Clinical and Laboratory Features of Anticonvulsant Cutaneous Reactions

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Abstract

Background: Cutaneous drug reaction is a common side effect of antiepileptic drugs (AEDs). In recent years, a significant increase in cases of cutaneous drug reaction due to AEDs and some changes in its pattern in our department have been noticed. Therefore, we carried out this study to present clinical and paraclinical characteristics of these cases.

Methods: All records of patients who were hospitalized at our hospital with a diagnosis of cutaneous drug reaction due to anticonvulsant therapy between March 2006 and September 2009 were reviewed.

Results: The most common offending drug was lamotrigine. The main indication of anticonvulsant therapy was for idiopathic seizures. The most frequent type of cutaneous reaction was maculopapular and/or erythrodermic rash. Eosinophilia was detected in 56.5% of the patients.

Conclusions: Although serious reactions with AEDs are not common, they may be life threatening. So, timely and accurate diagnosis can prevent fatal reactions and affects subsequent anticonvulsant treatment options. *(Iran J Dermatol 2009;12: 123-126)*

Keywords: cutaneous drug reaction, drug eruption, anticonvulasant, antiepileptic, side effect, adverse effect

Introduction

Cutaneous drug reaction is a common side effect of antiepileptic drugs (AEDs) and a frequent cause of treatment discontinuation. Such reactions range from the common and mild maculopapular rashes to Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [1].

Among the traditional AEDs, the aromatic compounds phenytoin, phenobarbital and carbamazepine have been associated with relatively higher incidences of cutaneous reactions in up to at least 10% of the patients [2-4]. Some of the newer drugs also frequently induce this problem, especially lamotrigine [5,6]. oxcarbazepine [7], and felbamate [8]. Skin reactions may remarkably restrict the use of these AEDs. Although serious reactions are not common, they may be life threatening [9].

The pathogenesis of cutaneous reactions seems to be multifactorial and has in many cases been explained by the hapten hypothesis of drug hypersensitivity, which implies both metabolic and immunological mechanisms. An imbalance between metabolic bioactivation and detoxification of the drug may lead to an accumulation of reactive metabolites, which may bind irreversibly to endogenous proteins [10].

In recent years, we have noticed a significant increase in cases of cutaneous drug reaction due to AEDs and some changes in its pattern in our department. Therefore, we carried out this study to present clinical and paraclinical characteristics of these cases.

Patients and Methods

All records of patients who were hospitalized at Loghman Hakim Hospital with a diagnosis of cutaneous drug reaction due to anticonvulsant therapy between March 2006 and September 2009 were reviewed.

Clinical details including age, sex, history of drug ingestion, interval between drug ingestion and cutaneous reaction, general and dermatologic examination findings, and laboratory parameters were recorded. The diagnoses were made by dermatologists based on clinical and morphologic observation and in some cases by skin biopsy. Stevens–Johnson syndrome (SJS) was diagnosed

when there was severe mucosal involvement, with skin erosions, bullae or peeling of less than 10% of the body surface area. TEN was diagnosed in the presence of bullae, skin erosions or peeling more than 30% of the body surface area in addition to severe mucosal involvement. Any abnormal hematologic, biochemical, and microbiologic results were recorded. The overall treatment given to patients and the mortality were also studied

Results

A total of 23 subjects (9 males, 14 females), who were hospitalized in Loghman Hakim hospital between March 2006 and September 2009 due to cutaneous eruptions after starting anticonvulsant therapy were included in this study. The subjects had an age range from 3 to 75 years, and the mean age was 33.9 years with a median of 32 years. Seventeen (73.9%) patients were admitted to the dermatology unit, three (13.1%) to the neurology unit, two (8.7%) to the pediatric unit, and one (4.3%) to the infectious disease unit.

