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Original Research Article

MULTIPLE RARE ADVERSE EFFECTS ASSOCIATED WITH LONG TERM USE OF CARBAMAZEPINE

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Abstract
Carbamazepine an anticonvulsant and mood stabilizer drug is used primarily in the treatment of seizures in epilepsy and bipolar disorders. Also used in conditions like trigeminal neuralgia, schizophrenia and attention deficit hyperactivity disorders, the drug belongs to one of the world health organization's list of essential medicines in a basic health system. Its use is associated with short term and long term adverse effects which range from mild to moderate to severe to fatal. The adverse reactions are also either common or rare. This article discusses a case report of a young adult female who reported with multiple rare adverse reactions to the drug involving joint, face, feet and oral cavity. Every clinician should know the possibility of such adverse reactions to help him differentiate associated conditions or diseases.

Key words: Allergy, hypersensitivity, epilepsy, tegretol

Introduction

Among most common neurological diseases of the world, epilepsy affects more than 50 million people worldwide. Since the introduction of carbamazepine *(5H-dibenz [b,f] azepine-5-carboxamide)* in the early sixties, most forms of the epilepsy are being treated presently with this drug. CBZ (carbamazepine) is an imminodibenzyl derivative that contains two of its derivatives (BIA 2-093 and BIA 2-024). The drug is metabolized in the liver and only 1 % of the administered dose is excreted in unchanged form. The main oxidative pathway involves formation of an active metabolite, carbamazepine-10, 11- epoxide which possesses anticonvulsant properties similar to those of CBZ. [1,2]The drug acts by reducing polysynaptic responses and blocking the post tetanic potentiation. The drug, despite its short half-life, can be given twice daily if an extended – release formulation is used. The drug is given mostly as a monotherapy regime

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and is initiated with a low daily dosage that is slowly increased till optimal effect is obtained.
Use of CBZ is also associated with adverse effects that range from reactions with other drugs to edible fruits. [4,5,6] Fatal cases of CBZ overdose were also recorded where patients were manifested with cardiac arrhythmias, abnormal movements, and seizures.[7]The occurrence of CBZ overdose is usually accidental, and in most times it is secondary to the co- administration of other substances. [8-13]Commonly found adverse reactions include blurred or double vision and involuntary eye movements, confusion, agitation, drooling, fear, irritability, loss of appetite and balance control. Amongst the rare adverse effects include bloody urine or stools, chest pain, fainting, muscle cramps, rapid weight gain, skin rashes, uncontrolled body movements, joint pain, slurred speech, swelling in the leg or foot, face, hands and swollen or painful glands. This article describes a clinical case of an adult female who reported with multiple rare adverse effects associated with the drug over a period of time.

Clinical case report

An adult female, aged 32 years reported to the department of Prosthodontics for treatment of temperomandibular joint pain and replacement of missing mandibular tooth with a fixed partial denture. Medical history revealed that the patient was under medical treatment for seizures, which had started 8 years back and was under medication for the condition since that time. Dental history revealed that the patient had lost mandibular left first molar due to caries six years back and had not sought any dental treatment. Extra oral examination revealed a diffuse swelling on the right side of the lower third of the face in the malar region with obliterated lower third of the naso labial groove and enhanced modiolus**(Fig.1)**.The right side temperomandibular joint was tender to palpation without any evidence of degenerative disc disorder. Palpation of extra oral and intra oral musculature did not produce any tender response from the patient. Intra oral examination revealed missing left mandibular first molar along with chronic generalized gingivitis with localized periodontitis in relation to posterior mandibularpremolars. Buccal corridor on the patients left region was obliterated and swelling of the external face was more visible intraorally than from outside. Clinical examination of the teeth revealed no evidence of wear or any interference of teeth in mandibular movements.

To complete the diagnosis the patient was referred to oral physician. Meanwhile to rule out joint pain because of occlusal problems, primary impressions were made with Irreversible hydrocolloid (Jeltrate, Alginate, Fast Set; Dentsply Intl, York, Pa) and then poured with Type-III dental stone (Pankaj Industries, Mumbai, India). Diagnostic casts, thus obtained were then mounted on a Hanau Widevue semi adjustable articulator (Waterpik, Ft Collins, CO, USA) with the help of a face bow (Quick Mount Face-Bow; Whip Mix Corp). After mounting the casts, the articulator was programmed using a protrusive interocclusal record and Hanau formula to simulate the mandibular movements. Diagnosis was completed when the patient returned for the next appointment for dental treatment after consultation of the physician. The patient was asked to undergo liver function tests to confirm evidence of hepatotoxicity. The joint pain in the temperomandibular region was not associated to occlusion even though a single molar was missing.

