

Cutaneous adverse drug reactions in a hospital-based Chinese population

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Summary

Background. Cutaneous adverse drug reactions (CADRs) are common skin adverse reactions associated with drugs.

Aim. To assess recent trends in CADRs and the drugs associated with them, using data from the past 5 years in the largest single database available on a hospital-based population in China.

Methods. All clinical records of inpatients admitted with a diagnosis of CADR to the Dermatology Ward, Huashan Hospital from January 2004 to December 2008 were retrospectively studied.

Results. In the 734 patients, the three most common types of CADRs were nonsevere reactions, erythema multiforme (EM)-like eruptions ($n = 255$), urticaria ($n = 192$) and exanthematous reactions ($n = 159$), followed by three severe reactions: Stevens–Johnson syndrome ($n = 58$), toxic epidermal necrolysis ($n = 29$) and exfoliative dermatitis ($n = 22$). The most common single drug associated with the development of all drug eruptions was allopurinol, followed by amoxicillin, cephalosporins, antiepileptic agents and antipyretic/analgesic agents. However, the most common single drugs associated with severe reactions were antiepileptic agents, followed by allopurinol, antipyretic/analgesic agents and cephalosporins. In contrast to patients with nonsevere reactions, patients with severe reactions were more likely to be male ($P < 0.001$) and to have a greater mean age of onset ($P < 0.001$), a longer latency period ($P < 0.001$) and a longer duration of hospitalization ($P < 0.001$).

Conclusion. In contrast to previous studies, we found allopurinol to be the most common single drug associated with CADRs followed by antibiotics (amoxicillin and cephalosporins), and antiepileptic, especially carbamazepine. A higher incidence of EM-like eruptions and urticaria was also seen.

Introduction

The frequency of occurrence of cutaneous adverse drug reactions (CADRs) is strongly related to the propensity of a given drug to induce the reaction, and the frequency of

its use in a given population. As a considerable number of new drugs have been introduced into the market and prescribed during the past decade, the incidence of CADRs has markedly increased. Eruptions were seen in 0.1–1% of treated patients in premarketing trials of most drugs.¹ A number of drugs currently used are associated with higher rates of skin eruptions: 5–7% for aminopenicillin, 3–4% for antibacterial sulfonamides and 5–10% for many antiepileptics.¹

Having the largest number of dermatology patients (average daily outpatient visits > 3000) in the entire country of China, the dermatology department at

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Shanghai Huashan Hospital, Fudan University Medical School, provided outpatient care to over 920 000 patients in 2007 and 1.06 million in 2008. Such a large patient database provides an excellent opportunity to survey trends in medications associated with drug reactions. Taking advantage of this large patient database, this study aimed to access recent trends in CADR and their associated drugs.

Methods

All clinical records of inpatients who were admitted to the Dermatology Ward, Huashan Hospital, from January 2004 to December 2008, were examined. These inpatients had been diagnosed at an outpatient clinic as having CADR, according to a consistent diagnostic algorithm (Fig. 1). The latency period between the intake of the drug and the onset of the skin eruption was recorded. Cases of CADR were included in this study only if latency periods were within 6 weeks. For multiple drug use cases, all suspicious drugs were considered.² Previous reports of drug eruptions were reviewed to help identify the associated drugs.^{3–6} All clinical charts of these patients were reviewed and comprehensively analysed, and the cases classified into two groups according to the severity of eruptions. The numbers of cases caused by either single drug use or multiple drug use were also recorded in both groups.

With regard to severe (S)-CADRs including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis

(TEN) and exfoliative dermatitis (ED), involvement of mucous membrane was carefully noted. For SJS, the diagnosis was made based on the appearance of mucous membrane erosions and epidermal detachment (positive Nikolsky sign) of < 10% of the body surface area (BSA).² Cases with detachment of 10–30% of BSA are normally considered to be overlap of the two syndromes;² in our study, these overlapped cases were categorized as SJS. Patients with > 30% of BSA of detached or ‘detachable’ epidermis, in addition to severe mucosal involvement were diagnosed as having TEN.² Diagnosis of ED was based on generalized erythema and swelling (oedema) involving > 90% of BSA, with oozing, and scaling 2–6 days after the onset of erythema as fine flakes or large sheets.⁷ For definition purposes, all CADR cases that did not fall in the S-CADR category are termed nonsevere (NS)-CADRs.

