Carbamazepine-induced dystonia in an adolescent

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Introduction

Dystonia is a relatively common clinical condition, identified by its characteristic features: Sustained muscle contractions, twisting, and abnormal postures.¹ The term “primary dystonia” is used to describe dystonia where no cause could be identified (idiopathic), while the term “secondary” is used to describe dystonia which is found to result from an identifiable cause.¹

The clinical features of dystonia are often bizarre and can be varied as blepharospasms, aversive eye movements, trismus, mouth opening, tongue protrusion, grimacing, distortion of lips, displacement/rotation of head and neck, hyperpronation, finger/wrist posturing, opisthotonus, and other axial distortions and gait disturbances. Dysarthria, dysphagia, jaw dislocation, tongue amputation, and respiratory cyanosis with stridor may follow. A cramp-like discomfort or tightness of jaw or tongue may occur, making chewing, swallowing, or speaking difficult.¹ It produces substantial disability and from a therapeutic perspective, the available treatments are for the most part unsatisfactory.

Drug-induced acute dystonia (DID) is one of the most common forms of secondary dystonia. This complication is seen with varying frequency, with varying rates being reported, based on differences in the population under study, specific drugs prescribed, and indications for the drugs being prescribed.² Drugs with antidopaminergic properties, such as first and second generation antipsychotics are among the agents most commonly implicated in drug-induced dystonia.³ Less frequently, other drug classes, like anti-emetics such as metoclopramide and prochlorperazine, anticonvulsants such as phenytoin, antidepressants such as nefazodone, citalopram, escitalopram, bupropion and duloxetine, and antivertigo agents such as cinnarizine and flunarizine are involved in this type of complication.¹ The dystonia can occur immediately after ingestion of a single dose, over the course of several days of therapeutic dose administration, after dose increase, or as a manifestation of overdosage.¹ Most cases occur in the first 72 h of medication use, often with dramatic symptoms, especially in children.¹ Patients at higher risk for DID include those with younger age, of male gender, a previous history of similar reactions, recent use of cocaine, comorbidity with mood disorders, and metabolic abnormalities (hypokalemia, dehydration, hypoparathyroidism, etc.).¹

ABSTRACT

Dystonia is sustained muscle contraction, which may be primary or secondary to other causes. Drugs comprise one of the most important causes for the secondary dystonia, the usual mechanism being a dopaminergic blockade. There are very few reports describing dystonia resulting from carbamazepine (CBZ) administration. In this case report, a 16-year-old male with mental retardation and seizure disorder developed dystonia at therapeutic blood levels of CBZ.

KEY WORDS: Carbamazepine, dopamine, dystonia

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Here, we discuss the case of an adolescent, who developed dystonia at therapeutic doses of carbamazepine (CBZ). Very few studies previously report such an effect with this medication.

**Case Report**

A 16-year-old male with moderate mental retardation presented to our clinic with 2 years history of multiple episodes of chewing movements accompanied by a state of altered consciousness, during which he would not respond to his name being called out and would continue to give a vacant stare in one direction. There was no history of unconsciousness, repeated rhythmic movements of the limbs, loss of tone resulting in falls, tongue bile, and urinary incontinence. Each episode was abrupt in onset and lasted about 5–10 min, after which the patient would spontaneously become responsive to the surroundings once again. A clinical impression of complex partial seizure was made based on the semiology, and the patient was started on CBZ 200 mg twice daily (8 mg/kg/day) for the same.

The patient was brought to the emergency department 4 days later with acute dystonia of the neck which had started approximately 2 h back. His neck was found to be held firmly in an extended position with the head tilted toward the right. He had been fully conscious, oriented, and responsive to external stimuli throughout this period, though he was noticed to be agitated. He was administered promethazine 50 mg intramuscularly with the dual purpose of achieving sedation, as well as using its anticholinergic properties to relieve the dystonia. The dystonia was seen to resolve completely within the next 25–30 min. A serum CBZ level estimation was done, and levels of 8 mcg/ml were obtained. Since it was within the normal range (5–12 mcg/ml), it was considered unlikely that the CBZ toxicity could have led to the dystonia. A literature review also confirmed that there was very little likelihood of the dystonia resulting from the use of CBZ, especially below toxic levels.

Therefore, the patient was advised to continue CBZ and kept under observation. He developed the cervical dystonia once again after 3 days. Supportive care was provided and promethazine 50 mg was administered via the intramuscular route. The dystonia resolved within a period of 25–30 min. It was considered that CBZ could be the offending agent, responsible for the episodes of dystonia. Thus, it was decided to stop CBZ and shift the patient over to another anticonvulsant drug.

The patient was shifted over to sodium valproate at 1200 mg/day (24 mg/kg/day) for seizure prophylaxis and was followed up for a 2-week period during which the patient remained seizure free, and no recurrence of dystonia was found.

**Discussion**

CBZ is a drug that is widely used all over the world for epilepsy, bipolar disorder, and trigeminal neuralgia, apart from off-label indications such as restless legs syndrome. While stabilization of sodium channels is believed to be the mechanism behind its antiepileptic properties, researchers have been looking into a possible action at the level of the dopaminergic system too. Scientific literature on the connection between CBZ and dopamine blockade, however, is far from conclusive at this point. Animal studies have shown CBZs ability to increase acetylcholine in striatum and inhibit dopamine transmission, with the latter being observed particularly at subtherapeutic levels, an effect which wanes as the concentration of CBZ increases in the blood, thus indicating the possibility of dystonias resulting from the administration of CBZ, at subtherapeutic blood concentrations. Other literature points toward CBZ causing a dyskinetic syndrome only in toxic doses, due to dopamine blockade. Other studies, exploring the antipsychotic effects of CBZ, have shed some light on its role in dopaminergic transmission, with indications that the antipsychotic effects of CBZ might result from reduced sensitivity of presynaptic dopamine receptors. Indeed, presynaptic effects after administration of CBZ showed reduced synthesis of dopamine and a reduced rate of disappearance of dopamine after tyrosine hydroxylase inhibition, indicating a reduction in turnover. Researchers have also used this basis to explain how CBZ causes a slight increase in prolactin levels, similar to neuroleptics which act by blocking D2 receptors.

Rare instances of dystonias associated with CBZ have been reported in literature, but this has been largely confined to patients with overdoses/toxic blood levels or drug combinations. Literature regarding this happening at therapeutic levels is scant, especially in the case of adolescents. In this case, the patient developed dystonia at therapeutic levels of CBZ, with the adverse drug reaction corresponding to a level of “definite causality” on the Naranjo et al. adverse drug reaction probability scale and of “certain causality” based on the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre scale. However, we wish to caution the readers that findings from a single case should not be generalized, in spite of the high probability of causality being indicated by the scale used. This case merely serves to indicate the possibility of CBZ causing dystonia at blood levels within the therapeutic range, with the aim to usher in further research in this direction.

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**Conflicts of Interest**

There are no conflicts of interest.

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