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Successful clozapine rechallenge following clozapine-induced neuroleptic malignant syndrome

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Abstract

Neuroleptic malignant syndrome (NMS) is a potential life-threatening adverse effect of antipsychotics. Characteristic signs and symptoms of NMS include hyperthermia, muscle rigidity, altered mental status, and autonomic instability. Treatment of NMS includes discontinuation of any antipsychotic or other potentially offending agents. This report describes the details of a patient diagnosed with NMS induced by clozapine with subsequent successful rechallenge. Given limited therapeutic options for patients with treatment-resistant schizophrenia, clinicians should be cognizant of potential risks but aware of the possibility of successful rechallenge with clozapine.

Keywords: clozapine, neuroleptic malignant syndrome, rechallenge

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Background

Neuroleptic malignant syndrome (NMS) is a potential life-threatening adverse effect of antipsychotics or other dopamine antagonists with characteristic signs and symptoms, including fever, muscle rigidity, altered mental status, and autonomic instability.[1] Rates of NMS vary from 0.02% to 3% among individuals treated with antipsychotics.[1,2] Reported mortality rates for NMS vary (10% to 20%) and may be improving due to increased recognition and appropriate treatment.[2] Almost all antipsychotic agents (including clozapine) have reports associating them with NMS, but it is more often associated with first-generation and higher-potency agents (eg, haloperidol, fluphenazine).[2,3] Abrupt discontinuation of dopamine agonists has also been reported to cause NMS.[4] Additional risk factors associated with development of NMS include higher antipsychotic dosage, requirement of parenteral administration, and history of NMS.[5,6]

Appropriate and timely diagnosis and treatment of NMS are critical. The diagnosis of NMS includes recent exposure to a dopamine antagonist (eg, antipsychotic), hyperthermia (> 38°C), profuse diaphoresis, severe muscle rigidity, altered mental status, and autonomic instability. Additionally, elevations in creatine kinase (CPK) or leukocytosis are often seen.[2] Other laboratory findings in cases of NMS may include elevated lactate dehydrogenase (LDH), elevated transaminases, and low serum iron.[7] Rating scales are sometimes used to assist in assessment of potential NMS cases.[8]

Treatment of NMS is mostly supportive and includes discontinuation of any antipsychotic or other potentially offending agents. Other therapies, such as a dopamine agonist (ie, bromocriptine), benzodiazepines, a skeletal muscle relaxant (ie, dantrolene), or electroconvulsive therapy may be employed in certain cases. Antipsychotic therapy can be restarted after a recommended minimum of 2 weeks, generally utilizing a different antipsychotic than the offending agent. A lower-potency agent (eg, clozapine, quetiapine) is generally preferred.[3] Reported rates of recurrence of NMS when restarting antipsychotics vary but range as high as 30%.[7]

Case Report

NP is a 53-year-old white female with a past medical history significant for treatment-resistant schizophrenia, type II diabetes mellitus, and seizure disorder. She was transferred from an outside hospital for psychiatric stabilization. Approximately 2 months prior to admission to our facility, she had been diagnosed and treated in an intensive care unit for clozapine-induced NMS at a nearby medical hospital. She had historically been maintained on clozapine (up to 600 mg daily) for years. The diagnosis of NMS was based on the patient being found unresponsive with hyperthermia (42.5°C) and severe muscle rigidity. Laboratory evaluation showed a CPK of 1806 international units per liter and a white blood cell count of 11.5/mm^3. Blood urea nitrogen, serum creatinine, and transaminases were within normal limits. No clozapine levels, LDH, or serum iron levels were obtained. She was successfully managed with supportive care, scheduled lorazepam, and discontinuation of clozapine.

Immediately prior to admission to our facility, she was treated for 18 days at a nearby psychiatric hospital and discharged on quetiapine (200 mg every morning and 600 mg every evening) and medical medications (metformin 500 mg twice daily, topiramate 100 mg every morning and 200 mg every evening, and potassium chloride SR 10 mEq daily). The patient presented to our facility with profound psychotic symptoms, including disorganized speech (word salad) and behavior. She was noted to be intrusive and aggressive with staff and other patients. Her previous regimen of quetiapine (total of 800 mg per day) was restarted. On hospital day 4, the patient continued to display severe psychotic symptoms and was cross-titrated onto olanzapine therapy (up to 30 mg per day). Olanzapine was initiated at 15 mg per day and increased by approximately 5 mg every 4 days. She tolerated the medication change without issue but continued to show no evidence of response to antipsychotic therapy.

On hospital day 20, family members indicated this was far below the patient's baseline, and the patient had historically only responded to clozapine therapy. Following a literature search and interdisciplinary discussions, the patient was restarted on clozapine therapy at 12.5 mg daily at bedtime and was increased by approximately 25 mg every other day. Olanzapine was slowly tapered as her clozapine dose was eventually increased to 400 mg daily. She was monitored closely for any signs or symptoms of NMS, including fever and elevated CPK, and tolerated without issue. Her psychotic symptoms improved substantially, and she was able to participate in community reintegration. She was discharged on hospital day 69 without any subsequent episodes of NMS.

Discussion and Conclusion

A PubMed search revealed only 6 previous case reports of clozapine rechallenge following clozapine-induced NMS. Each of the patients was being treated for a psychotic disorder, and patient ages ranged from 24 to 49 years. Four of the patients were female, and the onset of NMS during clozapine treatment varied widely (< 1 week to 364 weeks). In each of the cases, rechallenge with clozapine using a slow titration was successful. Time to rechallenge varied from 1 to 36 weeks.[9-14]

In cases of NMS, rechallenge is generally performed with an agent other than one that precipitated the event. Additionally, a lower potency agent (eg, clozapine, quetiapine) is normally chosen. This case highlights the challenge when the precipitating agent is one of the lowest potency agents available and the only medication indicated for treatment-resistant schizophrenia.

In this case report, a patient with treatment-resistant schizophrenia was successfully rechallenged with clozapine despite a previous adverse reaction presumed to be clozapine-induced NMS. As with many cases, additional information regarding her history and presentation to the outside hospital may have helped clarify the NMS diagnosis. However, the treatment team was required to make a pharmacotherapy decision with this determination by previous providers. Given limited therapeutic options for patients with treatment-resistant schizophrenia, clinicians should be cognizant of potential risks but aware of the possibility of successful rechallenge with clozapine.

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