Drug-induced skin events in hospitalized patients in Tehran, Iran: a 6-year case series study

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Abstract

Introduction: Drug reactions are commonly seen in the skin but their frequency has not been determined in Tehran yet. We aimed to evaluate adverse cutaneous drug events (ACDE) in hospitalized patients.
Material and methods: A 6-year case series study (from 2000 to 2006) including all hospitalized patients in two referral dermatology wards of Loghman-Hakim and Shohada Hospitals was performed.
Results: A total of 54 patients (31 female and 23 males) were included. Adverse cutaneous drug events was slightly more frequent in females (1.34 : 1). Thirty three and 22% of the patients were in the age group of 31-40 and 41-50, respectively. The most commonly seen dermatoses were maculo-papular rashes (60%), erythroderma (10%), and urticaria (10%). Drugs most frequently associated with ACDE were anticonvulsants and antibiotics, with rates of 31 and 28%, respectively. No mortality due to ACDE was seen. In most of the patients (50%), the duration of hospitalization was 3-7 days. Most of the patients (74%) had no previous history of allergy. In most cases (65%), the adverse events began during the first day to first month after drug exposure.
Conclusions: Although the prevalence of ACDE in this study was found to be lower than reported data in the literature suggest, the results confirm that ACDE is a notable public health concern. Early and rapid recognition of severe ACDE and prompt withdrawal of the offending drug are the most important actions to minimize morbidity associated with drug use.

Key words: adverse drug reaction, drug eruption, drug hypersensitivities, hospitalized patients, skin, toxicity.

Introduction

All drugs can potentially produce untoward consequences, even when used according to recommended methods of administration [1, 2]. Adverse drug events (ADE) are an important challenge in modern medicine. They have a considerable negative impact on both health and healthcare costs [3], and their incidence has been reported to range from 5.9 to 22.3% of all emergency department admissions [4]. It is estimated that approximately 10-20% of hospitalized patients are usually affected [5].

Adverse drug events can involve every organ and system of the body and are frequently mistaken for signs of underlying disease. The skin

reaction may mimic a spontaneously occurring skin disorder and is therefore included in the differential diagnosis of most skin diseases. Alternatively, the drug may produce specific changes. A drug-induced skin reaction can develop after the first dose, or after a period of sensitization. Pigmentation, nail changes or effects on hair may take a few months to become apparent. Skin reactions range from mild rashes to severe, life-threatening reactions including angioedema, Stevens-Johnson syndrome, vasculitis, and toxic epidermal necrolysis (TEN). It is estimated that 30% of reported ADE involve the skin [1, 5].

Adverse drug events has been shown to prolong hospitalization by 1 and 7 days, respectively, in 6 and 12% of patients affected by common diseases [6, 7]. In a general medicine department, pharmacological therapy was found to be longer in 3.8% of hospitalized patients because of ADE and 5% of these patients had life-threatening ADE [6].

Unknown drug reactions will probably develop because new drugs are continuously becoming available [8]. A number of ADE can be lethal [9-11], with 0.2-29.3% of all adverse cutaneous drug events (ACDE) requiring hospitalization [9]. It is estimated that ACDE affect 2-3% of hospitalized patients; most of them are fortunately not severe, but a few are fatal [12].

However, there are more than 30 drug/poison information and surveillance centres in Iran [13], but the rate of ACDE in hospitalized patients has not been determined yet. In the present study, two main dermatology centres of Tehran, Iran that serve a daily population of about 1.7 million as referral centres for most drug-related reactions have been selected and a case series study was carried out to explore reliable data on existence of ACDE in Iranian patients.

Material and methods

A 6-year case series study (from 2000 to 2006) including all hospitalized patients in dermatology wards of Loghman-Hakim and Shohada Hospitals was performed. All hospitalized patients were examined by a dermatologist and diagnosis was confirmed on the basis of morphology and distribution of the lesions. Biopsies were taken in 100% of cases to corroborate the diagnosis. Stevens-Johnson syndrome and TEN were excluded from this study because of their admission in the intensive care unit (ICU) and also because they are quite rare.

