by the total number of hospitalized patients in that period. Finally, the reported incidence rates of SCADRs in Haidian district were estimated by: total number of SCADRs diagnosed among inhabitants of Haidian district divided by the standard number of inhabitants in Haidian district, multiplied by the number of years investigated.

Results

The proportions of hospitalizations due to SCADRs among hospitalized patients

During the study period, 153 966 patients were admitted to the hospital. There were 247 patients admitted to the hospital due to cutaneous ADRs (CADRs), of which 46 cases were SCADRs. The proportion of hospitalizations due to all CADRs among hospitalized patients was 1.6/1000. The proportion of hospitalizations due to SCADRs among hospitalized patients was 0.3/1000. Of these patients, 20 patients had SJS, 15 had ED and 6 had TEN. There were nine cases of DRESS diagnosed, of which four overlapped with other SCADRs (two were SJS–DRESS overlap, one could be also diagnosed as TEN, and the other could also be diagnosed as ED). The proportions of hospitalizations due to SJS, ED, TEN and DRESS among hospitalized patients were 0.12, 0.10, 0.04 and 0.06 per thousand, respectively.

The risk of SCADRs among hospitalized patients

During the study periods, four patients hospitalized for other diseases developed SCADRs from systemic drugs while in the hospital; three had SJS and the other ED. One patient with SJS could be also diagnosed as DRESS. The risk of SCADRs from systemic drugs among hospitalized patients was 0.03/1000 (0.02/1000 for SJS, 0.01/1000 for ED and DRESS).

The prevalence rates of SCADRs among hospitalized patients

During the study period, the total number of CADRs found in the hospital was 251 (247 patients admitted for CADRs and 4 newly developed cases of SCADRs). The classifications of CADRs are shown in Table 1. The total number of SCADRs was 50 (46 patients admitted for SCADRs and 4 newly developed SCADRs) including 23 SJS, 16 ED, 6 TEN and 10 DRESS (5 cases of DRESS overlapped with other SCADRs). The total number of hospitalized patients was 153 966. The prevalence rates

Table 1 Clinical aspects of CADR.

Clinical classification (n = 251)	Cases, n (%)
Exanthema	120 (48)
Urticaria	31 (12)
Erythema multiforme	29 (12)
SJS	23 (9)
ED	16 (6)
Fixed type	12 (5)
Vasculitis	10 (4)
DRESS*	10 (4)*
TEN	6 (2)
Lichen planus type	2 (1)
Eczema	2 (1)

*All of them could be also diagnosed as other CADRs (3 SJS, 1 TEN, 1 ED and 5 exanthema). CADR, cutaneous adverse drug reaction; SCADRs, severe cutaneous adverse drug reaction; SJS, Stevens–Johnson syndrome; ED, exfoliative dermatitis; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms.

for overall SCADRs, SJS, ED, TEN and DRESS among hospitalized patients were 0.32, 0.15, 0.10, 0.04 and 0.07 per thousand, respectively.

The reported incidence of SCADRs in Haidian district

The standardized population in Haidian district was 2 191 813. During the study period, 35 cases of SCADRs were inhabitants of Haidian district. Considering that some patients with SCADRs from Haidian district might not be admitted to our hospital, we estimated that the reported incidence of SCADRs in Haidian district was not less than 1.8 per million person-years (see above for method for calculation). Among these patients, there were 12 patients with ED, 16 with SJS and 2 with TEN. Therefore, the reported incidence of ED, SJS and TEN in Haidian district was not less than 0.6, 0.8 and 0.05 per million person-years, respectively. Eight cases of DRESS were found; three of them overlapped with other SCADRs (one with ED, one with SJS and one with TEN). We estimated the reported incidence of DRESS in Haidian district was not less than 0.4 per million person-years (see above for method for calculation).

Age and gender of patients with SCADRs

Mean age \pm standard deviation of the SCADRs patients was 40.0 ± 20.0 years (range 15–86). Most patients were in the age ranges 21–40 and 61–70 years. The male : female ratio was 1.2 (28 : 24). There were more male patients with ED (12/16,

75.0%) and more female patients with SJS (15/23, 65.2%) ($P < 0.05$, χ^2 test).

Causative drugs and the underlying diseases justifying the use of drugs

The underlying diseases justifying the use of drugs are shown in Table 2. The most common disorders were infection, pain-related disorders and epilepsy. Infection comprised 56% (28/50) of all diseases, 16% (8/50) were pain-related diseases and 6% (3/50) of cases were epilepsy. Of the 28 infections, 20 (71%) were upper respiratory tract infections. Most were treated with antibiotics, and some patients were given two or more antibiotics simultaneously.

The culpable drugs are shown in Table 3. Antibiotics were the most common offending drugs, followed by anticonvulsants and traditional Chinese medicine (TCM). Antibiotic monotherapy was responsible for 56% cases of ED, 30% cases of SJS and 20% cases of

DRESS. Carbamazepine was used in seven patients, but only one patient had epilepsy. The other six comprised two patients with herpes zoster, two with headaches, one with chest pain and one with ischias. TCM and phenytoin were used for the other two patients who developed epilepsy.

