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Research Paper: Anticonvulsant Drugs and Severe Adverse Cutaneous Drug Reactions: A Longitudinal Observational Study

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ABSTRACT

Background: Severe Adverse Cutaneous Reactions to Drugs (SACRDs) are skin eruptions due to drugs, which can cause morbidity and morbidity in patients.

Objectives: The aim of this study was to determine the offending drug/agents and clinical phenotypes of SACRDs leading to admissions to the hospital.

Materials & Methods: We conducted a retrospective cross-sectional study during one year (March 2012-2013) on patients admitted to the department of Dermatology at Razi Hospital of Rasht, Iran. First, the clinical and drug history of all patients were collected. Then, two dermatologists examined them and diagnosed drug eruptions according to the clinical types of adverse drug reactions included in the study. Collected data were analyzed in SPSS V. 18 software by using Chi-squared test, Fisher's Exact test, and one-way ANOVA. The significance level was set at $p<0.05$.

Results: Forty-six patients were diagnosed with SACRDs. The most common SACRDs were toxic epidermal necrolysis/stevens Johnson syndrome (TEM/SJS) and Drug Reaction with eosinophilia and systemic symptom syndrome (DRESS) syndrome (30.5% and 2.1%, respectively). The most common culprit drugs were anticonvulsants (43.5%) and antibiotics (26.1%). Peripheral blood eosinophilia was observed in 30.4% of patients.

Conclusion: Anticonvulsants were the most common cause of ACDRs, leading to the hospitalization of the patients.

Keywords: Drug eruptions; Anticonvulsants; Skin

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Highlights

- Drug Eruption with Eosinophilia and Systemic Syndromes (DRESS) and Stevens-Johnson/Toxic Epidermal Necrolysis were the most common severe adverse cutaneous drug reactions due to anticonvulsant drugs.

- Carbamazepine, phenytoin, Lamotrigine, Sodium valproate were the most common culprit agents.

Introduction

Adverse drug reaction (ADR) are unwanted and harmful reactions of medicinal product that cause morbidity in patients and account for about 15-20% of their hospital budgets. The incidence of ADRs in developed countries is about 1-3%, and in developing countries, around 2-5% [1, 2]. Fortunately, only 2% of the adverse cutaneous drug reactions (ACDRs) are severe, requiring admission to hospital or prolonged hospitalization. toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome are some of these severe ACDRs. The mortality rate due to drug reactions, including systemic and or cutaneous reactions among patients ranges from 0.1 to 0.3% [3]. Factors such as age, i.e., too old or too young, alcohol consumption, race, pregnancy, breastfeeding, kidney problems, liver function, drug dose, female sex, and multiple drug use can affect in developing ADRs [4]. Immunologic effects (drug allergy) cause 20-25% and non-immunologic effects (drug intolerance) cause 75-80% of ADRs [5].

ACDR may appear in a wide variety of clinical manifestations including itching, maculopapular eruption, hives and angioedema, fixed drug eruption, phototoxic and photoallergic reactions, serum sickness and erythema multiforme (EM), stevens Johnson syndrome (SJS), TEN, DRESS, and acute generalized exanthematous pustulosis (AGEP) [6, 7]. Angioedema, anaphylaxis, SJS, and TEN are severe ACDRs that can be associated with mortality. The mortality rate varies from 5% for AGEP, 10% for DRESS syndrome, and 25% for TEN/SJS [8-10]. The diagnosis of different types of ACDR is based on medical history, physical examination, and pathologic findings [11, 12]. Sometimes it is difficult to distinguish ACDRs from viral exanthema, collagen vascular disease, neoplasia, bacterial infection, psoriasis, and autoimmune blistering disease. It is also difficult to determine a culprit drug which has caused an eruption [13].

ACRDs with acute onset are urticaria, angioedema, EM, SJS, TEN, and hypersensitivity syndrome, while those with chronic onset are pigmentary changes, drug-induced autoimmune bullous diseases, lupus, pseudolymphoma, and acneiform eruptions [14]. Skin is the most common organ in which ADRs occur (9-30%). Given that the genetic context, the method of prescription, and the types of medications affect the occurrence of ADR, in this study, we attempted to investigate the causes of hospitalization in patients with ACDR.

