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CASE SERIES

Neuroleptic Malignant Syndrome Improved with Intramuscular Administration of the Anticholinergic Agent, Biperiden

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Abstract: Anticholinergic drugs, such as biperiden, benztropine, and diphenhydramine, were used for neuroleptic malignant syndrome (NMS) in the 1980s and 1990s. However, they have not been recommended for pharmacotherapy in NMS since 2000, as they may prevent a decrease in body temperature by suppressing sweating. However, whether anticholinergic drugs actually exacerbate NMS remains unclear. This study highlights the usefulness of anticholinergic drugs, which are no longer attracting attention as current pharmacological treatments for NMS. I treated four NMS patients using anticholinergic drugs. Two patients were treated with biperiden alone, and the other two patients were treated with a combination of biperiden and other drugs, including dantrolene, amantadine, or diazepam. Intramuscular injection of biperiden improved muscle rigidity, tremors, dysphagia, and akinetic mutism. Psychiatrists are familiar with anticholinergic drugs as they are used for antipsychotic-induced akathisia and Parkinsonism. My study suggests that anticholinergic drugs, especially injectable formulations, can be a therapeutic option for NMS.

Keywords: anticholinergic drug, dantrolene, intramuscular injection, Parkinsonism

Introduction

Neuroleptic malignant syndrome (NMS) is one of the most serious side effects of antipsychotic drugs. In recent years, treatment with antipsychotic drugs has shifted from first-to second-generation antipsychotics. In addition, the recognition of NMS has spread, and early detection and treatment have been achieved. Consequently, NMS mortality is declining. A recent report showed a mortality rate of 7.6% for NMS.[1] However, it remains the most serious side effect of antipsychotics.

Bromocriptine, amantadine, benzodiazepines, and dantrolene are listed as current therapeutic agents for NMS;[2] however, anticholinergics, including biperiden, benztropine, and diphenhydramine are not recommended as therapeutic agents for NMS. I recently treated four NMS patients in whom the intramuscular injection of biperiden, an anticholinergic drug, was effective. The intramuscular injection of biperiden rapidly relieved extrapyramidal symptoms and improved akinetic mutism. This study aimed to highlight the usefulness of anticholinergic drugs, which are no longer attracting attention as a treatment for NMS.

Case Reports

Case 1

A 54-year-old man with a history of depression had been receiving sulpiride (300 mg/day), lofepramine (150 mg/day), and bromazepam (15 mg/day); however, his depression worsened in early January. Therefore, perphenazine (6 mg/day) was added, but the patient developed Parkinsonism, including finger tremors and bradykinesia. On January 15, the patient voluntarily discontinued all medications. Subsequently, fever and sweating manifested, and he could not eat. He was admitted to my hospital on January 22 (the 1st day after hospitalization, Day 1). At that time, muscle rigidity, finger

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tremor, dysphagia, diaphoresis, and sialorrhea were observed; the body temperature was 38.0°C, and the pulse was 110 beats/min. Blood tests showed a serum creatine kinase (CK) level of 11,400 (normal range: 10–70) IU/L, white blood cell (WBC) count of 10,400/mm^3, and albumin level of 4.4 (normal range: 3.8–5.2) g/dL. Myoclonus and hyperreflexia were not observed. Pneumonia and urinary tract infections were ruled out. He was diagnosed with NMS. Fluid replacement was immediately performed. As dantrolene was not available in psychiatric hospitals at that time, biperiden (5 mg), a centrally acting anticholinergic agent, was injected intramuscularly with the consent of the patient's family, which dramatically reduced extrapyramidal symptoms. Biperiden was injected intramuscularly three times a day on the day of admission and twice a day from hospitalization day 2. The fever improved on January 24 (Day 3). The autonomic symptoms disappeared by January 27 (Day 6), and the extrapyramidal symptoms disappeared by February 3 (Day 10).

