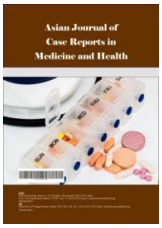

Asian Journal of Case Reports in Medicine and Health

4(3): 7-12, 2020; Article no.AJCRMH.63981

Antiepileptic Drug-Induced Skin Rash Revealing a Cross-Reactivity between Antiepileptic Drugs in a Patient with Anticonvulsant Polypharmacy

Z. Zeggwagh[1*], S. Kerroum[1], N. Ismaili[1], L. Benzekri[1], M. Meziane[1] and K. Senouci[1]

[1]Department of Dermatology and Venereology, University Hospital Ibn Sina, University of Mohammed V of Rabat, Rabat, Morocco.

Authors' contributions

This work was carried out in collaboration among all authors. Author ZZ have made contribution to acquisition of data and wrote the first draft of the manuscript. Authors ZZ, SK, NI, LB, MM and KS managed the literature searches and have been involved in revising the manuscript. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Arun Singh, Rohilkhand Medical College & Hospital, India.
Reviewers:
(1) Long Niu, Dalian Medical University, China.
(2) Romana Gjergja Juraški, Children's Hospital Srebrnjak, Croatia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/63981

Case Study

Received 10 October 2020
Accepted 15 December 2020
Published 09 January 2021

ABSTRACT

Aims: The cross-reactivity of antiepileptic drugs (AEDs) in the occurrence of drug eruption makes intrinsic accountability difficult. We are reporting on a case of drug eruption that occurred in a patient treated with four AEDs who had previously developed rashes with two other AEDs.
Presentation of Case: A 17-year-old epileptic patient with a history of rashes induced by phenobarbital and carbamazepine three years ago, and since ceased. Two months before admission, levetiracetam was added. Lamotrigine and clobazam were then added for generalized seizures. Two weeks later, a rash appeared on the neck, trunk and face with extension to limbs associated with pruritus and fever. On admission, the patient was febrile with tachycardia. Skin examination revealed a maculo-papular exanthema on the limbs, trunk and puffy face with negative Nikolski's sign. Biological assessment: leukopenia, thrombocytopenia and elevated CRP. The skin biopsy was in favor of toxiderma. The patient received paracetamol; imputability scores of the 4 antiepileptic drugs were calculated; and incriminated latromigine (C3S2B4) which was stopped with

**Corresponding author: E-mail: zeggwaghzineb@gmail.com;*

progressive increase of levetiracetam. The evolution was marked by a clinical and biological improvement.
Discussion: The incidence of AED-induced drug eruption ranged from 1.7 to 8.8%. The AEDs most at risk are aromatic AEDs. A high initial dose and rapid dose escalation are risk factors, especially for lamotrigine when metabolism is inhibited by valproic acid.
Conclusion: During anticonvulsant polypharmacy, caution should be taken when administering some AEDs to ensure that clinicians safely prescribe appropriate anti-epileptic medications considering the history of previous AED-related skin reactions.

Keywords: Antiepileptic drugs; cross-reactivity; rash.

1. INTRODUCTION

Drug eruption induced by antiepileptic drugs (AEDs) is known to physicians treating epilepsy and incidences can reach 10% [1-4]. Maculo-papular exanthema and delayed onset urticaria are the most commonly reported hypersensitivity reactions to AEDs [5]. However, even the most meticulous examination may not always lead to a diagnosis [6]. Moreover, the symptoms are rarely specific, the effect of stopping AED is not always conclusive, and several AEDs are often co-prescribed [6]. The combination of several AEDs increases the risk of skin adverse events [7]. For this reason, clinicians should be aware of the cross-reactivity of AEDs defined as the occurrence of an AED-related rash in a patient who had a skin rash during previous exposure to other AEDs [2,8].

Indeed, cross-reactivity of AEDs is a significant clinical problem, making their intrinsic imputability difficult during polypharmacy. In this respect, the present case of generalized exanthema illustrates a cross-sensitivity that occurred in a patient treated with four AEDs who previously developed drug eruption with two other AEDs [8].

