

Patterns of Antiepileptic Drug Reactions in Children: A Multicenter Study

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Abstract

Objectives

Antiepileptic drugs are among the most common triggers of cutaneous adverse reactions. About 5–17% of epileptic patients develop idiosyncratic skin reactions at some point during their treatment course, most of which occur within the first two months of drug initiation. This study aimed to investigate the pattern of cutaneous drug reactions associated with anticonvulsant use among the pediatric population in Iran to identify high-risk individuals.

Materials & Methods

In this retrospective descriptive study, medical records of children aged two months to 14 years, who were diagnosed with drug reactions due to anticonvulsant drugs between April 2007 and March 2018, were reviewed, and relevant information were extracted. This multicenter study was conducted in several provinces of Iran.

Results

A total of 186 cases with a final diagnosis of the antiepileptic drug-induced eruption were evaluated. The median age of participants was 36 months (range: 2-168), and 56% were male. In approximately 70% of the children, phenobarbital was the culprit. The median time interval between initiation of the causative drug and development of rash and fever was 10 and 7 days, respectively. The most common rash type was maculopapular rash (69%). Overall, 33% of the patients only received antihistamines after discontinuation of the causative drug.

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Conclusion

Similar to previously published studies in Iran, phenobarbital was the main cause of cutaneous drug reactions to antiepileptic drugs, indicating the necessity of paying more attention when prescribing phenobarbital for Iranian pediatrics.

Keywords: Fever; Anticonvulsants; Drug eruptions.

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Introduction

Epilepsy is a multifactorial chronic neurological disease that nearly 65 million people suffer from it globally, of whom 20% are children (1). It entails many seizure types and syndromes with different prognoses and responses to available treatment. The majority of patients under treatment with antiepileptic drugs (AEDs) show a desirable outcome in terms of seizure control; however, this success is not without adverse events. Drug side effects play an important role in patients' compliance with anticonvulsants and are responsible for early treatment discontinuation in about 25% of patients (2). They also affect the choice of therapy and are a major concern in achieving the optimal dose for a better clinical response. The complications associated with AEDs vary widely from CNS and skin involvement to hepatotoxic and hematologic events (3). Anticonvulsants, along with antibiotics, are among the most common causes of cutaneous adverse drug reactions (4). About 5–17% of epileptic patients develop idiosyncratic skin reactions at some point in their treatment course; however, it is assumed that they mostly occur in the first 2 months of drug initiation (3, 5). Cutaneous adverse events may manifest as mild maculopapular exanthema (MPE) or morbilliform rash, which often resolve spontaneously after drug discontinuation, or serious life-threatening events, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug hypersensitivity syndrome (HSS), which are associated with relatively high morbidity and mortality rate (6). Hypersensitivity syndrome is a rare, potentially fatal disorder defined as the presence of fever, skin eruptions, and lymphadenopathy. The term DRESS (drug rash with eosinophilia and systemic symptoms) is used to describe when HSS is also associated with systemic symptoms, such as abnormal liver function tests and eosinophilia (7).

Aromatic anticonvulsants, such as phenytoin, phenobarbital, and carbamazepine, have so far been suggested as the most frequent drugs involved in cutaneous adverse reactions (8). Risk factors that are assumed to increase the risk of developing cutaneous adverse reactions include high starting dose, rapid dose titration, and also host-related factors such as patients' age, and immunologic, and genetic vulnerability (9).

In this multicenter study, we aimed to investigate the pattern of cutaneous side effects, clinical manifestations, and laboratory findings associated with anticonvulsant use to identify high-risk individuals as well as to prevent the undesired consequences. This study also intended to identify the most common anticonvulsant drugs that account for cutaneous adverse reactions among Iranian pediatric patients.