Case 2

A 55-year-old man with schizophrenia was treated with haloperidol (15 mg/day), levomepromazine (150 mg/day), zotepine (175 mg/day), diazepam (10 mg/day), and trihexyphenidyl (6 mg/day) because of persistent hallucinations and delusions, agitation, and violent behavior. On February 12, he exhibited urinary retention, and had a fever of 38°C. The patient was diagnosed with a urinary infection and treated with antibiotics. His body temperature temporarily decreased to 36°C. On February 16, haloperidol was discontinued because high-dose antipsychotic drugs were suspected to have caused the urinary retention. Although the patient had dysphagia, he was being fed. On February 20, a sputum-producing cough was found, and his body temperature rose again to 37.6°C. Oxygen saturation (SpO_2) was 92%. Aspiration pneumonia was diagnosed on February 21. The psychotropic drugs were discontinued owing to his inability to take medication orally (the 1st day after discontinuation of psychotropic drugs, Day 1). On February 22 (Day 2), his body temperature was 37.2°C and SpO_2 was 96%. On February 26 (Day 6), his body temperature was 36.5°C, but his response worsened. On February 28 (Day 8), his body temperature increased to 38.6°C. Tremors, muscle rigidity, dysphagia, and diaphoresis were also observed, but myoclonus and hyperreflexia were not observed. His blood pressure and pulse were 139–94 mmHg and 136 beats/min, respectively. A blood test showed a WBC of 7600/mm^3 and a serum CK level of 40 (normal range: 62–287) IU/L. A blood test was performed again on March 1 (Day 9), and the WBC count, serum CK level, and albumin level were 11,500/mm^3, 88 IU/L, and 3.2 g/dL, respectively. Although the serum CK level was not elevated, NMS was suspected. As in Case 1, biperiden (5 mg, intramuscularly) was administered because an injectable form of dantrolene was not available and dantrolene could not be used immediately. Consequently, biperiden dramatically alleviated muscle rigidity and tremor and resolved akinetic mutism. Prior to biperiden administration, the patient had open eyes but did not respond to calls. However, after biperiden administration, he was able to perform actions, such as raising the upper limbs, according to instructions. I treated the patient with fluid replacement and injected biperiden (5 mg, intramuscularly) twice daily because its effects lasted only 12 h. On March 2 (Day 10), his body temperature dropped to 37°C. Muscle rigidity, finger tremor, and dysphagia gradually improved. His body temperature decreased to 36°C on March 6 (Day 14).

Case 3

A 74-year-old woman with bipolar I disorder had been hospitalized more than a dozen times. When the patient was 73 years old, she was admitted to a nursing home in October. However, in November of the same year, she developed depression and stupor and was unable to eat; therefore, she was admitted to my hospital. The patient's mental state alternated between times when she reacted well and was able to eat and when she reacted poorly and did not eat. Antidepressants, including sulpiride, maprotiline, and amoxapine, were administered, but depression was not improved. In February of the following year, olanzapine (5 mg/day) and amoxapine (70 mg/day) were administered. However, the effects remained unsatisfactory. She could not eat; therefore, tube feeding was performed, but she gradually became conspicuously thin (albumin level, 3.1 g/dL). On February 13, her body temperature was 35.6°C. On February 14 (the 1st day after appearance of fever, Day 1), the temperature increased to 38.1°C, and profuse sweating and finger tremors were observed. Blood and urine tests, and chest radiography were performed. Her SpO_2 was 99% and her C-reactive protein level was 1.07 (normal range: <0.3) mg/dL. Pneumonia and urinary tract infections were ruled out. On February 18 (Day 5), her body temperature was 40.7°C, and her pulse rate was 115/min. On February 20 (Day 7),

although the serum CK level was 93 (normal range: 40–160) IU/L. Myoclonus and hyperreflexia were not observed. NMS was suspected because of unknown high fever, a decreased level of consciousness, muscle rigidity, tremor, tachycardia, and diaphoresis. Therefore, treatment with olanzapine and amoxapine was discontinued. Biperiden (5 mg, intramuscularly) was first administered. After approximately 30 min, her muscle rigidity reduced and her response improved. As biperiden was effective, intramuscular injection of biperiden was continued. As the patient's body temperature exceeded 40°C, I administered dantrolene (60 mg, intravenously) and amantadine (400 mg) through a gastric tube. Her clinical symptoms gradually improved, and by March 10 (Day 25), all symptoms had subsided.

