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Case Report

BISOPROLOL-INDUCED DELIRIUM IN A PATIENT WITH ISCHEMIC STROKE: A CASE REPORT

Abstract

Delirium is a common neuropsychiatric syndrome that involves a number of symptoms including diffuse cognitive impairment, hallucinations, mood lability and disturbances in the sleep-wake cycle. Besides, delirium is a common condition associated with adverse outcomes, including increase in morbidity, mortality, and need of health services utilization. Even though the etiology of cognitive impairment is multifactorial, drugs also are known to be an important cause of delirium. In this study, we present a patient manifesting a bisoprolol-induced acute delirium, for whom the delirium symptoms completely disappear after bisoprolol was ceased. Bisoprolol is widely used in cardiology for the treatment of hypertension and arrhythmia. Beta-blocking agents have been recognized for some time to have central nervous system effects, which could adversely cause common psychiatric syndromes.

Key Words: Atrial Fibrillation; Bisoprolol; Delirium.

Olgu Sunumu

İSKEMİK İNMELİ BİR HASTADA BİSOPROLOLE BAĞLI DELİRYUM: BİR OLGU SUNUMU

Öz

Deliryum yaygın bilişsel bozukluk, hallüsinasyonlar, duygu-durum değişiklikleri ve uyku-uyanıklık döngüsünde bozulmalar gibi çok sayıda belirtiyi içeren yaygın bir nöropsikiyatrik klinik sendromdur. Hastaneye yatan tüm hastaların %10-30'unda görülmektedir. Ayrıca, Deliryum morbidite, mortalite ve sağlık hizmetlerinin kullanılmasında artmayı içeren kötü sonuçlarla ilişkili yaygın bir durumdur. Kognitif yetersizliğin etiyolojisi multifaktöriyel olarak düşünülse de, ilaçların da deliryumun önemli bir nedeni olduğu bilinmektedir. Bu çalışmada, bisoprololün neden olduğu akut deliryum tablosuyla gelen ve bisoprololün kesilmesiyle deliryum semptomlarının tamamen kaybolduğu bir hastayı sunuyoruz. Bisoprolol kardiyologlar tarafından hipertansiyon ve aritmi tedavisi için yaygın olarak kullanılmaktadır. Beta blokör ajanların bazen santral sistemi etkilerinin olabildiği ve bu nedenle yaygın psikiyatrik sendromların istenmeyen bir nedeni olabildikleri belirlenmiştir.

Anahtar Sözcükler: Atrial Fibrilasyon, Bisoprolol, Deliryum.

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INRODUCTION

Cerebrovascular diseases (CVD) are known to be among the most frequently encountered diseases causing disability, and mentioned in third rank as a cause of death after heart diseases and cancer. Cardioembolic strokes account for one fourth to one third of all types of ischemic strokes. Atrial fibrillation (AF), the prevalence of which increases with aging, is the most common cause of cardioembolic stroke. Paroxysmal atrial fibrillation (PAF) is associated with a comparable increase in risk of ischemic stroke as permanent AF. Delirium is a psychiatric disorder characterized with primarily a disturbance of consciousness, attention, cognition, and perception but can also affect sleep, psychomotor activity, and emotions (1). According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), it develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day. It may occur due to a general medical condition, a substance or medication (2). Delirium is a significant problem for older people and is associated with poor outcomes including longer stay in the hospital, increased risk of morbidity and mortality (3).

Bisoprolol is a widely used agent for the treatment of hypertension and arrhythmia. However, central nervous system effects of beta-blocking agents, and the fact that they can cause common psychiatric syndromes (5%–20%) is known for a long time (4,5). In this study, we present a patient manifesting a bisoprolol-induced acute delirium, for whom the delirium symptoms completely disappear after bisoprolol was ceased.

CASE

A 87-year-old woman with acute weakness and numbness in right arm and leg was admitted to our neurology unit. The patient's history was unremarkable and she had no history of smoking, alcohol, drug use, or any neurologic problems. The patient was aware of her name, and actual place and time. Neurological examination revealed right central facial paralysis, right hemiparesis and right hemihypoesthesia. The blood pressure of the patient was 130/75 mmHg. Laboratory tests (i.e. complete blood count, metabolic panel, thyroid-stimulating hormone, and urinalysis) were unremarkable. The initial cranial computed tomography (CT) was normal. In examinations to clarify the etiology of right-sided hemiparesis, patient's brain MRI (i.e. T2 hyperintense, T1 hypointense slices extending from left parietal to convexity, diffusion images of acute infarct region observed as diffusion restriction) revealed ischemic stroke. As soon as the diagnosis of ischemic stroke was made, the patient was put on 100 mg of acetylsalicylic acid treatment. The electrocardiography of patient who was consulted with a cardiologist to investigate the etiology of ischemic stroke, was viewed as a normal sinus rhythm. Paroxysmal atrial fibrillation (PAF) was found in patient's 24 hour holter electrocardiogram and his echocardiography was observed as EF: 55% PAB: 25 TY1° MY1°. Increase in bilateral carotid intima-media thickness was observed in doppler ultrasonography of carotid-vertebral. The patient, when history and clinical status taken together, was diagnosed with cardioembolic induced ischemic stroke. As consulted to cardiology clinic, the patient was started 5 mg bisoprolol and warfarin therapy. Within 12 hours of bisoprolol administration, the patient developed acute symptoms of delirium including agitation, disorientation, aggression, and generalized confusion. According to DSM-V, the patient was diagnosed with acute delirium. The investigations including hemogram, biochemical evaluation of renal and liver function, electrolytes, urinalysis, arterial blood gas analysis, electrocardiogram, and chest x-ray were repeated at each delirium episode, and found to be normal. After development of clinical condition, the patient's repeated physical and neurological examination was normal. Repeated cranial MRI revealed the same findings, and thus, any other possible intracranial etiologic causes were excluded. Therefore, we think that delirium could be caused by bisoprolol administration. After the drug was discontinued, patient's symptoms spontaneously resolved without any medication within the following twenty-four hours. It is worth to attention that delirium symptoms including confusion, distractibility, agitation, disorientation and perception disturbances recurred two more times after recommencement of bisoprolol. With bisoprolol started again, delirium table improved and the situation got better within 24 hours after the cease of medication. During the episodes of delirium, the blood pressure and fever of the patient was normal. There were no new neurological symptoms or findings. The patient was not given any antipsychotic medicine, in order to be able to follow the general course. Twenty-four hours later, the patient's delirium completely resolved and he was alert and oriented. Bisoprolol was stopped after 3 recurrences of delirium. Diltiazem was given for PAF, and no adverse effect was observed. In the follow-up period in hospital, the patient had no attack of delirium. After discharge of the patient, outpatient clinic controls have revealed mild right hemi-paresis with no delirium attack at all.

