Lamotrigine-Induced Blood Dyscrasias in Association with Rash

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INTRODUCTION

Lamotrigine is used to treat a number of disease states, including bipolar disorder. It is generally well tolerated, with dizziness, insomnia, and skin rashes being the adverse effects most often reported. The prevalence of rash among patients receiving lamotrigine is approximately 10%, but serious rashes associated with hospital admission are rare (0.3%).[1] Increased frequency of dermatologic events has been associated with more rapid initial titration of lamotrigine and with concomitant use of valproic acid, a known inhibitor of lamotrigine metabolism.[1] Blood dyscrasias associated with lamotrigine have been reported, but the numbers are too few to estimate the incidence.[1] We report here a case of lamotrigine-induced leukopenia (leukocyte count less than 4.0 x 10^9/L) and neutropenia (neutrophil count less than 1.5 x 10^9/L) associated with rash. This case illustrates the potential morbidity associated with lamotrigine-induced blood dyscrasias.

CASE REPORT

A 37-year-old woman with a significant psychiatric history was admitted to hospital for treatment of bipolar depression.* On admission, her home medications included divalproex 1000 mg PO hs, zopiclone 7.5 mg PO hs, risperidone 0.5 mg PO hs, sertraline 50 mg PO once daily, and quetiapine 25 mg PO prn q2h (maximum 4 doses/day). The patient was weeping and depressed on presentation to hospital, with suicidal ideation and displaying impaired judgement. She reported decreased appetite, decreased sleep, and anhedonia. She also stated that she was feeling anxious and overwhelmed.

The results of a physical examination were unremarkable. The results of laboratory testing at the time of admission were remarkable only for slight elevation of the mean corpuscular volume (99.5 fL/cell; normal range 80 to 96 fL/cell). The leukocyte count was 5.1 x 10^9/L. No other hematologic abnormalities were evident.

In hospital, a number of changes were made in the patient's medications. Because the patient appeared "weepy" and withdrawn on hospital day 2, sertraline was increased from 50 mg once daily to 100 mg once daily. On hospital day 6, the patient experienced hypomanic symptoms, specifically racing thoughts and increased energy. As a result, the sertraline was discontinued, as were quetiapine and risperidone. On the same day, olanzapine 5 mg PO q4h prn (maximum 3 doses/day) was added to help control her agitation. On hospital day 7, lamotrigine 12.5 mg hs was initiated, and divalproex was increased from 1000 mg qhs to 250 mg qam and 1000 mg qhs. On day 13, the patient continued to show signs of increased energy and anxiety; she also reported muscle aches. Lamotrigine was increased to 25 mg qhs. Laboratory investigations on day 19 revealed leukopenia (leukocyte count 3.5 x 10^9/L) (Figure 1). The patient also experienced abnormal (i.e., early) menses on this day. The platelet count was 163 x 10^9/L and remained within the reference range (150 x 10^9/L to 400 x 10^9/L) for the entire hospital stay. On day 20, an erythematous rash developed on the patient's upper chest, and her vision became blurry. Repeat laboratory analysis revealed leukocyte and neutrophil counts of 3.1 x 10^9/L and 1.3 x 10^9/L, respectively. The lamotrigine was discontin-

*Details that were not deemed essential to the understanding of this case have been omitted to protect patient confidentiality.

ued. On day 22 (2 days after discontinuation of lamotrigine), the rash resolved without medical management. By day 23, the leukocyte count had returned to normal (4.3 x 10^9/L). The neutrophil count increased to 2.3 x 10^9/L by day 28. The patient continued to receive divalproex throughout this period, and divalproex was continued after discharge, along with ongoing psychotherapy.

DISCUSSION

Given the time course of events, it was concluded that the leukopenia and neutropenia were likely associated with the use of lamotrigine. The development of a rash and the decrease in leukocyte count appeared 13 days after initiation of lamotrigine therapy, and resolved 2 to 5 days, respectively, after its discontinuation. The Naranjo adverse reaction probability score was calculated to assess the probability that this adverse hematologic reaction was associated with lamotrigine.[2] The score was 7, which indicates a probable adverse reaction. The mechanism is unknown.[3]

Concomitant use of divalproex might have contributed to the development of both the rash and the blood dyscrasias. Divalproex can reduce lamotrigine clearance by approximately 60%,[4,5] doubling the half-life of the latter drug and increasing its serum concentration by as much as 200%.[1,6] Hepatic metabolism is the primary route of elimination of lamotrigine (through N2-glucuronidation). The UDP-glucuronosyltransferase (UGT) enzymes responsible for lamotrigine elimination are UGT 2B7 and UGT 1A4. The interaction between valproic acid and lamotrigine arises from the inhibition of UGT 2B7, which leads to a decrease in lamotrigine clearance and an increase in serum concentration of the drug.[7] Such increases may in turn increase the risk of rash and also the risk of blood dyscrasias.