Materials & Methods

In this retrospective descriptive study, medical records of children aged two months to 14 years, who were diagnosed with drug reactions due to anticonvulsant drugs between April 2007 and March 2018, were reviewed. This study was conducted in university-affiliated hospitals in several provinces of Iran, including Tehran (Children's Medical Center), Hamadan (Besat Hospital), Shiraz (Namazi Hospital), Rasht (17 Shahrivar Hospital), Zanjan (Ayatollah Mousavi Hospital), and Kerman (Afzalipour Hospital). All included cases were treated as inpatients. The electronic Health Information System (HIS) of the mentioned hospitals was searched using the International Classification of Disease (ICD) codes for the following keywords: drug reaction, rash, reaction to phenobarbital, reaction to phenytoin, reaction to carbamazepine, reaction to sodium

valproate, and reaction to primidone. Then, medical records with a final and confirmed diagnosis of drug reaction due to anticonvulsant drugs were investigated by researchers, and relevant data were extracted and recorded, including demographic characteristics, causative drug, treatment, the time interval between initiation of the causative drug, and hypersensitivity symptoms like fever and rash, maximum temperature and duration of fever, types, and patterns of rash, clinical manifestations, and laboratory findings. Patients with a documented history of chronic liver disease, cancer, chronic renal failure, patients under treatment with immunosuppressive drugs, and patients with autoimmune disorders were excluded from the study.

The continuous variables were presented as mean and standard deviation, and the categorical variables as frequency and percentage. The chi-square test was used to compare each complication between gender and age groups. In addition, the Kruskal-Wallis rank test was used to compare complications between the used drugs. Data analysis was administered using SPSS version 14.2 with a statistical significance of 0.05.

The study was approved by ethics committee of Hamadan University of Medical Sciences. (Ethical approval code: IR.UMSHA.REC.1397.459)

Results

A total of 186 cases with a final diagnosis of AED-induced drug eruption were evaluated in this study. Of the total cases, 42, 42, 41, 31, 22, and 8 patients were from Hamadan, Rasht, Tehran, Zanjan, Shiraz, and Kerman, respectively. The median age of the included patients was 36 months (range 2-168), and 104 (55.9%) cases were male. For 130 (69.9%)

patients, phenobarbital was the culprit, followed by carbamazepine (n=25), sodium valproate (n=25), lamotrigine (n=9), phenytoin (n=4), primidone (n=4), and other anticonvulsant drugs (topiramate, clobazam, diazepam, and clonazepam) (10 cases), in descending order (Fig 1). Approximately 83% of the ADRs were caused by aromatic AEDs (phenobarbital, phenytoin, carbamazepine, and primidone). The median time interval between initiation of the causative drug and development of rash was 10 days (range 1-365), and the median time interval between initiation of the causative drug and development of fever was 7 days (range 1-365). The median temperature (equal to oral temperature) of febrile patients was 39 °C (range 37.5-41). On average, the duration of fever was 2 days, with a range of 1-37 days.

The most common rash type was maculopapular rashes (68.8%), mostly observed in children under five years of age (p= 0.001). Of 13 patients who developed macular rashes, 11 (84.6%) were male (p= 0.03). In most of the patients, rashes were spread over the body, extremities, and the face (74.4%, 66.3%, and 60.2%, respectively). The majority of patients with rashes on their palms were less than 10 years old (92.9%) (p= 0.04). Pruritus was a common manifestation that was observed in 66 (35.5%) patients, whereas other symptoms, such as abdominal pain, nausea, vomiting, diarrhea, red eyes, adenopathy, hepatomegaly, mucosal involvement, and finger peeling, each occurred in less than 10% of patients. Interestingly, no patient developed splenomegaly (Table 1).

The values for laboratory tests are presented in Table 2; as shown, the mean levels of alanine

transaminase (ALT) and aspartate aminotransferase (AST) were 72 U/l and 80 U/l, respectively. The mean erythrocyte sedimentation rate (ESR) was 20.14 mm/h, and the mean C-reactive protein (CRP) was 28.09 mg/l (Normal ESR<30 mm/h, Normal CRP<3 mg/dl).

Of 11 patients with red eyes, there was a difference between males and females (3 vs. 8, p= 0.05). Also, adenopathy was more common among males (p= 0.05), while mucosal involvement developed more frequently in females (p= 0.01). There was a significant difference between the three age groups (i.e., under 5 years, 5-10 years, and above 10 years) with respect to itching and finger peeling (p< 0.001 and p= 0.01, respectively).

