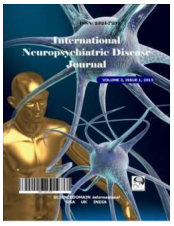

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Lamotrigine-induced Neutropenia Followed by Drug Eruption: A Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Author DIJ designed the study and wrote the protocol. Author UH managed the literature search and wrote the first draft of the manuscript with assistance from authors MHJ and NH. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

A 55-year-old female with no physical problems was initially hospitalized for psychotic mania but soon discharged. A month later she was rehospitalized for bipolar depression and treated with lamotrigine (25 mg/day), olanzapine (10 mg/day), and lorazepam (0.5 mg/day). On day 22, lamotrigine was stopped because of neutropenia. On the same day, the patient developed skin rashes with pruritus, which gradually spread. We present this case as evidence that neutropenia and pruritic rash are rare side effects of lamotrigine, and could have causal relationships with each other. Clinicians should be aware of the potential for these effects when using lamotrigine.

Keywords: Lamotrigine; neutropenia; bipolar depression; drug eruption.

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1. INTRODUCTION

Neutropenia is defined as a peripheral neutrophil count less than 2.0 x 10^9/L. Neutrophil counts below 0.5 x 10^9/L, a condition called agranulocytosis, enormously increases risk of recurrent infections. Common symptoms of neutropenia include skin rash, mouth ulcers, thrush, lymphadenopathy, mucous membrane abnormalities, fever, infections, and diarrhea. A reduction in circulating neutrophils can result from inadequate or ineffective granulopoiesis or accelerated removal of neutrophils from the blood. Either of these may be induced by various drugs, but the pathogenesis of neutropenia is not fully understood.

Drug-induced cutaneous eruption (briefly, drug eruption) is a relatively common adverse reaction to various drugs including some psychiatric mediacations [1,2]. Its exact mechanism is unknown but assumed as a combination of alterations in drug metabolism, drug detoxification, antioxidant defenses, and immune reactivity. Specifically, Type IV hypersensitivity reactions may involve an antibody-dependent, cell-mediated cytotoxic response [3]. Type IV cell-mediated reactions are not dose-dependent, usually begin 7-20 days after the medication is started or increased, involve blood or tissue eosinophilia, and may recur in response to the same drugs. Although drug eruption is closely linked to immune response, few reports indicate a connection with neutropenia.

Lamotrigine is a triazinic anticonvulsant and is also approved for the treatment of bipolar disorder [4-6]. Skin rashes are its most common side effect. Though various hematologic abnormalities associated with lamotrigine have been reported [7-9], these include only a few cases of neutropenia [10-12].

A similar case presenting neutropenia and Stevens-Johnson syndrome (SJS) under treatment with lamotrigine was recently reported [10], but unlike our case with characteristic exanthematous manifestations, high fever and severe skin rash occurred first, followed by neutropenia. In SJS and toxic epidermal necrolysis, both severe forms of skin rash, neutropenia is known to occur in about one-third of patients and correlates with a poorer prognosis. We present a case of a patient who became neutropenic immediately prior to development of drug eruption while taking lamotrigine.

2. PRESENTATION OF CASE

A 55-year-old woman was initially hospitalized for treatment of psychosis which occurred as part of a manic episode of bipolar I disorder. She had no personal or family history of psychiatric illness. At admission, her white blood cell (WBC) count and absolute neutrophil count (ANC) were 4,300 cells/mm^3 and 2,659 cells/mm^3, respectively. Her overall laboratory test results, including hepatic and renal function, were within normal range. She was treated with olanzapine (20 mg, Zyprexa, manufactured by Lily) and clonazepam (0.5 mg, Rivotril, manufactured by Roche), which led to partial improvement of symptoms and she was discharged against medical advice.