Results

General trend of incidence

In total, 734 inpatients with CADR were included in this study, covering a 5-year period. Although the numbers of total CADR increased every year, from 113 in 2004 to 216 in 2008, especially for the last 2 years (2007–2008) of this study period, we found that the percentage of S-CADR within these remained relatively constant, at 10.85–18.58% (Fig. 2). As these increased numbers of patients admitted for CADR were

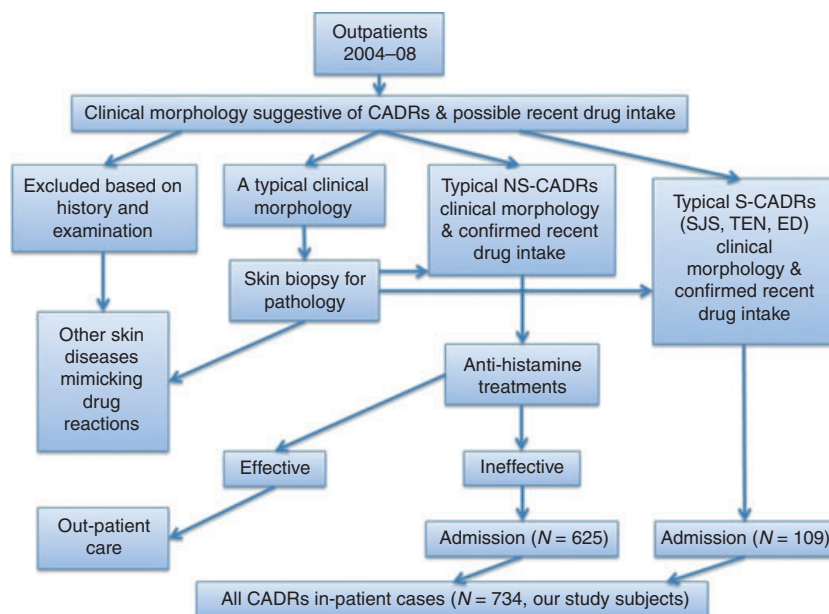


Figure 1 Diagnostic algorithm for cutaneous adverse drug reactions.

Figure 2 Total number of patients with cutaneous adverse drug reactions (CADRs) and severe (S)-CADRs, and percentage of patients with CADRs admitted annually in the period 2004–2008, showing an increasing trend for CADRs, even though the percentage of S-CADRs remained relatively constant.

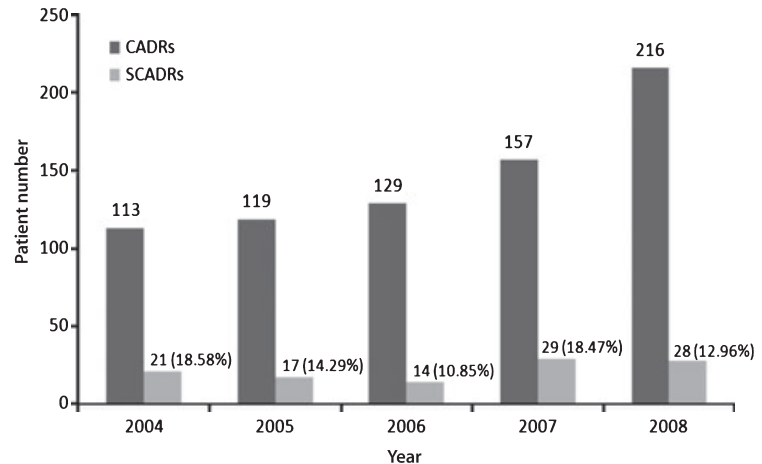
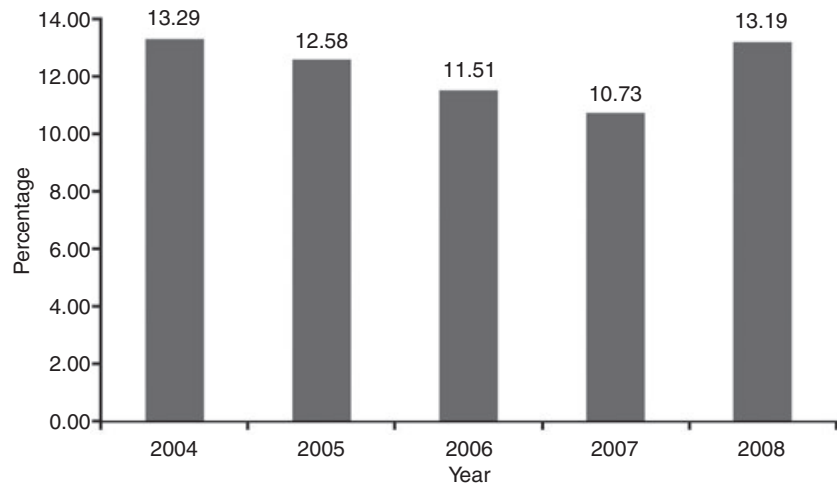


