

Probable Case of Neuroleptic Malignant Syndrome Following Administration of Antituberculous Drugs in a Chlorpromazine-Treated Patient

Neuroleptic malignant syndrome (NMS), a potentially fatal adverse reaction to neuroleptics, is known to occur more often in the initial stage of antipsychotic treatment. We describe a patient with chronic schizophrenia who, in a few days after the addition of antituberculous drugs to his antipsychotic regimen, developed probable NMS without pyrexia. We reasoned that rifampin, a strong hepatic enzyme inducer, decreased the plasma chlorpromazine concentration of the patient, with the result of cholinergic hyperactivity and finally, the symptoms of NMS. Therefore, physicians should be aware of drug interactions and the likelihood of NMS, and consider antipsychotic dose adjustment when prescribing drugs that may influence pharmacokinetic properties of antipsychotics in a patient with schizophrenia receiving long-term antipsychotic treatment.

Key Words : Neuroleptic Malignant Syndrome; Rifampin; Chlorpromazine

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon but potentially lethal adverse reaction to neuroleptic drugs that is characterized by autonomic instability, extrapyramidal symptoms (EPS), hyperthermia, and altered mental status (1). Dehydration, exhaustion, and psychomotor agitation have been reported to increase the risk of NMS (2).

In this report, we describe a patient with chronic schizophrenia who developed probable NMS following the addition of antituberculous drugs to his antipsychotic regimen.

CASE REPORT

A 42-yr-old man who had been in and out of psychiatric hospitals repeatedly since having been diagnosed with schizophrenia in his late teens, according to DSM-IV criteria, presented to the emergency room (E.R.) with an immediate history of vomiting, rigidity, and tremor. The patient had been treated with chlorpromazine 600 mg and benztropine 1 mg daily on an outpatient basis before coming to the E.R. Several months before visiting the E.R., the patient had a cough, felt chilled, and experienced a cold sweat. He visited the internal medicine department of another hospital for these symptoms and he was diagnosed with active pulmonary tuberculosis. Six days before visiting the E.R., he started taking anti-

tuberculous drugs (rifampin 600 mg, isoniazid 400 mg, and pyrazinamide 1,500 mg, daily). Four days before visiting the E.R., his sleep became disturbed, and his speech became limited. Rigidity in all four extremities and tremor in both arms were observed at this time. He also vomited twice before being taken to the E.R. of the university hospital.

His arterial blood pressure was 126/76 mmHg, heart rate was 120 beats/min, and body temperature was 37°C. The patient was delirious, and his verbal output was sparse. He showed severe "lead pipe" rigidity and frequent hand tremor. Abnormal laboratory findings included elevated serum creatine kinase (CK 2296.9 IU/L and CK-MB 11.2 ng/mL), uric acid (16.4 mg/dL), aspartate aminotransferase (AST 57 IU/L), glucose (158 mg/dL), myoglobin (557.4 ng/mL), and decreased serum blood urea nitrogen (BUN 6 mg/dL). The serum electrolyte panel (sodium 140 mM/L, potassium 3.7 mM/L, chloride 107 mM/L, carbon dioxide 25 mM/L) and calcium (8.9 mg/dL) were within normal ranges. Leukocytosis was not present, and the pre- and postcontrast brain CT scan did not reveal any abnormal findings.

On the first day in the E.R., chlorpromazine, benztropine, and antituberculous drugs were discontinued simultaneously, and vigorous intravenous hydration and Foley catheter insertion were carried out to prevent acute renal failure. On the third day in the E.R., the patient was alert and oriented, and subjective improvement was reported. The serum myoglobin level was also normal (46.0 ng/mL). On the fourth

day in the E.R., the rigidity in all four extremities improved, but he was still unable to sit up in bed without assistance. The Foley catheter was removed, but hydration was maintained. On the fifth day in the E.R., the serum CK level decreased to 403 IU/L. The patient was alert, ambulatory with help, and was discharged with a psychiatric appointment 1 week later, but without an antipsychotic prescription. One week after discharge, he was rechallenged with an antipsychotic, risperidone 1 mg daily, because of aggravated psychotic symptoms. About 3 months after discharge, he has not shown any specific neuropsychiatric sequelae of NMS and has taken antipsychotics and antituberculous drugs regularly without any serious adverse events.

DISCUSSION

The diagnosis of NMS has been based on clinical manifestations because the definite cause of NMS is still unknown. Levenson (1) suggested that the diagnosis of NMS is highly likely when three major symptoms (fever, muscle rigidity or EPS, and elevated CK level) or two major and two minor symptoms (tachycardia, abnormal blood pressure, tachypnea, altered consciousness, diaphoresis, and leukocytosis) are present. These criteria differ slightly from the DSM-IV TR criteria, in which severe muscle rigidity and elevated temperature are essential for the diagnosis of NMS. Fever is generally considered to be an essential feature of NMS, but a few reported cases have had many features of NMS without fever, or without initial fever (3-5). Woodbury and Woodbury (6) suggested that it may be a stage in the progression toward NMS and proposed that there is a spectrum of NMS. Although the patient did not exhibit a fever, he showed severe muscle rigidity, an elevated CK level, tachycardia, and an altered mental status. In addition, his symptoms markedly improved after neuroleptic and antituberculous drugs were discontinued and vigorous intravenous hydration was carried out. After considering all the above factors, we concluded that this was an atypical NMS, namely, NMS without pyrexia.

The other interesting feature of this case is that the NMS developed shortly after the coadministration of antituberculous drugs in a patient taking chlorpromazine alone for schizophrenia. Rifampin is a strong inducer of hepatic cytochrome P450 (CYP) 3A enzymes and increases the hepatic metabolism of many drugs (7). Most dopamine receptor antagonists are metabolized by the cytochrome P450 2D6 and P450 3A enzymes. Accordingly, the plasma concentrations and therapeutic effects of antipsychotics can be reduced by the administration of rifampin. Kim et al. (8) reported that a decrease in the plasma haloperidol concentration due to rifampin administration developed rapidly and that the extent was large in several patients. Gorski et al. (7) demonstrated that there is a large interindividual variability in the extent of CYP

3A induction by rifampin. Thus, we reasoned that this patient's chlorpromazine blood level was decreased by the administration of rifampin.

A few cases of NMS after the discontinuation of antidopaminergic or anticholinergic treatment have been reported (9, 10). Chronic treatment with haloperidol and piperazine phenothiazines actually inhibits the release of acetylcholine due to the induction of supersensitivity to dopamine (11). Moreover, long-term treatment with neuroleptics induces an up-regulation of muscarinic receptors (mAChR) (12). NMS following antipsychotic withdrawal, especially in the case of long-term treatment with antipsychotics, is probably related to cholinergic overdrive in addition to a dopaminergic 'imbalance' or dysregulation. Amore and Zazzeri (12) suggested that on neuroleptic withdrawal, a cholinergic hyperactivity can occur, resulting in a state of relatively reduced dopaminergic transmission, and that cholinergic hyperactivity seems to be a critical point in precipitating NMS. Chlorpromazine, which was taken in the present case, has marked anticholinergic properties. Consequently, we hypothesized that the plasma chlorpromazine concentration of the patient was decreased after the administration of rifampin, with the result of cholinergic hyperactivity and finally, the symptoms of NMS.

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