

Adverse cutaneous drug reactions: Eight year assessment in hospitalized patients

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Background: Adverse cutaneous drug reactions (ACDRs) are the most commonly reported adverse drug events. The causative drugs and clinical patterns of ACDRs are different in various populations. This study was conducted to identify the clinical patterns, causative drugs and reasons for drug administration in patients hospitalized due to ACDR. **Materials and Methods:** This retrospective study was carried out in a referral university hospital, Isfahan, Iran. The medical records of all patients who were hospitalized in the Dermatology Department due to ACDRs were reviewed covering an 8-year period between December 2006 and August 2013. **Results:** A total number of 282 patients with the mean age of 29.48 ± 21.18 years were hospitalized in this time period, of which 61% were females. The most common clinical patterns regarding the final diagnosis were Stevens-Johnson syndrome (SJS) (32%), exanthematous drug eruptions (24.5%) and toxic epidermal necrolysis (TEN) (11%). Anticonvulsants were the most frequently implicated drug group (51.8%) followed by antibiotics (33.7%) and analgesics and non-steroidal anti-inflammatory drugs (5.7%). The most common cause of drug administration was seizure (30%) and then upper respiratory tract infections (12%). The frequency distribution of clinical types of reactions was different between age groups ($P < 0.001$). The severe types (SJS, TEN, drug rash with eosinophilia and systemic symptoms and overlap syndrome) were more frequent in the patients aged ≤ 50 years old (55.2%) compare to those aged ≤ 50 years (28%) ($P = 0.001$). **Conclusion:** The main causative drugs of ACDRs were anticonvulsants and antibiotics. However, the sever types of reactions were more prevalent.

Key words: Adverse drug events, cutaneous drug eruption, drug reaction, hospitalization, patients

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INTRODUCTION

Adverse drug events (ADEs) are among the major challenges in modern medicine. Admissions related to drug reactions accounted for 3.31-16% of Medicine Department admissions^[1,2] and these reactions occur in 10-20% of all hospitalized patients.^[3] Adverse cutaneous drug reactions (ACDRs) are among the most frequent ADEs and comprise approximately 10 to 30% of total ADEs^[4] affecting 0.7-3% of all hospitalized patients.^[5,6] Urticaria,^[7,8] maculopapular eruption,^[9,10] and morbilliform rashes^[11] have been reported to be the most common clinical types of ACDRs in different studies. Although the majority of ACDRs are mild and self-limiting, severe manifestations such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are associated with a significant morbidity and might be fatal.^[12] On the other hand, these reactions could prolong hospital stay, generate excess costs and result in the discontinuation and change of the treatment.^[12,13] Factors such as female gender, obesity, age over 60 and immune dysregulation and underlying conditions like, pregnancy, hepatic failure and renal insufficiency

have been shown to be associated with the risk of ACDRs.^[14] Most of the studies reported anticonvulsants and antibiotics as the most common causative drug groups^[10,15-17] an non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly reported drugs in many studies.^[7,18,19] According to the previous studies on ACDRs, the epidemiological aspects, clinical patterns and the drugs causing these reactions differ between various populations.^[5,6,18,20] In Iran, separate reports of ADEs are collected from all over the country and released periodically by Center of Adverse Drug Reactions affiliated to Food and Drug Organization, Ministry of Health and Medical Education, but a published comprehensive and reliable data set on ACDRs in our setting is lacking. Several reports from various centers in Iran showed that antibiotics and anticonvulsants were the most common imputed drugs in patients hospitalized with ACDRs, females were more affected, and most prevalent dermatoses were maculo-papular rashes, erythroderma and urticaria.^[21-24]

Due to the importance of ADR which may affect patients compliance or make life threatening event, the 8 year

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assessment of ADR in hospitalized patients in an referral university hospital were conducted. We determined the prevalence of ACDRs, the clinical pattern of reactions and the drugs causing adverse reactions and the reasons for drug administration in patients hospitalized with ACDRs in our center.

