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The Increased Frequency of Seizures Caused by Carbamazepine Overdose: A Case Report

Karbamazepin Doz Aşımına Bağlı Sıklaşan Epileptik Nöbetler: Bir Olgu Sunumu

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Summary

Carbamazepine (CBZ) overdose is a problem occasionally seen that could be fatal. In the event of intoxication, complications such as cardiac arrhythmia, breathing depression and neurologic symptoms can be noted, extending even to causing a coma. In this report, we present a 22 year old epileptic patient who has an increased frequency of seizures due to high doses of CBZ. After noting the blood drug level as 24 µgr/ml (normal range: 4-12), necessary precautions were taken to reduce the drug overdose. The CBZ dose was reduced, the seizures did not recur. The increased frequency of seizures does not necessarily indicate an inadequate drug dose in an epileptic patient; on the contrary, it can be an indication of drug overdose.

Key words: Blood drug level; carbamazepine overdose; epilepsy.

Özet

Karbamazepin (KBZ) doz aşımı zaman zaman karşılaşılan ve yaşamı tehdit edebilen bir problemdir. İntoksikasyon durumunda kardiyak aritmi, solunum depresyonu ve komaya kadar ilerleyebilen nörolojik belirtiler görülebilir. Burada tedavi amaçlı yüksek doz KBZ kullanımının arkasından nöbetleri sıklaşan 22 yaşında bir hasta sunduk. Hastanın ilaç kan düzeyi 24µgr/ml (Normal: 4-12) olarak saptandığında ilaç doz aşımına yönelik tedavisi başlandı, KBZ dozu azaltıldı. Tedavi sonrasında nöbetleri tekrarlamadı. Epileptik bir hastada nöbet sıklığının artması mutlaka yetersiz ilaç dozu anlamına gelmemelidir; tam tersine bu durum ilaç doz aşımının bir göstergesi de olabilir.

Anahtar sözcükler: Kan ilaç düzeyi; karbamazepin doz aşımı; epilepsi.

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Introduction

Carbamazepine (CBZ) inhibits the secretion of glutamate and glutamate-like transmitters by blocking presynaptic voltage gated sodium channels in the central nervous system.[1] It also blocks N-methyl D-aspartate and adenosine receptors. It has been used for the treatment of postherpetic neuralgia, phantom extremity pains, and manic depressive disorders, except in those patients undergoing treatment for epilepsy.[1,2] The therapeutic dosage of CBZ is 15-25 mg/kg and serum CBZ levels should be between 4-12 µg/ml. Dizziness, headache, increase in epileptic activity, diplopia, blurred vision, tremor, rigidity, dysarthria, and nystagmus are adverse effects that have been reported with overdose of this drug on the central nervous system.[1-3] To diminish gastrointestinal involvement during the treatment of overdose, activated charcoal is given to the patient at repetitive doses (at 4-6 hour intervals).[2] In the event of life-threatening conditions, activated charcoal hemodialysis and hemoperfusion are applied.[4,5] Since high serum levels of CBZ can cause undesirable effects, the blood drug levels have to be controlled.

Here, we present a case taking a high therapeutic dose of CBZ that resulted in an increased frequency of epileptic seizures.

Case Report

A 22-year-old patient was admitted to our emergency clinic with seizures. The patient had been under care for simple partial epilepsy for the past 21 years, had been receiving 2x500 mg CBZ treatment, and has had seizures less frequently than once a month. The patient's relatives reported that he first had contractions on the right side followed by the left. These contractions lasted for nearly 15 minutes, and he could communicate with them during the seizure. He did not clamp down on his teeth, had no salivation or staring, but he had had 3 seizures since the night before. The patient also had occasional complaints of diplopia. Two days earlier, the patient had come to our emergency clinic suffering a simple partial seizure lasting for one minute. At that time, the CBZ dose that he had been using, 2x400 mg was considered as inadequate and changed to 2x500 mg. On his present arrival to our emergency clinic, he was conscious, oriented, cooperative, and had mild mental retardation. The patient's physical examination revealed that his blood pressure was 130/85 mmHg, his pulsation was 83/min rhythmic, his respiratory rate was 20/min, and his body temperature was 36.6°C. An ECG examination revealed that the heart was at normal rhythm with a heart rate of 80/min. In a neurological examination, his pupillary was isochoric, his direct and indirect light reflexes were positive, and his eye movements were normal in all directions. In a motor examination, his right arm exhibited slight weakness. Deep tendon reflexes were normoactive bilaterally. A blood analysis revealed that his leucocyte was 4.850/mm^3, hemoglobin was 15.1 g/dl, thrombocyte was 229000/mm^3, total protein was 6.4 g/dl (normal: 6.3-8.7), albumin was 3.4 g/dl (normal: 3.5-5.4), blood urea nitrogen was 7.1 mg/dl, creatinin was 0.84 mg/dl, sodium was 134 mEg/L, potassium was 3.77 mEg/dL, AST was 20 U/L, and ALT was 8 U/L. Upon recurrence of focal motor seizure while in the emergency room, I.V. diazepam treatment was administered. When the patient's blood CBZ levels reached 24 µg/ml (normal level is 4-12 µg/ml), a combination of 1000 cc Isotonic, 1000cc 5% Dextrose, and 100 mEq $NaHCO_3$ was given to him, since the seizures were attributed to CBZ toxicity.