2. CASE REPORT

A 17-year-old epileptic patient, treated with valproic acid (500 mg three times a day) since the age of 8 and without morbidity, is admitted to the Dermatology Department for a maculo-papular rash. He reported a 'drug eruption' with phenobarbital and carbamazepine prescribed 3 years earlier and stopped since. Two months before admission, levetiracetam was added (500 mg two times a day) to valproic acid by the neurologist. Despite this, the patient presented generalized tonic-clonic seizures that led to hospitalization in the Neurology Department where an electroencephalogram supported a diagnosis of epilepsy. Because the patient has a previous diagnosis of epilepsy with previous imaging, repeat imaging was not needed with subsequent seizures. Two other AEDs were added – lamotrigine (25 mg two times a day for 5 days then 50 mg two times a day) and clobazam (5 mg two times a day). Two weeks later, a skin rash appeared on the neck, trunk and face with extension to the limbs associated with pruritus and fever.

On admission, the patient, weighing 55 kg, was febrile at 39.5°C, with tachycardia (110/min), normal blood pressure, respiratory rate of 20 cycles/min and conjunctival hyperhemia. Skin examination revealed a maculo-papular exanthema on the limbs (Fig. 1), trunk (Fig. 2) and puffy face with a negative Nikolski's sign. There were no pustules or lesions involving the mucosa, palms or soles of the feet. There was no periorbital or perioral edema. The abdomen was soft without hepatosplenomegaly. The chest examination was normal. The rest of the examination was also normal. The biological abnormalities noted were leukopenia at 2470/mm3, thrombocytopenia at 89000/mm3 and CRP at 50 mg/l. Bacteriological results were negative. Skin biopsy showed pericapillary lymphocytic infiltration in the dermis, suggestive of drug eruption. The HLA analysis was not performed. The French imputability scores was denoted with chronology (C), semiology (S) and bibliography (B) scores of the four AEDs: C3S2B4 for lamotrigine; and C1S1B4 for levetiracetam, valproic acid and clobazam respectively. After a neurological consult, lamotrigine was discontinued with a gradual increase in levetiracetam. The dose was increased by 250 mg twice a day every 2 weeks to a total dose of 1000 mg twice daily. The skin rash gradually disappeared, as did the fever and tachycardia, with normalization of the laboratory abnormalities at D+7. The patient was seen 3 months later and was doing well with the same antiepileptic treatment at discharge.

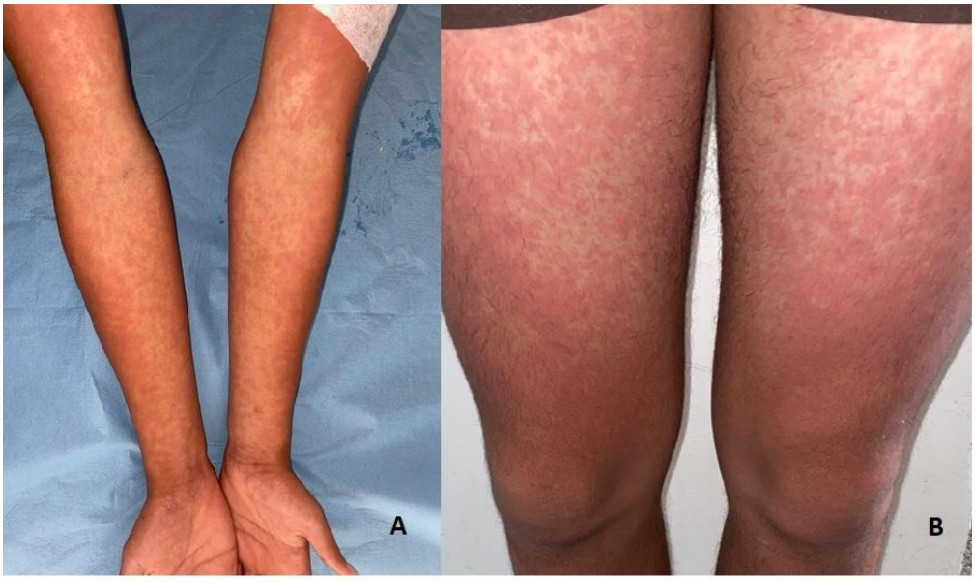

Fig. 1. A patient's drug rash and systemic symptoms from antiepileptic drugs, having maculo-papular exanthema over (A) upper limb, (B) lower limb.