MATERIALS AND METHODS

This retrospective study was conducted between June 2013 and December 2013 in Al-Zahra Teaching Hospital of Isfahan University of Medical Sciences, Isfahan, Iran. The study protocol was approved by ethical committee of the same university (Research Project Number 293060).

The records of patients hospitalized due to cutaneous drug reactions were reviewed, covering an 8-year period between December 2006 and August 2013. The review and data collection was completed by the same physician.

The following data was scrutinized from each patient's medical records: Age, gender, date of admission, drug history, the type of cutaneous lesions for which patients was admitted and the final diagnosis of ACDR, reasons for drug administration, duration between the use of drug and the onset of ACDR. The diagnosis of ACDR, type of lesion and clinical pattern was diagnosed by dermatologists.

Cases were excluded if more than 50% of the data was missing.

All statistical analyses were performed using SPSS 19.0 (Chicago, IL, USA). Descriptive statistics were generated and expressed as mean \pm standard deviation or number (percentage). One way ANOVA was used to compare the intervals between age groups and Categorical data was analyzed using the χ^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

A total number of 291 hospitalized patients were diagnosed with cutaneous drug reactions between December 2006 and August 2013. Nine patients were excluded from further analysis because of missing data in records and, therefore, 282 cases with the mean age of 29.48 ± 21.18 years (ranged 5 month to 90 years old) were included in the final analysis. Females constituted 60.8% ($N = 177$) of the cases.

Sixty-Six percent of the patients were hospitalized by emergency medicine services, 19% were referred from dermatologists' offices or dermatology clinics and 5.3% were referred by other services or admitted through consultation. The remaining 3.5% of the patients were admitted

through other ways. Forty-Three (15.2%) patients have been admitted to pediatric wards. Twelve patients (4.3%) required ICU care during their hospitalization. Mortality was observed in five cases.

The most common drug group causing adverse reactions was anticonvulsants (51.8% of all patients) followed by antibiotics (33.7%) and analgesics and NSAIDs (5.7%). The frequency of drug groups causing adverse reactions has been presented in Figure 1. The most frequent offending drugs were as follows; lamotrigine (17% of all patients), carbamazepine (12.4%), phenobarbital (10.6%), penicillin (6%), co-trimoxazole (6%), phenytoin (5%), cefixime (3.5%), sulfasalazine (2.8%), amoxicillin (2.5%) and ibuprofen (2.1%), sodium valproate (1.8%). Of the cases, 11.7% of patients had used a combination of two or three drugs. A combination of sodium valproate and lamotrigine constituted 2.1% of all cases, and the frequency percentage of other combinations was lower than 1%. Only 3 patients had kidney disease, and no patient had hepatic disease as the underlying disorder.

The most frequent drug groups causing adverse reactions and the interval between drug use and presence of skin eruptions in different age groups have been presented in Table 1. As the table shows, the most frequent drug group causing adverse reactions includes anticonvulsants or antibiotics across all age groups. No statistically significant difference was noted between various age groups regarding the interval between drug administration and the presence of signs or symptoms.

Table 1: Number of patients, interval between drug administration and presence of symptoms and the most frequent drug groups in different age groups

Age	n*	Interval (days)	The most frequent drugs (%)
0-10	65	14.22 \pm 9.90**	Anticonvulsants (71), antibiotics (29)
11-20	31	12.80 \pm 6.76	Anticonvulsants (53), antibiotics (40), analgesics (6)
21-30	55	17.33 \pm 13.35	Anticonvulsants (48), antibiotics (36), analgesics (5)
31-40	45	15.15 \pm 12.94	Anticonvulsants (56), antibiotics (33), analgesics (6)
41-50	20	14.22 \pm 14.12	Anticonvulsants (50), antibiotics (18), analgesics (9)
51-60	19	12.73 \pm 10.40	Antibiotics (45), analgesics (22), anticonvulsants (18),
61-70	13	20.92 \pm 18.70	Anticonvulsants (50), antibiotics (28), thyroid drugs (7)
71-80	8	14.75 \pm 8.81	Antibiotics (50), analgesics (22), anticonvulsants (12)
>80	6	17.33 \pm 21.21	Antibiotics (50), anticonvulsants (33)
P		0.506 [#]	<0.001 ^{###}

