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Flumazenil-induced Ballism

Flumazenil, an imidazobenzodiazepine, is the first benzodiazepine antagonist and is being used to reverse the adverse pharmacological effects of benzodiazepine. There have been a few reports on the central nevous system side effects with its use. We report a patient with generalized ballism following administration of flumazenil. The mechanism through which flumazenil induced this symptom is unknown. It is conceivable that flumazenil may antagonize the GABA-benzodiazepine receptor complex and induce dopamine hypersensitivity, thus induce dyskinesic symptoms.

Key Words : *Ballism; Flumazenil; GABA; Dopamine*

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INTRODUCTION

Flumazenil, an imidazobenzodiazepine, is the first benzodiazepine antagonist and is being used to reverse the adverse pharmacological effects of benzodiazepine. Other potential indications include hepatic encephalopathy, and other forms of coma (1). Flumazenil is a relative safe drug, with rare central nevous system (CNS) side effects, such as seizure, agitation and anxiety (2-4).

We report a case of ballistic movements that developed following the administration of flumazenil.

CASE REPORT

A 58-yr-old woman was found suffering from drowsiness and was transported to the emergency room. The patient had been treated with hemodialysis for chronic renal failure for the previous 10 yr. Her medication included 100 mg aspirin, 10 mg baclofen, and 5 mg amitriptyline hydrochloride. She had never been on any neuroleptic or dopaminergic drugs and there was no past history of neurological disease.

On admission, she was confused, disoriented and drowsy, with a blood pressure of 120/90 mmHg, a regular heart beat of 96 beats/min, and a temperature of 36.8℃. Physical examination did not demonstrate any pathologic findings. Neurologic findings were as follows: slightly dilated pupils, responsive to light, normal corneal, oculocephalic, and gag reflexes, decreased deep tendon reflexes, and symmetrical muscle flaccidity.

Laboratory tests included a sodium level of 141 mEq/L, potassium 4.1 mEq/L, creatinine 3.1 mg/dL, blood urea nitrogen 37.3 mg/dL, glucose 131 mg/dL, HbA1C 6.2%, white blood cell count 8,700/μL, hemoglobin 13.1 g/dL, platelet count 313,000/μL, and normal thyroid function. A brain MRI obtained on admission did not demonstrate any abnormality.

To diagnose and treat unexplained decreased mentality, intravenous flumazenil was administered in increments of 0.25 mg/min. The patient regained full consciousness following a total dose of 1.0 mg of flumazenil. One hour later, the patient developed ballistic movements of the proximal portion of the upper and lower limbs. The movements could be described as flexion/extension writhing movements of her limbs and grimacing of her face. These movements disappeared when she was asleep. On neurological examination, the patient was found to be alert and attentive. The cranial nerves were normal. There was no evidence of pyramidal disturbance. Power was full in all muscle groups. There was no abnormal subjective or objective sensory disturbance. Deep tendon reflexes were symmetric and normoactive and both plantar were flexor. All drugs were discontinued and her symptoms resolved within 3 days.

DISCUSSION

Experimental chorea models can be produced by injecting a γ-aminobutylic acid (GABA) antagonist into the external pallidum (GPe) or subthalamic nucleus (STN) (5, 6). The interruption of GABAergic transmission from the striatum to the GPe would lead to an abnormally increased GPe neu-

ronal activity, which exerts an inhibitory action upon the STN (7). Increased STN inhibition would result in the loss of its control on the internal pallidum (GPi). Besides excitatory STN inputs (8), the GPi neurons also receive inhibitory afferent inputs directly from the striatum. The imbalance between the indirect excitatory and direct inhibitory pathways would ultimately lead to a disinhibition of the motor thalamus.

Benzodiazepines exert their main action on the central nevous system primarily by an enhancement of GABAergic synaptic transmission (9). These effects are mediated by the interaction of benzodiazepines with specific neuronal membrane proteins, the benzodiazepine receptors, which are localized, at least in part, in the GABAergic synapses (10). These GABAmimetic activities have been used effectively in the treatment of acquired and non-acquired chorea/ballism (11).

Flumazenil selectively antagonizes the central actions of benzodiazepines by competitive interaction at the GABA-benzodiazepine receptor level. In addition, animal studies have shown that flumazenil can influence dopamine metabolism in the central nervous system. Flumazenil has been shown to increase the extracellular dopamine of mesolimbic dopaminergic neuron following repeated administration of benzodiazepine receptor partial agonists. Therefore, the administration of flumazenil may increase dopamine availability, in turn increasing dopamine receptor sensitivity (13).

The occurrence of a ballistic movement in our patient following the administration of flumazenil suggests a possible relationship between flumazenil and ballism, although the mechanism is not known and the short half-life of flumazenil effect makes flumazenil-related ballism unlikely. Since the drug was completely eliminated from the body within 48-72 hr following infusion of flumazenil (1), the effect of flumazenil did correlate with the duration of the patient's symptom. A potential explanation is that flumazenil may antagonize the GABA-benzodiazepine receptor complex and/or induce dopamine hypersensitivity and, therefore, cause dyskinesic symptoms.

It is of course possible that this symptom may be unrelated to flumazenil. In addition, as previously reported (14), other drug such as baclofen cannot be ruled out in relation to this condition. However, the long-term use of this drug without specific side-effects makes baclofen-induced dyskinesia unlikely in our case.

In summary, the temporal relationship to the administration of flumazenil and the absence of a clear etiology on the MRI support the association between flumazenil and ballism, despite the fact that a cause-and-effect relationship cannot be clearly inferred.

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