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Neuroleptic Malignant Syndrome Induced by Lamotrigine

Masamichi Ishioka, MD, Norio Yasui-Furukori, MD, PhD, Kojiro Hashimoto, MD, and Norio Sugawara, MD, PhD

Abstract: This case report describes a 54-year-old man with bipolar I disorder who was treated with aripiprazole (ARP) and lithium. The patient was admitted to our hospital because of aggravation of depressive symptoms, and treatment with lamotrigine (LTG) was initiated. Two weeks after admission, we discontinued administration of ARP after the appearance of a tremor. Three weeks after discontinuing ARP, the patient developed a high fever, rigidity of the arms, diarrhea, dysphagia, and diaphoresis. We suspected these symptoms were consistent with neuroleptic malignant syndrome and therefore removed the application of LTG. After 2 days, most of the patient’s symptoms and blood results had improved, leading us to conclude that the LTG treatment had induced neuroleptic malignant syndrome. Thus, the purpose of this case report was to warn psychiatrists against therapy with LTG, as it may be conducive to neuroleptic malignant syndrome.

Key Words: lamotrigine, neuroleptic malignant syndrome

CASE REPORT

A 54-year-old man with bipolar I disorder was admitted to our psychiatric hospital because of the exacerbation of depressive symptoms. The patient presented with an 8-year history of bipolar I disorder but had neither a prior history of substance use nor any systemic illness. He had been treated with several antipsychotics in the past without any development of neuroleptic malignant syndrome. However, the development of a tremor during treatment with sertraline (SER; 25 mg) was initiated because of the development of a tremor. At the same time, treatment with lamotrigine (LTG) was initiated.

The patient was treated with aripiprazole (ARP; 6 mg/d) and lithium (Li; 400 mg/d). Subsequently, a 50-mg/d dose of LTG was added, and this dosage was increased by 50 mg/wk. Two weeks after admission, we discontinued ARP because of the development of a tremor. At the same time, treatment with sertraline (SER; 25 mg) was initiated because of the continued symptoms of depression. Five weeks after admission, at which time the patient was receiving LTG at 200 mg/d, Li at 400 mg/d, and SER at 25 mg/d, he developed a fever of 39.1°C with rigidity of the arms, diarrhea, dysphagia, and diaphoresis; rash was not observed. A heart rate of 100 to 120 beats/min, blood pressure of 140/100 mm Hg, and diaphoresis were observed during the physical examination. Laboratory tests indicated the levels of white blood cells at 6000/μL, CPK at 4000 IU/L, alanine aminotransferase (AST) at 121 IU/L, and C-reactive protein at 0.17 mg/L. A neurological examination ruled out a possible brain infection, inflammation, or malignancy. The level of inflammatory markers 1 week later, and the signs of infection were no longer observed at this point. Two weeks after recovery, the patient was treated with electroconvulsive therapy, which was effective at abating his depressive symptoms.

DISCUSSION

To our knowledge, this is the first reported case of NMS induced by LTG. Based on the diagnostic criteria for NMS outlined by Pope et al,1 we believe that our patient developed this syndrome because his episode presented all 3 major manifestations, including hyperthermia (>37.5°C), severe extrapyramidal effects (rigidity, diarrhea, and dysphagia), and symptoms of the autonomous nervous system (tachycardia and diaphoresis). Lamotrigine is the most likely causal agent of NMS in this patient because the patient was treated with Li and SER after the initial NMS symptoms, and no further NMS symptoms occurred, although the spontaneous occurrence of an NMS-like syndrome cannot entirely be ruled out.

Several drugs are known to be implicated in the onset of NMS. In a review of the literature, we found more than 20 different compounds to be associated with NMS, particularly first-generation antipsychotics and atypical antipsychotics (Table 1). Several other classes of drugs with dopamine-blocking pharmacologic effects (eg, amoxapine and metoclopramide) may also cause NMS symptoms. However, it is known that LTG does not directly affect the dopaminergic system2; instead, LTG blocks sodium channels and inhibits the release of glutamate and aspartate, along with inhibiting acetylcholine and γ-aminobutyric acid (GABA) release.3 Lamotrigine is also known to serve as a weak blocker of T-type calcium channels.
We hypothesize that the GABA-associated properties of LTG may have been responsible for the NMS observed in our patient. Although the exact mechanism for how NMS is associated with the GABAergic system is not yet completely understood, it is known that the GABAergic medication baclofen may cause symptoms of NMS.10

Of course we cannot exclude the possibility that this patient’s NMS was induced by ARP. However, 3 weeks elapsed after halting the prescription for ARP before the NMS symptoms developed. According to most case reports,11,12 NMS typically occurs within 1 week of either an initiation, increase, or interruption of ARP treatment. In particular, initiations and increases are responsible for most cases of NMS. A literature search for NMS caused by the withdrawal of a dopaminergic drug (mainly levodopa) identified a study of 11 cases, which indicated that the patients had an average latency period of 92.72 ± 13.24 hours before developing NMS.13 Other studies show a similar time to onset. We therefore concluded that there was little possibility that ARP induced the NMS symptoms. Instead, we believe it is likely that LTG caused the NMS symptoms in our patient and therefore recommend the use of caution when administering LTG.

REFERENCES


TABLE 1. List of Drugs Inducing NMS

<table>
<thead>
<tr>
<th>Action Mechanism of the Drug</th>
<th>Drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical antipsychotics</td>
<td>Haloperidol, chlorpromazine, fluphenazine, perphenazine, prochlorperazine</td>
<td>Jahan et al6</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Clozapine, olanzapine, risperidone, paliperidone</td>
<td>Trollor et al7</td>
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<tr>
<td>Dopaminergic agents</td>
<td>Metoclopramide, amoxapine</td>
<td>Trollor et al7</td>
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<tr>
<td>GABAergic drug</td>
<td>Amanatidine, l-dopa</td>
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<tr>
<td>Monoamine oxidase inhibitors</td>
<td>Bacrofen</td>
<td>Trollor et al7</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Linezolid</td>
<td>Trollor et al7</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Lithium, carbamazepine, sodium valproate</td>
<td>Trollor et al7</td>
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