

Risperidone-Induced Neuroleptic Malignant Syndrome

From the Department of Pharmacy Practice, Wayne State University,^{*} and the Departments of Emergency Medicine[†] and Pharmacy Services,[‡] Detroit Receiving Hospital, Detroit, MI.

Received for publication July 25, 1996.
Revision received January 27, 1997.
Accepted for publication March 21, 1997.

Copyright © by the American College of Emergency Physicians.

Iman Bajjoka, PharmD*
Tushar Patel, MD†
Tami O'Sullivan, PharmD**

Risperidone is an antipsychotic drug used for the treatment of schizophrenia. It was expected that this atypical neuroleptic agent would not cause dystonia or neuroleptic malignant syndrome (NMS) owing to its unique mechanism of action with attenuated antidopaminergic activity and more potent antiserotonergic activity. We report the case of a geriatric patient in whom signs and symptoms consistent with NMS developed after 3 weeks of risperidone therapy. The patient presented with fever, mental status changes, tremor, and rigidity. His laboratory findings were significant for increased serum creatine phosphokinase, hypernatremia, and metabolic acidosis. There have been few reported cases of risperidone-induced NMS. Health care providers should be aware of the risk of risperidone-induced NMS.

[Bajjoka I, Patel T, O'Sullivan T: Risperidone-induced neuroleptic malignant syndrome. *Ann Emerg Med* November 1997;30:698-700.]

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a drug-induced disorder that results from dopaminergic antagonism. Risperidone is a relatively new antipsychotic agent with potent antiserotonergic activity and less antidopaminergic activity. It was expected that NMS would not be a complication of risperidone therapy. We present a case of NMS associated with risperidone therapy.

CASE REPORT

A 75-year-old man presented to the ED from a nursing home for evaluation of emesis and possible seizure activity. His medical history included senile dementia with agitation and atherosclerotic heart disease. Medications included risperidone .5 mg orally twice daily for the preceding 21 days, torsemide 20 mg orally once daily, nebulized metaproterenol 5% .3 mL three times daily, and cefaclor 250 mg orally three

times daily. He had not received other treatment for his acute condition. He had no known drug allergies.

Blood pressure was 110/80 mm Hg; pulse 168 (intermittently irregular), respirations 22, and temperature 39.1° C. The mucous membranes were dry, the neck rigid, and the lungs both clear on auscultation. The cardiac examination revealed an intermittently irregular rhythm and tachycardia. Abdominal findings were unremarkable. Guaiac-negative stool and normal sphincter tone were noted, as were poor skin turgor and equal peripheral pulses. The patient spontaneously moved all extremities but was disoriented and did not follow commands. He had 2+ deep-tendon reflexes bilaterally with downgoing plantar reflex. Shaking tremors and cogwheel rigidity of the arms and lead-pipe rigidity of the legs were noted.

Initial laboratory investigation revealed a serum sodium of 173 mEq/dL (173 mmol/L), potassium of 3.9 mEq/dL (3.9 mmol/L), chloride of 129 mEq/dL (129 mmol/L), bicarbonate of 15.0 mEq/dL (15.0 mmol/L), blood urea nitrogen of 61 mg/dL (21.8 mmol/L), creatinine of 2.7 mg/dL (238.7 mol/L), and glucose of 190 mg/dL (10.5 mmol/L). Anion gap was 29 mEq/L (29 mmol/L) with a serum lactate of 4.1 mmol/L. The leukocyte count was 8,600/mm³ (8.6×10⁹/L), hematocrit 50.7% (.51), and platelet count 195,000/mm³ (195×10⁹/L). Initial creatine kinase (CK) was 475 U/L (7.90 μKat/L). Arterial blood gas on room air showed pH 7.38, Pco₂ 20.6 mm Hg, Po₂ 78.5 mm Hg, and O₂ saturation 94.4%.

The electrocardiogram revealed multifocal atrial tachycardia with a rate of 168 beats/minute. Chest radiograph showed mild bibasilar atelectasis. Computed tomography of the head without contrast revealed marked atrophy. Cerebrospinal fluid was normal. Serum and urine drug screens for opiates, cocaine, barbiturates, benzodiazepines, acetaminophen, propoxyphene, cannabinoids, phencyclidine, methadone, and ethylene glycol were negative. Urine analysis revealed a specific gravity of 1.025, pH 5, blood 2+, 5 to 10 red blood cells per high-power field, fewer than 5 leukocytes per high-power field, and no ketones. Urine myoglobin was 2+.

A diagnosis of NMS was made and management of dehydration, hypernatremia, rhabdomyolysis, metabolic acidosis, and multifocal atrial tachycardia initiated. Supportive care included discontinuation of risperidone, alkalization of the urine, and intravenous fluid administration. Treatment with dantrolene, benzodiazepines, paralytics, or dopamine agonists was not used. His fever was initially refractory to therapy with acetaminophen and reached a maximum of 39.7° C on the day of admission. Broad-spectrum antibiotics were initiated empirically, but all cultures of urine, cerebrospinal

fluid, and blood were negative. His peak CK was 6,974 U/L (116.05 μKat/L) on the second day of hospitalization but decreased to 656 U/L (μKat/L) by the sixth hospital day. His mental status, fever, and rigidity returned to baseline within 3 days.

