

Neuroleptic Malignant Syndrome Associated with Quetiapine

Natalie Roy, Paula L. Diaz, and John Howard

INTRODUCTION

Neuroleptic malignant syndrome is a rare adverse effect of antipsychotic agents. The most common signs and symptoms are hyperthermia, muscle rigidity, changes in mental status, and autonomic instability.¹ The prevalence of neuroleptic malignant syndrome in association with the use of typical antipsychotics is estimated at 0.5% to 1%.¹ Atypical antipsychotics such as quetiapine have greater affinity for serotonin 5-HT_{2A} receptors than for dopamine D₂ receptors. Therefore, it is believed that atypical antipsychotics are less likely to cause this condition. This article describes a patient treated with quetiapine who presented with biochemical and clinical evidence of neuroleptic malignant syndrome.

CASE REPORT

A 46-year-old woman with schizoaffective disorder was transferred from a local psychiatric hospital to the Emergency Department of a tertiary care centre for assessment of deteriorating mental and physical status. Approximately 2 weeks before the admission, the patient's medication regimen had been changed from clozapine and lamotrigine to quetiapine and clonazepam in response to the development of leukopenia. The quetiapine dose was 50 mg in the morning and 25 mg at bedtime. Concomitant medications included divalproex (750 mg in the morning and 1000 mg in the evening) for seizures and an oral contraceptive. After the change in medications, the patient became confused and agitated, and she experienced fever, tachycardia, diaphoresis, hypertension, and rigidity (including neck rigidity). The evening before the admission, the patient had been too agitated to sleep. She had been moved to a private room, where she paced continuously.

On admission, her serum creatine kinase level was 469 U/L (normal range 35 to 230 U/L); her serum troponin I level was normal at 0.5 µg/L (normal range 0.0 to 1.0 µg/L). The white blood cell count was 10.8 x 10⁹/L (normal range 4.0 to 10.0 x 10⁹/L), and serum creatinine level was 183 µmol/L (normal range 55 to 120 µmol/L). Her temperature was 38.5°C, her blood pressure 148/90 mm Hg, and her pulse 133 beats/min. Cerebrospinal fluid was unremarkable, and the results of computed tomography of the head were normal. Quetiapine was discontinued, and IV administration of fluids was initiated. Vancomycin 1 g and cefotaxime 2 g were administered intravenously as a precautionary treatment for encephalitis. A trial of bromocriptine (a dopamine agonist) 1.25 mg PO tid was initiated, but this drug was discontinued approximately 2 days later when the patient experienced nausea and vomiting. Lorazepam was administered as necessary for agitation. The maximum creatine kinase level, 1759 U/L, occurred on day 2; creatine kinase decreased to 169 U/L by discharge on day 7. Temperature, blood pressure, heart rate, and degree of muscle rigidity gradually returned to normal by the day of discharge.

DISCUSSION

Gurrera has hypothesized that sympathetic nervous system hyperactivity is responsible for most of the features of neuroleptic malignant syndrome.² Velamoor has suggested that the antidopaminergic activity of neuroleptics is the predominant cause of neuroleptic malignant syndrome.³ Dopaminergic systems are involved in temperature regulation, as well as regulation of muscle tone and movement.³ Although the atypical antipsychotics have lower affinity for D₂ receptors, some cases of neuroleptic malignant syndrome have been

reported in association with these agents.⁴⁻⁷ Quetiapine is considered an atypical antipsychotic because it has binding affinity for dopamine D₁ and D₂, serotonin 5-HT_{1A} and 5-HT_{2A}, histamine H₁, and adrenergic α_1 and α_2 receptors.⁸ Quetiapine has a higher affinity for serotonin 5-HT_{2A} receptors than for dopamine D₂ receptors.⁸

The incidence of neuroleptic malignant syndrome in clinical trials with quetiapine has been reported as 0.09%.⁹ In addition, as of December 31, 1999, 24 cases of this syndrome had been reported to the manufacturer after 109 000 to 164 000 patient-years of exposure to the drug.* Recently, another report of neuroleptic malignant syndrome associated with the use of quetiapine was published.¹⁰

Risk factors associated with the development of drug-induced neuroleptic malignant syndrome include organic brain syndrome, mood disorders, dehydration, agitation, exhaustion, rapid or parenteral administration of antipsychotics, and catatonia.^{3,11} Some risk factors are modifiable, and the risk may be reduced by interventions such as hydration, minimization of agitation and hyperactivity (to prevent exhaustion), administration of the lowest effective antipsychotic dose, use of benzodiazepines for sedation (to prevent the need for excessive doses of antipsychotics), and regular monitoring of temperature.¹¹ In addition, administration of anticholinergics may be considered, but these drugs should be used with caution in patients with elevated temperature, as they may cause anhidrosis resulting in fatal hyperthermia. Other options for reducing the risk include decreasing the antipsychotic dose or substituting a less potent antipsychotic agent at the onset of extrapyramidal rigidity or catatonia.^{3,12} The patient described here presented with the following risk factors: a mood disorder, agitation, dehydration, and exhaustion.