Figure 3 Cutaneous adverse drug reactions (CADRs) as a percentage of all inpatients admitted annually in the period 2004–2008.



substantial (Fig. 2), we next analysed whether these increases represented an increase in the percentage of the total inpatient population. We found that there was no substantial increase in the percentage of inpatients diagnosed with CADRs (10.73–13.29%) (Fig. 3).

Age and gender

The mean age of all patients in the study was 43.87 years (range 8–93). Patients with NS-CADRs and S-CADRs had a mean age of 43.1 years (range 8–87) and 18.4 years (range 15–93), respectively. Mean age of onset for patients with S-CADRs was significantly lower than that of patients with NS-CADRs ($P < 0.001$). Of the 734 patients with CADRs, female patients ($n = 487$; 66.3%) outnumbered male patients ($n = 247$; 33.7%; $P < 0.001$). The ratio of female to male for patients with NS-CADRs (2.2 : 1.0) was

substantially greater than that of patients with S-CADRs (1.0 : 1.0) ($P < 0.001$).

Types of drug reactions and associated drug use

After review and comprehensive analysis of all cases ($n = 734$, both single drug- and multiple drug-associated) we found that the three most common drug reactions were all NS-CADRs: erythema multiforme (EM)-like eruptions ($n = 225$; 34.74%), urticaria ($n = 192$; 26.15%) and exanthematous reactions ($n = 159$; 21.656%). The next most common were the S-CADRs: SJS ($n = 58$; 7.90%), TEN ($n = 29$; 3.95%) and ED ($n = 22$; 3.00%) (Table 1). When we separated cases associated with single drug use from those with multiple drug use, we found almost equal numbers of patients in the NS-CADRs and S-CADRs groups (Table 2).

Table 1 Type of drug eruption of all patients with CADR.

Type of drug eruption	<i>n</i> (%)
EM-like eruptions	255 (34.74)
Urticaria	192 (26.15)
ER	159 (21.66)
SJS	58 (7.90)
TEN	29 (3.95)
ED	22 (3.00)
Purpura	9 (1.23)
Fixed drug eruption	9 (1.23)
Lichenoid eruptions	1 (0.13)

CADRs, cutaneous adverse drug reactions; ED, exfoliative dermatitis; EM, erythema multiforme; ER, exanthematous reactions; FDE, fixed drug eruption; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Table 2 Categorization of patients by severity of eruptions and associated drug use (single or multiple drugs).

Causative drug(s)	Types of reaction, <i>n</i>		
	NS-CADRs	S-CADRs	Total, <i>n</i>
Single	250	52	302
Multiple	375	57	432
Total	625	109	734

NS-CADRs, non-severe cutaneous drug reactions; S-CADRs, severe cutaneous drug reactions.

