Chronic Diseases Journal

DOI: 10.22122/cdj.v7i4.412 Published by Vesnu Publications

Cutaneous reactions to carbamazepine in children with epilepsy

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Original Article

Abstract

BACKGROUND: The main components in controlling and treating seizures are antiepileptic drugs (AEDs). Mostly, the systemic side effects of these drugs are regarded very important; however, these drugs can also cause serious mucocutaneous side effects. Carbamazepine is a drug which is used to treat epilepsy. Side effects of this drug can range from skin rash to toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS). The purpose of this study was to evaluate skin complications of carbamazepine in children with epilepsy.

METHODS: This study was performed on 99 children, aged 2 months to 11 years, with the diagnosis of skin complications after taking carbamazepine. Records were examined and their initial profiles including their medical skin conditions and rashes were recorded within the checklist. Data were entered into SPSS software. Measures of central tendency and dispersion were achieved. Finally, the relationship between the drug and the cutaneous reactions of these patients was analyzed using the chi-square test.

RESULTS: The most common complications among the patients were maculopapular lesions and skin erythroderma, with the prevalence of 37.4% for each. Other types of skin lesions included papules with 14.1%, macules with 8.1%, and SJS with 3.0%. A significant association (P = 0.02) between the types of the skin lesion and the dose of carbamazepine was observed; the more the dosage was, the more severe skin lesions were.

CONCLUSION: The most common cutaneous reactions to carbamazepine were erythroderma and maculopapular rash in the patients. The findings of this study also revealed that the lack of drug compliance was of high importance.

KEYWORDS: Carbamazepine, Epilepsy, Cutaneous Adverse Drug Reactions, Antiepileptic Drugs

Date of submission: 15 Sep. 2018, **Date of acceptance:** 12 Dec. 2018

Citation: Zamiri A, Amoiyan S, Mostafavi-Toroghi S, Babaei-Hatkehlouei M, Moaddabi A, Ebrahimzadeh-Hassanabadi M, et al. **Cutaneous reactions to carbamazepine in children with epilepsy.** Chron Dis J 2019; 7(4): 240-5.

Introduction

Anticonvulsants play the main role in controlling and curing seizures. The prevalence of seizures in Iran is about 1% and various anticonvulsants are used in this country. Mostly, the systemic side effects of these medications are considered, e.g., hepatitis and kidney failure; however, they can cause mucocutaneous lesions leading to discontinuance or replacement of the medicine. Some of the most prevalent cutaneous side effects are: exanthema, hypersensitivity syndrome, lymphoma-like symptoms, erythema multiforme (EM), erythroderma, toxic epidermal necrolysis (TEN), drug-induced lupus erythematosus (DILE), Stevens-Johnson syndrome (SJS), acneiform eruptions, vasculitis, gingival hyperplasia, hypertrichosis, hair loss, and hair

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color changes.[1] Among the anticonvulsants, aromatic compounds such as phenytoin, phenobarbital, and carbamazepine are more likely to cause skin lesions which sometimes may require hospitalization. The pathogenesis of these skin problems looks multifactorial.[2,3]

The side effects of anticonvulsants are the major cause of morbidity and sometimes mortality during the treatment of epilepsy in patients, which would probably affect their quality of life and burden of disease. The exact incidence rate of adverse reactions to these drugs is not available due to the outpatient treatment for both epilepsy and the adverse drug reactions (ADRs) in majority of the cases. Most of these side effects are mild and will not get the patients hospitalized. In outpatient treatment, the side effects are not properly reported or recorded; therefore, it is difficult to estimate the incidence rate of these complications.

Carbamazepine is a common drug used for treating epilepsy. The skin reactions range from maculopapular eruptions to SJS and TEN.[1] The drug-induced skin eruptions are distinguished from the non-drug-related cases, based on the patient's history, the clinical examination, and the features of the eruptions. The purpose of this study was to evaluate the cutaneous reactions to carbamazepine in epileptic patients who were treated with this medicine and were recorded in Taleghani Hospital of Gorgan, Iran, in 2012.