Discussion

Delirium is defined as a mental disorder with reversible acute continuing with confusion, mental status disorder, emotional liability, hallucinations or illusions and inappropriate, impulsive, unrealistic and harsh treatment. Conditions such as infection, fever, metabolic imbalances, renal or hepatic dysfunction, endocrine dysfunction, thiamine deficiency, drug intoxication or failure, postoperative conditions, severe blood loss, cardiac arrhythmias and cardiac insufficiency, hypertensive encephalopathy, head trauma, epileptic attacks, drug side effects, some focal brain lesions (medial aspect of the right parietal lobe and occipital lobe), sensory deficiency (blindness, deafness) are known to cause delirium. In order to explain delirium table, in patients who have the decline of neurotransmitters, cerebral oxidative metabolism deficiency, cholinergic dysfunction, inflammation or infection, theories such as lymphokines have been proposed (6).

Bisoprolol is widely used in cardiology for the treatment of hypertension and arrhythmia. Bisoprolol, a potent B1-selective, is a beta-blocker and it is almost completely absorbed from the gastrointestinal tract. It binds to serum proteins approximately 30% and reaches to peak plasma concentration within 2-4 hours. It is eliminated equally via liver and kidney, approximately 50% unchanged in the urine and the rest in the form of inactive metabolites. Bisoprolol is the most selective ,-blocker and it is suitable for the suppression of PAF (7).

However, beta-blocking agents have central nervous system effects and can cause common psychiatric syndromes (5%–20%), which have been recognized for a long time (4,5). Delirium associated with ,-blocker use can result in symptoms such as confusion, disorientation, agitation, aggression, and visual and auditory hallucinations. There are documented cases of delirium associated with the use of propranolol, atenolol, metoprolol, carvedilol (8-11).

Bisoprolol is a lipid soluble drug whose penetration to the central nervous system is allowed. Given lipophilicity, bisoprolol could certainly penetrate the central nervous system. Additionally, beta-blocker therapy has common side effects including hypotension and bradycardia, which could result in diminishing cerebral oxygen supplies and reduced cerebral perfusion pressure. In a study conducted with aged hypertensive rats treated with propranolol, it has been showed that cerebral blood flow decreases and cognitive function deteriorates compared to animals treated with captopril (12).Among the well-known side effects of beta-blocker therapy are delirium, hallucinations, sleep disturbances, depression, ataxia, drowsiness, and psychosis (13-15). Beta-blockers are also known to interact competitively with serotonin sensitive adenylate cyclase system known to be involved in pathogenesis of delirium, besides it is related to beta adrenergic receptors (16-18). Another reason that may explain delirium is changes in cholinergic system. Deficiency in cholinergic neurotransmitter reveals delirium symptoms (19). Cholinergic neurons spanning from pons and basal forebrain to the cortex renders the input information of cortical neurons ready. The reduction in acetylcholine level leads to a reduction in frontal cortical perfusion. Hypoglycemia, hypoxia and other metabolic changes can cause changes in the acetylcholine mediative functions (20). Although no anticholinergic effect of bisoprolol is known, advanced age is an important predisposing factor for development of delirium. Loss of cholinergic reserves due to aging is becoming more and more associated with age increase. It has been speculated that cerebral neurotransmitter changes associated with age (especially cholinergic reduction) contributes to the development of delirium (21).

The reasons which made us think that the presented clinical condition is due to bisoprolol is as follows: (1) Our case did not have a previously known systemic disease and long-term used medication, (2) delirium table has developed right afterwards the onset of bisoprolol treatment started for PAF, (3) no other factors that could cause delirium were not detected for the case, (4) the fact that delirium symptoms resolved spontaneously and multiple times without any need to any other treatment after the discontinuation of the medication.

Another thing worth to attention is that our case is 87 years old, as increased age makes patients more vulnerable to the side effects of drugs. Moreover, as patient's age increase, the expectation of positive effects of drugs by the physicians, tend to also amplify the possibility of the adverse effects and any other negative consequences. Our case suggests that bisoprolol should be considered among the medications that could cause or at least associated with delirium. The fact that heart diseases are still the leading group among all diseases also bring up the conclusion that cardiologists should also pay more attention to drug choices in elderly patients.

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