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RESEARCH ARTICLE

Adverse cutaneous drug reactions among hospitalized patients: five year surveillance

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Abstract

Context: Cutaneous Adverse Drug Reactions (CADRs) are observed in 2–3% of hospitalized patients. The clinical presentation of the CADRs varies among different populations.

Objective: To study the CADRs in hospitalized patients and their outcome.

Materials and methods: Patients hospitalized at our department between 2005 May and 2010 May were retrospectively reviewed for the diagnosis of CADRs.

Results: A total of 94 patients (3.3%) were diagnosed with CADR among 2801 hospitalized patients. Of them, 56 patients were female (59.6%) and 38 patients were male (40.4%). The culprit drugs were antibiotics (24.5%), non-steroid anti-inflammatory drugs (NSAID) (22.4%), anticonvulsants (13.8%), antihypertensive agents (8.5%), paracetamol with or without pseudoephedrine or phenylephrine (6.4%), intravenous contrasts (3.2%), terbinafine (2.1%), biologic agents (2.1%) and various other medications (17.0%). The most common clinical type of CADRs was morbilliform exanthemas in 59.6% of the patients, followed by erythroderma (6.4%), drug reactions with eosinophilia and systemic symptoms (6.4%), lichenoid drug reaction (5.3%), urticaria and angioedema (4.3%), acute generalized exanthematous pustulosis (4.3%), drug-induced vasculitis (3.2%), drug induced psoriasis (2.1%), Stevens–Johnson syndrome/toxic epidermal necrolysis overlap (2.1%), psoriasiform drug reaction (2.1%). Fixed drug reaction, erythema multiforme, bullous drug reaction, drug induced panniculitis were observed in one each. No deaths occurred on the follow-up. Fever was observed in 35.1% of the patients. Eosinophilia was present in 51.1% of them. Latency period ranged between 0–15 days in 59 patients (62.8%), 15–30 days in 19 patients (20.2%), 30–90 days in 13 patients (13.8%), 90–120 days in three of them (3.2%). The latency for anticonvulsant drugs was statistically longer than the other group of drugs (p : 0.027).

Discussion and conclusions: CADRs were more common in women and most of them were caused by antimicrobial agents followed by NSAIDs and anticonvulsants. Latency period of anticonvulsants were longer than the other groups.

Keywords: Cutaneous, adverse drug reaction, hospitalized patients

Introduction

Cutaneous adverse drugs reactions (CADRs) are estimated to be about 30% of all adverse drug reactions and observed in 2–3% of hospitalized patients (1). Antibiotics, anticonvulsants and non-steroidal anti-inflammatory drugs are the most common cause of CADRs. The cutaneous drug reactions show varying clinical features changing according to the type and severity (2–6). The CADRs are classified by World Health Organization

(WHO) as mild, moderate or severe (7). Morbiform rash is the most common clinical presentation of CADRs in most of the previous studies (2–6). Severe cutaneous drug reactions include Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reactions with eosinophilia and systemic symptoms (DRESS) (8). As well, the other reported reactions are urticaria/angioedema, erythema multiforme, fixed drug reaction,

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bullous eruptions, lichenoid dermatitis, erythema nodosum, erythroderma, vasculitis, skin necrosis (8,9). In this study, we aimed to assess the clinical features and causative agents of CADRs among hospitalized patients at a dermatology clinic of an university hospital.

Materials and methods

The Turkish patients hospitalized at Ege University Medical Faculty Department Dermatology, a tertiary hospital in Aegean region of Turkey, between 2005 May and 2010 May reviewed retrospectively. Patients with a diagnosis of CADR were included into the study. Diagnosis was based on the presence of a skin rash which had developed after the intake of a new drug together with the histopathologic examination in most of them. Data including age, gender, drugs involved, clinical type of drug reaction, fever, laboratory findings, associated dermatological disease, treatment were all documented. The normal range of leukocyte count was defined as 4500/ μ l to 11,000/ μ l. Eosinophil above 4.5% was defined as "Eosinophilia". The normal C reactive protein (CRP) level was lower than <0.5 mg/dl and erythrocyte sedimentation rate (ESR) was lower than 20 mm/h.