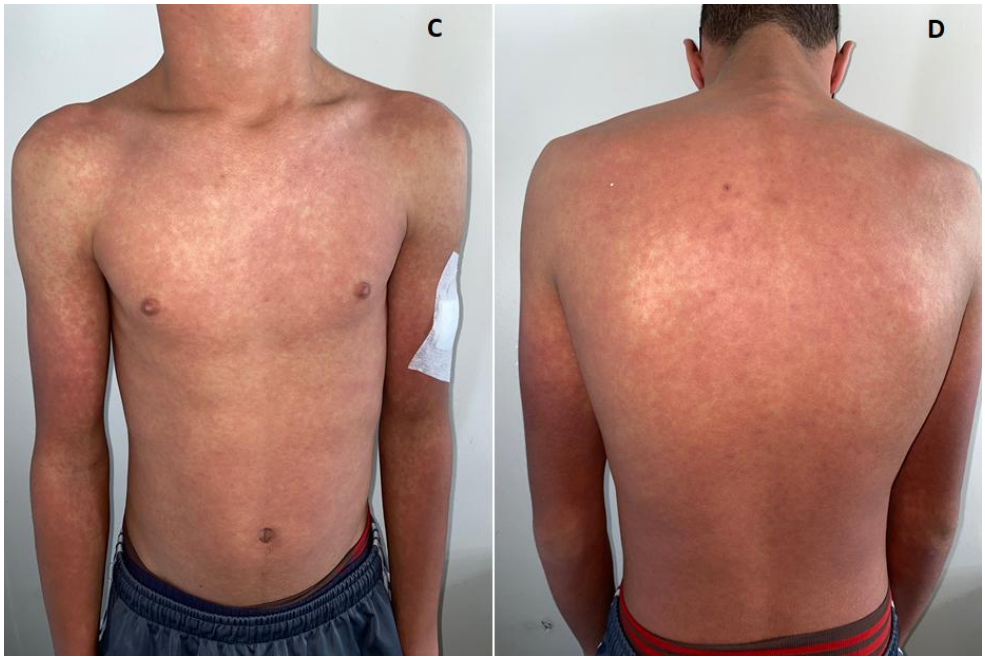

Fig. 2. A patient's drug rash and systemic symptoms from antiepileptic drugs having maculo-papular exanthema over trunk (C) front, (D) back

3. DISCUSSION

Toxidermias are cutaneous side effects of drugs. More than 90% of these drug hypersensitivity reactions are benign (maculopapular exanthema, urticaria, pruritus, photosensitivity, etc.) and evolve rapidly after discontinuation of the causative drug [9]. Yet there are severe systemic and cutaneous forms that are potentially fatal, such as anaphylaxis, acute generalized exanthemous pustulosis, and especially Stevens-Johnson syndrome and Lyell's syndrome.

Fortunately, these forms remain rare [9]. AEDs are also quite often associated with a rash, that can be mild to fatal. Incidence vary according to the type of rash, the AED used, and the history of rash, with rates ranging from 1 to 10% [1,3,4]. In addition, 86% of hypersensitivity reactions were observed within 3 months of initiation of AEDs [3]. Most of the skin reactions occur in relation with aromatic AEDs, such as phenytoin, carbamazepine, phenobarbital, and some of the newer ones, such as oxcarbazepine and lamotrigine [3].

Lamotrigine appears to be involved in cross-reactions less often than carbamazepine, oxcarbazepine and phenobarbital [8]. This is probably what prompted neurologists to prescribe lamotrigine to our patient, although drug eruptions were reported twice as frequently with aromatic AEDs than with non-aromatic AEDs [10]. Levetiracetam, lacosamide and zonisamide are rarely associated with these adverse events with a risk of less than 1% [3,4].

Three of the AEDs incriminated in the occurrence of drug eruption in our observation were aromatic: phenobarbital and carbamazepine initially, then lamotrigine secondarily. It should be recognized that the risk of developing an AED rash is approximately three to five times higher in patients who have had another AED rash compared with those without [1,10]. Indeed, once a hypersensitivity reaction occurs, the likelihood of cross-sensitivity to another AED increases among other aromatic AEDs. Few studies have determined the frequency of toxidermal cross-sensitivity in patients taking multiple AEDs [2]. Among aromatic AEDs, toxidermal cross-sensitivity is estimated to occur in 40-66% of patients [2,6]. For example, two-thirds of patients who presented hypersensitivity reactions to phenobarbital developed skin reactions to carbamazepine, as did our patient [6].