Materials and Methods

This cross-sectional study was carried out on the children who were treated with carbamazepine as a medication for epilepsy and were hospitalized by virtue of skin lesions and had hospital records. The sample size was determined 99 cases, based on 80% power and 95% level of confidence considering the missing information in the records. Data in the records were extracted based on a checklist that included skin problems caused by taking medications, drug-induced rashes, basic information of the patients, etc. The data were encoded and entered into SPSS software (version 18, SPSS Inc., Chicago, IL, USA). Measures of central tendency and variability and the relationship between cutaneous side effects of the drug and demographic characteristics of these patients were analyzed using the chi-square test.

Results

During the year 2012, 123 cases were hospitalized in Taleghani Hospital due to cutaneous lesions which were appeared while taking carbamazepine. Of all these patients, 20 were excluded: 5 for lacking proper medication compliance and failure to comply with the right drug consumption as written in their prescriptions, 3 for incomplete hospital records, and 12 for consulting with other health services, e.g., allergy and infection units and accordingly for the probability of being diagnosed with a medical complication other than carbamazepine-induced cutaneous reactions. Finally in this study, of the remaining 103 patients, 99 children aged from 2 months to 11 years were randomly chosen and examined. They were admitted to Taleghani University Hospital of Gorgan and were diagnosed with carbamazepine-induced cutaneous lesions. In terms of age frequency, the average age of the hospitalized patients that participated in this study was 44.49 months and the standard deviation (SD) was 33.22. The minimum age among the patients was 2 months and the maximum was 11 years. 25% were less than 16 months, 25% were 16 to 37 months, and the other 50% were aged between 37 and 67 months.

According to figure 1, while assessing the types of skin reactions caused by carbamazepine in patients, we observed that the most prevalent reactions were erythroderma and mucopapular eruptions with the portion of 37.4% for each. SJS was the most infrequent reaction with the prevalence of 3.0%. The prevalence of papules

and macules was 14.1% and 8.1%, respectively.

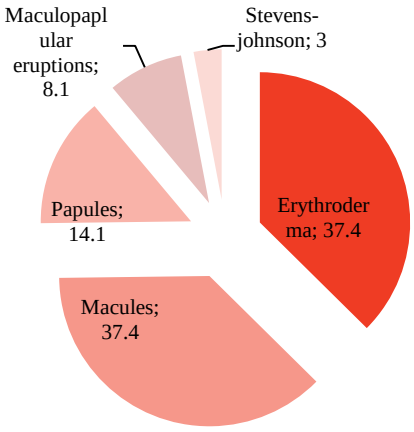

Figure 1. Absolute frequencies of different types of rash in children treated with carbamazepine

In this survey, the number of males who were affected with rashes due to using carbamazepine was higher. In terms of ethnicity, 41 patients (41.4%) were Fars, 18 patients (18.2%) were Turkmen, 26 patients (26.3%) were Sistani, and 14 patients (14.1%) were of other ethnic groups.

Studying the patients, it was found out that the majority of them (77.8%) had no history of allergic reactions to any foreign matter or medicine. Among the types of seizure, generalized seizures were more prevalent happening to 60 patients (60.6%) and partial seizures were less seen with the prevalence of 39.4%. The relationship between the types of skin lesions and the types of seizures are compared in table 1. It should be noted that no meaningful significant relationship was observed between sex and the type of skin reaction after the drug use (P = 0.06).

The average duration of drug use in patients was 12.82 ± 6.56 days. The minimum and maximum intervals between taking the drug and onset of the reactions were 4 days and 30 days, respectively. Concerning the interval between emergence of skin lesions and going to the hospital, the average time was 3.25 ± 3.07 days; the minimum interval was 1 day (going on the same day that rashes appeared) and the maximum interval was 5 days. The relationship between types of skin lesions and the time each takes to appear is evaluated in figure 2.

