Amisulpride and Neuroleptic Malignant Syndrome

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Neuroleptic malignant syndrome (NMS) is a rare but lethal complication of neuroleptics. Its incidence ranges between 0.02% and 3%. Amisulpride, a second generation neuroleptic, was associated with rhabdomyolysis in one report and NMS in 2 reports. Although the precise pathogenesis is still unclear, dopamine receptor blockade is theorized to play a central role. Conventional presentations include hyperthermia, muscle rigidity, and elevated creatine kinase concentrations. However, similar to other second generation neuroleptics, amisulpride induces an atypical form of NMS, which presents with lower degrees of hyperthermia and elevation of creatine kinase than the typical form. This phenomenon makes it difficult to identify early signs of NMS. This study describes the first case of amisulpride-induced NMS in Taiwan, together with a review of the current knowledge on NMS. In this case, the correlation between NMS and amisulpride was categorized as "probable" on the Naranjo adverse drug reaction probability scale. *(Chang Gung Med J 2011;34:536-40)*

Key words: amisulpride, atypical neuroleptics, neuroleptic malignant syndrome

Dopamine D2 receptor antagonistic agents (typical neuroleptics) have been used to treat psychotic symptoms since 1954,[1] and patients soemtimes develop lethal neuroleptic malignant syndrome (NMS).[1] The newer atypical neuroleptics can also induce NMS in susceptible patients.[2] Amisulpride, one of the atypical neuroleptics, has also been reported to induce NMS.[3-5] This study describes a case of amisulpride-induced NMS in Taiwan.

CASE REPORT

A 25-year-old woman with schizoaffective disorder who had discontinued all psychiatric medication for one month was admitted to our emergency department with severe auditory hallucinations, religious delusions, and hallucinatory behaviors. The patient was administered previously prescribed neuroleptics, amisulpride (400 mg twice daily without titration), triazolam (0.5 mg every night), and diphenhydramine (50 mg nightly).

The following day, the patient had an elevated body temperature (37.7°C), tachycardia (111 beats/minute [bpm]), consciousness change, nystagmus, mild muscle rigidity, and mutism. Her blood pressure was 101/55 mmHg. Laboratory investigations revealed leukocytosis (white blood cell count [WBC] 11,500/mm^3) without a left shift and elevated C-reactive protein (CRP 6.05 mg/L). Alanine aminotransferase (ALT) was elevated (52 U/L), blood urea nitrogen (BUN) was 9 mg/dL, and creatinine was 0.7 mg/dL. Creatine kinase (CK) and myoglobin levels were markedly elevated (CK 7215 U/L, myoglobin 957.1 μg/L). Other laboratory results including routine urinalysis, and electrolyte and alkaline phosphatase levels were normal.

On the third day, catatonic features and severe muscle rigidity with action tremor over the bilateral upper limbs were noted. She also exhibited hyporeflexia and decreased muscle power, but pupil size

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and light reflex were normal. Her body temperature (maximum of 38.2°C) was intermittently elevated but an infection source was not evident. Autonomic dysfunction (tachycardia, 98 bpm; elevated blood pressure, 162/120 mm Hg) was also found. NMS was impressed under the presentation with diagnostic criteria, and the correlations between amisulpride and NMS were in the "probable" category on the Naranjo adverse drug reaction (ADR) scale (Table 1). Amisulpride, triazolam, and diphenhydramine were all discontinued. Bromocriptine (7.5 mg four times daily), clonazepam (0.5 mg four times daily), and supportive treatment were administered for 2 weeks.

After this 2-week treatment, the patient fully regained lucidity. Nystagmus and catatonic features were markedly improved. No hyporeflexia or decreased muscle power was noted. The fever and autonomic dysfunction improved (body temperature 36.8°C, heart rate 79 bpm, and blood pressure 110/75 mm Hg). Other laboratory results (blood levels) were normal (WBC 6200/mm^3, CRP 0.89 mg/L, ALT 34 U/L, BUN 12 mg/dL, CK 91 U/L, myoglobin 32.3 μg/L). Bromocriptine and clonazepam were gradually reduced during the following week. Quetiapine (50 mg every night) was prescribed to treat her ongoing psychotic symptoms. After 2 more weeks, quetiapine was titrated to 600 mg nightly and the psychotic symptoms improved considerably. The patient was then discharged from the hospital without further complications.

DISCUSSION

The incidence of NMS is 0.02-3% in patients undergoing neuroleptic therapy.[6,7] Although the mortality rate of NMS has declined from 76% before 1970 to 10-30% recently,[8] cautious prescription of neuroleptics is recommended. Amisulpride, a second-generation neuroleptic, blocks pre- and postsynaptic dopamine D2 and D3 receptors when given in low and high doses, respectively.[9]

Amisulpride-induced rhabdomyolysis was previously described in one article; amisulpride-induced NMS was described in two articles.[3-5] Within these three articles, only one case fulfilled the diagnostic criteria for NMS according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision (DSM-IV-TR), the Caroff and Mann criteria, and Levenson criteria.[3,6,10,11] The case we presented also fulfills all three sets of diagnostic criteria.

