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An epidemiological and clinical analysis of cutaneous drug eruption: A cohort of 164 patients

Kutanöz ilaç erüpsiyonunun epidemiyolojik ve klinik analizi: 164 hastadan oluşan kohort çalışması

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Abstract

Aim: Drug reactions are important and frequent complications of medical treatments. In this study we aimed to investigate the patients hospitalized with a diagnosis of cutaneous drug eruptions, implicated drugs, and related skin manifestations considering the literature.

Methods: This retrospective cohort study was performed in Haydarpaşa Numune Training and Research Hospital, Dermatology and Venereology Department. The study comprised 164 patients that were diagnosed with cutaneous drug eruption between January 2010 and December 2016. Some parameters, such as demographic characteristics, type of the reaction, culprit drug groups, multiple drug usage, time between the onset of the drug intake and beginning of the eruption were recorded. Age, gender, symptoms, laboratory tests, diagnosis and treatment information were obtained through patient files. Causal relationship was assessed by Naranjo algorithm. Adverse drug reactions were categorized as definite, probable, possible, and absent. All values were expressed in percentages. The severity of the reaction caused by the drug was assessed with Hartwig's Severity Assessment Scale.

Results: Among 164 patients, there were 104 females and 60 males with a mean age of 46.3 (18.8) years. The most commonly encountered type of drug reactions were urticaria and angioedema (42.1%), followed by morbilliform drug eruption (31.7%). More cutaneous reactions were noted with NSAIDs (18.9%), antibiotics (15.2%) and the combination of NSAIDs and antimicrobial agents (9.8%). Time between the onset of eruption and the intake of the drug varied by hours to months. Some of these patients also described similar reactions related to drugs in the past.

Conclusion: Knowledge of these drug eruptions, the causative drugs and the prognostic factors is important for clinicians. It is recommended to advise patients to carry a list in their wallets indicating their drug allergies and/or intolerances, especially if they had a severe reaction before. We conclude that a careful follow-up should be performed with NSAIDs, antibiotics and anti-epileptics. The combination of drugs, including NSAIDs and antibiotics should be avoided as much as possible.

Keywords: Cutaneous drug eruptions, Reaction patterns, Epidemiological and clinical features, Scales

Öz

Amaç: İlaç reaksiyonları medikal tedavinin önemli ve sık bir komplikasyonudur. Bu çalışmada ki amacımız, kutanöz ilaç reaksiyonu tanısı ile kliniğimizde yatırılan olgularda, sorumlu ilaçlar ve bu ilaçların neden olduğu klinik tablolar literatür bilgileri eşliğinde incelemektir.

Yöntemler: Çalışmaya Ocak 2010-Aralık 2016 tarihleri arasında kutanöz ilaç erüpsiyonu tanısı ile Haydarpaşa Numune Eğitim Araştırma Hastanesi Deri Ve Zührevi Hastalıkları Kliniğinde yatırılarak tedavi edilen 164 olgu alınmıştır. Hastaların yaşı, cinsiyeti, semptomları, laboratuar tetkikleri, tanı ve tedavi bilgileri hasta epikrizlerden incelenerek elde edildi. Demografik özellikler, reaksiyonun tipi, reaksiyona yol açtığı düşünülen ilaç grupları, multipl ilaç kullanımının varlığı, ilaç alımından döküntünün başlangıcına kadar geçen süre gibi parametreler kayıt edildi. Nedensellik ilişkisi Naranjo algoritması ile değerlendirildi. KİE'ler,
kesin, muhtemel, olası ve yok olarak gruplandırıldı. Bütün değerler yüzdelik olarak ifade edilmiştir. İlacın yol açtığı reaksiyonun şiddeti Hartwig's Ciddiyet Değerlendirme Skalası ile değerlendirildi.

Bulgular: Çalışmaya alınan 164 hastanın 104'ü kadın (%63,4) ve 60'ı erkek (%36,6) idi. Hastalarımızın yaşları 4 ile 97 arasında değişmekle birlikte yaş ortalaması 46,3 (18,8) idi. En sık reaksiyon tipi %42,1 oranında saptadığımız ürtiker ve anjiyoödemdi. Bunu sırasıyla, %31.7 olarak saptanan makülopapüler ilaç erüpsiyonu izlemekteydi.kutanöz reaksiyonlara en sık yol açan NSAİİ'ler (%18,9), antibiyotikler (%15,2) ve bunları izleyen NSAII ve antbiyotiklerin kombinasyonu idi (%9,8). İlacın ilk alınmasından döküntünün başlangıcına kadar geçen süre saatler ile aylar arasında değişmekteydi. Bu olguların bir kısmı da öyküde geçmişte ilaçlarla ilişikli benzer reaksiyonlar tanımlamaktadır.