Sensitizing drugs and type of eruption

To determine the frequency of a given drug in association with CADR, further analyses focused on patients who had taken a single medication before the skin symptoms appeared ($n = 302$); these cases were listed and separately analysed for NS-CADRs and S-CADRs (Table 3). Of the 250 patients with NS-CADRs, the four most commonly incriminated drugs were amoxicillin ($n = 42$; 16.80%), cephalosporins ($n = 41$; 16.40%), antipyretic/analgesic agents ($n = 36$; 14.40%) and allopurinol ($n = 31$; 12.40%) (Table 3). By contrast, the four drugs most often associated with S-CADRs ($n = 52$) were antiepileptic agents ($n = 20$; 38.46%), allopurinol ($n = 18$; 34.62%), antipyretic/analgesic agents ($n = 4$; 7.69%) and cephalosporins ($n = 3$; 5.77%; Table 3). Of the 40 cases (20 NS-CADRs, 20 S-CADRs) associated with antiepileptic agents, 36 (90%) were related to carbamazepine (CBZ) and 4 (10%) to phenytoin. We next analysed the four most common single drugs in association with each of the top three types of NS-CADRs and S-CADRs (Table 4). Finally, the top five single drugs associated with CADR (both NS-CADRs and S-CADRs) and the four most common types

Table 3 Single drug usage in association with NS-CADRs and S-CADRs.

Associated drugs	<i>n</i> (%)
NS-CADRs	
Amoxicillin	42 (16.80)
Cephalosporins	41 (16.40)
Antipyretics/analgesics	36 (14.40)
Allopurinol	31 (12.40)
TCM	26 (10.40)
Antiepileptics	20 (8.00)
Macrolides	16 (6.40)
Penicillin	15 (6.00)
Quinolones	8 (3.20)
Sulfonamides	5 (2.00)
Tetracyclines	5 (2.00)
Anti-amoebic/anti- <i>Trichomonas</i>	5 (2.00)
S-CADRs	
Antiepileptic agents	20 (38.46)
Allopurinol	18 (34.62)
Antipyretics/analgesics	4 (7.69)
Cephalosporins	3 (5.77)
Penicillin	2 (3.85)
Amoxicillin	2 (3.85)
Quinolones	1 (1.92)
TCM	1 (1.92)
Sulfanilamides	1 (1.92)

NS-CADRs, non-severe cutaneous drug reactions; S-CADRs, severe cutaneous drug reactions; TCM, Traditional Chinese medicine. Fewer types of drugs were recorded in association with S-CADRs than with NS-CADRs.

of CADR associated with each of these top five drugs were analysed (Table 5).

Latency period

Of the total 734 cases, 624 (545 NS-CADRs and 79 S-CADRs) had their latency period clearly recorded. The mean latency period of these 624 patients was 7.64 ± 8.32 days. Mean latency was 6.9 ± 7.7 days for patients with NS-CADRs ($P < 0.001$) and 12.4 ± 10.5 days ($P < 0.001$) for patients with S-CADRs. After discounting the possible confounding factor (year difference), the difference in latency period between patients with NS-CADRs and patients with S-CADRs was significant ($P < 0.001$). With regard to the single drug most associated with CADR ($n = 302$), the latency periods were 22.1 ± 13.1 days for allopurinol ($n = 44$), 15.4 ± 9.1 days for antiepileptics ($n = 37$), 5.1 ± 4.5 days for cephalosporins ($n = 44$), 3.9 ± 5.0 days for antipyretic/analgesic agents ($n = 39$) and 3.9 ± 4.2 days for amoxicillin ($n = 41$). A separate analysis found that the latency period of the major single agents associated with S-CADRs was 22.6 ± 11.9 days for allopurinol, 14.3 ± 5.8 days for antiepileptics,

Table 4 The four most common single drugs linked to the development of top three types of NS-CADRs and S-CADRs.