The following information was obtained from each patient during hospitalization: age (child cases are referred to children's hospitals, so paediatric patients were not included in this study), sex, history of previous disease and drugs used, history of previous ADE and allergies, type of ACDE, duration between use of drug and onset of ACDE, treatment, duration of hospitalization, and mortality.

Results

A total of 54 patients, 31 female and 23 males, were recorded. ACDE were slightly more frequent in females (1.34 : 1) but no significant difference between men and women was observed according to type of ACDE and clinical manifestation. No significant change in the number of patients with ACDE in the years of study was observed.

Patients' age ranged from 18-80 years; 33 and 22% of the patients were in the age group 31-40 and 41-50, respectively.

Biopsies corroborated the clinical diagnosis of ACDE. The most common ACDE were maculo-papular rashes (60%), erythroderma (10%), and urticaria (10%). One of the 54 patients (1.7%) presented a less common drug reaction, drug-related pustulosis (Table I). No mortality due to ACDE was observed. In most of the patients (50%), the duration of hospitalization was 3-7 days (Figure 1).

Most of the patients (74%) had no previous history of allergy. In most cases (65%), the adverse reactions began during the first day to first month after drug exposure (Figure 2). The most frequently involved drugs were anticonvulsants and antibiotics, with rates of 36 and 32%, respectively (Table II). As indicated in Table III, the most common cause of the drug prescription was epilepsy (24.6%) and pharyngitis (24.6%). Most of the patients (32%) had no underlying concomitant disease (Table IV). The most frequent treatments included intravenous administration of antihistamine and corticosteroids.

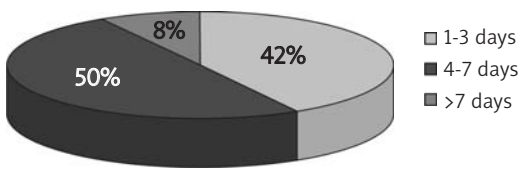

Figure 1. Distribution of patients according to duration of hospitalization

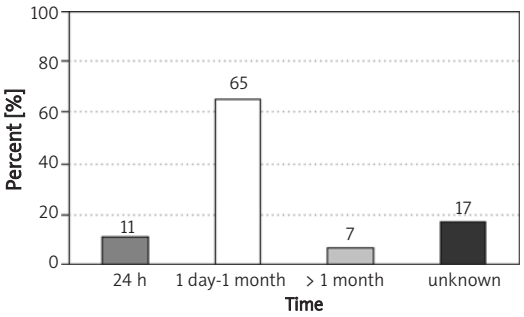

Figure 2. Distribution of patients according to time interval between use of drug and onset of ACDE

Table I. Distribution of patients according to type of ACDE

Type of ACDE	Type of immunological reaction	Number*	Percent [%]
Maculo-papular rashes	Hypersensitivity type IV	36	60
Erythrodermia	Hypersensitivity type IV	6	10
Urticaria	Hypersensitivity type I	6	10
Fixed drug eruption	Hypersensitivity type IV	3	5
Vesiculo-bolus lesions	Hypersensitivity type IV	3	5
Desquamating lesions	Hypersensitivity type IV	3	5
Vasculitis	Hypersensitivity type III	2	3.3
Drug-related pustulosis	Hypersensitivity type IV	1	1.7
Total		60	100

**A number of patients showed more than one ACDE*

Table II. Distribution of patients according to causal drugs

Type of drugs	Name of drugs	Number*	Percent [%]
Antiepileptic drugs	Phenytoin	10	17.9
	Carbamazepine	7	12.5
	Phenobarbital	2	3.5
	Lamotrigine	1	1.8
	Total	**20**	**36**
Antibiotics	Amoxicillin	6	10.7
	Trimethoprim-sulfamethoxazole	3	5.4
	Penicillin	2	3.5
	Ciprofloxacin	2	3.5
	Vancomycin	1	1.8
	Ampicillin	1	1.8
	Clindamycin	1	1.8
	Ceftriaxone	1	1.8
	Idocinol	1	1.8
	Total	**18**	**32**
$NSAID_S$	Ibuprofen	3	5.4
	Diclofenac sodium	2	3.5
	Indomethacine	1	1.8
	Total	**6**	**10.7**
Cardiovascular drugs	Propranolol	1	1.8
	Enalapril	1	1.8
	Captopril	1	1.8
	Verapamil	1	1.8
	Diltiazem	1	1.8
	Total	**5**	**8.9**
Antidepressants and sedative drugs	Oxazepam	1	1.8
	Amitriptyline	1	1.8
	Total	**2**	**3.5**
Others	Cilax	1	1.8
	Hyoscine	1	1.8
	Tramadol	1	1.8
	Metocarbamol	1	1.8
	Dimenhydranate	1	1.8
	Total	**5**	**8.9**
Total		**56**	**100**