The distribution of clinical characteristics and lab values between various drugs are demonstrated in Table 3. AST>100 was found in 21/156 cases, while ALT>100 occurred in 26/156 cases; these adverse effects were both statistically significant between drugs (p< 0.001). Adenopathy was more commonly observed as the adverse effect of lamotrigine and phenobarbital, as approximately 11% and 8% of the cases developed adenopathy, respectively. This adverse effect also was statistically significant between drugs (p= 0.004). The highest percentage of leukopenia (WBC< 3500) occurred with phenytoin use (75%), as a significant between-drug variability was also observed in respect to leukopenia (p< 0.001). Of all patients, 117 (62.9%) cases received medications for their hypersensitivity symptoms after the offending drug had been ceased, with the majority (32.5%) receiving antihistamines alone (Fig 2).

Table 1. Clinical manifestations of patients based on gender

Clinical sign		Male N (%)	Female N (%)	Total N (%)	p-value
Rash type	Macule	11 (84.62%)	2 (15.38%)	13 (8.44%)	0.031
	Papule	7 (70.00%)	3 (30.00%)	10 (6.49%)	0.356
	Maculopapule	60 (56.60%)	46 (43.40%)	106 (68.83%)	0.827
	Vesicle	4 (100.00%)	0 (0.00%)	4 (2.60%)	0.073
	Erythroderma	5 (35.71%)	9 (64.29%)	14 (9.09%)	0.113
	Other types of rash	2 (28.57%)	5 (71.43%)	7 (4.55%)	0.137
Rash location	Face	60 (53.57%)	52 (46.43%)	112 (60.22%)	0.429
	Body	74 (53.24%)	65 (46.76%)	139 (74.73%)	0.206
	Extremities	65 (53.28%)	57 (46.72%)	122 (66.3%)	0.409
	Palm	8 (57.14%)	6 (42.86%)	14 (7.53%)	0.923
	Sole	10 (66.67%)	5 (33.33%)	15 (8.06%)	0.382
Other manifestations	Jaundice	2 (40.00%)	3 (60.00%)	5 (2.69%)	0.467
	Abdominal pain	5 (62.50%)	3 (37.50%)	8 (4.30%)	0.701
	Diarrhea	4 (80.00%)	1 (20.00%)	5 (2.69%)	0.271
	Nausea	8 (66.67%)	4 (33.33%)	12 (6.45%)	0.438
	Vomit	6 (54.55%)	5 (45.45%)	11 (5.91%)	0.925
	Itching	31 (46.97%)	35 (53.03%)	66 (35.48%)	0.068
	Red Eye	3 (27.27%)	8 (72.73%)	11 (5.91%)	0.049
	Finger Peeling	1 (25.00%)	3 (75.00%)	4 (2.15%)	0.208
	Mucosal involvement	2 (18.18%)	9 (81.82%)	11 (5.91%)	0.009
	Adenopathy	10 (83.33%)	2 (16.67%)	12 (6.45%)	0.048
	Hepatomegaly	1 (20.00%)	4 (80.00%)	5 (2.69%)	0.101

Table 2. Laboratory findings of patients

Variable	Objects	Mean	Standard Deviation
WBC (/ μL)	174	6367.90	4978.14
PMN (/ μL)	135	40.46	24.90
Lymphocyte (/ μL)	135	35.44	22.26
Eosinophil (/ μL)	111	2.63	5.43
Monocyte (/ μL)	100	1.92	1.93
Platelet (/ μL)	168	228266.50	141690.30
HB (g/dl)	170	11.23	1.66
ALT (U/L)	143	80.16	215.85

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Variable	Objects	Mean	Standard Deviation
AST (U/L)	144	72.15	126.03
ALKPH (U/L)	130	491.54	321.79
Bili T (mg/dl)	72	0.59	1.47
Bili D (mg/dl)	72	0.11	0.26
ESR (mm/h)	153	20.14	15.81
CRP (mg/l)	27	28.09	25.19