Latency period between the time of administration of the medication and the onset of the rash was noted. In patients receiving more than one drug, the most frequent class of drug associated with the appearance of a rash was attributed as the culprit drug.

Diagnosis of drug reactions with eosinophilia and systemic symptoms (DRESS) was established according to the criteria proposed by European Registry of Severe Cutaneous Adverse Drug Reactions (RegiSCAR) including (i) hospitalization, (ii) acute onset of exanthema with fever >38°C, (iii) enlarged lymph nodes, (iv) involvement of at least one internal organ, (v) eosinophilia >10% or >700/ μ l or atypical lymphocytes or lymphopenia <4000/ μ l or lymphocytosis or thrombocytopenia. The patients presenting with four or more criteria diagnosed as DRESS (10). Statistical analyses were performed using SPSS 13.0 for Windows. χ^2 -Tests were used to analyze the categorical data.

Results

A total of 94 patients (3.3%) with CADRs were included into the study among 2801 hospitalized patients. Of them, 56 patients were female (59.6%) and 38 patients were male (40.4%). Mean age of the patients was 55.38 ± 19.5 (range 1–84 years). Five patients were receiving more than one drug. The others were receiving the culprit drug as monotherapy. The suspected drugs were antibiotics (23 patients, 24.5%), non-steroid anti-inflammatory drugs (NSAID) (21 patients, 22.4%), anticonvulsants (13 patients, 13.8%), antihypertensive agents (8 patients, 8.5%), paracetamol with or without pseudoephedrine or phenylephrine (6 patients, 6.4%), intravenous contrasts (3 patients, 3.2%), terbinafine (2 patients, 2.1%), biologic agents including adalimumab and imatinib (2 patients, 2.1%) and various

other medications (16 patients, 17.0%). The causative agents of drug reactions have been detailed in Table 1.

Fifty-six patients (59.6%) had morbilliform exanthemas, 6 patients (6.4%) had erythroderma, 6 patients (6.4%) had DRESS, 5 patients (5.3%) had lichenoid drug reactions, 4 patients (4.3%) had urticaria and angioedema, 4 patients (4.3%) had acute generalized exanthematous pustulosis (AGEP), 3 patients had drug-induced vasculitis (3.2%), 2 patients (2.1%) had drug induced psoriasis, 2 patients (2.1%) had SJS/TEN overlap, 2 patients (2.1%) had psoriasiform drug reaction. Fixed drug reaction, erythema multiforme, bullous drug reaction, drug induced panniculitis were observed in one each. Severe CADRs including DRESS, SJS/TEN overlap and AGEP were observed totally in 12 patients (12.7%). The causative drugs of these serious reactions have been given in Table 2. There were no any statistical relation between the culprit drug and the clinical type of the drug reaction. No deaths occurred on the follow-up.

Mucosal involvement was observed in 17 patients (18.1%). There were erosive lesions and erythematous areas on oral mucosa of 14 patients (14.9%). Oral mucosa involvement were accompanied by conjunctival involvement in 6 patients (6.4%) and were accompanied by genital mucosal involvement in 4 patients (4.2%). In two of them, lichenoid lesions were together with erosive areas on oral mucosa. In three patients (3.2%), conjunctivas were involved alone.

Fever (>37.5°C) was observed in 33 patients (35.1%) at the admission. Of them, all patients with DRESS had a fever higher than 38°C. Previous drug reaction history was present in 10.6% (10 patients) of the patients. Eosinophilia was present in 48 patients (51.1%). The mean eosinophilia was 15.09% (range 5.40–40.00%). Twenty-six patients (27.6%) had leukocytosis (range 11300–30700/ μ l), while four of them (4.2%) had mild leukopenia (range 2540–4300/ μ l). Twenty patients (12.8%) had elevated liver transaminases and 9 patients (9.6%) had elevated blood urea nitrogen together with elevated creatinine levels. CRP level (range 0.56–27.44 mg/dl) and ESR (26–110 mm/h) were elevated in 63 (67.0%) and 25 patients (26.6%), respectively. All of the altered biochemical parameters returned to normal limits after cessation of the culprit drugs. Latency period ranged between 0–15 days in 59 patients (62.8%), 15–30 days in 19 patients (20.2%), 30–90 days in 13 patients (13.8%), 90–120 days in three of them (3.2%). The latency period of anticonvulsants was statistically longer than the other group of drugs (p : 0.027). The mean latency period for anticonvulsants was 47.5 days (range 7–120 days).