Case 4

A 68-year-old woman with schizophrenia was on psychotropic medications olanzapine (10 mg/day), quetiapine (12.5 mg/day), and flunitrazepam (2 mg/day). Furthermore, she was taking Kampo drugs, including glycyrrhizin derivatives and licorice derivatives, for hepatic disorders. On August 24, the patient complained of weakness in her lower extremities. A blood test was performed on August 26, revealing a serum potassium level of 1.8 mEq/L. Pseudoaldosteronism due to glycyrrhizin and licorice was diagnosed; therefore, both drugs were discontinued, and replacement of fluids containing potassium was initiated. The patient continued to experience anorexia, muscle weakness, bradycardia, and ventricular extrasystoles. The psychotropic drugs were discontinued on August 31 (the 1st day after the discontinuation of psychotropic drugs, Day 1) because improving her physical condition was a priority. On September 4 (Day 5), a fever of 37.7°C manifested. She became less responsive to addressing, and dysphagia appeared. On September 5 (Day 6), finger tremors were observed. On September 6 (Day 7), her body temperature was 38.4°C, and the pulse rate was 118/min. Nuchal rigidity, finger tremors, muscle rigidity, and diaphoresis were observed. Myoclonus and hyperreflexia were not observed. NMS was suspected, and a blood test revealed leukocytosis of 10,100/mm^3 and a slightly elevated CK level of 191 (normal range: 40–160) IU/L. Her albumin level was 3.7 g/dL. Biperiden (5 mg, intramuscularly) was injected and after approximately 30 min, tremor and nuchal rigidity improved. Biperiden 5 mg was injected intramuscularly twice daily for 2 days. As the dysphagia improved on September 7 (Day 8), biperiden (6 mg/day) was administered orally, followed by the oral administration of dantrolene (75 mg/day) and diazepam (10 mg/day). On September 12 (Day 13), her body temperature decreased to 36°C.

Discussion

Serotonin syndrome (SS) is a disease that presents clinical symptoms similar to those of NMS as a differential diagnosis.[3] However, none of my four patients received serotonergic drugs. In addition, myoclonus and hyperreflexia, which are characteristics of SS, were not observed. Therefore, SS was ruled out. Moreover, other physical diseases were ruled out and all four patients met the diagnostic criteria for NMS proposed by Caroff et al[4] as well as in accordance with the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR).[5]

Next, the characteristics of the four cases of NMS are described. Concerning the severity of NMS classified by Woodbury and Woodbury,[6] Patient 1 was in a mild condition, while Patients 2–4 were in a moderate condition. In Patients 1, 2, and 4, NMS had developed after the discontinuation of psychotropic drugs. Antipsychotic drugs exert considerable anticholinergic effects and reportedly develop NMS after antipsychotics discontinuation.[7] Additionally, NMS was developed because of an abrupt reduction in γ-aminobutyric acid (GABA) agonist activity.[8] Therefore, Patients 1, 2, and 4 were considered to have developed NMS due to withdrawal of antipsychotic drugs with anticholinergic effects or discontinuation of benzodiazepines with GABAergic agonists. The serum CK levels were not elevated in Patients 2 and 3. In general, the serum CK levels are elevated in >90% of NMS cases; however, there are a few cases, in which it is not elevated[9,10] due to factors, such as malnutrition. Patients 2 and 3 had extremely low albumin levels, suggesting that malnutrition was a factor in the absence of elevated serum CK.