WBC: white blood cells, PMN: polymorphonuclear leukocyte, HB: hemoglobin, ALT: alanine transaminase, AST: aspartate aminotransferase, ALKPH: alkaline phosphatase, Bili T: total bilirubin, Bili D: direct bilirubin, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

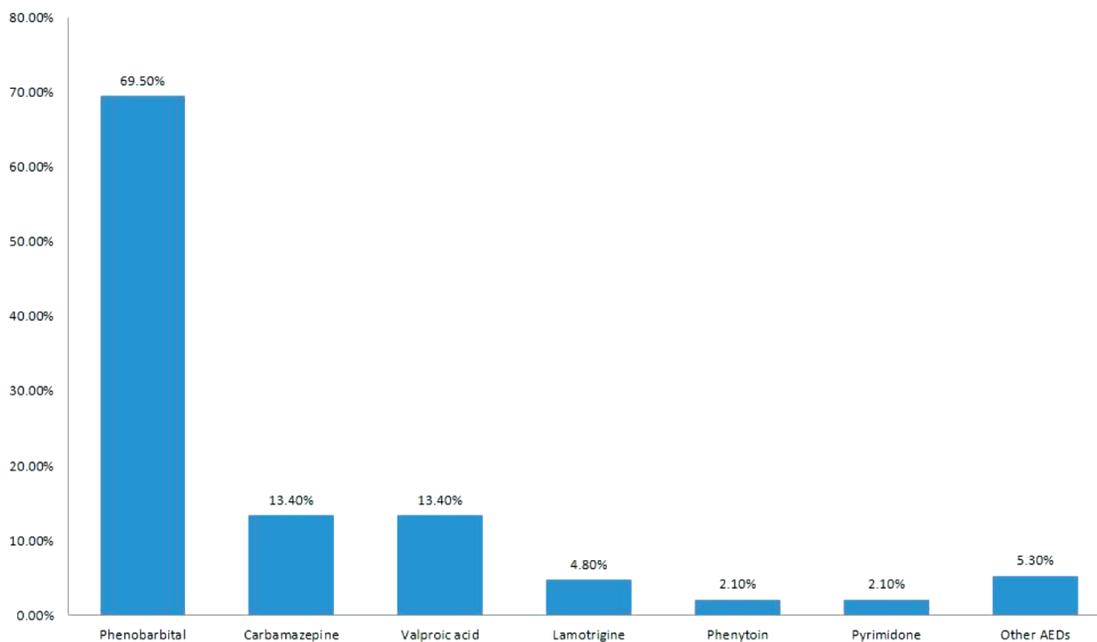


Figure 1. Frequency of patients treated with specific antiepileptic drugs (Note: Some patients had received more than one drug)

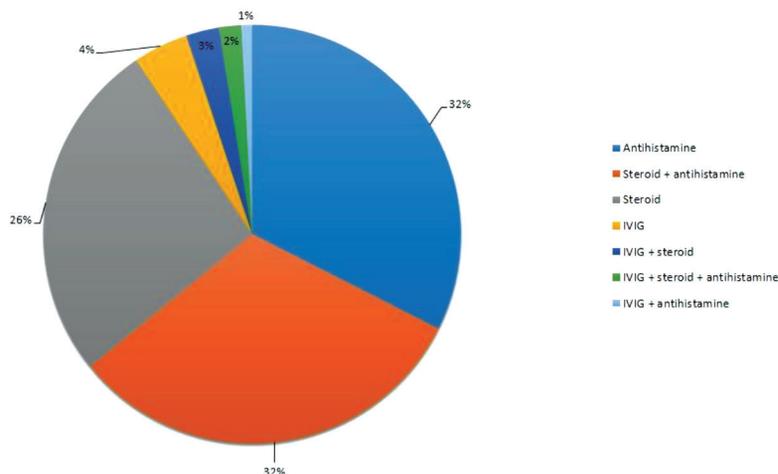


Figure 2. Medications prescribed for AED-induced drug eruption, IVIG: Intravenous immunoglobulin

