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Case Report

Remitting-Relapsing Carbamazepine Overdosage Mimicking Vertebrobasilar Transient Ischemic Attacks

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Abstract

The objective of this article is to describe an atypical, remitting-relapsing presentation of carbamazepine toxicity due to its interaction with nebivolol. The method we use is a case report of an elderly epileptic patient in treatment with antiepileptic drugs (AEDs) and antihypertensive drugs, manifesting transient neurological symptoms in association with high blood pressure values. The case report is of a 72-year-old male by forty years of age had tonic-clonic seizures related to the presence of a cerebral arteriovenous malformation. Seizures had been successfully controlled for many years by the same dosage of carbamazepine and lamotrigine, and recently total serum carbamazepine levels resulted within the “therapeutic range.” He had also a history of controlled essential hypertension, but lately he manifested a

scarce control of his blood pressure values. Few days after a modification of his antihypertensive therapy, the patient had two transient episodes of dysarthria, ataxia, and dizziness. At the emergency department, his blood pressure values were 190/110 mmHg, ECG and routine blood tests were normal, and a brain CT did not show acute lesions; about two hours later, his neurological examination was normal. Morning fasting carbamazepine serum levels were “normal” too; therefore, his symptoms were initially interpreted as vertebrobasilar transient ischemic attacks. However, the recurrence of similar episodes despite the normalization of his blood pressure suggested a carbamazepine intoxication. Indeed, its dosage resulted too high just in occasion of one of his attacks. A moderate reduction of carbamazepine was followed by cessation of toxicity. This case reminds us to be aware of adverse consequences of other drugs

in patients assuming carbamazepine: in this case, its toxicity was consequential to a likely metabolic interaction with nebivolol.

Keywords: TIA, carbamazepine toxicity, elderly, drug-drug interaction.

Introduction

Carbamazepine (CBZ) represents a “first-line” drug for the treatment of epilepsy, and it is also widely used to treat various disorders with a significant prevalence among the adult and the elderly population, including mood disorders, fibromyalgia, and other forms of chronic pain (Bertilsson, 1978; Diaz et al., 2008; Hosia-Randell et al., 2008). Given to its pharmacological kinetic properties (Lordos et al., 2009), the chance of occurrence of CBZ-related adverse effects is increased in patients who need multiple drug use as a consequence of drug interactions (Bertilsson, 1978; Diaz et al., 2008; Hosia-Randell et al., 2008).

Neurological manifestations of CBZ toxicity include a wide range of symptoms, among which ataxia, somnolence, and eye

abnormalities are common: their acute onset with stable or progressive course can require, especially in elderly patients, a differential diagnosis with a vertebrobasilar stroke; however, the detection of increased total or free CBZ serum levels usually allows a correct diagnosis.

Here, we describe an atypical neurological presentation of CBZ overdosage in an old epileptic and hypertensive patient in treatment with multiple drugs, including CBZ, characterized by a remitting-relapsing course mimicking vertebrobasilar transient ischemic attacks. In this case, CBZ overdosage could be documented only in occasion of one of his attacks while routine fasting CBZ levels had resulted normal. The etiology of CBZ overdosage is reasonably due to its interaction with nebivolol,

recently added on to his morning therapy to manage high blood pressure values.

Case Report

Our patient, a 72-year-old male, by forty years of age had secondarily generalized epilepsy due to the presence of a large right temporal arteriovenous malformation (AVM). His seizures were successfully controlled by a long-term association of CBZ (400 mg every 12 hours) and lamotrigine (100 mg q.d.), and recently his serum carbamazepine levels were within the "therapeutic range," while lamotrigine levels had never been checked.

He was also affected by primary hypertension: two weeks prior, because of a scarce control of his systolic blood pressure values, his clinician added nebivolol 5 mg q.d. to his usual antihypertensive therapy (barnidipine 20 mg q.d., candesartan-hydrochlorothiazide 32/25 mg q.d., and canrenone 50 mg q.d.).

The patient came to the emergency department of our hospital for the sudden onset of dysarthria, dizziness, and gait instability; the day before, he had refused the admission at another hospital for a similar episode associated with high blood pressure values.