Sonuç: Kutanöz ilaç Erüpsiyonu ve ona neden olan ilaçların ve prognostik faktörlerin bilinmesi klinisyenler için büyük önem arz etmektedir. Bu durumda hasta bilinçlendirilmeli ve uyarıcı olarak yanında daha önce hangi ilaçların reaksiyonlara sebep olduğunu gösteren alerji kartı ya taşınması sağlanmalıdır. NSAİİ'ler, antibiyotikler ve bunları içeren kombine ilaç kullanımından mümkün olduğunca kaçınılması, antibiyotikler ve antiepileptikler konusunda dikkatli bir izlem yapılması, uzun süreden beri kullanılan ilaçların da irdelenmesi gerektiği sonucuna varıldı.

Anahtar kelimeler: Kutanöz ilaç erüpsiyonları, Reaksiyon paternleri, Epidemiyolojik ve klinik özellikler, Ölçekler

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Introduction

Cutaneous drug eruptions (CDE) or cutaneous drug reactions (CDR) are defined as undesirable toxic reactions when drugs are administered at standard doses for the diagnosis, treatment, or prophylaxis of a particular disease [1,2]. The clinical manifestation of CDE varies widely, from a simple asymptomatic skin rash to life-threatening emergencies [3]. Drug reactions are frequently encountered by dermatologists in clinical practice. Most frequent cause of cutaneous drug eruptions are antibiotics, especially penicillins, cephalosporins and nonsteroidal anti-inflammatory drugs (NSAIDs). CDEs are seen in 1-8% of the population and 0.1-16.8 % of the hospitalized patients [4-5].

Materials and methods

This retrospective study was conducted in Haydarpaşa Numune Training and Research Hospital Dermatology and Venereology (DVL) Department located in Istanbul, between January 2010 and December 2016. A total of 2757 inpatient diagnoses were analyzed retrospectively, and 164 patients with definite diagnoses of adverse drug reactions were evaluated. In 73 cases, histopathological examination of the skin was performed. Laboratory findings that may be helpful in the diagnosis such as liver and renal function disorders and presence of eosinophilia were evaluated. Infectious diseases, which are often similar to drug reactions, and other etiological factors had been ruled out in all patients with appropriate laboratory investigation. Patients were categorized according to their age as children and adolescents (0-19 years), adults (20-64 years) and elderly (age 65 and over). The time between the suspected drug intake and adverse cutaneous drug reaction was categorized into three groups, as follows: 0-3 weeks, 3 weeks-3 months and 3 months-1 year. Causative drugs were grouped as antibiotics, NSAIDs, anticonvulsants, antihypertensives, antiepileptics, vitamins, common cold medications, chemotherapeutics, spasmolytics and combined drugs. In patients with combined drug usage, cutaneous drug eruptions were assessed for causality with Naranjo's algorithm.

Naranjo Algorithm is a questionnaire designed by Naranjo et al. [6] for determining the likelihood of whether a cutaneous drug eruption is due to the suspected drug rather than the result of other factors, and probability is divided into four categories: Definite, probable, possible, or unlikely.

The severity and preventability of the reported reactions were assessed with modified Hartwig categorization as mild, moderate, and severe with seven levels of severity [7].

Ethics committee approval

The approval for this study was obtained from the Haydarpaşa Numune Traininig and Research Hospital Ethics Committee of Clinical Studies (decision number: 2017/07). All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committees and 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analysis

The SPSS / Windows (version 21.0) was used to perform descriptive analysis (mean, standard deviation, minimum, median, maximum). For quantitative variables, one sample Kolmogorov-Smirnov test was used to detect normality of distribution. Mann-Whitney *U* test was later used based on the results. Binary outcomes were compared between groups using the Chi-square test for assessing significance. *P*-value <0.05 was considered significant. The analyses were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

Of the 164 patients included in the study, 104 were female (63.4%) and 60 were male (36.6%). The age range of the patients was 4–97 years with a mean age of 46.3 (18.8) years. The most common age peak was the 6th decade, and the data were presented in Figure 1.