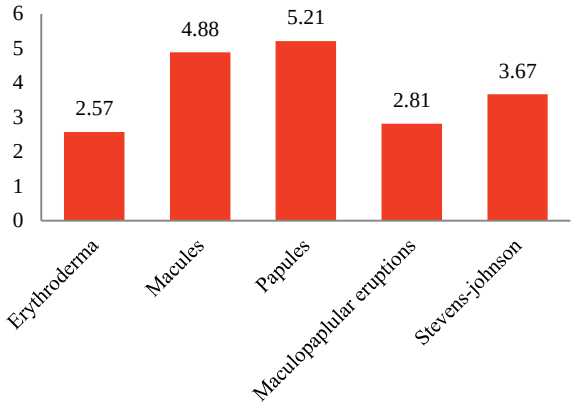

Figure 2. Relationships between types of skin lesions and rash start time

In terms of the relation between types of skin lesions and the daily drug dosage used by the patients, analysis of variance (ANOVA) statistical test showed that there was a significant correlation here; the more the dosage was, the more severe lesions were.

With regard to the possible influence of ethnicity on the occurrence of skin reactions during treatment with this medicine, chi-square analysis was used to assess this hypothesis.

Table 1. Comparison of relations between types of skin lesions and convulsions among the patients (in terms of the number of people)

Type of seizure	Erythroderma	Macules	Papules	Maculopapular	SJS	P
Generalized	25	5	6	22	2	0.61
Partial	12	3	8	15	1	

SJS: Stevens-Johnson syndrome

Findings indicated that erythroderma and maculopapular rash were more prevalent in Fars patients and macules were more common in Turkmen ones. Statistically, this difference was not a significant correlation (P = 0.28) (Table 2).

Table 2. Comparison of relation between types of skin lesions and the daily drug dosage

Type of skin lesions	Average (mg/day)	SE	P
Erythroderma	237.84	13.75	0.02
Macules	256.25	22.03	
Papules	321.43	32.61	
Maculopapular	347.57	12.73	
SJS	350.00	76.37	

SJS: Stevens-Johnson syndrome; SE: Standard error

Discussion

This study was performed on 99 children aged 2 months to 11 years who were referred to Taleghani Hospital of Gorgan, in 2012, and were diagnosed with adverse skin reactions after carbamazepine therapy. In terms of age frequency, the average age of hospitalized patients that participated in this study was 44.49 ± 33.22 months.

The minimum age among the patients was 2 months and the maximum was 11 years. 25% were less than 16 months, 25% were 16 to 37 months, and the other 50% were aged between 37 and 67 months. Mamishi et al. reported 7 Iranian children with severe skin reactions caused by barbiturates. These children were aged 2 to 11 years. Their symptoms began 1-2 weeks after taking the drug. Early prodromal symptoms were fatigue, fever, cough, anorexia, and then the mucocutaneous manifestations started to appear and worsen gradually. The skin reactions ranged from skin rashes to large blisters.[4]

In our study, the majority of patients were male with the frequency of 61.6%. About ethnicities of patients with skin lesions caused by carbamazepine, the majority was Fars, and after that, the number of Sistani and Turkmen patients was respectively higher. In this survey, 77.8% of the patients had no specific history of allergy to any food or drug and only 22.2% of them had histories of allergies. Comparing the relationships between the types of skin lesions and the patients' allergy backgrounds did not indicate any significant correlation. Concerning the family relationship between parents of the children, 37 children had relative parents and the other 62 did not. The statistical analysis showed that there was a correlation about this in the patients. Assessing types of seizure after the initial diagnoses indicated that 60.6% of the seizures were generalized and the other 39.4% were partial. The average time of carbamazepine treatment was 12.82 ± 6.56 days among patients. Garcia et al. reported a patient with severe carbamazepine-induced cutaneous reaction in the treatment of post-herpetic neuralgia (PHN). The patient was treated with carbamazepine and amitriptyline due to neuralgia. After 15 days, she developed malaise, muscle pain, with a mild non-specific cutaneous rash. Carbamazepine was discontinued immediately. One week later, she was hospitalized with urticaria, generalized exanthema, bullae, and maculopapular rashes all over her body. She evolved with progressive worsening of her symptoms, with increase in the number and size of cutaneous lesions besides areas of necrosis and loosening of the epidermis in different parts of her body. Eventually, this worsening evolved to septic shock followed by death.[5]