The cardinal symptoms of neuroleptic malignant syndrome are changes in mental status, muscle rigidity, hyperthermia, and autonomic dysfunction.¹² The elevation in temperature may be mild or severe.³ Autonomic instability may result in labile blood pressure or tachycardia.¹² Mental status is virtually always altered, and a range of symptoms may be seen, including mutism, confusion, stupor, or coma.^{3,12} The syndrome is variable in presentation,^{3,12} and the diagnosis must be made by a process of exclusion. However, there exists a relatively common pattern of symptom progression,³

whereby muscle rigidity and changes in mental status precede hyperthermia and autonomic dysfunction.³ The time to onset is variable, but the syndrome usually appears within 4 weeks of the initiation of antipsychotic treatment, and approximately two-thirds of cases develop within the first week.^{3,12} However, neuroleptic malignant syndrome may develop after months of treatment at a constant dose.^{3,12} The patient described here showed signs and symptoms approximately 2 weeks after initiation of quetiapine therapy. These consisted of altered mental status (confusion and disorientation), fever, tachycardia, diaphoresis, hypertension, muscle rigidity, and elevated creatine kinase level. The clinical presentation was consistent with that discussed in previous reports.³ Other reported signs and symptoms of neuroleptic malignant syndrome include dysphagia, tremor, incontinence, and leukocytosis.³

Treatment involves replacing fluids; reducing the patient's temperature by IV administration of cold saline, application of ice for surface cooling, and use of a hypothermia blanket; monitoring cardiac, respiratory, and renal function; and discontinuing all antipsychotic agents (or other dopamine antagonists).^{3,12} The use of dopamine agonists or dantrolene may also be considered.^{3,12} In most cases, the signs and symptoms eventually resolve.³ Mortality rates have ranged from 10% to 20%. Causes of death included renal failure, arrhythmias, pulmonary emboli, and aspiration pneumonia.³ The patient described here required 1 week to fully recover. She was treated by discontinuation of the quetiapine, rehydration, administration of benzodiazepines to manage her agitation, and monitoring of cardiac, respiratory, and renal function. Although bromocriptine was initiated, it was discontinued approximately 2 days later when the patient developed nausea and vomiting.

If the patient continues to require treatment for a psychiatric disorder, consideration should be given to nonneuroleptic therapies (such as lithium, benzodiazepines, or electroconvulsive therapy) as initial management.¹¹ The patient or the patient's family should be involved in any decision to reinstitute antipsychotics.¹¹ If administration of an antipsychotic agent is determined to be in the best interest of the patient, neuroleptics in a different chemical class and with a lower affinity for D₂ receptors should be considered.¹¹ Rechallenge should not take place until 2 weeks after the patient has recovered from the episode of neuroleptic malignant syndrome.³

The atypical antipsychotics allow patients to avoid the extrapyramidal side effects commonly associated with typical antipsychotic agents. This case demonstrates

*T. Melo, medical information associate, AstraZeneca, Mississauga, Ontario, personal communication, November 28, 2000.



that the atypical antipsychotic quetiapine may cause neuroleptic malignant syndrome. Other atypical antipsychotics, including risperidone, clozapine and olanzapine, have also been reported to cause this syndrome.⁴⁻⁷ On the basis of the observations reported here, it is recommended that patients receiving quetiapine be monitored for the signs and symptoms of neuroleptic malignant syndrome, which may occur within 2 weeks following initiation of therapy.

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Natalie Roy, BScPhm, is a Staff Pharmacist at the London Health Sciences Centre, London, Ontario.

Paula L. Diaz, BSc(Hons), MRPharmS, is a Clinical Specialist Pharmacist at the London Health Sciences Centre, London, Ontario.

John Howard, MD, FRCPC, is Site Chief of the Victoria South Street Campus Department of Gastroenterology and Pediatrics, London Health Sciences Centre, London, Ontario.

Address correspondence to:

Natalie Roy
12 Lochern Road
London ON
N5Z 4L6
e-mail: natalie.roy@home.com