*Number of patients; **Data are expressed as mean \pm SD; [#]Comparison of between drug administration and presence of symptoms using One-way ANOVA; ^{###} χ^2 -test; SD = Standard deviation

The most common cause of administration of these drugs was seizure (in 30% of the patients) followed by upper respiratory tract infections (12%), bipolar disorders (5.3%), headache (2.5%) gynecologic infections (2.1%), pneumonia (2.1%) and urinary tract infection (1.8%). Reasons for which the patients received drugs have been classified in Figure 2.

The primary cutaneous morphological type which patients were admitted with was as follows: Maculopapular rash in 191 cases (67.7%), urticaria in 30 cases (10.6%), target lesions in 19 cases (6.7%), blisters and erosions in 14 cases (5%) and other types of lesions in the remaining 10%. The frequency of different clinical types of cutaneous drug reactions according to the final diagnosis and their most common drugs causing adverse reactions has been presented in Table 2. The most incident pattern of cutaneous

drug reactions was SJS (31.9%) followed by exanthematous drug eruptions (24%).

No association was seen between the gender and clinical pattern of reactions (Cramer's V = 0.18, and P = 0.55).

The frequency distribution of clinical types of reactions was different between age groups [Table 3, χ^2 test, P < 0.001]. The severe types (SJS, TEN, drug rash with eosinophilia and systemic symptoms [DRESS] and overlap syndrome) were more frequent in the patients aged ≤ 50 years old (55.2%) compare to those aged > 50 years (28%) and the difference was statistically significant (Fisher's exact test, P = 0.001). Pattern of causative drugs were different between this two age groups. In age group ≤ 50 years, anticonvulsants (57.5%),

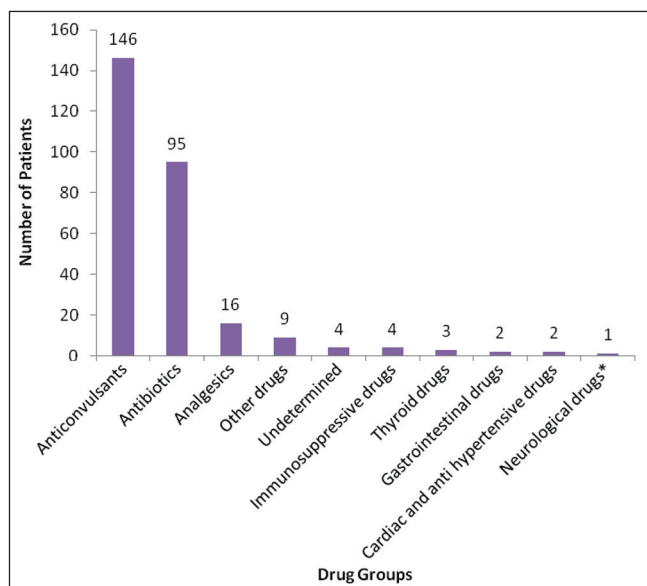


Figure 1: Drugs implicated in adverse cutaneous drug reactions (*neurological drugs other than anticonvulsants)