**In a number of cases more than one drug has been prescribed*

Table III. Distribution of patients according to reason for drug prescription

Reason for drug prescription	Number*	Percent [%]
Convulsion	14	24.6
Pharyngitis	14	24.6
Cardiovascular disease	4	7
Musculo-skeletal pain	4	7
Gastroenteritis	3	5.3
Constipation	2	3.5
Sleep disorder	2	3.5
Tic	2	3.5
Pelvic infection	2	3.5
Fever of unknown origin	2	3.5
Pyelonephritis	2	3.5
Depression	2	3.5
Migraine	2	3.5
Dental surgery	2	3.5
Total	**57**	**100**

**In one case more than one reason for drug prescription was present.*

Discussion

No drug is completely harmless, even when used correctly, and all may cause ADE [3, 4, 7]. It is well established that ADE has a considerable adverse impact, not only on the health of the population, but also on healthcare costs [24, 29, 30]; thus epidemiological investigations of drug usage and untoward events are necessary to establish means to prevent adverse consequences [6, 31, 32].

Adverse effects in the skin are induced by immunological, non-immunological and unknown mechanisms. Most adverse skin drug reactions occur by non-immunological mechanisms. Immunological reactions require activation of host

Table IV. Distribution of patients according to underlying disease

Underlying disease	Number*	Percent [%]
No underlying disease	20	32
Cardiovascular disease	12	19
Epilepsy	7	11
Diabetes mellitus	7	11
Thyroidal dysfunction	4	6.3
Cerebro-vascular accident	2	3.2
Migraine	2	3.2
Brain tumour	2	3.2
Renal stones	1	1.6
Tic	1	1.6
Hypophysial tumour	1	1.6
Brain abscess	1	1.6
Non-Hodgkin's lymphoma	1	1.6
Asthma	1	1.6
Psoriasis	1	1.6
Total	**63**	**100**

**In a number of cases more than one underlying disease was present. No underlying disease means that the patient was not diagnosed for a specific disease by any physician and thus the drug has been used on his/her own intent*

immunological pathways and are designated as drug allergies. Drug reactions occurring through non-immunological mechanisms may be due to activation of effector pathways, overdose, cumulative toxicity, side effects, ecological disturbance, and interactions between drugs, metabolic alterations, and exacerbation of pre-existing dermatological conditions, or inherited protein or enzyme deficiencies. Notably, the mechanism of most drug reactions is unknown. Multiple factors determine the capacity of a drug to elicit an immune response, including the molecular characteristics of the drug and host factors. Route of administration, degree of drug exposure, individual variability in absorption and metabolism, and frequency of high-dose and interrupted courses of therapy are important risk factors for the development of drug allergy [14].

Adverse drug events may affect any organ, and the skin is a common site of presentation [9, 15]. In a prospective study, Hallas *et al*. reported that 8.4% of hospitalizations were drug related [16]. In a meta-analysis of 37 studies conducted between 1966 and 1989, drug-induced hospitalizations accounted for about 5% (range: 0.2-21.7%) of all admissions [17]. Some studies report that ACDE are infrequent, with an incidence of 0.4-1.2 in 1.2 to 6 million people per year [18], occur at any age and include Stevens-Johnson syndrome, TEN, hypersensitivity syndromes, serum sickness and angioedema. However, in our study the prevalence was considerably lower than that reported in the literature [19], maybe because we purposefully excluded Stevens-Johnson syndrome and TEN, which represent up to 4.9 and 2.4% of the cases reported elsewhere. On the other hand, patients seem to be unaware of special skin hospitals and thus they admit to general hospitals. Regarding the mean admission range of hospitalized skin-related patients in these two hospitals that was 220, the other reason is possibly that many of the patients are treated as outpatients in emergency rooms, or they may be treated by other colleagues.