Materials and Methods

This research project was designed as a longitudinal observational study in Razi Hospital, Rasht City, Iran, in one year (March 2012-2013). Of 6758 hospitalized patients, 440 patients were admitted to the Department of Dermatology. Of them, 46 cases were because of ACDR. Having other skin diseases, lesions with diagnostic overlap with other diseases, and having no clear pharmacological history were the exclusion criteria. The collected data were analyzed in SPSS V. 18 by using the Chi-squared test, Fisher's exact test, and one-way ANOVA. All information extracted from the questionnaires was kept confidential.

Results

ACDRs account for 0.68% of admissions to the hospital and 10.5% of hospitalization in the Dermatology Department. Most ACDRs were the side effects of using anticonvulsants (43.5%), antibiotics (26.1%), sedatives (15.2%) and other drugs (allopurinol, methotrexate, dimenhydrinate, carvedilol, losartan, hydrochlorothiazide, and radiocontrast agents). Among anticonvulsants, lamotrigine, phenytoin, and carbamazepine account for 95% of severe ACDRs and sodium valproate for the remaining 5% admitted to the hospital. The majority of patients need to be hospitalized for one to two weeks. Severe ACDRs caused by anticonvulsants was found to be more common in men (52.6%); 64.7% aged less than 30 years and 23.1% over 50 years. Overall, the incidence of ACDRs was higher in women (58.7%).

Table 1. Laboratory test results in patients with ACDRs (n=46)

Laboratory Test	No. (%)
Leukocytosis	7(8.6)
Leukopenia	2(2.5)
High absolute eosinophil	14(17.3)
High SGOT	21(25.4)
High SGPT	20(24.7)
Hematuria	7(8.6)
Leukocyturia	10(12.4)
Total	81(100)

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The Mean±SD time between the use of anticonvulsants and the onset of ACDR was 26.7±21.47 days, and based on the results of one-way ANOVA, there was no statistically significant difference between the types of the drugs. All patients with ACDR following anticonvulsants consumption had adverse noncutaneous effects such as fever, lymphadenopathy, purpura, facial swelling, arthritis, and arthralgia; in 40% of them, mucosal involvement was also observed. Among the admitted patients, 38 had abnormal laboratory results (Table 1).

In this study, anticonvulsants were the most common causes of increased peripheral blood eosinophilia (50%); the most common ACDR leading to peripheral blood eosinophilia was DRESS syndrome, which in 45% of patients, systemic corticosteroid was used for

Table 2. Type of ACDRs observed in patients (n=46)

ACDR	Type of Drug				Total
	No. (%)				
	Antibiotics	Sedatives	Anticonvulsants	Others	
Urticarial and angioedema	0(0)	0(0)	1(5)	0(0)	1(2.2)
Exanthematous eruption	2(16.7)	0(0)	2(10)	1(14.3)	5(10.9)
SJS/TEN	4(33.3)	2(28.6)	6(30)	2(28.6)	15(30.5)
DRESS	2(16.7)	1(14.3)	9(45)	0(0)	12(26.1)
AGEP	3(25)	1(14.3)	0(0)	0(0)	4(8.7)
Erythroderma	0(0)	0(0)	1(5)	1(14.3)	2(4.3)
Generalized fixed drug eruption	1(8.3)	1(14.3)	0(0)	1(14.3)	3(6.5)
Lichenoid eruption	0(0)	2(28.6)	0(0)	1(14.3)	3(6.5)
Photoallergic dermatitis	0(0)	0(0)	1(5)	1(14.3)	2(4.3)
Total	12(100)	7(100)	20(100)	7(100)	46(100)

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SJS: Stevens-Johnson syndrome; TEN: Toxic epidermal necrolysis; DRESS: Drug reaction with eosinophilia and systemic symptoms; AGEP: Acute generalized exanthematous pustulosis

its treatment. According to the results shown in Table 2, the most common clinical manifestations of ACDRs in patients were SJS/TEN, DRESS, exanthem eruption, AGEP, lichenoid eruption, and fixed drug eruption, in this order. According to Fisher's exact test results, there was a significant relationship between the type of ACDR and the type of used drug (P=0.036). In this regard, SJS/TEN and DRESS syndrome were highly associated with the use of anticonvulsants; while AGEP had more association with the use of antibiotics, and lichenoid eruption highly associated with sedatives consumption (Table 2). The tissue eosinophil infiltration was observed on 13% of skin biopsies of the patients.

