

Severe Neuroleptic Malignant Syndrome: Successful Treatment with High-dose Lorazepam and Diazepam: A Case Report

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Neuroleptic malignant syndrome (NMS) is an idiosyncratic and potentially fatal adverse complication of antipsychotic medications and other dopamine-modulating agents. It is characterized by hyperthermia, muscle rigidity, autonomic dysfunction and alteration in mental status. Here, we report a patient with severe NMS who was successfully treated with high-dose lorazepam and diazepam. A 61-year-old man with bipolar I disorder was admitted to the hospital because of manic episodes. Fever, muscle rigidity, tachycardia, diaphoresis, elevated blood pressure and delirium occurred following intramuscular injection of haloperidol and NMS was diagnosed. Supportive treatment included hydration, alkalized fluids and correction of abnormal electrolytes without the use of dantrolene, dopaminergic agents or electroconvulsive therapy. The Francis-Yacoub NMS rating scale was employed for evaluation of clinical improvement, and scores were 55 on the first day and 0 at discharge. The patient was followed up for 6 months and was free of NMS. In conclusion, this is the first report of rapid relief of NMS with high-dose lorazepam and diazepam in a Taiwanese patient. (*Chang Gung Med J* 2010;33:576-80)

Key words: neuroleptic malignant syndrome, lorazepam, diazepam

Neuroleptic malignant syndrome (NMS) was first described by Delay and Deniker in 1968. NMS is an idiosyncratic, serious and sometimes fatal complication of antipsychotic drug treatment. It is characterized by muscle rigidity, fever, autonomic dysfunction, and altered mental status.^(1,2) Although the pathophysiology of NMS has not been established, circumstantial evidence suggests the possible involvement of the brain dopamine system in its pathogenesis. Serotonin-enhancing drugs and norepinephrine-enhancing antidepressants have shown an association with this disorder.⁽³⁾ Treatment of NMS with dantrolene, bromocriptine, amantadine, lorazepam and electroconvulsive therapy has been attempted. Supportive treatment including volume resuscitation and correction of electrolyte abnormali-

ties or alkalized fluids to prevent renal failure is important. Lorazepam may ameliorate symptoms and hasten recovery.^(4,5) Here, we report a case of severe NMS induced by antipsychotic drug intake and its successful treatment with high-dose lorazepam and diazepam. This is the first report of rapid NMS relief induced by high-dose administration of lorazepam and diazepam in a Taiwanese patient.

CASE REPORT

A 61-year-old man with bipolar I disorder was admitted to the hospital because of irritable mood, hypertalkativeness, decreased sleep requirement, inflated self esteem, flight of ideas, and delusion of

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persecution. Twelve hours prior to admission, he received intramuscular injections of haloperidol (5 mg) at another hospital. Because of aggressive behavior, he was also given another an intramuscular haloperidol (5 mg) injection 12 h following admission. Fever (39.4°C), muscle rigidity, delirium, diaphoresis, high blood pressure (150/100 mmHg) and tachycardia (109 beats/min) were observed 24 h later. Laboratory findings showed a creatine phosphokinase (CPK) level of 14918 U/L (normal range 15-130 U/L), a myoglobin level of 7368 ug/L (normal range < 80 ug/L), and an aspartate aminotransferase (AST) level of 259 U/L (normal range 0-37 U/L). He had no prior history of hypertension. A diagnosis of NMS with rhabdomyolysis was made. He received supportive treatment with intravenous hydration and acetaminophen at the required doses. Urine alkalinization with intravenous sodium bicarbonate was prescribed to prevent renal failure related to rhabdomyolysis. During the first 5 days after NMS onset, the patient was administered 8 mg lorazepam daily (and intramuscular lorazepam in required doses for agitation) and 30 mg diazepam daily (10 mg intravenously in normal saline every 8 h). On the fifth day, we prescribed 5 mg of injectable biperiden for mild muscle rigidity. On the sixth day, the fever and muscle rigidity demonstrated considerable improvement and his confusion subsided; therefore, we discontinued the diazepam. The lorazepam

was continued for 6 days and gradually tapered to 3 mg daily. Then, we administered 400 mg/d valproate sodium for manic symptoms. The Francis-Yacoub NMS rating scale yielded a reading of 55 on the first day and 0 on the 26th day (Table 1). On the 7th day, muscle rigidity, fever, and autonomic dysfunction resolved and the patient was alert. The abnormal laboratory data, including serum CPK, myoglobin and serum transaminase (AST and ALT) levels started to decrease. On the 8th day, abnormal laboratory tests, included AST 120 U/L, myoglobin 335 ug/L, and CPK 3043 U/L. On the 11th day, the CPK level decreased to 564 U/L, myoglobin to 116 ug/L, and AST to 59 U/L. We prescribed 5 mg/d olanzapine for worsened psychotic symptoms and no recurrence of NMS symptoms was noted. He was discharged from the hospital in stable condition on oral 10 mg/d olanzapine, 1000 mg/d sodium valproate, 3 mg/d lorazepam, and 30 mg/d flurazepam daily. He was followed up for 6 months and did not demonstrate NMS recurrence.