After discharge, she had not taken any medication until she was hospitalized again about a month later due to a major depressive episode. Her WBC count and ANC were 4,400 cells/mm^3 and 3,010 cells/mm^3, and other laboratory results were within normal range. Following diagnosis of bipolar I disorder with current depression, treatment with lamotrigine (25 mg/day, Lamictal, manufactured by GSK), olanzapine (10 mg/day), and lorazepam (0.5 mg/day, Ativan, manufactured by Ildong) was initiated. On day 14, the lamotrigine dose was increased to 50 mg/day according to a regular titration schedule, and olanzapine remained at the same dose. On day 18, her WBC count began to indicate neutropenia (3,200 cells/mm^3) and her ANC was 1,755 cells/mm^3. Also, her aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were slightly increased to 50 IU/L and 93 IU/L, respectively. As there were no other observable symptoms or signs, treatment was continued under careful observation. On day 22, liver function appeared normal; liver CT showed only one small simple cyst. However, her WBC and ANC continued to decrease to 2,900 cells/mm^3 and 1,720 cells/mm^3, respectively. Despite the reduced neutrophil count, other blood cells and platelets were within normal range. At that time, lamotrigine was discontinued immediately because of its potential to cause skin rash, while the other drugs were maintained. At the same day, the patient complained of pruritus and rash on both legs. She had no previous history of allergy. Under close observation with frequent blood tests, oral antihistamines and steroid ointment were prescribed to relieve her itch.

A hematologic consultation ruled out other possible causes of neutropenia with serial follow

up for CBC and peripheral blood smear. Her WBC and ANC normalized within six days after discontinuation of lamotrigine, but the drug eruption became worse and broadened to cover her entire body, particularly both deltoids and both thighs, with characteristic exanthematous (maculopapular) manifestations. The next day, considering the possibility of a more severe dermatologic condition such as SJS, she was transferred to the dermatology department, where a skin biopsy was performed and she was treated with intravenous antihistamines and steroids. The dermatologist recommended minimizing all drug doses, so olanzapine was reduced to 5 mg/day and lorazepam was discontinued. A few days after recovery from neutropenia, both her pruritus and rash resolved completely without any complications.

3. DISCUSSION

In this case, we conclude that lamotrigine is the only cause of both neutropenia and drug eruption for four reasons. (1) Neutropenia developed a few days after the lamotrigine dose was increased from 25 mg/day to 50 mg/day (olanzapine and clonazepam were previously exposed to her during first admission). (2) Neutropenia began to improve soon after discontinuation of lamotrigine, while other drugs were continued at the same doses. (3) Until onset of drug eruption, lamotrigine was the only drug whose dose was changed. (4) Drug eruption resolved after the recovery of neutropenia.

Our case scores a total of six points on the Naranjo algorithm [13,14], a commonly used as a tool to assess adverse drug reactions, indicating that lamotrigine is the probable cause of the side effects (Table 1). A few cases indicating that lamotrigine may induce neutropenia (or agranulocytosis) have been reported [7-12]. These papers have carefully concluded that neutropenia induced by lamotrigine occur rapidly following treatment initiation and results from dose escalation rather than the dosage itself; the presentation of this case also supports those speculations. Nevertheless, this case is unique for its presentation of both neutropenia and skin rash in temporal correlation. We suggest that development of neutropenia while taking lamotrigine increases vulnerability to drug eruption as well as infections.

The mechanisms by which lamotrigine causes both its therapeutic and adverse effects are not yet thoroughly understood [15-19]. Nonetheless, a likely explanation is that lamotrigine decreases neutrophils in the peripheral blood via a temporary malfunction in the immune system that also attacks basal keratinocytes in the skin, causing a rash [20]. Whether neutropenia and drug eruption are directly or indirectly related, or are both the results of a single underlying pathophysiology, remains unclear. Nevertheless, considering that both conditions are immunological problems that occurred close together in time, neutropenia may be indicative of potential for drug eruption. Thus, we recommend that clinicians should cautiously monitor the occurrence of neutropenia when starting and titrating lamotrigine dosage. Once neutropenia develops, clinicians should be advised to discontinue lamotrigine and carefully monitor for skin rashes.