Types of drug eruption	Most common single drug	<i>n</i>
EM	Cephalosporins	33
	Amoxicillin	24
	Allopurinol	23
	Antiepileptics	15
Urticaria	Antipyretics/analgesics	8
	Amoxicillin	7
	Cephalosporins	6
	TCM	6
	Antipyretics/analgesics	14
	Amoxicillin	10
	Penicillin	6
	Allopurinol	5
SJS	Antiepileptics	16
	Allopurinol	14
	Cephalosporins	2
	Antipyretics/analgesics	2
TEN	Allopurinol	3
	Antiepileptics	2
	Antipyretics/analgesics	2
ED	Cephalosporins	1
	Allopurinol	4
	Antiepileptics	2
	Amoxicillin	1
	Quinolones	1

ED, exfoliative dermatitis; EM, erythema multiforme; ER, exanthematous reactions; NS-CADRs, non-severe cutaneous drug reactions; S-CADRs, severe cutaneous drug reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; TCM, traditional Chinese medicine.

3.0 ± 4.0 days for antipyretic/analgesic agents and 7.0 ± 5.2 days for cephalosporins. The difference in latency period between allopurinol and other agents was significant ($P < 0.001$).

Length of hospitalization

Mean duration of hospital stay was 8.68 ± 6.84 days for the 734 CADR cases. It was 7.3 ± 3.9 days for NS-CADRs, which was significantly shorter than the 16.6 ± 12.4 days for S-CADRs ($P < 0.001$). Duration of hospitalization was 22.4 ± 20.2 days for patients with TEN, which was significantly longer than the 15.8 ± 7.4 days for patients with SJS and 10.7 ± 4.6 days for patients with ED ($P < 0.01$).

Discussion

Retrospective studies of drug eruptions have been reported by many countries and regions,^{8–11} but a retrospective study of inpatients with CADRs in China,

Table 5 The five most common single drugs linked to the development of CADRs and their four most often associated skin reactions.

Top five single drug	Most common type of drug eruption	<i>n</i>
Allopurinol	EM	26
	SJS	11
	ED	4
	TEN	3
Amoxicillin	EM	24
	ER	10
	Urticaria	7
	ED	1
Cephalosporins	EM	33
	Urticaria	6
	SJS	2
	TEN	1
Antiepileptics	SJS	16
	EM	15
	ED	2
	TEN	2
Antipyretics/analgesics	ER	14
	EM	13
	Urticaria	8
	SJS	2

ED, exfoliative dermatitis; EM, erythema multiforme; ER, exanthematous reactions; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

the developing country with the largest population in the world, has not previously been reported, to our knowledge. Over a period of 5 years, the average percentage of inpatients admitted with a diagnosis of CADRs (12.2%) in our hospital increased substantially compared with that of a previous survey (8.6%) conducted for the period 1983–1992.¹² This rising incidence might be associated with increasing use and frequent application of new drugs. Moreover, the use of multiple drugs, which was associated with 380 cases (51.77%) of CADRs in our study, is becoming a major factor, and makes the task of determining the true incriminating medication more difficult.

In our study, gender and age at disease onset for all CADRs were different from those reported in previous studies in both East and South Asian populations,^{8,13,14} with a relatively older age (mean 43.9 years) and a higher female predominance (66.3%). Furthermore, patients with S-CADRs were older (mean 48.4 years) than those in previous reports.^{2,13} In addition, higher incidences of EM-like eruptions and urticaria were seen in our study compared with previous studies.^{8,15}

The most common single drug in association with all CADRs was found to be allopurinol (Table 5). When we analysed NS-CADRs and S-CADRs separately, although

allopurinol was no longer the prime associated drug, it was still important, accounting for 12.4% of all NS-CADRs and 34.62% of all S-CADRs (Table 3). Amoxicillin and cephalosporins were the second and third most common associated drugs for all CADR (Table 5). Amoxicillin and cephalosporins were the top two CADR-associated antibiotic drugs, and our study found that antibiotics accounted for 29.14% of all CADR cases with a history of single drug use (Table 5). When all antibiotic drugs were combined in the analysis, this group of drugs accounted for 48.34% of total CADR cases associated with single drug intake. This finding is in general agreement with the study on 104 patients described by Gerson *et al.*,¹⁶ which also found that the most common category of drug associated with the appearance of a rash was antibiotics, followed by antiepileptic agents. Our data are also in partial agreement with a study from Bangkok, which reported that amoxicillin was the most common associated antibiotic agent in CADRs, followed by trimethoprim-sulfamethoxazole and cloxacillin.⁸ Similar to other studies,^{8,9,15} our study confirms that antiepileptics and antipyretic/analgesic agents are also some of the most commonly associated drugs for CADRs in general. Kamaliah *et al.*¹⁷ reported that the most common associated drugs were anticonvulsants (CBZ and phenytoin), followed by antibiotics (sulfonamides and penicillin). Li and Ma¹³ reported in their epidemiological study that anticonvulsants, especially CBZ, were the second most common type of offending drug for inpatients with S-CADRs in a Chinese region over an 8-year period. Recent research suggested that allopurinol plays a major role in the induction of the S-CADRs SJS and TEN in Asian, European and Israeli populations.^{11,18} Allopurinol has been implicated repeatedly in life-threatening S-CADRs including SJS and TEN.^{19,20} In our study, allopurinol was found to be the most common associated drug for S-CADRs, followed by CBZ.

