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Carbamazepine and Clobazam induced severe iron deficiency Anemia - A rare case report

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Abstract

Carbamazepine and Clobazam are antiepileptic's used to control various types of seizures. Carbamazepine is an iminostilbene, and it is a front-line drug in antiepileptics. It acts on the voltage-dependent sodium channel. Clobazam is a benzodiazepine used for seizures, Lennox-gestalt syndrome, and febrile seizures in children. Both drugs had a good profile of efficacy to control seizures and some severe side effects like aplastic anemia, ataxia, SJS, Etc. In our case, the patient is a known case of seizure disorder and has used carbamazepine for 25 years and Clobazam for eight years. She developed an adverse drug reaction called severe iron deficiency anemia, which is classified as probable ADR using the Naranjos ADR probability scale. As per the modified shumock and thornton preventability scale, it is a preventable ADR.

Keywords: Carbamazepine (CBZ), Clobazam, iron deficiency anemia, dechallenge, ADR assessment

Introduction

The uncontrolled and aberrant brain electrical impulse that causes a seizure. Changes in consciousness, behavior, memory, and feelings are the result of this. Partial or generalized seizures are the two categories of seizures. The most frequent type of seizure in adults is a partial seizure, which begins with the activation of one region of the cortex and may show as simple symptoms like a motor or sensory phenomenon. Epilepsy affects about 50 million individuals worldwide, making it one of the most prevalent neurological conditions worldwide. People with epilepsy make up over 80% of the population in low- and middle-income nations. According to estimates, 70% of epilepsy sufferers could avoid seizures if their condition was adequately identified and treated.

The most popular method of treating epilepsy is using AEDs. In about 7 out of 10 people, they aid in seizure management. AEDs function by altering the balance of substances in your brain. They cannot treat epilepsy, but they can prevent seizures. Most antiepileptic drugs (AEDs) cause bone marrow toxicity and cause aplastic anemia, but in my case, AEDs caused iron deficiency anemia which is a rare phenomenon with unknown mechanism, there aren't many research that show the kinetics of Clobazam and Carbamazepine. We learned several fascinating things, such as the fact that these medications affect the mucosal layer and gastrointestinal pH, which reduces the absorption of dietary iron. Carbamazepine is an iminostilbenes class of

antiepileptics. It treats epilepsy, trigeminal neuralgia, and acute manic and mixed episodes of bipolar disorder. It modulates the voltage-gated sodium channels (VGSC), causing inhibition of action potentials and decreased synaptic transmission. It had side effects like dizziness, drowsiness, ataxia, nausea, vomiting, headache, abdominal pain, and increased blood pressure. Hematologic disorders include thrombocytopenia, leukopenia, neutropenia agranulocytosis, aplastic anemia, pure red cell aplasia, leukemia, or eosinophilia.[1] Clobazam is a benzodiazepine whose primary goal is to provide greater efficacy with fewer benzodiazepine-related side effects. Clobazam used as an adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in patients two years or older. Non-FDA-approved indications include adjunctive therapy for seizures seen with Dravet syndrome, adjunctive therapy for refractory status epilepticus, and adjunctive therapy for refractory focal epilepsy and anxiety. Clobazam had severe side effects, like hypothermia, with unknown mechanisms. Carbamazepine undergoes enzyme biotransformation through epoxidation with the formation of its metabolite, carbamazepine-10,11-epoxide (carbamazepine epoxide). Determining carbamazepine epoxide is clinically significant in therapeutic drug monitoring as it decreases the risk of toxic reactions and increases the possibility of reaching the expected therapeutic result.[2] The first carbamazepine overdose was reported in 1967, and significant toxicity occurs at levels higher than 40 mg/L (the normal therapeutic levels are 4 to 12 mg/L**).**[3] Clobazam was not excreted in its unchanged form by all species. The primary metabolite in the plasma of monkeys, dogs, and humans was N-demethylclobazam, which is assumed to cause side effects on long-term use.[4] However, in our case, the patient developed drug-induced iron deficiency anemia, which is a novel side effect that needs to be addressed to prevent its complications.

Case Report

A 48-year-old female patient known case of seizure disorder using carbamazepine 200mg two times a day for 25 years and clobazam 5mg two times a day for eight years as per physician advice, and suddenly she developed symptoms like shortness of breath, body weakness, legs pain, pale skin, on examination we observed brittle nails, glossitis, tachycardia, so physician suggested some lab test like CBP, thyroid profile, liver functioning test, total iron, vitamin B12, as we suspected a patient had Hemoglobin of 6gm/dl and iron less than 15mcg/dl this shows severe iron deficiency anemia, then immediately we suggested parenteral iron infusion therapy and neurologist opinion to withdraw the carbamazepine and clobazam as these are the suspected drugs causing anemia in this case. After the neurologist's opinion, we dechallenged both suspected drugs and started a combinational tablet of sodium valproate 133.5 mg and valproic acid 58 mg with controlled release. Both doses account for 200 mg twice daily, to avoid complications of anemia we prescribed ferrous ascorbate equivalent to elemental iron of 100mg + folic acid 1.5mg once daily for one month. Upon review after one month, Hb was improved to drastically to 11.4gm/dl and iron to 30mcg/dl. These results show positive dechallenge of suspected drugs. We thought rechallenge was unethical because re-exposure to suspected drugs may cause severe complications. Naranjo's assessment made to obtain the relationship between ADR and the suspected drug is probable with a score of 6, as per WHO-UMC criteria for causality assessment, which showed the association between ADR of iron deficiency anemia and suspected drugs was certain.

Discussion

No solid pharmacological evidence exists to prove carbamazepine and clobazam-induced iron deficiency anemia. The pathogenic mechanisms are still unknown; they may be related to an immunological mechanism, but drug pharmacokinetics and pharmacodynamic interactions also play an essential role. Further research is needed to assess the pathogenic mechanism and to establish evidence for hematological complications caused by antiepileptics.[5] However, there is one statement to be noted: a toxic metabolite of carbamazepine that is 10,11CBZ epoxide had significant inhibitory action on erythroid progenitor cells of the bone marrow, which causes aplastic anemia. We assume this toxic metabolite of CBZ had inhibitory action on dietary iron absorption by an unknown mechanism of action. However, one hypothesis is that this toxic metabolite makes gastric ph alkaline, which is not favorable for iron absorption. Clobazam has its metabolites N-desmethyl Clobazam and 4-hydroxy Clobazam. These interfere with folic acid and vitamin B12 absorption with unknown mechanisms and make gastric ph alkaline. These factors cause aplastic anemia, megaloblastic anemia, and iron deficiency anemia. The patient is taking vitamin B12 750mcg tablet as a neuroprotective agent for peripheral neuropathy, and this prevents megaloblastic anemia. As per WHO-UMC, the criteria of casualty assessment established the association between ADR and drugs. Naranjo's assessment to obtain the relationship between ADR and the suspected drug is probable with a score of 6; Hartwig's severity assessment proved this as moderate level 4(b); and as per the preventability scale by Shumock & Thornton, this is preventable ADR. So this drug was withdrawn from the patient, and appropriate treatment was given to help her recover better and faster

Conclusion

This ADR is preventable through patient counseling and clinical advice regarding therapy.Anti epileptics ADRs can be provided through a patient information leaflet by the manufacturer, but this practice still needs to be followed. The patient has not consulted the doctor for eight years due to a lack of awareness of therapy and its side effects.

So we conclude that iron deficiency anemia was induced by carbamazepine and Clobazam, established by our assessment scales, laboratory data, and positive dechallenge.

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