Rapid initial titration of lamotrigine might have increased the risk of these adverse reactions in the patient described here. According to the manufacturer's guidelines, the dose of lamotrigine should be increased slowly every 2 to 3 weeks over a period of 6 to 7 weeks for patients who are also taking valproate; the initial dose of lamotrigine should be no more than 12.5 mg daily or 25 mg every 2 days.[1] Even at this slow initial titration rate, there is a risk of serious rash, and titration should proceed with caution.[1,8] Thus, both the rapid initial titration of lamotrigine and the concomitant use of divalproex may have played a role in the development of rash and blood dyscrasias in this patient.

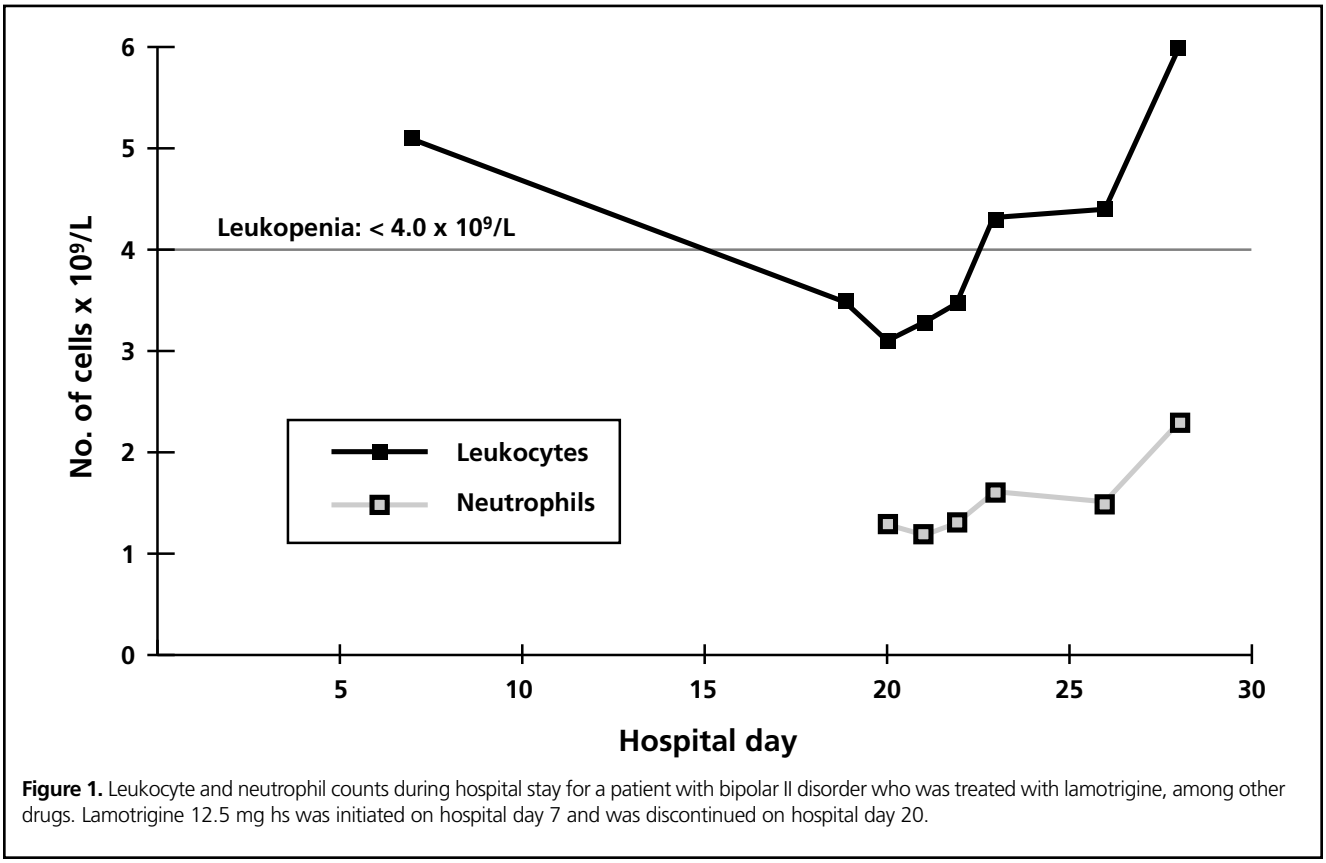

Figure 1. Leukocyte and neutrophil counts during hospital stay for a patient with bipolar II disorder who was treated with lamotrigine, among other drugs. Lamotrigine 12.5 mg hs was initiated on hospital day 7 and was discontinued on hospital day 20.

Although divalproex has been documented to cause rash (in up to 6% of patients taking this drug) and rarely neutropenia,[9] the timing of rash and blood dyscrasias in this case suggests that lamotrigine was involved. Furthermore, the abnormalities disappeared after discontinuation of lamotrigine, despite continuation of divalproex.