SCADRs induced by TCM monotherapy were found in seven patients including three with TEN, two with SJS, one with ED, and one ED–DRESS overlap. Therefore, TCM monotherapy accounted for two cases (13%) of ED, two cases (9%) of SJS, three cases (50%) of TEN and one case (10%) of DRESS. TCM was also frequently used with antibiotics and other drugs. The ingredients of TCM used in three of the seven patients were unknown. All four patients were administered a different type of TCM. Paishi Chongji and Shilintong Pian were used in one patient for renal lithiasis, Fenghanganmao Chongji was used in another patient for the common cold, and Danshentong was used for the third patient for acne vulgaris. The fourth patient was treated with Yinxiadi

Table 2 The underlying diseases justifying the use of drugs.

SCADRs	Infection, n (%)	Others, n (%)
SJS (n = 23)	12 (52)	Epilepsy (2), pain-related diseases (7), acne (1), arteriosclerosis (1)
TEN (n = 6)	1 (17)	Psoriasis (2), herpes zoster (1), fever (1), bromhidrosis (1)
ED (n = 16)	11 (69)	Epilepsy (1), depression (1), gout (1), eczema (1), renal lithiasis (1)
DRESS (n = 10)*	4 (40)	Epilepsy* (2), pain-related diseases* (1), fever *(1), renal lithiasis* (1), renal dysfunction (1)
Total	28 (56)	22 (44)

*Overlapped with other SCADRs. SCADRs, severe coetaneous adverse drug reaction; SJS, Stevens–Johnson syndrome; ED, exfoliative dermatitis; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms; TCM, traditional Chinese medicine.

Table 3 The culpable drugs for SCADRs.

Drug(s)	ED (n = 16)	SJS (n = 23)	TEN (n = 6)	DRESS (n = 10)*
Antibiotics	9 (56)	7 (30)	0	2 (20)
Antibiotics + NSAID	0	0	0	1 (10)
Antibiotics + TCM	0	2 (9)	0	0
Antibiotics + NSAID + TCM	0	1 (4)	1 (17)	1 (10)
Anti-convulsants	0	7 (30)	1 (17)	3 (30)
NSAID	1 (6)	0	0	0
NSAID + TCM	1 (6)	1 (4)	0	0
Antivirals	1 (6)	0	0	0
Anti-depressants	1 (6)	0	0	0
TCM	2 (13)	2 (9)	3 (50)	1 (10)
Gout preparations, allopurinol	1 (6)	0	0	1 (10)
Sulfonamide	0	0	0	1 (10)
Sulfonamide + TCM	0	1 (4)	0	0
Sulfonamide + anticonvulsants	0	1 (4)	0	0
Nitrofurans, furazolidone	0	0	1 (17)	0
Calcium antagonist	0	1 (4)	0	0

Results are n (%). SCADR, severe coetaneous adverse drug reaction; SJS, Stevens–Johnson syndrome; ED, exfoliative dermatitis; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms.

Table 4 Contents of the TCMS used.

Paishi Chongji (排石冲剂)	Herba* Glechomae (连钱草)	<i>Glechoma</i> spp., probably <i>G. longituba</i>
	Semen Plantaginis (车前子)	<i>Plantago</i> spp., <i>P. asiatica</i> L. or <i>P. depressa</i> Willd. (seed)
	Caulis Lonicerae (忍冬藤)	<i>Lonicera</i> spp., <i>L. japonica</i> (stem)
	Folium Pyrrosiae (石韦)	<i>Pyrrosia</i> spp. (leaf)
	Radix Cynanchi Paniculati (徐长卿)	<i>Cynanchum paniculatum</i> (root)
	Pulvis Talci (滑石)	Talcum powder
	Fructus Malvae (冬葵子)	<i>Malvae</i> spp., probably <i>M. verticilla</i> (fruit)
	Caulis Aristolochiae Manshuriensis (关木通)	<i>Aristolochia manshuriensis</i> (stem)
	Herba Desmodii Styracifoli (广金钱草)	<i>Desmodium styracifolium</i>
	Shilintong Pian (石淋通片)	Herba Ephedrae (麻黄)
Radix Puerariae (葛根)		<i>Pueraria</i> spp., <i>P. lobata</i> or <i>P. thomsonii</i> (root)
Folium Perillae (紫苏叶)		<i>Perilla</i> spp., <i>P. frutescens</i> (leaf)
Radix Saposhnikoviae (防风)		<i>Saposhnikovia</i> spp., <i>S. divaricata</i> (root)
Ramulus Cinnamomi (桂枝)		<i>Cinnamomum</i> spp., <i>C. cassia</i> (twig)
Radix Angelicae Dahuricae (白芷)		<i>Angelica dahurica</i> (root)
Salvia Miltiorrhiza (丹参)		<i>Salvia miltiorrhiza</i>
Yinxiedi (银犀敌)	Zaocys (乌梢蛇)	<i>Zaocys</i> spp., <i>Z. dhumnades</i> (flesh)
	Herba Schizonepetae (荆芥)	<i>Schizonepeta</i> spp., <i>S. tenuifolia</i>
	Radix Saposhnikoviae (防风)	<i>Saposhnikovia</i> spp., as above
	Periostracum Cicadae (蝉蜕)	<i>Cryptotympana pustulata</i> (nymph shell)
	Olibanum (乳香)	<i>Boswellia</i> spp., <i>B. carterii</i>
	Radix Glycyrrhizae (甘草)	<i>Glycyrrhiza</i> spp., <i>G. glabra</i> or <i>G. uralensis</i> , <i>G. inflata</i> (root)

