Acneiform Rash Caused by an Unlikely Drug: Topiramate

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Established Facts

- It is necessary to report all adverse effects of a drug to assess its safety and to know how to act in case of an adverse reaction.

Novel Insights

- Aromatic antiepileptic drugs may cross-react in 40–58% of the cases, so patients with a documented rash to these medications should be prescribed the less likely drug to produce it. This particular case report is useful because there are no reports of skin rashes induced by topiramate used for migraine prophylaxis.

Keywords

Topiramate · Migraine · Adverse event · Rash

Abstract

Topiramate is an antiepileptic drug that can also be used for migraine prophylaxis, weight control, and even for methamphetamine dependence; the dosage margin is wide, and the list of side effects is shorter than with other anticonvulsants. We present the case of a 35-year-old man with a disseminated rash of the trunk and extremities after treatment with 25 mg of topiramate daily as a prophylactic migraine treatment. This case report is useful, as this patient was not polymedicated and had a score of 7 on the Naranjo Adverse Drug

Reaction Probability Scale. The patient was diagnosed as atypical DRESS syndrome and resolved satisfactorily with symptomatic treatment and topiramate withdrawal; slowly, the lesions regressed. He required no further drugs for the dermatologic condition.

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Introduction

Topiramate is an antiepileptic drug classified in the atypical enzyme-inducing group as this induction is dose dependent. It has also been used for migraine prophylaxis, weight control [1], and even for methamphetamine dependence [2].

Fig. 1. Maculopapular rash.

Fig. 2. Close-up of maculopapular rash.

Topiramate is a sulfamate-substituted monosaccharide, and although its mechanism of action in migraine treatment is not fully understood, it does block sodium and calcium channels, increases GABA concentrations, and enhances inhibitory effects, while stabilizing cortical excitability and inhibiting glutamate receptors and carbonic anhydrase [3, 4].

Even though the most common antiepileptic drugs to cause rash are aromatic anticonvulsants, any of them can cause it. For topiramate, the dosage margin is wide. In migraine prophylaxis, the dosage is 25 mg/day, while as an antiepileptic drug the dosage can be as high as 600 mg/day with a maximum of 1,600 mg/day. The list of side effects is shorter than for other anticonvulsants, but there are still many cases with a wide variety of manifestations.

Case Report

We present the case of a 35-year-old man with the only relevant condition of chronic migraine unmanageable with analgesics. He initiated treatment with 25 mg topiramate daily as a prophylactic migraine treatment with good therapeutic response. After 10 weeks of treatment, he sought dermatological attention for an asymptomatic rash spread over the trunk and received prednisone 50 mg daily for 2 weeks, tapering the dosage. The lesions resolved but soon reappeared after steroid discontinuation. Now, the lesions were spread over the trunk and extremities. They appeared as erythematous papules, some confluent and with eczematous appearance (Fig. 1, 2), and continued to be asymptomatic.

This time, a punch biopsy was performed, and the histological report was of a vacuolar interface dermatitis with superficial lichenoid infiltrate by lymphocytes and eosinophils (4.2%, with a normal range of 1–4%), for which hypersensitivity syndrome with

eosinophilia (drug reaction with eosinophilia and systemic symptoms; DRESS syndrome) had to be ruled out. The patient reported unquantified fever, but this could not be corroborated, since whenever we saw the patient he was found normothermic. The complete blood cell count was within normal ranges except for eosinophils that were reported as slightly elevated. The liver function tests were unremarkable, and consequently, an atypical DRESS syndrome was diagnosed. So, the final diagnosis was a drug reaction, with a score of 7 on the Naranjo Adverse Drug Reaction Probability Scale (Table 1).

As the dermatosis was asymptomatic, he was conservatively treated with soap substitutes and skin moisturizer, with which the lesions very slowly regressed, and he required no further drugs for the dermatologic condition.

Conclusions

Despite the fact that this drug has almost ideal pharmacokinetic properties (the same as gabapentin and vigabatrin) as it is rapidly absorbed and excreted by urine and as there are no intermediate metabolites and fewer drug reactions in comparison with older anticonvulsants [5], still, several reports of side effects mention kidney stones, heatstroke [6], metabolic acidosis, respiratory alkalosis, increased metabolism of ethinylestradiol and progestogens, possibly a teratogenic effect, acute myopia and angle closure glaucoma, impaired concentration, dizziness, emotional lability, and psychosis [7, 8]. Among the dermatological complaints are urticaria and angioedema as well as photosensitivity and pigmentary changes that return to normal after the discontinuation of the drug. Also, alopecia cases have been reported, although in a lower

Table 1. Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do not know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total score				7

According to Naranjo et al. [16].

percentage than for other mood stabilizers. The drug causes nonscarring alopecia that may be localized or generalized and is apparently associated with telogen effluvium and, thus, reversible. Exanthema, pruritus, fixed drug eruption, acneiform eruptions, and hyperhidrosis can also be related [9, 10]. Mild adverse effects might not even be reported by the patients; however, pruritus has warranted case reports [11, 12].

So, we conclude that topiramate is a mood stabilizer and notably has fewer side effects than other drugs in the same group, such as carbamazepine or lamotrigine. Nevertheless, it apparently accounts for almost 2% of the skin rashes caused by this group of drugs, which is often really difficult to evaluate, as patients usually receive more than one of these drug [13].

We based our final diagnosis of a drug reaction on the clinical aspect and histopathology, supported by the Naranjo Adverse Drug Reaction Probability Scale, which assesses whether there is a causal relationship between an identified adverse clinical event and a drug, using a simple questionnaire to assign probability scores. Total scores range from -4 to +13; the reaction is considered definite if the score is 9 or higher, probable if it is 5–8, possible if it is 1–4, and doubtful if it is 0 or less (Table 1 shows that the patient had a score of 7).

The atypical DRESS syndrome was based on the unquantified fever, peripheral eosinophilia, and persistence of symptoms several weeks after the discontinuation of the drug. This syndrome, originally thought to be caused only by anticonvulsants, is known to have a different pathophysiology from that of toxic epidermal necrolysis. In this case, Treg cells appear and downregulate the im-

mune response, causing milder lesions than those seen in toxic epidermal necrolysis, although both have participation of CD4 T-cell lymphocytes [14].

It is important to remember that aromatic antiepileptic drugs may cross-react in 40–58% of the cases [15], so patients with a documented rash due to these medications should be prescribed the less likely drug to produce it. This is why we think that this case report is important for further reference.

We consider that adverse effects are important to document. This particular case is useful, since this patient only received topiramate and no other medication. Fortunately, this case resolved satisfactorily.

Statement of Ethics

The patient’s identity will be kept in confidentiality and anonymity at all times. According to the guidelines for human study and animal welfare regulations, the authors state that the patient gave his informed consent for all the tests performed. This is not a protocol, so it has not been submitted to the institution’s committee on human research. This report did not involve any study on animals.

Disclosure Statement

The authors state that they have no conflicts of interest and ensure the quality and integrity of this report.

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