In addition to diagnostic criteria, the ADR scale assesses the causal relationship between the suspected drug and undesired clinical reactions. Naranjo and his colleagues developed the ADR probability scale in 1981, and this 10-item questionnaire provides a simple valid, reliable method to assess the correlations.[12] It categorizes the correlations into definite,

Table 1. Patient Score on the Adverse Drug Reaction Probability Scale

	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes	+1
2. Did the adverse event appear after the suspected drug was administered?	Yes	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes	+1
4. Did the adverse reaction reappear when the drug was re-administered?	Do not know	0
5. Are there possible alternative causes that could have caused the reaction?	No	+2
6. Did the reaction reappear when a placebo was given?	Do not know	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	No	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	No	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
10. Was the adverse event confirmed by any objective evidence?	Yes	+1
Total score		+7

Adapted from Naranjo et al., 1981[5].

probable, possible, and doubtful.[12] As several drugs are used at the same time, the drug with the highest score will be the most likely cause of the undesired reaction.[12] With the elimination of alternative reactions, such as between diphenhydramine and NMS (Naranjo ADR scale categorized as "possible"), a correlation between amisulpride and NMS was "probable" according to the Naranjo ADR scale.[12,13]

The pathogenesis of NMS, however, is still unclear. Dopamine receptor blockade plays an important role in two major theories of NMS, namely alteration of a central neuroregulatory mechanism and abnormal reaction of predisposed skeletal muscle.[8]

Hyperthermia and muscle rigidity are distinctive symptoms in many diagnostic criteria sets.[6,10,11] Progressive rigidity may profoundly elevate the CK level, which reflects myonecrosis secondary to intense muscle contracture.[8] CK elevation often results in acute myoglobinuric renal failure, which is associated with a mortality risk of approximately 50%.[6,8] Alterations in consciousness, autonomic dysfunction, and other laboratory findings, including leukocytosis and elevated hepatic enzymes, are reportedly signs of NMS.

Atypical neuroleptic-induced NMS presents atypical features, an atypical course, and a risk of lethality.[2,14] Compared with typical NMS, atypical NMS may exhibit benign temperature elevation, fewer tremors, or mild rigidity.[2] Additionally, more than three-fourths of cases of atypical neuroleptic-induced NMS present with extrapyramidal syndrome.[14] In reports of amisulpride-induced NMS, manifestations included a minor form, with no temperature elevation over 39°C and a rare case of CK as high as 10,000 IU/L.[3,4,5] These atypical forms make atypical neuroleptic-induced NMS difficult to diagnose early.

NMS usually develops in the first 2 weeks of neuroleptic therapy. Amisulpride-induced NMS develops earlier, in the range of 1-4 days after exposure.[8] Amisulpride-induced NMS also resolves within 2 weeks, similar to typical NMS.[10,15]

High neuroleptic doses, rapid dose titration, and parenteral administration have been identified as pharmacologic risk factors in some controlled studies of NMS.[8] Dehydration, malnutrition, infection, organic brain disease, and sympathoadrenal hyperactivity are all risk factors for NMS.[8] Berardi and colleagues observed a significantly higher incidence of catatonia in NMS patients than in controls.[16] The specific characteristics of different D2 receptor binding sites with low and high amisulpride dosages make marked D2 receptor blockade change in the transition of escalation.[4]

Removal of the causative agent is the most important management step in NMS; supportive treatment is also suggested because it prevents lethal complications such as dehydration, electrolyte imbalance, epilepsy, hyperthermia, and acute renal failure associated with rhabdomyolysis.[8,17] Drug treatment for NMS should continue for 2-3 weeks until symptoms remit.[18] Amisulpride-induced NMS reportedly improves markedly after removal of amisulpride and administration of dantrolene and bromocriptine, with no neurological sequelae.[3-5] Additionally, recommendations for rechallenging the patient with neuroleptics include the following: a symptom-free interval of at least 2 weeks, lower potency agents, a lower initial dose, avoidance of concomitant use of lithium, and close monitoring for recurrence of NMS.[7,15]

Amisulpride-induced NMS is difficult to diagnose as early r as NMS induced by other atypical agents. Early detection of symptoms and signs, aggressive intervention, and a thorough understanding of the etiology are essential to reducing NMS mortality.

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Amisulpride 及抗精神病藥物惡性症候群

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抗精神病藥物惡性症候群 (NMS，簡稱惡性症候群) 是在抗精神病藥物使用時少見卻具致命性的副作用。發生率介於 0.02% 至 3%。Amisulpride 引發的橫紋肌溶解症及惡性症候群過去分別在一篇及兩篇的報告中提出。雖然致病機轉仍未定論，但一般認爲多巴胺 (dopamine) 阻斷與惡性症候群的發生相關。惡性症候群典型表現包括體溫升高、肌肉僵硬及肌酸磷酸脢 (creatine phosphokinase，CK) 上升。具較低多巴胺阻斷效價的新一代抗精神病藥物，其導致的惡性症候群在臨床症狀、病程、致命性具體溫上升幅度較少、較少顫抖、或輕微的肌肉僵硬的不典型表現。比較目前與過去四篇報告，amisulpride 所導致的臨床症狀同樣具不典型的表現，包括體溫未超過攝氏 39 度、肌酸磷酸脢上升僅在一篇報告超過 10,000 IU/L。此表現將導致在惡性症候群發展初期難確立診斷及即早處置。我們報告了台灣地區首例因 amisulpride 導致的惡性症候群並整理關於惡性症候群的最新觀念。另外，根據評估藥物副作用相關性的量表 (Naranjo adverse drug reaction probability scale)，此報告落在「具可能性的」相關性上。(長庚醫誌 2011;34:536-40)

關鍵詞：amisulpride，新一代抗精神病藥物，抗精神病藥物惡性症候群

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