DISCUSSION

The incidence of NMS in patients treated with neuroleptics is 0.01%-0.02% and the mortality rate is 14.28%.^(6,7) There is no general consensus on the specific treatment for NMS and associated evidence is incomplete, because this disorder is rare, heteroge-

Table 1. Laboratory Data and Diazepam and Lorazepam Dosages during the Treatment Course

Items	1st	2nd	3rd	4th	5th	6th	7th	8th	11th	26th
Serum CPK (U/L)	14918	12703	9237	9830	7728	3970		3043	564	57
Body temperature (°C)	39.4	39.9	39.8	39.3	38.0	37.3	36.0	36.3	36.0	36.4
AST (U/L)	259	255	224	195	168	111		120	59	31
Serum iron level (ug/dL)			90			57				
Myoglobin (ug/L)	7368	1489	1929	1472	1744	743		335	116	
Francis-Yacoub NMS Rating Scale score	55	57	56	49	29	15	8	8	7	0
Diazepam (mg/day)	30	30	30	30	30	0	0	0	0	0
Lorazepam (mg/day)	4	14	14	12	8	8	8	8	6	3

Abbreviations: CPK: creatine phosphokinase; AST: aspartate aminotransferase; NMS: neuroleptic malignant syndrome.

neous and unpredictable. Woodbury and Woodbury presented a treatment algorithm for NMS, including supportive and pharmacological treatment, according to the clinical presentation by illness stage or severity.⁽⁸⁾ Lorazepam and other benzodiazepines are administered to treat NMS symptoms; these drugs may reduce recovery time in NMS.^(5,9) Diazepam is effective in the treatment of NMS by enhancement of the GABAergic system.^(10,11) The cerebrospinal fluid (CSF) level of gamma-aminobutyric acid (GABA) is significantly decreased in the active phase and the GABAergic system is considered hypofunctioning in NMS.⁽¹²⁾ Reducing the recovery time with benzodiazepine treatment may be related to the effects of these drugs on GABAergic hypofunction.

In our patient, severe NMS with rhabdomyolysis was observed; we prescribed high-dose lorazepam and diazepam for treatment.⁽¹³⁾ In Woodbury's treatment algorithm for NMS, dopaminergic agents, including bromocriptine and amantadine, may be prescribed in severe NMS. In our patient, muscle rigidity, consciousness alterations, and autonomic dysfunction resolved by Day 7 and residually elevated CPK, myoglobin, and serum transaminase levels were observed. The Francis-Yacoub NMS rating scale showed scores ranging from 55 to 8 between the first and 7th day. The persistently abnormal CPK, myoglobin, and serum transaminase levels may have remained elevated because of the rhabdomyolysis. In general, peak CPK levels occur within 24-36 hours of muscle injury and decrease by approximately 39% per day (Table 1).⁽¹⁴⁾ In addition, we successfully administered olanzapine 5 days after NMS resolution, which was quicker than in another report that delayed its antipsychotic treatment until approximately 2 weeks following the NMS resolution.⁽⁹⁾

In NMS, controlling of fever is a significant factor.⁽¹⁵⁾ Supportive treatment, including antipyretic medications such as non-steroidal anti-inflammatory drugs or acetaminophen, and external cooling are frequently administered. Endovascular cooling has been reported in an NMS patient.⁽¹⁶⁾ Hypothalamic dopamine blockade, muscle rigidity, increased muscle metabolism and autonomic dysfunction are related to hyperthermia.⁽⁹⁾ In our patient, hyperthermia improved with high-dose lorazepam and diazepam administration (Table 1). However, the mechanism of interaction between benzodiazepines and hyperther-

mia is still unknown.

Low serum iron levels in NMS have been associated with poor responses to benzodiazepines and patients with normal iron serum levels show good responses to benzodiazepines.⁽¹⁷⁾ In our patient, the normal iron serum level with a good response to benzodiazepines was noted. However, the relationship between low serum iron and treatment resistance to benzodiazepines is still unknown.

In conclusion, this is the first report of rapid relief of severe NMS with a good outcome using high-dose lorazepam and diazepam in a Taiwanese patient.

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嚴重抗精神病藥物惡性症候群： 成功使用高劑量的 lorazepam 和 diazepam 治療之個案報告

蔡孟璋 黃條來

抗精神病藥物惡性症候群是使用抗精神病藥物所引起的一種很嚴重甚至會致命的副作用。臨床上的表現會出現體溫高、肌肉僵硬、發汗、心率過快、血壓升高或易變動、意識不清、吞嚥困難、大小便失禁等症狀。在本文我們提出一個成功使用高劑量的 lorazepam 和 diazepam 治療的嚴重抗精神病藥物惡性症候群個案。這位個案為 61 歲男性，診斷為雙極性、躁症發作，個案出現抗精神病藥物惡性症候群（包括體溫高、肌肉僵硬、發汗、心率過快、血壓升高、意識不清）之前的 48 小時內，共使用肌肉注射 haloperidol 10 mg。除了使用高劑量的 lorazepam 和 diazepam 治療外，支持性的治療，如經靜脈補充足夠的水分，給予 sodium bicarbonate 和矯正體內不正常的電解值數值。我們使用 Francis-Yacoub NMS rating scale 來評估個案的臨床嚴重程度。此個案在治療前的 Francis-Yacoub NMS rating scale 分數為 55 分，治療後出院時的分數為 0 分。在本文我們也討論 lorazepam 和 diazepam 對於治療抗精神病藥物惡性症候群的可能機轉。(長庚醫誌 2010;33:576-80)

關鍵詞：抗精神病藥物惡性症候群，lorazepam，diazepam

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