At admittance, his neurological symptoms had improved, only showing a lateropulsion to the left in the standing position and during gait. His blood pressure values were 190/110 mmHg. ECG and routine blood tests were normal, and brain CT scan did not

show acute lesions. Administration of nifedipine controlled his blood pressure, and about one hour later his neurological examination was normal, so these episodes were interpreted as a vertebrobasilar transient ischemic attack related to hypertension. During the following days, the patient underwent extensive diagnostic tests. Glucose metabolism, renal, and hepatic functions were normal; serum fasting carbamazepine resulted within “therapeutic levels” (9 μg/ml, normal range 2.0-10.0 μg/ml), while lamotrigine determination was not available at our laboratory. An EEG Holter documented a right temporal theta activity without epileptic discharges or spikes. Echocardiography documented a left ventricular hypertrophy. A brain MRI, including both angiographic and DWI studies, confirmed the presence of a huge right temporal AVM, but excluded acute or subacute ischemic lesions. Doppler ultrasound

studies revealed nonstenotic fibrocalcific atherosclerotic plaques in both internal carotids, but the increased risk of intracranial bleeding related to the AVM contraindicated antiplatelet therapy. Modification of antihypertensive therapy, consisting of withdrawal of hydrochlortiazide and canrenone and introduction of furosemide 25 mg q.d. and amlopidine 10 mg q.d., achieved a good control on patient's blood pressure values, but he still presented other transient neurological episodes: their recurrence about 5–7 hours after the intake of the morning dose suggested their relation to transient CBZ overdosage likely caused by the recent modification of the patient's therapy, adding on nebivolol. Indeed, serum CBZ levels determination during one of his attacks exceeded the "therapeutic range" (15.5 μg/ml). Reducing the morning dose of carbamazepine to 200 mg, patient's symptoms resolved. This reduction did not affect the

control on epilepsy during four months of follow up, and serum carbamazepine levels stayed within the “therapeutic range” (8.7 μg/ml).

Discussion

The occurrence of transient neurological deficits in an old patient with epilepsy and hypertension was previously reported (Marini et al., 2004): in such case, the addition of CBZ for the control of epilepsy was associated with the occurrence of a marked uncontrolled hypertension and of transient episodes of dysarthria, vertigo, and unstable gait. Additional antihypertensive medications did not reduce his blood pressure, while a substantial reduction of his carbamazepine dose resulted in the control of his blood pressure and no recurrence of his

symptoms. The authors proposed a causal relationship between the introduction of CBZ and the hypertension and interpreted the neurological episodes as hypertension-related, transient ischemic attacks.

Instead, in this case, several findings support an opposite causal relationship between the antihypertensive treatment and the occurrence of CBZ toxicity, since our patient developed a primary hypertension, many years after he had started CBZ as a treatment for his epilepsy. During his long-term CBZ treatment, he never showed any related side effects, and his hypertension was generally controlled by antihypertensive drugs. Only recently, evidence of raised blood pressure values required an adjustment of his antihypertensive therapy, and indeed our patient started to manifest transient neurological symptoms

right in concomitance of this change. Finally, his blood pressure values were again controlled by a further modification of his antihypertensive treatment, while he was still taking his usual CBZ dose.

The diagnosis of CBZ overdosage in our patient was challenging because (i) in an elderly patient with cerebrovascular risk factors, transient neurological symptoms concomitant with high blood pressure values support a diagnosis of TIA; (ii) he was on long-term therapy with the same CBZ dosage, and his serum CBZ levels were repeatedly normal, including the routine fasting determination during his last hospitalization; and (iii) symptoms and signs of carbamazepine toxicity were markedly fluctuating with interictal neurological examinations completely normal,

including ocular motility, and in fact overdose serum CBZ levels could be detected only during one of his attacks.

Symptoms and laboratory findings indicative of CBZ toxicity occurred in our patient about 5–7 hours after the intake of the morning dose, with a time interval corresponding to its peak plasma concentration (Lordos et al., 2009); therefore, this issue strongly suggests that the transient CBZ overdosage would result from its interaction with other drugs taken in the morning as well.

Although there are no data in the literature regarding specific drug-drug interactions with CBZ, this observation strongly suggests that nebivolol, recently added on in therapy and constantly taken together with the morning dose of CBZ by our

patient, would induce transient CBZ overdosage either affecting its binding to serum carrier proteins or delaying its hepatic metabolism by CYT P450 (Patsalos PN et al., 2002). According to this hypothesis, a selective reduction of the morning carbamazepine dose completely resolved patient's symptoms. On the other hand, although we could not rule out the occurrence of lamotrigine overdosage, which manifests with similar symptoms, we believe that this event is very unlikely because the metabolism of lamotrigine is not regulated by CYT P450 and, furthermore, CBZ overdosage is known to enhance lamotrigine metabolism (Patsalos et al., 2002).

In conclusion, in agreement with previous studies (Bertilsson, 1978; Diaz et al., 2008; Hosia-Randell et al., 2008; Marini et al., 2003), this report underlines the importance of always keeping

in mind the effects of drugs interaction in the therapeutic management of adult patients with comorbidities requiring multiple drug use.

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