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Short communication

A review of published cases of severe cutaneous reactions associated with the use of the most frequently prescribed antiepileptic drugs

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Introduction

Epilepsy is one of the most common neurologic disorders with an annual incidence of 50 per 100,000 persons per year in developed countries (Kim et al., 2020). The first-generation antiepileptic drugs (AEDs) which were introduced between 1912 and 1978 include carbamazepine, phenobarbital, phenytoin, primidone, and valproate. Gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate or vigabatrin are members of the second generation and the newest AEDs (or the third generation) are brivaracetam, eslicarbazepine acetate, lacosamide and perampanel.

In more than 25% of the patients, adverse drug reactions (ADRs) are the main reason for discontinuation of the treatment with antiepileptic drugs after the initial antiepileptic drugs are administrated. Up to 33% patients are refractory to multiple AEDs and such cases may potentially lead to recurrent adverse drug reactions and drug interactions (Mohanraj and Brodie, 2005). Hypersensitivity to AEDs is less common, but the risk of severe allergy is higher in this group (Fowler et al., 2019). Adverse skin reactions occur in 3% of individuals who receive antiepileptic drugs and are the most common reason for discontinuation of the treatment. Although most of them are usually mild, occasionally they may be severe when occurring as part of the syndromes of erythema multiforme, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) (Kim et al., 2020).

Materials and methods

For the purpose of this review, electronic literature search was conducted in through comprehensive screening using built logical sequences. Case reports or case series which reported detailed clinical description of the patients diagnosed with SJS, TEN and DRESS which were suspected or caused by the antiepileptic drugs levetiracetam, lamotrigine and lacosamide were included in the review. The review of the published case reports or case series covered period of 10 years starting from 01.05.2012 until 01.05.2022.

Results and discussion

44 publications describing a total of 52 patients which fulfilled the inclusion criteria for severe cutaneous reactions were included in the review. The age of the patients ranged from 2 years to 73 years (median: 32.7 years) and for 1 patient age was not reported. 32 of the patients were female (61.53%) and 20 male (38.47%) patients. DRESS, SJS and TEN were diagnosed in 15 (28.85%), 15 (28.85%) and 22 (42.30%) patients, respectively.

Levetiracetam

9 case reports (17.31%) related with levetiracetam use induced severe cutaneous reactions were identified during the review. 4 patients were diagnosed with DRESS and all of them completely recovered. 1 patient diagnosed with SJS completely recovered. 4 case reports related with levetiracetam induced TEN were identified. From them, 3 patients fully recovered and 1 was still recovering at the time when the article was published.

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Lamotrigine

42 case reports (80.77%) related with lamotrigine use were detected during the search of the PubMed/MEDLINE database. 10 patients (23.81%) were diagnosed with DRESS, and only one of the patients was with unknown outcome, while the other patients completely recovered. 14 patients (33.33%) were diagnosed with SJS. 9 of them have fully recovered, 1 patient recovered with sequelae, 1 patient had fatal outcome and 3 patients had unknown outcome. 18 patients with TEN (42.86%) were associated with lamotrigine use. 7 patients completely recovered, 4 patients were with status recovering at the period when the articles were published, 2 patients recovered with sequelae, 2 patients had fatal outcome and for 3 patients there was not specified the outcome from the ADRs.

Lacosamide

1 case report (1.92%) with DRESS related with lacosamide use was identified during the review. The patient fully recovered after the adverse drug reaction. In the retrieved case reports and case series, the onset of the severe cutaneous drug reactions was in range from 1 day to 6 months after initiating the anticonvulsant therapy. In most of them, the onset was approximately 2 weeks after the initiation of the AEDs. The therapy used for the patients with severe cutaneous drug reactions consisted mainly of corticosteroids, cyclosporine, immunoglobulins and antibiotics. The choice of antiepileptic drug depends on a variety of factors, including the type of seizure, drug response, side effects, and patient comorbidities (Man Kei Fong and Sheng, 2017). Aromatic AEDs such as phenytoin, carbamazepine and phenobarbital as well as some newer drugs, including lamotrigine have been related with eliciting a whole spectrum of hypersensitivity reactions, ranging from simple maculopapular skin eruptions to a severe life-threatening condition (Scaparrotta et al., 2011). During our literature review for published case reports and case series of the PubMed/MEDLINE database, 80.77% of the case reports with severe cutaneous reactions were associated with lamotrigine use. Severe cutaneous reactions due to lamotrigine have been shown to be associated with human leukocyte antigen (HLA) alleles in the population and the chances of these adverse effects are higher when lamotrigine is combined with valproate (Srivastava et al., 2017). These data are in line with the data obtained during our review as from the 42 identified case reports associated with lamotrigine, valproate was identified as concomitant drug in 16 cases. For levetiracetam, which is AED that does not contain an aromatic ring in their molecule, nine case reports of severe skin reactions were identified.

According to Li et al (2020), lacosamide is safe and effective in antiepileptic treatment, and its common side effects are dizziness, headache, drowsiness, diplopia, and cardiovascular abnormalities. Only one case report with lacosamide was identified during our review in which cross-reactivity with the drug was suspected in view of the rapid onset of DRESS syndrome after the initial rash resolution and soon after the introduction of the lacosamide (Man Kei Fong and Sheng, 2017).

Conclusion

The risk for an adverse event represents the probability for the event to occur among a defined exposed population and cannot be determined solely by literature screening. The conducted literature review for period of ten years suggested that when hypersensitivity skin reactions occurred, the aromatic AED lamotrigine was associated with higher risk of SJS/TEN/DRESS compared with levetiracetam and lacosamide. The frequency of lamotrigine induced DRESS and TEN is very rare (<1/10000) and for the lamotrigine induced SJS the frequency is defined as rare (≥1/10000 to <1/1000) (SmPC, Lamal, 2021). Levetiracetam as non-aromatic AED and lacosamide as one of the newest third-generation AED were associated with lower number of severe cutaneous reactions. These literature data also correlated with the data obtained from the EudraVigilance database regarding AEDs induced severe cutaneous reactions.
The benefits provided by the use of the antiepileptic drugs lamotrigine, levetiracetam and lacosamide far outweigh the risks that are related with them and therefore are safely used in everyday clinical practice for treatment of epilepsy.

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