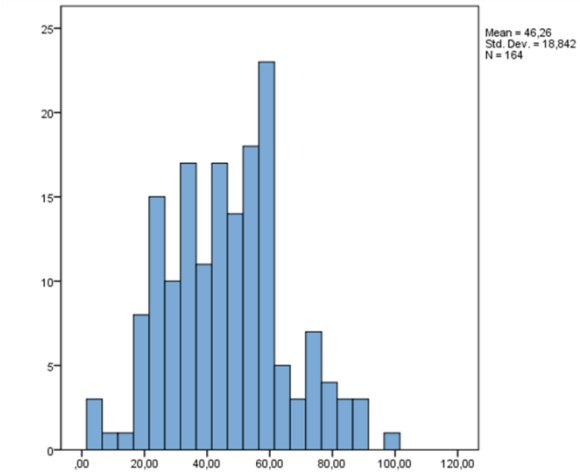

Figure 1: Mean age of inpatients with cutaneous drug eruption

Among all, 87.2% of the patients had drug reactions for the first time, while 12.8% reported a history of a previous adverse drug reaction. A systemic illness was present in 64% of the patients. In terms of patient characteristics, 13 patients (7.9%) had a history of atopy. The most common drug group causing cutaneous drug reactions was NSAIDs (18.9%), followed by antimicrobial drugs (15.2%). Antibiotic+ NSAID combined drug use was the third most common cause for cutaneous drug reactions (9.8%) (Table 1). Cutaneous drug eruption was mostly caused by flurbiprofen (34.5%) and metamizole (20%) from the NSAID group, by cephalosporins (32.8%) and penicillins (29.5%) among antimicrobial agents, and by phenytoin (50%), lamotrigine, and carbamazepine from the anticonvulsant group. Antihypertensive drugs caused CDE in 6 patients. The most common were beta blockers (75%), followed by ACE inhibitors (25%).

The most frequent cause of the use of drugs causing CDE was an upper respiratory tract infection (34.1%). Epilepsy was another common cause (4.3%). The time from drug intake to the development of the reaction was between 1 day and 1 year. More than half (87.4%, n=144) of the cutaneous drug eruptions occurred within hours to days of drug ingestion, 19 (11.6%) occurred between 3 weeks and 3 months, 1 occurred between 3 months-1 year. There was no significant relationship between the duration of drug use and the reaction pattern (Fisher Exact test *P*=0.752).

Table 1: Causative agents for the three most common types of cutaneous drug reactions

Drugs	n	%
NSAIDs	31	18.9
Antibiotics	25	15.2
Antiepileptics	7	4.3
Antispasmolytics	7	4,3
Antihypertensives	6	3.7
Anticonvulsants	6	3.7
Antifungals	6	3.7
Common cold medications	5	3.0
Unknown	5	3.0
Antineoplastics	4	2.4
Antipyretics	4	2.4
Common cold drug+ NSAID	3	1.8
Antibiotic + antipyretic	3	1.8
Antiepileptic + NSAID	3	1.8
Antigout (allopurinol)	3	1.8
Antibiotic + common cold drug	2	1.2
Antibiotics+spasmolytics	2	1.2
Antibiotic + contrast agent	2	1.2
Antidepressants	2	1.2
Antidiabetics	2	1.2
Antimalarials	2	1.2
Antivertigo drug	1	0.6
Antianemic	1	0.6
Antibiotic + antipsychotic	1	0.6
Antibiotic + NSAID + expectorant	1	0.6
Antibiotic+antianemic	1	0.6
Antidepressant	1	0.6
Antipyretic+antidiabetic+antibiotic	1	0.6
Antiepiletic + antipsychotic	1	0.6
Anticonvulsant + antiepileptic	1	0.6
Antihyperlipidemic	1	0.6
Antimycotic + allopurinol	1	0.6
Spasmolytic + antifungal	1	0.6
Spasmolytic+antianemic	1	0.6
NSAID + paracetamol	1	0.6
NSAID + antispasmodic	1	0.6
Paracetamol	1	0.6
Vitamins	1	0.6
Agricultural medicine	1	0.6
Total	164	100.0

One of the commonest manifestations of CDE, urticaria, was found in 69 (42%) patients, morbilliform rash was observed in 46 patients (31.7%), followed by eosinophilia and systemic symptoms (DRESS) in 10 (6.1%) and acute generalized exanthematous pustulosis (AGEP) in 7 (4.3%) (Figures 2, 3) (Table 2).