Discussion

Drug reaction manifests in a spectrum from simple rashes to the involvement of internal organs [15]. In this study, the samples had severe ACDRs that required hospitalization. The anticonvulsant drugs were the most common cause of severe ACDRs in our samples. In other studies, it was also reported that anticonvulsants are the most common cause of ACDRs associated with life-threatening hepatic and renal failures [16]. In most studies, ACDR prevalence has been reported higher in women, but severe type of ACDR caused by anticonvulsants is more common in men [17]. Consistent with these reports, our results also showed that severe ACDR caused by anticonvulsants was higher in men, while those induced by antibiotics and sedatives were common in women.

Among hospitalized patients in our study, the most common ACDRs were SJS/TEN and DRESS mostly followed by using anticonvulsants. Some studies have indicated the role of the genetic factors, especially the change in the HLA-B genes, in the incidence of severe ACDRs in patients treated with some anticonvulsants, including phenytoin and lamotrigine, although the non-genetic factors such as the concurrent use of anticonvulsants with omeprazole are also considered as an effective factor [18, 19]. Eighty percent of the patients with severe ACDR followed by anticonvulsants stayed in the hospital more than a week, while in 58.3% of patients with ACDR caused by antibiotics, the duration of hospitalization was less than one week. About one-third of the patients had mucosal involvement; the most common drug with mucosal side effects were anticonvulsants (43.5%) and antibiotics (26.1%), although there was no relationship between the type of drug and mucosal side effects.

Mucosal complications due to nutritional problems cause the patient to feel uncomfortable. Despite the high prevalence of mucosal complications in patients undergoing chemotherapy, in one study, mucosal complications were not reported in any patient which indicate the preventability of many side effects with proper preventive cares [19].

Most patients had also adverse noncutaneous drug reactions, the most important of which were fever and facial swelling. Laboratory disorders such as leukocytosis, high absolute eosinophil, high levels of liver enzymes, and urinary problems were also observed in more than 80% of hospitalized patients. Among these, liver disturbance was the most common lab disorder followed by peripheral blood eosinophilia. The latter was detected in one third of patients particularly in DRESS syndrome. Anticonvulsants were the most common offending drugs in patients with peripheral eosinophilia.

There are various reports of DRESS syndrome incidence following the use of anticonvulsants and psychotropic drugs such as lithium [15, 20-22]. The manifestation of this syndrome starts two to six weeks after drug initiation for the first time and in a shorter time with re-exposure. Fever and rash are the most common manifestations of this syndrome. In most patients, these eruptions are initially morbilliform and gradually become vesicular or pustular eruptions. Edema of the face is the hallmark of this drug reaction, but it is not observed in all patients. Lymphadenopathy and liver involvement are the most common noncutaneous manifestations of this syndrome. Other organs like lung, joints, heart, kidney, and brain can also be involved. Involvement of thyroid and heart can delay DRESS syndrome even after drug withdrawal. The most common causes of DRESS syndrome are aromatic anticonvulsants (carbamazepine, phenytoin, and phenobarbital), sulfonamides, and allopurinol. Sodium valproate with lamotrigine also increases the risk of this complication [1, 15]. Withdrawal of the causative drug and corticosteroid therapy are novel treatments; in case of resistance to corticosteroid, cyclophosphamide, cyclosporine, and intravenous immunoglobulin (IVIg) are recommended [15, 23].

Conclusion

Anticonvulsants were the most common cause of ACDRs, leading to the hospitalization of the patients.The most common SACRDs were toxic epidermal necrolysis/stevens Johnson syndrome (TEM/SJS) and drug reaction with eosinophilia and systemic symptom syndrome (DRESS) syndrome.

Epidemiological studies of severe ACDRs are still in the early stages. It is difficult to determine the incidence rate of drug reactions accurately. Due to the greater frequency of severe ACDRs following the use of aromatic anticonvulsants, the use of this drug group should be prescribed with caution, and skin rashes in the first weeks of treatment should be taken into account by doctors as an important factor. This research can pave the way for new decisions by neurologists to use drugs with fewer side effects.

Ethical Considerations

Compliance with ethical guidelines

All the study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013.

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The study protocol is based on the thesis of Hosein Abdi with registration No. 727, Department of Dermatology, School of Medicine, Guilan University of Medical Sciences.

Authors contributions

Writing the draft: Maryam Hosseini & Shirin Zaresharifi; Writing-reviewing, & editing the draft: All authors; Study design and data collection: Narges Alizadeh, Abbas Darjani & Hossein Abdi

Conflict of interest

The authors declared no conflict of interest.

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