DISCUSSION

Risperidone is an antipsychotic agent that binds with high affinity to serotonergic and dopaminergic receptors. It is effective in the treatment of the positive, negative, and affective symptoms of schizophrenia. NMS has rarely been associated with its use.¹⁻⁸

The mechanism of NMS is presumed to be striatal dopamine receptor blockade and involvement of hypothalamic dopaminergic tracts. Risperidone has antagonistic activity at both serotonin and dopamine receptors but has a higher relative affinity for serotonin receptors. This property was thought to render risperidone unlikely to induce NMS, dystonia, and extrapyramidal side effects.

The principal features of NMS are autonomic instability, extrapyramidal symptoms (EPS), and hyperthermia. Typically, the first sign is severe skeletal muscular rigidity, followed by progressive pseudo-Parkinsonian features, such as bradykinesia, tremors, and masked facies. Changes in mental status can occur within 1 to 3 days and may progress to stupor and even coma in severe cases. Other features include fever, profuse diaphoresis, tachycardia, tachypnea, labile blood pressure, and urinary incontinence or retention.⁹ Pertinent laboratory abnormalities include increasing serum sodium due to water depletion, leukocytosis, and increase in serum CK and other muscle enzymes.

Of nine cases of risperidone-associated NMS reviewed in the medical literature, three patients were older than 65 years of age,^{1,5} and the time of onset of NMS was 12 hours to 23 days after institution of risperidone therapy.¹⁻⁸ All patients but one had a history of EPS from other antipsychotics.^{1-4,6-8} Most of the nine patients exhibited EPS or muscle rigidity,¹⁻⁸ hyperthermia,^{1,3-5,7,8} and autonomic instability.^{1,3-8} Eight had increased serum CK.^{1-4,6-8} Most had alterations in mental status,^{1,3-8} and a few patients were diaphoretic^{1,2,4,7,8} and incontinent of urine.^{1,2,7,8} Most patients recovered,¹⁻⁸ but one died of pneumonia 1 week after the onset of NMS.¹

As illustrated by our case, a disproportionate number of reported risperidone-induced NMS cases have occurred in older persons. It has been suggested that the dosage of risperidone studied in younger persons in clinical trials may be inappropriate for the elderly owing to changes in pharmacokinetics or pharmacodynamics. Furthermore, this syn-

RISPERIDONE-INDUCED NMS

Bajjoka, Patel & O'Sullivan

drome may be underdiagnosed, especially in elderly persons, because of misattribution of the signs and symptoms to underlying psychiatric illness, an acute infectious process, Parkinson's disease, delirium, or dementia.¹

Another difficulty in diagnosis of NMS is its similarity to serotonin syndrome. Serotonin syndrome produces behavioral or cognition abnormalities, autonomic nervous system dysfunction, and abnormal neuromuscular activity, all of which closely resemble NMS. A main differentiating feature is that neuroleptic agents most commonly induce NMS, whereas serotonergic agents, including antidepressant agents, most commonly induce serotonin syndrome.¹⁰ The distinction is important clinically because the management of the syndromes differs.

NMS is a potentially fatal illness that is most commonly induced by antipsychotic agents with potent antidopaminergic activity. Because of its potent serotonergic antagonism, it was mistakenly believed that risperidone would not induce NMS. Practitioners in the ED should consider the possibility of risperidone-induced NMS in patients recently instituted on risperidone therapy who present with muscle rigidity, autonomic instability, and fever.

REFERENCES

1. Webster P, Wijeratne C: Risperidone-induced neuroleptic malignant syndrome [letter]. *Lancet* 1994;344:1228-1229.
2. Raitasuo V, Vataja R, Elomaa E: Risperidone-induced neuroleptic malignant syndrome in young patient [letter]. *Lancet* 1994;344:1705.
3. Swanson CL, Price WA, McEvoy JP: Effects of concomitant risperidone and lithium treatment [letter]. *Am J Psychiatry* 1995;152:1096.
4. Dave M: Two cases of risperidone-induced neuroleptic malignant syndrome [letter]. *Am J Psychiatry* 1995;152:1233-1234.
5. Singer S, Richards C, Boland RJ: Two cases of risperidone-induced neuroleptic malignant syndrome [letter]. *Am J Psychiatry* 1995;152:1234.
6. Murray S, Haller E: Risperidone and NMS? [letter]. *Psychiatr Serv* 1995;46:951.
7. Najara JE, Enideev ID: Risperidone and neuroleptic malignant syndrome: A case report [letter]. *J Clin Psychiatry* 1995;56:534-535.
8. Sharma R, Trappler B, Ng YK, Leeman CP: Risperidone-induced neuroleptic malignant syndrome. *Ann Pharmacother* 1996;30:775-778.
9. Knezevic W, Mastaglia F, Lefroy R, et al: Neuroleptic malignant syndrome. *Med J Aust* 1984;140:28-30.
10. Mills KC: Serotonin toxicity: A comprehensive review for emergency medicine. *Top Emerg Med* 1993;15:54-73.

Reprint no. 47/1/83296

Address for reprints:

Tami O'Sullivan, PharmD
Pharmacy Department
Saint Joseph Mercy Hospital
5301 East Huron River Drive
Post Office Box 995
Ann Arbor, MI 48106-0995