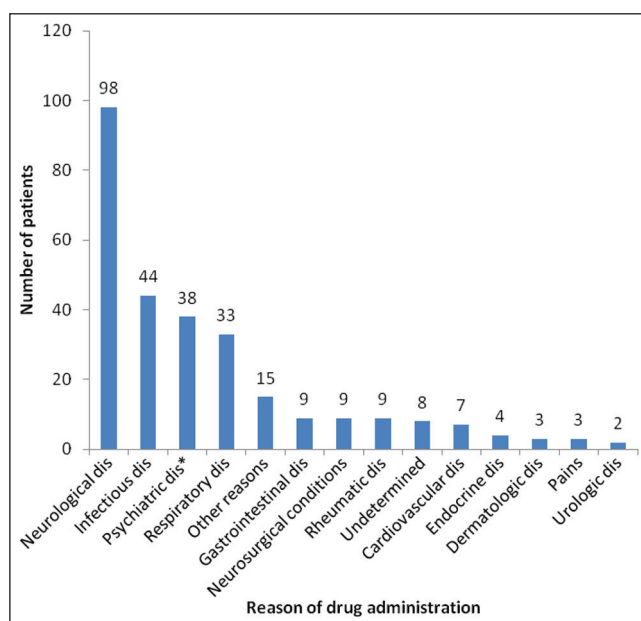


Figure 2: Distribution of patients according to reason for drug prescription *dis: Diseases/disorders

Table 2: Frequency and causative drugs of different types of cutaneous drug reactions

Clinical classification	n*	Percentage	Most common imputable drug (%)
SJS	90	31.9	Lamotrigine 30, carbamazepine 19, phenobarbital 12
TEN	31	11.0	Carbamazepine 16, phenobarbital 13, lamotrigine 13
DRESS syndrome**	18	6.4	Carbamazepine 22, lamotrigine 11, vancomycine 11
EDE	69	24.5	Lamotrigine 20, phenobarbital 18, carbamazepine 12
AGEP	8	2.8	Hydroxychloroquine 25, allopurinol 25
Min EM	16	5.7	Co-trimoxazole 25, ibuprofen 12.5, cefixime 12.5
Major EM	4	1.4	Lamotrigine, ampicillin, lamotrigine + sodium valproate, doxycycline + fluconazole
Utricaria	29	10.3	Cefixime 13, aspirin 10
FDE	11	3.9	Co-trimoxazole 18 diclofenac 18 naproxen 9
SS	1	0.4	Co-trimoxazole
Overlap (SJS/TEN)	3	1.1	Carbamazepine, sodium valproate
Erythroderma	2	0.7	Sodium valproate, sodium valproate + phenytoin
P			<0.001**

*Number of patients; **DRESS = Drug reaction with eosinophilia and systemic symptoms; *** χ^2 -test; TEN = Toxic epidermal necrolysis; SJS = Stevens–Johnson syndrome; EDE = Exanthematous drug eruptions; AGEP = Acute generalized exanthematous pustulosis; Min EM = Minor erythema multiforme; Major EM = Major erythema multiforme; FDE = Fixed drug eruption; SS = Serum sickness; Overlap = Overlap of SJS/TEN

Table 3: Frequency of different clinical types in age groups

Age group (years)	Clinical type of ACDR											
	SJS (%)	TEN (%)	DRESS (%)	EDE (%)	AGEPT (%)	Min EM (%)	Major EM (%)	Urticaria (%)	FDE (%)	SS (%)	Erythroderma (%)	Overlap (%)
<10	23 (33.8)	5 (7.4)	1 (1.5)	25 (36.8)	0	9 (13.2)	1 (1.5)	2 (2.9)	0	1 (1.5)	0	1 (1.5)
10–20	15 (46.9)	5 (15.6)	4 (12.5)	6 (18.8)	0	1 (3.1)	0	1 (3.1)	0	0	0	0
21–30	22 (36.7)	10 (16.7)	5 (8.3)	10 (16.7)	0	3 (5.0)	0	8 (13.3)	1 (1.7)	0	0	1 (1.7)
31–40	18 (36.7)	6 (12.2)	4 (8.2)	6 (12.2)	1 (2.0)	1 (2.0)	3 (6.1)	8 (16.3)	2 (4.1)	0	0	0
41–50	4 (17.4)	2 (8.7)	2 (8.7)	7 (30.4)	4 (17.4)	0	0	4 (17.4)	0	0	0	0
51–60	2 (9.1)	1 (4.5)	1 (4.5)	8 (36.4)	1 (4.5)	1 (4.5)	0	4 (18.2)	3 (13.6)	0	0	1 (4.5)
61–70	3 (21.4)	1 (7.1)	1 (7.1)	4 (28.6)	0	1 (7.1)	0	2 (14.3)	1 (7.1)	0	1 (7.1)	0
71–80	2 (25.0)	0	0	2 (25.0)	1 (12.5)	0	0	0	3 (37.5)	0	0	0
>80	1 (16.7)	1 (16.7)	0	1 (16.7)	1 (16.7)	0	0	0	1 (16.7)	0	1 (16.7)	0