The high incidence of allopurinol-induced S-CADRs may be associated with increased exposure to allopurinol in populations, because of increased sales of the medication.¹¹ It was reported that the use of ≤ 200 mg of allopurinol daily at the beginning of treatment was associated with a higher risk for SJS or TEN compared with lower daily doses.¹¹ Furthermore, a drug interaction between allopurinol and other medications, including aminopenicillin and angiotensin-converting enzyme inhibitors, has been suspected in causing allopurinol-induced eruptions.²¹ It is noteworthy that in our study, allopurinol-induced CADRs seemed to develop after a longer latency period, with allopurinol-induced S-CADRs developing after 22.6 ± 11.9 days,

which was significantly longer than the time taken for CADRs associated with other drugs: 14.3 ± 5.8 days for antiepileptics, 3.0 ± 4.0 days for antipyretic/analgesic agents and 7.0 ± 5.2 days for cephalosporins ($P < 0.001$).

There were 20 cases of S-CADRs in our study associated with antiepileptic agents, and of these, 17 (85%) were associated with CBZ as a single drug. Thus, we found a more significant role for CBZ in the induction of S-CADRs compared with a previous report, which found that only 44% of the total S-CADR cases caused by antiepileptic agents were induced by CBZ.²² One possible reason may be due to the wider use of this antiepileptic agent, especially for the control of pain. Another reason may be due to genetic predisposition, as it has been recently reported that CBZ-induced SJS/TEN is strongly associated with the human leucocyte antigen (HLA) genotype B*1502 in a Han Chinese population.²³ An extended genetic study suggested that HLA-B*1502 could contribute to the pathogenesis of CBZ-induced SJS/TEN and that genetic susceptibility to CBZ-induced S-CADRs is phenotype-specific.²⁴

It is noteworthy that both multiple drug use (51.77% of all CADRs) and traditional Chinese medicine (TCM) monotherapy (3.68%) were associated with CADR development in our study. Combined use of ≥ 2 different antibiotics or antipyretic/analgesic agents were the most common forms of multiple drug use. Drug-drug interaction is a possible cause of CADRs even if each drug does not cause CADR if given individually. TCM has been widely practised in China for thousands of years and is generally considered natural and safe. However, TCM can also induce S-CADRs.¹³ In our study, 27 patients (1 case of TEN, 11 cases of EM and 15 cases of other types) had taken only TCM before the symptoms developed, thus the TCM was considered the most probable associated drug in these cases. Although it is clear that some TCM can cause CADRs and interact with conventional medicines,²⁵ the complex composition of most TCM formulations makes it difficult to identify the causative ingredient.

In summary, our study, in contrast to previous studies, found that the most common drug associated with CADR development overall was allopurinol, followed by amoxicillin, cephalosporin, antiepileptic agents and antipyretic/analgesic agents. Allopurinol and CBZ stand out as the major culprits for development of S-CADRs.

There are several limitations to this study. It was a retrospective study. A few patients refused treatment and discharged themselves after only a short time, therefore reducing the length of follow-up.

Nevertheless, we found the CADRs make up an important group of hospital admissions. As people live longer and are likely to require multiple drug treatments, identification by safe methods of the offending drug in cases of CADR will pose an important challenge in the future.

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