Eight (34.8%) cases were due to lamotrigine, 7 (30.4%) cases to phenytoin, 5 (21.8%) cases to carbamazepine, 2 (8.7%) cases to phenobarbital and 1(4.3%) case to valproic acid. In 50% of the cases with cutaneous drug reaction to lamotrigine, valproic acid was being used as a co-treatment; however, in all these cases, valproic acid had started several months prior to lamotrigine. Cutaneous eruption appeared 1-35 days (mean: 16 days) after the intake of the offending agent.

The indication of anticonvulsant therapy was idiopathic seizures in 10 (43.5%) patients, post-traumatic seizure in 4 (17.4%) patients, and psychiatric disorders in 4 (17.4%) patients. Five other patients (21.7%) were receiving anticonvulsants due to astrocytoma, brain metastasis of lung cancer, eclampsia, cerebrovascular accident and addiction treatment.

The type of skin rash was maculopapular and/or erythrodermic in 11 (47.8%) patients. Eight (34.8%) patients had Stevens–Johnson syndrome (SJS), two (8.7%) had toxic epidermal necrosis (TEN), one (4.35%) had acute generalized exanthematous pustulosis and one (4.35%) had skin burning sensation without any visible eruptions. Table 1 shows different clinical features according to offending drugs. Mucosal involvement was recorded in 10 (43.5%) patients, all of whom had SJS/TEN. Among patients with mucosal involvement, oral mucosa was affected in all cases, ocular mucosa in 90% of the cases, genital mucosa in 50% of cases, and nasal mucosa in 30% of cases. Nine (39.2%) patients had palmoplantar involvement. Fever was noted in thirteen (56.5%) patients. One of the patients with TEN developed sepsis. Fourteen (60.9%) patients had pruritus.

Details of the results of some laboratory parameters are shown in Table 2. One or more hepatic enzymes were elevated in 9 (39.2%) patients, ranging from a minimal elevation less than a two-fold increase above the upper limit to a 7-fold increase; however, clinically apparent icterus was observed in none of the patients. Evaluation of renal function by blood urea nitrogen and serum creatinine and serum electrolytes revealed hyperuremia in 2 (8.7%) patients and hyponatremia and hyperkalemia in 1 (4.3%) patient.

Thirteen (56.5%) patients had peripheral eosinophilia with absolute eosinophil counts >350/µl. Blood dyscrasia (pancytopenia) was recorded in only 1 (4.3%) patient.

The first step in treatment of anticonvulsant cutaneous reaction was to discontinue the offending drug and if necessary, to use another anticonvulsant agent according to the neurologist's perscription. Four (17.4%) patients were treated with "only antihistamine", eight (34.8%) with "antihistamine and topical steroid", and eleven (47.8%) with a combination of "antihistamine, topical steroid and prednisolone (20 mg/d)". The dose was gradually reduced in 3–4 weeks in accordance with the clinical resolution. All patients responded favorably. Two patients with TEN were referred to the Intensive Care Unit for the severity of the lesions and poor general status, one of whom expired after several days.

Discussion

As in a study by Alvestad et al, we found that drug-induced skin reactions due to AEDs were more frequent in women [1]. A possible explanation is that sex hormones influence T-cells, the production of specific antibodies and proinflammatory mediators [11]. In general, female sex hormones enhance immune responses in both physiological and pathological states, whereas androgens attenuate inflammatory responses even more than endogenous glucocorticoids [12,13].

As in previous studies, aromatic anticonvulsants (phenytoin, phenobarbital and carbamazepine), had the highest incidence of cutaneous adverse reactions (60.8% vs. 39.2%). However, when we evaluated skin rashes for each single drug, we found the highest incidence of cutaneous reactions with lamotrigine. Several studies have suggested

Table1. *Types of cutaneous reactions and offending drugs*

	Lamotrigine	Phenytoin	Phenobarbital	Carbamazepine	Valproic Acid
Maculopapular/ Erythrodermic	3 (13.1%)	4 (17.4)	2 (8.7%)	1 (4.3%)	1 (4.3%)
SJS	2 (8.7%)	3 (13.1%)		3 (13.1%)	
TEN	2 (8.7%)				
AGEP				1 (4.3%)	
Burning sensation	1(4.3%)				

SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis; AGEP: acute Generalized exanthematous pustulosis

Table 2. *The distribution of laboratory findings in patients with anticonvulsant cutaneous reactions*

	Total number of cases (%)
Elevated ALT	5 (21.8)
Elevated AST	5 (21.8)
Elevated Alk.ph	3 (13)
Hypoproteinemia	6 (21.6)
Elevated LDH	10 (43.5)
Elevated CPK	4 (17.4)
Eosinophilia	13 (56.5)
Pancytopenia	1 (4.3)
CRP(+)	5 (21.8)
Hyperglycemia	2 (8.7)
Hyperuremia	2 (8.7)
Hyponatremia	1 (4.3)
Hyperkalemia	1 (4.3)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Alk.ph: alkaline phosphatase; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; CRP: C-reactive protein.

significantly higher risk of cutaneous rashes when lamotrigine is administered by patients already taking valproate since valproic acid inhibits the metabolism of lamotrigine [14,15]. In our study, 50% of the cases with cutaneous drug reaction to lamotrigine were also taking valproic acid as a co-treatment. This rate has been reported to be between 40% and 60% in previous studies [2,16].

As Mansur et al reported, the indication of antiepileptic drugs has expanded in recent years to include the treatment of neuropathic pain and psychiatric disorders [2]. Accordingly, 8 (34.8%) patients were using anticonvulsant drugs (3 carbamazepine, 2 lamotrigine, 2 phenytoin, and 1 valproic acid) for disorders other than epilepsy in our study.

Cutaneous drug reaction to AEDs appears to be much more severe in patients undergoing concomitant radiotherapy and it has been reported that cranial radiotherapy during treatment with anticonvulsants acts as a trigger for TEN. The offending anticonvulsant has been phenytoin in most of the reported cases [17,18]. However, we could not evaluate this relationship as none of our patients was receiving radiotherapy. However, Baba et al reported that most of their cases developed cutaneous drug reaction after craniotomy, and they suggested that surgical trauma could have been involved in decreasing the activity of enzymes in these subjects (as reported in rats) [19], due to their exposure to anaesthetic agents and other drugs [20].

Different types of skin lesions and systemic involvement including fever, lymphadenopathy, nephritis, hepatitis, pneumonia, conjunctivitis and hematologic disorders such as leucocytosis, eosinophilia, and lymphocytosis have been reported with AED. Multi-organ involvement is thought to be related to differences in the expression of enzymes responsible for the detoxification of drugs or detoxification of metabolites, alternate pathways of metabolism, or immunologic reactivity [21,22]. Mansur et al reported maculopapular and/or erythrodermic rashes as the most common cutaneous reaction to anticonvulsant agents [2]. Similar to this observation, in our study, 47.8 % of the patients

developed maculopapular and/or erythrodermic rashes, followed by SJS and TEN.

Studies have shown that hepatitis is the cause of liver failure-the most common cause of death-in patients with anticonvulsant hypersensitivity syndrome. The overall mortality is 18-40% when the liver is involved [23]. Almost 40% of our patients showed abnormal liver function tests, but all recovered as these patients were diagnosed and offending drugs were discontinued as soon as possible.

The most important step in the management of cutaneous drug reaction to AEDs is to identify and discontinue the offending drug. It is believed if the reaction has developed because of aromatic anticonvulsants, valproic acid would be the safest alternative for seizure control [24,25]. In favor of this suggestion; the treatment in most of our patients switched to valproic acid and none of them experienced exacerbation or recurrence.

In conclusion, cutaneous drug reaction to AEDs is a frequent medical problem, which usually requires a close monitoring and management. Its timely and accurate diagnosis can prevent life- threatening reactions and affects subsequent anticonvulsant treatment options.

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