*Most ingredients are plants; where the Latin medicinal name does not include the species, the genus name is given with probable species, otherwise the full species is given, where known, and the part of the plant/animal used. 'Herba' generally refers to the aerial parts of the plant.

for psoriasis vulgaris, and developed TEN. Details of the medicines are shown in Table 4.

Discussion

The epidemiology of SCADRs has been studied in many countries and regions;¹⁻⁹ however, an epidemiological study of SCADRs in China, the largest developing country in the world, has not been reported.

Using a retrospective study, we investigated primarily the epidemiology of SCADRs in a city district of China. The clinical aspects of CADRs in our hospital are similar to those of a French survey.¹⁴ The prevalence of SCADRs in hospitalized patients in the French group was 0.75/1000 (10/13 294), which was also close to our result (0.32/1000). These results indicate that SCADRs are not uncommon in China.

The risk of SCADRs from systemic drugs among hospitalized patients has not been reported in China. During the study period, four inpatients experienced SCADRs (three with SJS and one with ED) from systemic drugs while in the hospital for other underlying diseases. The risk of SCADRs from systemic drugs among hospitalized patients was 0.03/1000 (0.02/1000 for SJS, 0.01/1000 for ED and DRESS). These results were much

higher than the incidence of SCADRs reported in the general population.^{2-5,9} Our results suggested that hospitalized patients in China were at greater risk of developing SCADRs and should be studied further.

We estimated that the reported incidence of ED, SJS, TEN and DRESS in Haidian district was not less than 0.6, 0.8, 0.05 and 0.4 per million person-years, respectively (see Methods for calculation). These results were relatively lower than the incidence reported in other areas.^{2-5,9} The possibility that some patients were not admitted to our hospital and the different diagnostic criteria used in various studies may have resulted in the lower rate. However, because of the huge population in China, SCADRs could still be a serious problem.

A male predominance was found in patients with SCADRs, consistent with previous studies.^{1,5} However, in our study, there were more female patients in the SJS group; the reason for this is unclear.

Infection comprised 56% of all underlying diseases justifying the use of drugs (Table 2). This result is consistent with previous studies.^{1,5,6,8} In our study, 20 out of 28 infections (71%) were upper respiratory infections, and most of the patients were treated by antibiotics. In some cases, two antibiotics were given simultaneously. These results suggest that some

SCADRs in the study could have been avoided if antibiotics were used more strictly.

Similar to other studies, antibiotics were also the most common offending drugs for SCADRs, followed by anticonvulsants, especially carbamazepine.^{1,5,6,8} Carbamazepine is a drug approved for epilepsy, trigeminal neuralgia, neuralgia of diabetes mellitus and glossopharyngeal neuralgia. Seven patients in our study had been administered carbamazepine, but only one patient had epilepsy. In the other six cases, two patients had herpes zoster, two had headaches, one had chest pain and one had pain around the ischia. Stricter use of carbamazepine might also avoid such SCADRs.

Allopurinol was found to be the most common drug responsible for TEN and SJS.⁷ In our study, one case of allopurinol-induced ED and one case of DRESS was found (Table 3).

TCM is very commonly used in China. TCM monotherapy accounted for 13% of ED, 9% of SJS, 50% of TEN and 10% of DRESS cases (Table 2). TCM was also frequently used with antibiotics and other drugs. These results suggest that TCM, although generally considered a natural and safe medicine, could also induce SCADRs and must be investigated further. Because most TCM are complex and many TCM products, especially decoctions, are unlabelled, it is very difficult to identify the culprit ingredient in the medicine. It is already known that some TCM can cause ADR and react with conventional medicines. In addition, some TCM may also contain conventional medicines.¹⁵

A retrospective study has several limitations. Our data may not include all the patients with SCADRs because some of them may not have been admitted to our hospital. However, as our hospital is the largest in Haidian district and is the only hospital in the area with a dermatology ward, most patients with SCADRs should be admitted here. Our reported incidence of SCADRs in Haidian district might still be an underestimate. Under-reporting of TEN was found to be a serious problem in Canada.³ Although our result was relatively lower, SCADRs could be still a serious problem because of the huge population in China. Stricter regulations are needed to increase the report of SCADRs in China. Finally, another possible reason is the type of hospital; different types of hospital may admit different patients. However, when the incidence of ADR was studied in another report, such a difference could not be demonstrated.¹⁶

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