Table 3. Adverse drug reactions based on the anticonvulsant prescribed for patients

Complication	Phenobarbital N (%)	Phenytoin N (%)	Carbamazepine N (%)	Valproate Na N (%)	Lamotrigine N (%)	Primidone N (%)	Other drugs N (%)	p-value
Macular rash	8 (6.15%)	-	2 (8.00%)	1 (4.00%)	-	1 (33.33%)	1 (10.00%)	0.017
Papular rash	6 (4.62%)	-	2 (8.00%)	2 (8.00%)	1 (11.11%)	-	1 (10.00%)	0.027
Maculopapular rash	78 (60.00%)	1 (25.00%)	14 (56.00%)	13 (52.00%)	6 (66.67%)	2 (66.67%)	6 (60.00%)	<0.001
Vesicular rash	3 (2.31%)	-	1 (25.00%)	-	-	-	-	0.083
Erythroderma	10 (7.69%)	-	2 (8.00%)	3 (12.00%)	1 (11.11%)	-	-	0.002
Other types of rash	3 (2.31%)	-	2 (8.00%)	1 (4.00%)	-	-	-	0.082
Itching	43 (33.08%)	1 (25.00%)	12 (48.00%)	13 (52.00%)	-	2 (66.67%)	3 (30.00%)	<0.001
Mucosal involvement	8 (6.15%)	-	-	3 (12.00%)	1 (11.11%)	1 (33.33%)	-	0.007
Adenopathy	10 (7.69%)	-	1 (4.00%)	-	1 (11.11%)	-	-	0.004
Hepatomegaly	4 (3.08%)	-	1 (4.00%)	1 (4.00%)	-	-	1 (10.00%)	0.112
WBC (/ μ L) <3500	24 (18.46%)	3 (75.00%)	7 (28.00%)	8 (32.00%)	3 (33.33%)	1 (25.00%)	6 (60.00%)	<0.001
Platelet (/ μ L) <150000	23 (17.69%)	2 (50.00%)	2 (50.00%)	9 (36.00%)	-	-	6 (60.00%)	<0.001
PLT(/ μ L) >450000	6 (4.62%)	-	-	-	-	-	-	-
AST (U/L) >100	11 (11.00%)	-	5 (25.00%)	2 (11.76%)	2 (25.00%)	1 (25.00%)	-	<0.001
ALT (U/L)>100	15 (15.00%)	-	4 (20.00%)	3 (17.65%)	2 (25.00%)	1 (25.00%)	1 (16.67%)	<0.001
ESR (mm/h) >40	8 (7.62%)	-	2 (9.09%)	1 (4.00%)	1 (12.50%)	-	3 (37.50%)	0.007

WBC: white blood cells, AST: aspartate aminotransferase, ALT: alanine transaminase, ALKP: alkaline phosphatase, ESR: erythrocyte sedimentation rate

Discussion

A total of 186 inpatients with a final diagnosis of AED-induced drug eruption from six provinces of Iran were evaluated in this multicenter study. The obtained findings are consistent with previous studies, which indicated that approximately 83% of the ADRs were caused by aromatic AEDs (10-13). Among aromatic AEDs, phenobarbital was the most common culprit. Although carbamazepine and lamotrigine are known as the most prevalent drugs for adverse skin reactions according to several studies, a previously published study in Iran reported phenobarbital as the leading cause of skin reactions (11, 14-16). The consistency of the findings of two studies conducted in Iran can be due to evaluating a younger age group because a higher percentage of phenobarbital prescriptions for controlling different types of seizures is observed among this age group.