*Data are expressed as number (%); SJS = Steven–Johnson syndrome; TEN = Toxic epidermal necrolysis; DRESS = Drug reaction with eosinophilia and systemic symptoms; EDE = Exanthematous drug eruptions; AGEPT = Acute generalized exanthematous pustulosis; Min EM = Minor erythema multiforme; Major EM = Major erythema multiforme; FDE = Fixed drug eruption; SS = Serum sickness; Overlap = Overlap of SJS/TEN; ACDR = Adverse cutaneous drug reaction

antibiotics (32.5%) and analgesics and NSAIDs (4.4%) were the most common causative drug groups and in group >50 years, antibiotics (42%) were the most common drug group followed by, anticonvulsants (30%), analgesics and NSAIDs (12%).

DISCUSSION

Adverse cutaneous drug reactions are the most common ADEs and could result in hospital admission, prolonged hospital stay, increased morbidity or even mortality.^[12,13] In this study, we evaluated the clinical patterns and the drugs causing adverse reactions in patients admitted to the dermatology department of a referral center due to ACDRs.

Previous studies showed conflicting results about the incidence of ACDRs in different genders. Some studies reporting a male preponderance^[19,25] in hospitalized patients, but others showed a female preponderance.^[8,16] Male to female ratio in this study was 1:1.55. This predominance of females is in line with previous studies in Iran.^[22,23] More incidence of ADEs in females not only has been shown about inpatients, but also epidemiological studies and the analysis of spontaneous reports showed that female gender is a risk factor for ADEs.^[26,27] Difference in pharmacokinetics, body weight and composition, hormonal effects on drug metabolism have been suggested as a potential explanation for the effect of gender on the ADEs.^[28]

The mean age of patients in our study was 29.5 years that is younger than previous studies conducted in Iran and other countries.^[16,23] In this study, the most affected age group was 0-10 years that is not in line with previous studies. Other studies reported that the majority of patients belong to the age groups older than what we found.^[11,19,21,22] Our center in the majority of the period covered in our study was the main referral center for pediatric patients, and the pediatric wards was included in this study that. It could

be considered as one of the explanations for the younger study population.

The drugs causing adverse reactions for ACDRs are different for different populations. Saha *et al.*^[11] reported antibiotics as the most common implicated drug groups in outpatients. Pudukadan *et al.*^[29] reported co-trimoxazole (22.25%) and dapsone (17.7%), as the most common drugs. Many studies reported antibiotics or anticonvulsants as the most common culprit.^[10,13,16] In our study, the most common drug group affecting patients was anticonvulsants (51%) followed by antibiotics (33%) which are in keeping with previous studies carried out in Iran.^[21,22] Rahmati-Roodsari *et al.*^[22] reported anticonvulsants (36%) and antibiotics (32%) as the most common drugs causing adverse reactions in patients hospitalized in Loghman-Hakim Hospital (Tehran, located near the center of Iran) and the most common drugs were phenytoin, carbamazepine and then amoxicillin. Jelvehgari *et al.*^[21] reported anticonvulsants as the most common drug group and carbamazepine (28%), carbamazepine/valproate (20%) and a combination of co-trimoxazole-carbamazepine-diclofenac (26.7%) as the most common drugs causing adverse reactions in hospitalized patients in Sina Hospital of Shiraz (located in southwestern Iran). Other studies in Iran reported antibiotics as the most common drugs and then NSAIDs or anticonvulsants.^[23,24] In our study, NSAIDs were the third most frequent causative drug group. Many studies reported NSAIDs as one of the most common causative drug groups for ACDR after antibiotics and anticonvulsants.^[18,19] Although, the severe reactions are low in association to NSAIDs,^[30] this drug group has been reported as a common causative agent in the presence of SJS and TEN after anticonvulsants, antibiotics.^[31]