Drug induced vasculitis in three patients were due to diclofenac, clarithromycin, sodium fusidate. Generalized fixed drug reaction was due to mebeverine. Bullous drug reaction was due to chemotherapy including fludarabine and daunorubicin.

Histopathologic examination was done in 92 patients (97.8%). In the treatment, firstly the culprit drugs were ceased. Systemic steroids were used in 40 of them

Table 1. Culprit drugs in adverse cutaneous reactions.

Drugs	No. (%)
Antibiotics	23 (24.5)
Penicillins (Amoxicillin/Amoxicillin-Clavulanic acid:11, Ampicillin-Sulbactam:1)	
Cephalosporins (Cefuroxime axetil:2, Ceftriaxone:2, Cephalexin:1)	
Macrolides (Clarithromycin:2)	
Others (Trimethoprim/sulfamethoxazole:1, Clindamycin:1, Levofloxacin:1, Sodium Fusidate:1)	
NSAIDs	21 (22.4)
Diclofenac Na:10	
Naproxen: 4	
Etodolac:2	
Others: Meloxicam 1, Tiaprofenic acid:1, Ibuprofen:1, Flurbiprofen:1, Dexketoprofen:1	
Anticonvulsants	13 (13.8)
Carbamazepine:8	
Lamotrigine:3	
Phenytoin:2	
Diuretics and antihypertensive agents	8 (8.5)
Furosemide:2	
Indapamide:1	
Perindopril:1	
Valsartan/Hydrochlorothiazide:1	
Quinapril/ Hydrochlorothiazide:1	
Lisinopril/ Hydrochlorothiazide:1	
Irbesartan/ Hydrochlorothiazide:1	
Paracetamol with or without Pseudoephedrine or Phenylephrine	6 (6.4)
Intravenous contrasts	3 (3.2%)
Terbinafine	2 (2.1%)
Biologic agents	2 (2.1%)
Adalimumab:1, imatinib:1	
Others (each 1)	16(17.0%)
Allopurinol, Propylthiouracil, Rosuvastatin, Fluconazole, Progesterone, Metamizole, Disulfiram, Doksilamin suksinat, Mebeverine, Methylprednisolone, Betahistine dihydrochloride, Valacyclovir, Insecticide including Hexachlorobenzene, Daunorubicin and Fludarabine, Piracetam, Interferon.	

Table 2. Causative drugs of serious CADR.

Clinical reaction pattern	No.
DRESS syndrome	6 (6.4%)
Lamotrigine (2), carbamazepine (1), phenytoin (1), ceftriaxon (1) and paracetamol with pseudoephedrine (1).	
SJS/TEN overlap	2 (2.1%)
Lamotrigine (1) and amoxicilline (1)	
AGEP	4 (4.3%)
Diclofenac (1), levofloxacin (1), terbinafine (1) and clindamycin (1).	
Total	12 (12.7%)

(42.5%), as well topical steroid and antihistaminic agents were used in the rest of them.

Discussion

In this study, we documented the clinical presentation of CADR and their outcome in hospitalized patients. The causative agents and distribution of the types of the CADR vary from country to country. Although each drug has the potential of producing a CADR, in the literature, the most common culprit drugs have been reported as antimicrobials mainly the aminopenicillins,

sulphonamids, and anticonvulsants. As compatible with the literature, in our study, antimicrobials mainly the penicillins were the most common culprit drug group followed by NSAIDs, anticonvulsants and antihypertensive/diuretic agents, respectively (5,9). Diclofenac was the most frequent NSAID causing a CADR in our study. Different NSAIDs such as mefenamic acid (5), aspirin (9) or ibuprofen (11) have been attributed as the most frequent NSAIDs causing CADR in different populations. This is most probably related to the prescribing habits of different countries. Among antihypertensive agents, diuretics and angiotensin converting enzyme (ACE) inhibitors are implicated as the frequent cause of CADR (8). In our study, ACE inhibitors, angiotensin receptor antagonist and diuretics including furosemide, indapamide and hydrochlorothiazide were the responsible antihypertensive agents.