In our study, the median age of evaluated patients was 36 months, and about 56% of them were male. In 2018, a prospective observational study on adverse drug reactions to AEDs was performed in the UK on children under 18 years old with a median age of 11.2 years, in which 56 cases developed drug reactions (14). Another study in Turkey evaluated 570 children under 18 years old (61.3% male), with a median age of 7.3 years, of whom 31 cases were considered AED reactions (11). Karimzadeh et al. conducted a descriptive study on antiepileptic drug-related adverse reactions in Tehran, Iran. The study, which evaluated 70 inpatients under 14 years old, reported that 63% of the patients were male, and children under five years old had the highest percentage of reactions (16). This study is consistent with our study in terms of patients' age. This can be explained by the fact that both studies evaluated inpatients younger than 14 years

old, which have a higher need for hospitalization. In contrast, other studies evaluated outpatients younger than 18 years old. Also, it can be due to environmental factors or genetic features of the Iranians.

The median time interval between initiation of the causative drug and development of rash and fever was 10 and 7 days, respectively. Regarding these results, drug reactions should be considered in children with fever without focus, especially those under two years of age. In addition, a precise drug history is essential because fever usually presents sooner than skin eruptions (17). Karimzadeh et al. reported that for 84.2% of cases, the symptoms developed within the first week of drug initiation (16). According to another study in Iran, which investigated cutaneous reactions of AEDs in adults, the median time interval between drug initiation and the appearance of rashes was 74 days, and most of the cases (48%) developed reactions between two weeks to one month after drug initiation (10). In comparison, we can conclude that hypersensitivity manifestations appear sooner in children than in adults.

In this study, the most common rash type was maculopapular rashes (68.8%), which is consistent with similar studies (10, 16, 18, 19). Our study showed that the rashes were distributed all over the body in about 75% of patients. Also, Guvenir et al. reported that all patients with AED hypersensitivity presented with maculopapular rashes, of which 64.5% were generalized (11)]. In our study, mucosal involvement occurred in less than 10% of patients. In comparison, according to Guvenir et al., 16.1% of patients developed mucosal involvement (11)]. Pruritus, as a common manifestation, was observed in 35.5% of patients. In a previous study in Iran, pruritus was found in 60.9% of the patients,

although both children and adults were enrolled (13). Thus, it can be speculated that pruritus is more common among adults.

Elevated liver transaminase was present in more than 10% of cases, mainly as the result of lamotrigine, primidone, and carbamazepine use. This laboratory finding has also been reported by other studies (10, 13). There was no evidence of splenomegaly among children with drug-induced fever and rash, even in cases with leukopenia. Hence, if the child presents with splenomegaly, clinicians should initially rule out more probable differential diagnoses such as viral infections and malignancies. In patients with fever, maculopapular rash, redness of oral mucosa, and adenopathy, Kawasaki disease should be carefully differentiated from a drug eruption due to the overlap of symptoms. In our study, the mean ESR and CRP level was 20.14 mm/h and 28.09 mg/l, respectively, while in Kawasaki disease, ESR is consistently greater than 40 mm/h and CRP is greater than 30 mg/l; so, these factors should be assessed for a definite diagnosis of such patients (20).

It is necessary to mention some limitations and biases of our study. For example, some information were missed in patients' medical records due to the retrospective design of the study. Information regarding a definite diagnosis of DRESS, SJS, and TEN were incomplete in medical records and, therefore, could not be evaluated. Also, this study evaluated inpatients in a tertiary medical center; hence, the results cannot be generalized to outpatients. Further studies should be conducted in an outpatient setting.

In Conclusion

This study, which was conducted on children younger than 14 years old, showed that the most

common culprit for cutaneous drug reactions to antiepileptic drugs was phenobarbital. Considering the high percentage of adverse skin reactions associated with phenobarbital in the Iranian population, pediatricians should prescribe this drug with more caution and possibly substitute it with another anticonvulsant. Splenomegaly was not evident in any of the cases, suggesting that in children under treatment with AEDs, who manifest with skin rashes and splenomegaly, differential diagnoses other than adverse drug reactions should be considered. Moreover, the results of our study indicated that ESR and CRP can be used as discriminative biomarkers for differentiating between Kawasaki disease and AED-induced drug eruption in patients presenting with Kawasaki-like symptoms.

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The study was approved by ethics committee of Hamadan University of Medical Sciences. (Ethical approval code: IR.UMSHA.REC.1397.459)

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Conflict of interest

None

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