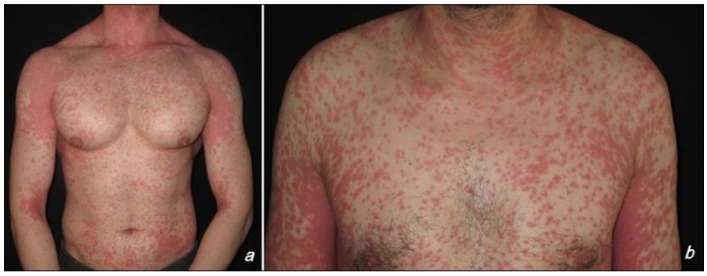

Figure 2: Morbilliform or Maculopapular drug reaction

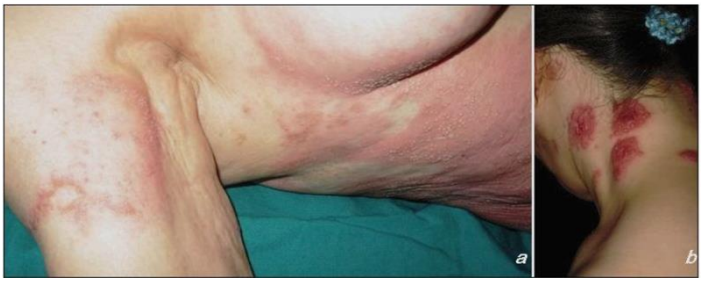

Figure 3: A: Acute Generalized Exanthematous Pustulosis (AGEP) Caused by Oral Retinoids, B: Sweet syndrome

In addition to clinical findings, 73 patients (44.5%) underwent histopathological examination, which revealed superficial perivascular dermatitis in 47 patients (64.4%), degeneration in dermoepidermal junction in 31 patients (42.5%), and dermal eosinophilic infiltration in 30 patients (41.1%). Small vessel vasculitis is found in 12 patients (16.44%) and keratinocyte necrosis was present in 7 patients (9.59%). The first treatment step consisted of cessation of the suspected drugs.

Table 2: Cutaneous manifestation of CDE

Clinical feature	n	%
Urticaria	69	42
Morbilliform rash	52	31.7
DRESS	10	6.1
Fixed drug eruption	7	3
Stevens Johnson Syndrome	5	3
Other patterns	5	3
Sweet Syndrome	4	2.4
Toxic epidermal necrolysis	4	2.4
Erythroderma	1	0.6
Total	164	100

In 90.9% (n=149) of the cases, the disease was controlled with both topical and systemic medical treatments, 7.3% (n=12) were treated with topical agents and 1.8% (n=3) received systemic medical therapy only.

The most used causality assessment modality is Hartwig's Severity Assessment Scale. The severity of cutaneous drug eruption is divided into 7 levels (Levels 1-2: Light, levels 3-4: Medium, levels 5-6-7: Severe). Among all, 78% of the patients were level 4, 15.9% were level 3 and 4.9% were level 5.

According to the Naranjo Algorithm, the drug reactions of 61.6% of patients were possibly related, that of 30.5% were probably related, that of 4.3% were unlikely to be related, and that of 3.7% were definitely related to the suspected drugs.

Discussion

Considering drugs are an essential component of medical therapy, drug-related adverse reactions are important and frequent complications of medical treatment. Cutaneous drug eruptions are seen more commonly in females compared to males [8-10]. In their study of 300 patients with CDE, Jelvehgari et al. [11] reported that the number of female patients were more than that of the male patients (♀ = 152, ♂ = 148). In our study, we also found that the proportion of female patients were greater than men. This may be because women are more likely to use drugs than men. Cutaneous drug reactions can occur at any age. While infants and children are at lower risk, adults and geriatric age groups are at higher risk for adverse drug reactions [12-13]. In our study, the mean age of the inpatients was 46.3 + 18.8 years, and the majority of the patients were 50 years and older. Our findings showed comparable results to other studies on cutaneous drug reactions. Using multiple drugs, especially due to systemic and chronic diseases, cross-reactivity among them, and diseases that lead to an inability to detoxify the toxic drug metabolites can all increase the chance of CDE development [12]. In our study, 64% (n=106) of the patients had at least one systemic disease and multiple drug use. In a 2-year retrospective study, Farshchian et al. [14] found that 20 of the 308 patients (6.5%) had a history of drug reaction which means that careful history taking can prevent recurrence of CDE in these patients. Among our patients, recurrence rate of CDE was 12.8%. These results show that patients do not adequately avoid the previously allergenic or cross-reacting drugs. In this case, the patient should be informed and should carry an allergy card or wristband to warn health care workers about which drugs can cause reactions.