The most common cause of administration of the implicated drugs was seizure (in 30% of patients) therefore; it is no surprise that the three most common drugs are lamotrigine (17% of all patients), carbamazepine (12.4%), and phenobarbital (10.6%) that are used as anticonvulsants

and mood stabilizers. These three were the most common drugs causing adverse reactions in severe types of ACDRs including SJS, TEN and DRESS in our study. Yang *et al.* reported that lamotrigine carbamazepine and phenobarbital were the major antiepileptic drugs for severe types of ACDRs in Asians.^[32]

Upper respiratory tract infections were responsible for 12% of all drug administrations in the study population. 83% of the drugs causing adverse reactions in these patients were antibiotics. Antibiotics are often prescribed to treat upper respiratory tract infections, even though they are mostly caused by viruses, and these antibiotics are ineffective.^[33,34] Rahmati-Roodsari reported the epilepsy (24.6%) and pharyngitis (24.6%) as the most common cause of the drug prescription each one accounting for 24.6% of drug prescriptions in study population.^[22]

Regarding the clinical patterns, previous studies have classified CADRs in various ways and reported the frequencies. In Rahmati-Roodsari's study the most frequent type of ACDR was Maculo-papular rashes, urticaria and erythroderma.^[22] Jelvehgari *et al.* reported the most frequent clinical patterns as follows: Erythroderma, maculopapular rash, SJS and TEN. Drug exanthems.^[21] DRESS and SJS/TEN spectrum were the most prevalent clinical pattern in Lee *et al.*'s study.^[16] Urticaria^[7,8] maculopapular eruption,^[9,10,35] and morbilliform eruption^[11] have been reported to be the most common clinical pattern of ACDRs in hospitalized patients in various studies. For more precise evaluation we classified the reactions according to the primary cutaneous presentation and final diagnosis. Regarding the primary presentation the most frequent type of lesions was maculopapular rash followed by urticaria. According to the final diagnosis, the most prevalent clinical pattern was SJS followed by exanthematous drug eruptions and TEN. It shows that in our study the proportion of severe cases is higher than other reports as the two out of three most frequent clinical patterns are among severe types of ACDRs. There is no clear explanation for this prevalence pattern. Al-Zahra hospital is the only referral center in the region, severe cases are referred to this center and milder cases might be managed in other centers. Although, the more prevalence of severe cases in the population and the different pattern of drug use could not be excluded, the referral policies might at least partially explain the more frequency of severe cases.

In our study, the severe types of reactions were more frequent in the patients aged ≤ 50 years old. In this age group anticonvulsants were more frequent compare to patients >50 , and as the Table 2 represents, the most common causative drugs for the severe types (SJS, TEN, DRESS and overlap syndrome) are anticonvulsants.

We faced some limitations in this study. First, there were some cases with missing data in the study and nine patients were excluded because of this. Second, diagnosis of the reactions was based on attending physician's opinion and may be the subject to inter-observer variation. However, our study was a retrospective one which makes these limitations inevitable.

CONCLUSIONS

The drugs are causing ACDRs were similar to those reported in the majority of previous studies, but severe types of reactions were more prevalent. Anticonvulsants and antibiotics were the most frequent imputed drugs, and seizure disorder and upper respiratory infections were the most frequent cause of administration. Therefore, selection of anticonvulsants and prescription of drugs (mainly antibiotics) for upper respiratory infections should be done more cautiously.

AUTHOR'S CONTRIBUTION

Study concept: FM and ZN. Study design: FM and ZN and BAN and AAE and SR. Data collection: FM and ZN and BAN and AAE and SR. Data entering and analysis: FM and ZN.

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