The dose of carbamazepine used by patients was also assessed. The average recommended dosage was 15 to 20 mg per kg of body weight. Unfortunately, not every family had effective medication compliance and some failed to live up to the dosage a neurologist had prescribed for them. This resulted in occurrence of cutaneous reactions and hospitalization. These patients were excluded from this study. The prevalence of different types of skin lesions

were as follows: 37.4% erythroderma, 37.4% maculopapular eruptions, 14.1% papules, 8.1% macules, and 3.0% SJS. According to the study of Huang et al.[6] maculopapular rash was the onset of symptoms in every patient. The incidence rates of erythroderma and SJS were 35.5% and 28.9%, respectively. 19.7% of the patients had TEN, 10.5% of them had maculopapular eruptions, and 5.0% had both maculopapular eruptions and urticaria. Phenytoin was the most common drug causing skin reactions. About the onset time of the side effects, the minimum time was 10 days and the maximum time was 5 years. The skin lesions were also assessed in hospitalized patients during 5 years. 734 patients showed symptoms for six types of skin lesion during this time. Three common non-serious lesions were urticaria, exanthema, and lesions looking like EM; and the rest were common serious complications such as SJS rash and exfoliative dermatitis. Anticonvulsants were the most common drugs causing serious skin reactions. Among patients with more serious skin reactions, the number of males and the average age were higher. They had been using the drug for a longer time and this prolonged their hospitalization time.[6]

Pharmacokinetics of carbamazepine in children is age- and body weight- dependent and highly variable due to influence of dosing regimen and comedication.[7] There is an association of variants of genes that regulate certain isoforms of cytochrome P450 enzymes (CYPs), some sodium channels, and drug transporters with either pharmacokinetics or pharmacodynamics of carbamazepine in children.[8] Genetic factors contribute to the high interindividual variability in response to antiepileptic drugs (AEDs). However, most genetic markers identified to date have limited sensitivity and specificity, and the value of genetic testing in guiding AED therapy is limited.[9] The use of genetic testing to guide epilepsy treatment is likely to increase in the future, as better understanding of the function of epilepsy genes will permit the application of precision medicine targeting the biological mechanisms responsible for epilepsy in the specific individual.[10].

Conclusion

The results of this study showed that skin reactions were one of the most frequent side effects of carbamazepine. Given the importance of the adverse reactions to this medicine, the appearance of these complications and particularly, the initial symptoms including skin reactions, should be noteworthy to the doctors. The findings also point out to the poor drug compliance in some families. They interfered in the dosage and the proper use of the medicine; thus, they could not live up to their medical prescription and this resulted in misusing of the drug in some children. Families should be perfectly justified about the exact dosage and timing of the drug and should be asked about how they are using the medication every time a doctor visits them. The average duration between the beginning of using the drug and admission of patients to the hospital was 21 ± 16 days. According to this, we could possibly say that generally, families did not pay enough attention to the danger of adverse reactions to carbamazepine and delayed in taking their children to a pediatric neurology center. In this study, the most prevalent skin lesions seen in the patients were erythroderma and maculopapular eruptions. According to this, if someone introduces these two types of skin lesion to the families as the most common ones caused by carbamazepine, it would be helping them get their children admitted to a medical center in a better time. Also according to the relationship between the dosage of medications and the incidence rate of each type of these lesions, increasing the dosage could cause severe and more extensive cutaneous reactions.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

Appreciation and thanks to the Deputy of Research and Technology of Golestan University of Medical Sciences, Gorgan, Iran, and the Health Research Center for Infants and Children of Taleghani Hospital who helped us in this research.

This study has been derived from an MSc thesis (No. 631) approved by Golestan University of Medical Sciences.

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