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Successful Readministration of Clozapine in a Patient With a History of Clozapine-Induced Elevation of Creatine Phosphokinase

To the Editor: Several previous case reports have shown that clozapine treatment occasionally induces elevation of creatine phosphokinase (CPK) levels.[1,2] We describe a patient with marked elevations of CPK after initiation of clozapine treatment.

Case report. Our patient was a 41-year-old woman who was first diagnosed with schizophrenia (*ICD-10*) at age 25 years due to auditory hallucination and delusions of persecution. Treatment with risperidone was effective in ameliorating her symptoms. Her poor adherence to medication resulted in repeated relapses. At age 41, she was admitted to our psychiatric ward because of aggressive behaviors and worsening of psychotic symptoms. Treatment with antipsychotics including quetiapine, olanzapine, and aripiprazole as well as with electroconvulsive therapy was ineffective. Clozapine was started on day 162 of admission and was effective in relieving her psychotic symptoms. The dose was increased to 600 mg/d by day 232. However, a generalized tonic-clonic seizure was observed on day 286, which was treated with intramuscular injection of diazepam. Because she had no past history of epilepsy, we suspected clozapine to be the cause of the seizure. Therefore, the dose was decreased to 400 mg/d the following day and was discontinued on day 291. Her serum levels of CPK were 1,079 U/L, 6,454 U/L, 7,509 U/L, and 5,224 U/L on days 287, 290, 291, and 293, respectively. An isoenzyme analysis indicated that the elevated CPK was almost exclusively of skeletal muscle origin. Malignant syndrome was ruled out due to the lack of fever, rigidity, and leukocytosis. Because clozapine was the only effective treatment for her psychotic symptoms, clozapine was restarted on day 297. After 56 days of treatment with clozapine 400 mg/d, no relapse of seizures or CPK elevation was observed.

A previous report[3] indicates that clozapine has myopathic side effects and may cause muscle weakness accompanied by CPK elevation. The time course of serum CPK levels led us to consider that clozapine was the direct cause of CPK elevation in the presented case. Our case illustrates a successful readministration of clozapine in a patient who previously experienced clozapine-induced elevation of CPK.

Clinical investigation of our patient discounted other possible causes of CPK elevation. The lack of increased levels of CPK of myocardial origin excludes the possibility of a cardiac lesion. No signs of skin myositis were observed. She engaged in no intense exercise. Other possible causes that must be considered were seizure and the muscle damage by intramuscular injection. A previous report showed that serum CPK levels markedly rise after a tonic-clonic seizure, usually with a delay of at least 3 hours and with a peak concentration after 36–40 hours.[4] Direct muscle damage generally causes CPK elevation within 6 hours with a peak level at 18 hours.[5] The CPK in our patient reached peak level 6 days after the seizure and the intramuscular injection. Therefore, it was unlikely that either the seizure or the intramuscular injection could fully explain the observed CPK elevation.

An elevated CPK level is one of the adverse events observed in patients prescribed clozapine. The present case suggests that readministration of clozapine with close monitoring is a treatment option for patients with previously experienced clozapine-induced CPK elevation.

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