In many studies, most drug reactions are caused by penicillins, cephalosporins, antibiotics, NSAIDs and anticonvulsants [3-15,16]. However, this rank varies according to demographic features like ethnicity and geographical region. For

example, in the study by Akpınar et al. [17] evaluating 106 cases in Turkey, the most frequent causative agents for CDE were antibiotics (40.5%), NSAIDs (31.1%) and antiepileptics. In an epidemiological study that examined 117 cases in a dermatology clinic in Brazil, severe drug reactions developed mostly against anticonvulsants (23.9%), antibiotics (22.1%) and with combination drugs [18].

When we compared the reports of previous studies to our study, NSAIDs (18.9%), antibiotics (15.2%), combined drug use (9.8%), and antiepileptics (4.3%) were the most common culprits of CDEs. This may be since NSAIDs can be obtained from pharmacies easily without prescription.

Cutaneous drug eruptions can present with all kinds of skin manifestations, but the most common types include morbilliform rash, urticaria and/or angioedema, erythroderma, and erythema multiforme [19-20]. However, the frequency of these patterns varies according to the geographical location, ethnic differences and the drugs used. Botelho et al. [16] examined 117 cases of CDE and reported the most common clinical forms as morbilliform rash (37.6%), DRESS (14.5%) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (12.8%). In India, Sasidharanpillai et al. [21] have noted SJS-TEN (5 SJS, 12 TEN) in 43 patients as the most common type of adverse drug reaction followed by morbilliform rash, DRESS, and fixed drug eruption. In these two studies, anticonvulsants were the predominant drugs causing CDE in different patterns. The most common forms of drug eruption in our study were urticaria-angioedema, morbilliform rash and DRESS, which were parallel to other researches from our country. In our study, the most common causes of urticaria were antibiotics and NSAIDs. This result was like the study of Naldi et al. [10] who observed the same reaction patterns in 2224 patients. In this study, which evaluated hospitalized patients only, urticaria was more common than morbilliform rash. This can be explained by the fact that morbilliform drug eruptions are relatively benign and mild forms do not require hospitalization. The interval between the offending drug intake and the eruption ranges from a few minutes to several hours for urticaria, and from a few hours to one week for morbilliform rash, DRESS, SJS and TEN. Akpınar et al. [17] studied the time between drug intake and the initial eruption and found that 84.6% of the cases occurred within the first two weeks and 7.5% of the cases occurred in between 1 to 3 months. In our study, akin to other results in the literature, the time between drug intake and CDE ranged from 0-3 weeks in 87.8% of patients and between 3 weeks-3 months in 11.6% of patients. This result suggests that the medications used in the last three weeks in patients with CDE need to be investigated more thoroughly. In our hospital, the patients included in the study were treated with combined topical and systemic therapy without consideration of the reaction pattern. Systemic treatments administrated most frequently were antihistamines and systemic steroids. In patients with DRESS, 40 patients received systemic corticosteroids, 1 patient received both systemic corticosteroids and IVIG, and 7 patients were treated conservatively.

In our study, we evaluated the causality of CDE in patients with Naranjo criteria, however, due to the inability of rechallenge test in our hospital and retrospective nature of this study, it led us to modify the Naranjo criteria. Similar to the other studies, causality relation was “probable” in 61.6%, “more likely” in 30.5% and “definite” in only a few.

According to Hartwig's scale, 78% of patients had “moderate” (level 4), 15.9% had “mild” (level 3) and 4.9% had “severe” (level 5) CDE.

Limitations

The most notable limitations of this study were its retrospective nature, and that the evaluation of some cases were limited to standard parameters. Incomplete documentation in patient files also resulted in loss of valuable data.

Conclusion

A detailed drug history and chronology of events should be investigated in detail for the patient presenting with CDE. Patients with a history of drug allergy should be informed, and the use of combined medication should be avoided as much as possible in the elderly population. All drugs should be considered potentially hazardous and the risk of drug reactions should be assessed in terms of the expected therapeutic benefit for each patient.

NSAIDs, antibiotics and antiepileptics, the most frequently accused agents, should draw special attention during history taking. Drug allergy history must always be taken from the patient or the patient’s relatives before prescribing. Using criteria that can be modified according to the conditions of our country, such as Naranjo criteria, will be guiding in determining the causality of drugs. Consequently, both the patient and the physician will be more cautious of riskier medications.

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