Table 1. Naranjo algorithm for adverse drug reaction assessment predicting causality in this case with lamotrigine-induced neutropenia

1. Are there previous conclusive reports on this reaction?	No	0
2. Did the adverse event appear after the suspected drug was administered?	Yes	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	Yes	1
4. Did the adverse event reappear when the drug was readministered?	Don't know	0
5. Are there alternative causes that could on their own have caused the reaction?	No	2
6. Did the reaction reappear when a placebo was given?	Don't know	0
7. Was the drug detected in 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?	Don't know	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: 6 (probable causality)		

4. CONCLUSION

lamotrigine may induce neutropenia, especially at the early phase of treatment, and this condition may increase the risk of drug eruption. Hematologic abnormality and rash resolved soon after discontinuation of lamotrigine in our case.

CONSENT

All authors declare that 'written informed consent' was obtained from the patient (or other approved parties) for publication of this case report.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wang XQ, Shi XB, Au R, Chen FS, Wang F, Lang SY. Influence of chemical structure on skin reactions induced by antiepileptic drugs-the role of the aromatic ring. Epilepsy Res. 2011;94:213-7.
2. Hsiao CJ, Lee JY, Wong TW, Sheu HM. Extensive fixed drug eruption due to lamotrigine. Br J Dermatol. 2001;144: 1289-91.
3. Gell PGH, Coombs RRA. The classification of allergic reactions underlying disease. In: Coombs RRA, Gell PGH, editors. Clinical Aspects of Immunology. London: Blackwell Sci; 1963.
4. Bowden CL, Singh V. Lamotrigine (Lamictal IR) for the treatment of bipolar disorder. Expert Opin Pharmacother. 2012;13:2565-71.
5. Rapoport SI, Basselin M, Kim H-W, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. Brain Res Rev. 2009;61:185-209.
6. Green B. Lamotrigine in mood disorders. Curr Med Res Opin. 2003;19:272-7.
7. Ahn YM, Kim K, Kim YS. Three cases of reversible agranulocytosis after treatment with lamotrigine. Psychiatry Investig. 2008;5:121-3.
8. Fadul CE, Meyer LP, Jobst BC, Cornell CJ, Lewis LD. Agranulocytosis associated with lamotrigine in a patient with low-grade glioma. Epilepsia. 2002;43:199-200.
9. Solvason HB. Agranulocytosis associated with lamotrigine. Am J Psychiatry. 2000;157:1704.
10. Yasui-Furukori N, Hashimoto K, Tsuruga K, Nakamura K. Comorbidity of Stevens-Johnson syndrome and neutropenia associated with lamotrigine: A case report. Gen Hosp Psychiatry. 2014;36:761:e9-11.
11. Das P, Ramaswamy S, Arora M, Samuels I, Gabel TL. Lamotrigine-induced neutropenia in a woman with schizoaffective disorder. Prim Care Companion J Clin Psychiatry. 2007;9:471-2.
12. Lambert O, Veyrac G, Armand C, Bourlon S, Bourin M, Jolliet P. Lamotrigine-induced neutropenia following two attempts to increase dosage above 50 mg/day with recovery between episodes. Adverse Drug React Toxicol Rev. 2002;21:157-9.
13. Belhekar MN, Taur SR, Munshi RP. A study of agreement between the Naranjo algorithm and WHO-UMC criteria for causality assessment of adverse drug reactions. Indian J Pharmacol. 2014;46:117-20.
14. Agbabiaka TB, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: A systematic review. Drug saf. 2008;31:21-37.
15. Ketter TA, Greist JH, Graham JA, Roberts JN, Thompson TR, Nanry KP. The effect of dermatologic precautions on the incidence of rash with addition of lamotrigine in the treatment of bipolar I disorder: A randomized trial. J Clin Psychiatry. 2006;67:400-406.
16. Hirsch LJ, Weintraub DB, Buchsbaum R, Spencer HT, Straka T, Hager M, et al. Predictors of lamotrigine-associated rash. Epilepsia. 2006;47:318-322.
17. Biton V. Pharmacokinetics, toxicology and safety of lamotrigine in epilepsy. Expert Opin Drug Metab Toxicol. 2006;2:1009-1018.
18. Messenheimer JA, Guberman AH. Rash with lamotrigine: dosing guidelines. Epilepsia. 2000;41:488.

19. Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother. 1999;33:1037-1042.

20. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: What is the pathogenesis? Arch Dermatol. 2001;137: 357-364.

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