Several risk factors for drug eruption induced by AED have been described, such as history of drug eruption with AED, advanced age, female gender, ethnicity, genetic predisposition, vitamin D deficiency, and the presence of co-morbidities [11,12]. The history of a previous AED-related skin reaction appears to be the most significant predictor of future rash [1,4]. Only this factor could be identified in our patient who reported the appearance of generalized skin rash following the prescription of phenobarbital and carbamazepine at the onset of his epilepsy, replaced by valproic acid.

In a study of factors associated with lamotrigine-induced drug eruption, co-medication with valproic acid did not appear to be an independent predictor of drug eruption. Yet a history of rashes with other AEDs and patients under 13 years of age appeared to be strong risk factors for developing lamotrigine rash [11]. Authors have suggested that children may have a higher risk for rash than adults due to increased drug metabolism resulting in higher concentrations of reactive metabolites [2,12].

The mechanisms causing drug eruption and cross-reactivity appear to be complex and diverse. There are several hypotheses about how the immune system responds to AEDs [5]. AEDs may act as haptens that induce an immune response by binding to T cells [8]. Indeed, a strong association has been found for aromatic AEDs and T-cell-mediated skin hypersensitivity reactions [10]. Similarly, a significant relationship of type I hypersensitivity with aromatic AEDs has been observed [10]. In addition to these immunological factors, cross-reactivity may be associated with individual pharmacogenetics involving the HLA system and responsible for genetic alteration of enzymatic processes [2,4,8].

Furthermore, it is suggested that patients predisposed to cross-reactions between aromatic AEDs have a deficiency in epoxide hydrolase - an essential enzyme for the detoxification of a metabolite produced by oxidation of aromatic benzene ring by cytochrome P450 [6]. On the other hand, phenobarbital and carbamazepine are well-known enzyme inducers resulting in increased metabolism and decreased serum concentration of the affected drug [7]. Thus, the half-life of lamotrigine is halved when it is given in combination with these AEDs [7]. Conversely, valproic acid is a well-known enzyme inhibitor and increases serum concentration of AEDs possibly associated with serious side effects [1,7]. For example, valproic acid triples the half-life of lamotrigine, thus increasing the risk of accidents in this combination [1,3,4,13]. Therefore, the toxicity of lamotrigine in our patient may have been potentiated by its combination with valproic acid. In addition, drug eruption may have been enhanced by initial high doses of lamotrigine exceeding the recommended dose escalation pattern for lamotrigine and valproic acid combination therapy [13]. It has been suggested that the initial rash could initiate the underlying basic mechanisms responsible for an idiosyncratic

response, and induce a second response that would not occur if the introduction of the second drug was delayed or administered very gradually [2]. Apart from clobazam, an aromatic AED administered to our patient following his epileptic condition, has been associated in the literature with rash, angioedema, Stevens-Johnson syndrome and Lyell's syndrome, but the rate of skin eruption is not high compared to other aromatic AEDs and the risk of cross sensitivity is lower [4].

Recognition of AED-related rash must be rapid because accurate diagnosis avoids potentially fatal re-exposure and impacts subsequent anticonvulsant treatment options [14].

The search for the cause of drug eruption associated with AEDs is based on several arguments, but none has an absolute outcome [6]. Some reactions, such as urticaria and maculopapular rashes, can result from interactions between viruses (HIV, EBV and VZV) and drugs that require a virological assessment as performed on our patient [15].

Furthermore, if a patient receiving multiple medications develops a rash, the most recently added drug should be considered [4]. In practice, to explore the causative drugs that lead to cutaneous eruptions, patch tests and lymphocyte transformation tests have proved to be useful tools for evaluating reactions to aromatic AEDs mediated by an immunologic mechanism.

The patch tests can be performed with good sensitivity and a proven usefulness during polypharmacy [7]. These patch tests reproduce the hypersensitivity reaction at the site of drug application and facilitate the identification of the causative drug [12]. However, their use is not recommended because the risk of developing a new reaction is not negligible [13]. In addition, only a few studies have evaluated the sensitivity of patch tests in the diagnosis of hypersensitivity reactions to AEDs [6].

Therefore, to decide which AED to withdraw, the assessment of the causal relationship between each one of the AEDs and the occurrence of an adverse event makes it possible to help the diagnosis and the appropriate approach to adopt. This causality assessment, used in pharmacovigilance and applied in our case, is measured by a score that integrates intrinsic chronological criteria (delay, evolution after discontinuation, recurrence after accidental reintroduction) and semiological criteria (history, compatible clinic, facilitating factors, exclusion of other diagnoses) as well as extrinsic bibliographical data [6,9].