A nasogastric catheter was applied to him for gastric drainage, and then he was given activated charcoal (1 g/kg). The activated charcoal was administered in 4 hour intervals a total of three times. In order to maintain the patient's treatment and to regulate medicine doses, he was hospitalized in the neurology service. During the service follow-ups, his CBZ dose was regulated to 2x300 mg, and his serum CBZ level, which was checked a few days later, was determined to be 12 µg/ml. The patient had no seizures and a normal EEG during the follow-up, and was discharged from the hospital.

Discussion

Carbamazepine is an antiepileptic drug that has tricyclic content. It has been used for the treatment of partial and generalized epilepsies, bipolar affection disorder, trigeminal neuralgia, postherpetic neuralgia, and phantom extremity pains. It inhibits sodium channels that are responsive to presynaptic voltage in the central nervous system. Because of the drug's lipophilic content, it is absorbed differently based on oral intake. It can reach plasma crest levels within 6-8 hours, and these levels can remain for up to 24 hours. After it is taken orally, it quickly passes to the brain because of its high lipid solubility.[1-3]

In the literature, the majority of the articles about CBZ have referenced chronic adverse effects. Symptoms and findings are contingent upon the dose and are proportional to the serum levels. Symptoms are often neurologic may change depending upon absorption from the gastrointestinal system.[2,3]

Many sources report that doses over 40 mg/kg are fatal.[1-3] While symptoms are generally neurologic (ataxia, nystagmus, mydriasis, movement disorders, anticholinergic toxidermia) for amounts taken over 20 mg/kg, doses over 50 mg/kg can lead to central nervous system problems such as unconsciousness, coma, seizure and cardiotoxicity, which can progress and become fatal.[3,4] The protein and albumin levels in our patient were close to the lower border line. In patients with lower protein and albumin levels, the toxic signs of CBZ and its active metabolites 'CBZ 10,11-epoxid' might be seen even for the lower doses, since both are highly bound to plasma proteins.[1,2,6]

Plasmapheresis is a technique that gives successful results and has recently been used for CBZ overdose.[7] For CBZ overdose, hemoperfusion and hemodialysis are recommended when supportive care is unattainable, and coma, seizure, and cardiovascular risks are high (serum CBZ level >50 mg/L).[8-11] Because the blood drug level was not high in our patient, hemoperfusion and hemodialysis were not needed.

The CBZ dose used for our patient was 1000 mg/day. For such a patient, development of neurological symptoms can be possible. The patient's blood drug level was 24 µg/ml, and he had increasingly frequent epileptic seizures. CBZ-induced hyponatremia and seizures have been well described before.[12] However, the sodium levels were within normal ranges in our patient. CBZ is a powerful anticholinergic drug, and therefore, increased seizures may occur as a result of the anticholinergic effect. This is most likely because this type of drug causes a blockade of the inhibitory presynaptic acetylcholine receptors, which are of the nicotinic type. This blockade would interrupt the normal feedback/control mechanism and allow for continued release of transmitters into the synapse.[6,13] In addition, CBZ is also an inhibitor of the central nervous system adenosine receptors. In case of massive overdose, the A2a receptor may lose selectivity. CBZ may inhibit A2a as well, behaving like the known adenosine receptor inhibitors theophylline and caffeine. Inhibition of adenosine receptors may cause the removal of the body's natural anticonvulsant mechanism.[6] With repetitive activated charcoal, the amount of drug penetrating to the enterohepatic circulation was kept at a minimum level, and therefore other possible adverse effects on the central nervous system and a need for intensive care were prevented.[3]

It is important to note that changing the treatment dose will not be a correct implementation without considering blood drug level of patients under CBZ treatment. Neurological findings obtained from patients who use CBZ must be taken into consideration. The amount of medicine that has been taken, the measured serum CBZ level, and symptoms and treatment findings must be used to determine further diagnosis and treatment. For example, evaluating an epilepsy patient in the emergency room, his/her blood drug level must be checked, rather than just increasing the dose, supposing that the medicine is at inadequate level. When the CBZ level is over 50 µg/ml, which has been considered to be fatal for the patient, a constant analysis of drug blood level is of vital importance.

The reasons for increased epileptic seizure frequency have been investigated in practice. However, at clinics, a drug overdose has to be considered, and the blood level and dose of all medicines that the patient is using must be evaluated together.

Conflict of Interest

The authors declares no conflict of interest related to this work.

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