Lamotrigine-induced blood dyscrasias have been reported previously. A MEDLINE search in November 2006 identified 10 case reports published in the English language.[10-19] These included 1 case of leukopenia,[11] 3 cases of neutropenia,[14,15,17] and 3 cases of agranulocytosis.[10,12,16] Two cases involving thrombocytopenia combined with neutropenia or leukopenia[13,19] and one report describing 2 separate cases of anemia[18] were among the other hematologic adverse reactions reported. These blood dyscrasias were observed as early as the first week and as late as 2 months after initiation of lamotrigine. Blood dyscrasias were often dose related[14] and usually resolved between 3 days and 2 weeks after discontinuation of lamotrigine, with the exception of the 2 cases of anemia, which did not improve until 2 months later.[18] Rash, usually erythematous or maculopapular, was observed in 4 of these cases, appearing most commonly in the first 2 to 3 weeks of therapy and resolving 5 days after discontinuation of lamotrigine.[11,12,18,19] Valproic acid was used concomitantly in 5 of the previous cases reported.[10,11,17,18] In the patient described here, neutropenia and an erythematous rash were discovered 13 days after initiation of lamotrigine, when the patient was receiving a relatively low dose (25 mg) at bedtime. Similar to other case reports, the rash and hematologic abnormalities resolved 2 and 5 days, respectively, after the lamotrigine was stopped.

Health care professionals should be aware of the potential for lamotrigine to cause blood dyscrasias. When initiating lamotrigine therapy, a slow dose titration is suggested to prevent the development of a serious rash. Lamotrigine titration schedules should also take into consideration the use of inducers or inhibitors of lamotrigine metabolism, as outlined by the manufacturer.

References

1. Lamotrigine product monograph. In: *Compendium of pharmaceuticals and specialties 2005*. Ottawa (ON): Canadian Pharmacists Association; 2005.
2. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30(2):239-245.
3. Knowles SR, Shapiro LE, Shear NH. Anticonvulsant hypersensitivity syndrome: incidence, prevention and management. *Drug Saf* 1999;21(6):489-501.
4. Weintraub D, Buchsbaum R, Resor SR Jr, Hirsch LJ. Effect of antiepileptic drug comedication on lamotrigine clearance. *Arch Neurol* 2005;62(9):1432-1436.
5. Gidal BE, Sheth R, Parnell J, Maloney K, Sale M. Evaluation of VPA dose and concentration effects on lamotrigine pharmacokinetics: implications for conversion to lamotrigine monotherapy. *Epilepsy Res* 2003;57(2-3):85-93.
6. May TW, Rambeck B, Jurgens U. Influence of oxcarbazepine and methsuximide on lamotrigine concentrations in epileptic patients with and without valproic acid comedication: results of a restrospective study. *Ther Drug Monit* 1999;21(2):175-181.
7. Rowland A, Elliot DJ, Williams JA, Mackenzie PI, Dickinson RG, Miners JO. In vitro characteristics of lamotrigine N2-glucuronidation and the lamotrigine–valproic acid interaction. *Drug Metab Dispos* 2006;34(6):1055-1062.
8. Ketter TA, Wang PW, Chandler RA, Alarcon AM, Becker OV, Nowakowska C, et al. Dermatology precautions and slower titration yield low incidence of lamotrigine treatment-emergent rash. *J Clin Psychiatry* 2005;66(5):642-645.
9. Epival product monograph. In: *Compendium of pharmaceuticals and specialties 2004*. Ottawa (ON): Canadian Pharmacists Association; 2004.
10. Solvason HB. Agranulocytosis associated with lamotrigine. *Am J Psychiatry* 2000;157:1704.
11. Nicholson RJ, Kelly KP, Grant IS. Leucopenia associated with lamotrigine. *BMJ* 1995;310(6978):504.
12. de Camargo OAK, Bode H. Agranulocytosis associated with lamotrigine. *BMJ* 1999;318(7192):1179.
13. Ural AU, Avcu F, Gokcil Z, Nevruz O, Cetin T. Leucopenia and thrombocytopenia possibly associated with lamotrigine use in a patient. *Epileptic Disord* 2005;7(1):33-35.
14. 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(3):157-159.
15. LeDrew K, Phillips L, Hogan M, MacCullum A. Lamotrigine-induced neutropenia. *Can J Psychiatr* 2005;50(4):242.
16. Fadul CE, Meyer LP, Jobst BC, Cornell CJ, Lewis LD. Agranulocytosis associated with lamotrigine in a patient with low-grade glioma. *Epilepsia* 2002;43(2):199-200.
17. Damiani JT, Christensen RC. Lamotrigine-associated neutropenia in a geriatric patient. *Am J Geriatr Psychiatry* 2000;8(4):346.
18. Esfahani FE, Dasheiff RM. Anemia associated with lamotrigine. *Neurology* 1997;49(1):306-307.
19. Alleyne S, Alao A, Batki SL. Lamotrigine-associated rash and blood dyscrasias in a methadone-treatment patient with hepatitis C. *Psychosomatics* 2006;47(3):257-258.

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