For patients requiring AEDs with high risk of cross-reactivity between them and drugs that have previously caused rash, special warnings and precaution for use are recommended [8]. In the presence of aromatic AED-related rash, other aromatic AEDs should be avoided and non-aromatic AEDs with low interaction should be used as potential alternatives [3,4,6].

To avoid a possible evolution towards severe toxidermia, the immediate cessation of lamotrigine was considered in our patient as recommended [13]. Taking into account the association of valproic acid and lamotrigine in our reported case, the doses of lamotrigine should have been significantly reduced to avoid elevated serum lamotrigine level in our patient [13].

Many AEDs have low or negligible risk of rash, such as gabapentin, vigapantin topiramate, levetiracetam and pregabalin [7]. Thus considering the cross-reactivity among aromatic AEDs, the choice of levetiracetam in our patient was considered a safe alternative.

4. CONCLUSION

Drug eruption can be a serious adverse skin reaction to AEDs, and should be assessed and treated promptly. Caution should be taken when administering some AEDs to ensure that competent clinicians safely prescribe appropriate anti-epileptic medications. It is important to ensure which AED is responsible for drug eruption before depriving the patient of it.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Arif H, Buchsbaum R, Weintraub D, Koyfman S, Salas-Humara C, Bazil CW, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology. 2007;68:1701-9.
2. Hirsch LJ, Arif H, Nahm EA, Buchsbaum R, Resor SR, Bazil CW. Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology. 2008;71:1527-34
3. Panda S. Cross-sensitivity of levetiracetam and carbamazepine induced skin rash. J Assoc Physicians India. 2019;67:89-90.
4. Mani R, Monteleone C, Schalock PC, Truong T, Zhang XB, Wagner ML. Rashes and other hypersensitivity reactions associated with antiepileptic drugs. A review of current literature. Seizure. 2019; 71:270-8.
5. Atanasković Marković M, Janković J, Tmušić V, Gavrović-Jankulović M, Ćirković Veličković T, Nikolić D, et al. Hypersensitivity reactions to antiepileptic drugs in children. Pediatr Allergy Immunol. 2019;30:547-52.
6. Ben Mahmoud L, Bahloul N, Ghozzi H, Kammoun B, Hakim A, Sahnoun Z, et al. Epicutaneous patch testing in delayed drug hypersensitivity reactions induced by antiepileptic drugs. Therapie. 2017;72: 539-545. [Article in French]
7. Maniu CM, Buss G, Feldmeyer L, Spertini F, Ribi C. Severe delayed drug hypersensitivity reactions. Rev Med Suisse. 2013;9:803-11. [Article in French]
8. Alvestad S, Lydersen S, Brodtkorb E. Cross-reactivity pattern of rash from current aromatic antiepileptic drugs. Epilepsy Res. 2008;80:194-200.
9. Thielen AM, Toutous-Trellu L, Desmeules J. Drug-eruptions. Rev Med Suisse. 2008; 4:1671-5. [Article in French]
10. Handoko KB, van Puijenbroek EP, Bijl AH, Hermens WA, Zwart-van Rijkom JE, Hekster YA, et al. Influence of chemical structure on hypersensitivity reactions induced by antiepileptic drugs. The role of the aromatic ring. Drug Saf. 2008;3:695-702.
11. Hirsch LJ, Weintraub DB, Buchsbaum R, Spencer HT, Straka T, Melissa Hager, et al. Predictors of lamotrigine-associated rash. Epilepsia. 2006;47:318–22.
12. Guvenir H, Dibek Misirlioglu E, Civelek E, Toyran M, Buyuktiryaki B, Ginis T, et al. The frequency and clinical features of hypersensitivity reactions to antiepileptic drugs in children: A prospective study. J Allergy Clin Immunol Pract. 2018;6:2043-50.
13. Faught E, Morris G, Jacobson M, French J, Harden C, Montouris G, et al. Adding lamotrigine to valproate: Incidence of rash and other adverse effects. Epilepsia. 1999; 40:1135-40.
14. Vittorio CC, Muglia JJ. Anticonvulsant hypersensitivity syndrome. Arch Intern Med. 1995;155:2285-90.
15. Haverkos HV, Amsel Z, Drotman P. Adverse virus-drug interactions. Rev Infect Dis. 1991;13:697-704.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/63981