The most common ACDE was maculo-papular rashes (60%), followed by erythroderma (10%), and urticaria (10%). Borch *et al*. in their study reported that urticaria and local reactions at injection sites were the most frequent reactions [20]. Also, in another study by the same team, they reported that symmetrically distributed maculo-papular exanthema and eczematous eruption are the most common types of skin reactions [21]. The lower frequency of some ACDE such as urticaria in the present work may be that most of these cases are not usually referred to dermatology wards. One of the 54 patients (1.7%) presented a less common drug reaction, drug-related pustulosis. Drug-related pustulosis is very uncommon [22]. It has been associated with β-lactam antibiotics, macrolides, quinidine, vancomycin, and methotrexate, and more frequently in immunosuppressed patients [8, 23]. The most common reactions seen in the Boston study were morbilliform exanthems (94%) and urticaria (5%).

We found that ACDE was caused mainly by anticonvulsants and antibiotics and commonly used drugs. Presumably for patients on multiple medications, it was not possible to establish the causal drug of the reaction. In agreement with other studies, ACDE were most frequently related to antibiotics, non-steroidal anti-inflammatory drugs ($NSAID_S$), and X-ray contrast media [8, 16, 19, 24]. According to the Boston Collaborative Drug Surveillance carried out in 37,000 patients [25, 26], 2-3% of all hospitalized patients developed an ADE. The drugs with the highest reaction rate were amoxicillin (51/1000), trimethoprim sulfamethoxazole (47/1000), ampicillin (42/1000), semisynthetic penicillins (29/1000), blood and blood products (28/1000) [27].

In our study, ACDE were slightly more frequent in females (1.34 : 1), which is supported by another study [8]. Although some studies report that dermatoses are not age related [28], and some suggest that ACDE are more frequent in young children and older adults, possibly because of a dysfunctional immune system or the inability

to metabolize the drugs [33], in our study dermatoses were more common in the age group of 31-50 years, and since children are referred to children's hospitals, paediatric patients were not included in this study.

In our study, most of the ACDE appeared within the first day to first month of drug exposure, which is similar to other studies [25, 27], and most patients had no prior history of allergy. A careful medical history is mandatory because human error as mentioned earlier can be responsible for an ADE. In another study, 1-3 weeks after drug ingestion was indicated as the most common period of ACDE; however, anticonvulsants have been associated with a longer presentation period of up to 8 weeks [34].

Although some studies indicate that ACDE have a mortality rate of up to 30% and the most frequently associated drugs are trimethoprim-sulfamethoxazole, carbamazepine and diphenylhydantoin [35, 36], in the present study no mortality due to ACDE was observed, which is supported by another report [19]. This may be due to the fact that severe ACDE such as Stevens-Johnson syndrome and TEN were excluded in our study.

As shown in Tables III and IV, the most common reason for drug prescription was epilepsy (24.6%) and pharyngitis (24.6%). Most of the patients had no underlying concomitant disease. Among those with underlying diseases, cardiovascular system disease was ranked first.

Although the present study does not show high incidence of ACDE in Tehran, regarding the high rate of drug-related poisonings in the country [37-39], and considering the average number of drugs per prescription in Iran that is 3.6, and the proportion of prescriptions with at least one injection out of the total number of prescriptions that is 47.4% [40], further surveys and especially meta-analysis studies are needed. The important agents of acute poisoning in Iran are drugs (69.13%), especially sedative-hypnotics, followed by opioids (12.34%) and pesticides, especially organophosphates (OPs) (6.21%). Regarding the different methodology used by various studies, a comparative meta-analysis [41] is needed to clarify the source of differences in total rate of ACDE reported from different countries. The small sample size of this study despite the long duration of observation in two referral centres is a study limitation. Of course, we believe that this preliminary report on ACDE is sufficient for researchers and policy makers to design further clinical studies with adequate follow-up on comparative evaluation of ACDE in outpatients and inpatients.

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