Dental treatment was carried for the patient and a fixed partial denture was fabricated in relation to missing left mandibular first molar. All necessary precautions were taken during clinical and laboratory procedures.

Discussion:

Adverse reaction of CBZ at therapeutic doses that affect central nervous and digestive system are related to acute CBZ toxicity and may include sedation, dizziness, diarrhea and even constipation. Signs of toxicity generally occur at plasma CBZ concentrations in excess of 10 to 12mg/L, with diplopia, nystagmus, and aplastic anemia being the most characteristic ones[14]Long term treatment on the other hand,

usually modifies plasma lipids, hyponatremia, and weight gain and may induce several allergic reactions. [2]Although the mechanism of action of CBZ is beyond the scope of this article, but to summarize, the drug is believed to inhibit sodium channel activity and voltage – gated calcium channels.[15-17]

Rare adverse reactions observed in this patient included temperomandibular joint pain, diffuse swelling on lower third of the face (swollen salivary gland), history of swelling of feet (one week ago) and slurred speech probably due to swelling. The swelling associated to this drug is so conspicuous that unless one does not observe carefully it might miss a naked eye. Facial swelling or facial edema has been associated to clinically apparent hepatotoxicity that occurs in the setting of anticonvulsant hypersensitivity syndrome in about half of the cases with onset of fever and rash. Hepatotoxicity can also occur without immuno – allergic features in which case the latency to onset can be after a long period of time.[18, 19]

Conclusion

Carbamazepine adverse reactions do include swelling of the face and feet, temperomandibular joint tenderness and pain, slurred speech though rare. In addition, intra oral features associated with swelling decrease buccal corridor space on the affected side. The patient may present symptom of inability to eat on the affected side due to tenderness of joints.

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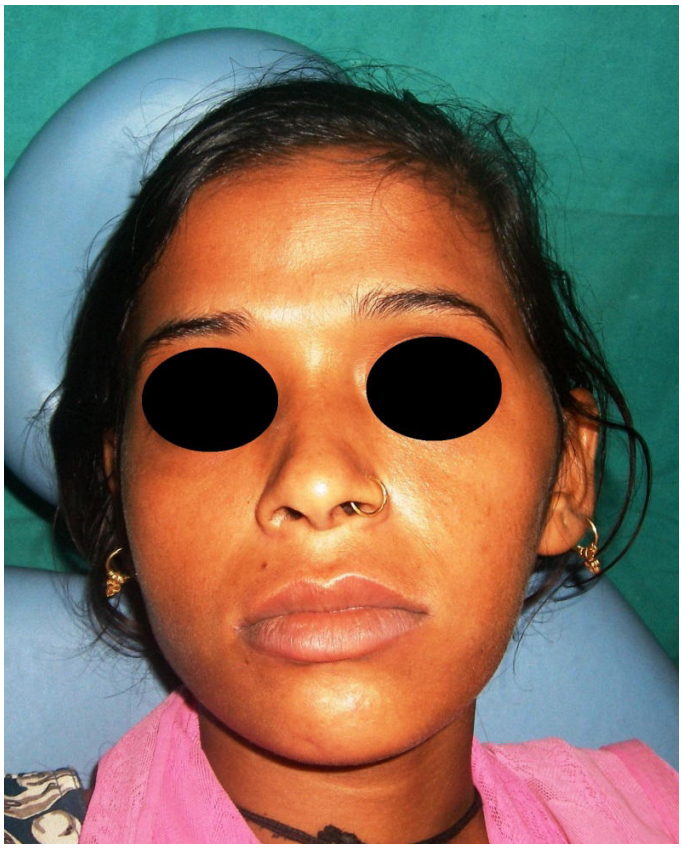

Figure 1: Extra oral view shows diffuse swelling of right lower third of face with obliteration of nasolabial groove in the region.