Maculopapular rash have been reported as the most frequent type of CADR in different percentages ranging from 31 to 94% in most of the previous studies (5,12–14). Our results also revealed maculopapular eruption as the most frequent clinical presentation of CADR in 60% of the patients. Urticaria and fixed drug eruption are another common presentations of CADR besides

maculopapular eruptions in many previous studies (11,12,15,16). Fixed drug reaction and urticaria frequencies were lower among hospitalized patients in our study. Fixed drug reaction usually does not require hospitalization and urticaria/angioedema patients are usually admitted to emergency departments or outpatient clinics. Thus, their hospitalization frequency may be lower than the other clinical type of drug reactions. This may explain the lower frequency of these reactions among the hospitalized patients in our study. Our results revealed that there was no relationship between the drug group and the clinical type of the CADR. Severe CADR including SJS/TEN overlap, AGEP and DRESS were observed in 12% of the patients. Fortunately, none of them died on the follow-up.

Differential diagnosis of drug reactions differs according to the clinical type of the reaction. Diagnosis of a CADR is mainly based on the clinical history of a drug usage and appearance of a rash after the drug intake. Histopathologic features of morbiliform reactions are usually not specific, whereas some of them such as fixed drug reaction, SJS, TEN have specific features (4). In this study, the diagnosis was mainly based on the anamnesis and clinical features. The association of a drug with a rash may easily be established in a patient who had a short latency period as one or two weeks after the drug intake. However, in a patient whose latency period is longer than 30 days, it may not be easy to assign the rash to the suspected drug. In such cases, the follow up period after cessation of the drug and histopathological features helped us to confirm the diagnosis. The diagnosis of a CADR may also be confirmed by skin tests including prick test, intradermal test and patch test. These tests help the physician to detect the causative agent in 72% of the patients. However, skin tests have the potential to induce the CADR again with serious results. Besides this, they are neither sensitive nor specific for the diagnosis of a CADR. Challenging the drug is also risky and therefore in daily routine it is impractical to use it for the confirmation of a drug reaction. (14). Finally, we did not perform any of the skin tests in establishing the diagnosis of a CADR.

Lamotrigine and aromatic anticonvulsants such as phenytoin, phenobarbital and carbamazepine have been frequently attributed to cause CADR (17,18). In this study, carbamazepine was the most causative anticonvulsant. Anticonvulsants have been reported as the culprit drug in 43.8% of life-threatening reactions such as SJS and TEN (6). In our study, although there was no statistical relationship between the causative agent and clinical pattern of the reaction, as compatible with the literature 41.6% of the severe reactions were due to anticonvulsants including lamotrigine, carbamazepine and phenytoin (Table 2). We observed that anticonvulsants had a longer latency period than the other drug groups. The mean latency period of anticonvulsants was 47.5 days in this study. In the literature, this interval has been found as 34.2 days by Teraki et al. (19).

Cutaneous adverse drug reactions are more common in women. Because women have been reported to be prescribed more drugs than men (1,2,12,17). Our result also revealed higher frequency of CADR among women.

Allopurinol has been reported as a frequent culprit drug in most of the studies (20,21). However, in our study, only one patient required hospitalization because of erythroderma due to allopurinol. This may be related to the ethnic variations of different populations. Recently, it has been shown that some drug reactions by some drugs have an association with certain HLA alleles. Pharmacogenomic studies revealed that carbamazepine-induced SJS/TEN is related with HLA-B*1502 in Southeast Asian patients, whereas it is failed to show an association in Caucasian and Japanese patients. As well, allopurinol induced CADR were found to be associated with HLA-B*5801(22). However, we did not study the pharmacogenetics of our study group.

Conclusions

The current study demonstrated that anticonvulsants had a longer latency period than the other groups of drugs. As well, this study supported that drug reactions also showed variation in our population, which may be due to different prescribing habits of Turkish physicians and pharmacogenetic properties of Turkish patients. Furthermore, new drugs are coming into market sometimes causing new types of drug eruptions. Therefore, studies about CADR should go on regarding pharmacogenetics.

Declaration of interest

There is no conflict of interest.

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