Strawn et al[2] proposed a treatment algorithm for mild, moderate, and severe NMS. The pharmacological agents include lorazepam, bromocriptine, amantadine, and dantrolene. Although benzodiazepines, such as lorazepam, are effective against catatonic symptoms in NMS, intravenous benzodiazepines can cause respiratory depression and hypotension in a dose-dependent manner. The precise pathophysiological mechanisms of NMS remain unknown; however, dopamine hypofunction in the striatum and hypothalamus is known to be involved in the development of

NMS.[2,4] From this perspective, the administration of dopamine agonists, such as bromocriptine and amantadine, seems to be reasonable for NMS treatment. As NMS is accompanied by dysphagia, drug forms that can be injected intravenously or intramuscularly are preferred. However, there are no injectable forms of bromocriptine and amantadine. Injectable form of dantrolene is a peripheral muscle relaxant that has been recognized as a specific drug for malignant hyperthermia caused by anesthetics, but it is not approved for NMS.[11]

Although anticholinergic agents are not adopted in the treatment algorithm for NMS,[2] I treated four NMS patients using an intramuscular injection of biperiden, an anticholinergic agent, in this study. Consequently, remarkable effects were observed, especially on extrapyramidal symptoms, such as tremor, muscle rigidity, dysphagia, and akinetic mutism. NMS was improved with fluid replacement and biperiden intramuscular injection in Patients 1 and 2. Biperiden, dantrolene, and amantadine were administered to Patient 3, whereas, biperiden, dantrolene and diazepam were administered to Patient 4. However, in these two cases, biperiden was injected intramuscularly before the concomitant use of dantrolene, amantadine, and diazepam, and I confirmed that biperiden relieved extrapyramidal symptoms and akinetic mutism within approximately 30 min. The exact mechanism of action of anticholinergic drugs in relieving NMS remains undetermined, although they may act by blocking the acetylcholine receptors and improve decreased dopamine activity.[12]

Case reports in the 1980s and the 1990s have reported the usefulness of anticholinergic agents as therapeutic agents for NMS.[13–17] However, many reports have shown that dantrolene and bromocriptine were effective against NMS from the 1990s to date.[11,18] Anticholinergic agents may prevent a decrease in body temperature because they suppress sweating.[19] Therefore, anticholinergic agents are not recommended as therapeutic agents for NMS in recent reviews.[20–22] However, it remains unclear whether anticholinergic agents exacerbate hyperthermia in NMS. Furthermore, in recent years, benztropine has reportedly been effective against NMS,[23] and biperiden and bromocriptine have been effective against NMS.[24] Dysphagia and sialorrhea are observed in many NMS patients, and both symptoms can trigger aspiration pneumonia associated with the risk of death. In this study, I observed rapid improvement of extrapyramidal symptoms, including muscle rigidity, tremor, dysphagia, and sialorrhea, by administering intramuscular injection of biperiden. This is considered beneficial for the prognosis of NMS. Anticholinergic drugs are familiar to psychiatrists as they are used for antipsychotic-induced akathisia, dystonia, and Parkinsonism. Therefore, in addition to bromocriptine, amantadine, benzodiazepines, and dantrolene, anticholinergic agents, particularly in injectable form, can be one of the therapeutic options for NMS.

Limitations

It is not possible to say with certainty that anticholinergic drugs are effective for all NMS patients. In fact, there are some reports that anticholinergic drugs have no effect on NMS.[25,26]

Furthermore, this study only included four patients, and it is necessary to accumulate more cases in the future and examine the effect of anticholinergic drugs on NMS. According to NMS classification by Woodbury and Woodbury,[6] Case 1 was mild, while Cases 2–4 were moderate; no case was severe. It is necessary to consider whether anticholinergic drugs are effective even in severe cases in the future.

Conclusion

As NMS etiology is not well understood, effective therapeutic agents with different mechanisms of action are needed. In this study, anticholinergic agent, biperiden improved and did not exacerbate, the clinical symptoms of the four NMS patients. Therefore, anticholinergic drugs, especially injectable formulations, can be used safely against NMS without causing respiratory depression and hypotension and can be one of the therapeutic options for treating NMS patients. However, the basic treatment of NMS is discontinuation of causative drugs and systemic management. Moreover, caution is needed when using off-label medicines.

Informed Consent for Publication

Written consent for publication of case details was obtained from all patients. Institutional approval was not required to publish the case details. This study was conducted in accordance with the tenets of the Declaration of Helsinki.

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