Research & Reviews: Journal of Hospital and Clinical Pharmacy

Lamotrigine Induced Pancytopenia and Sepsis: Case Report and Literature Review

Mira Parekh[1], Suad A. Al-Abri[2], and Thomas E. Kearney[3*]

[1]Clinical Pharmacist, Sharp Grossmont Hospital, San Diego, California

[2]Medical Toxicology Fellow, California Poison Control System – San Francisco,Division, University of California, San Francisco

[*3]Managing Director, Professor of Clinical Pharmacy, California Poison Control System – San Francisco Division, Department of Clinical Pharmacy, University of California, San Francisco, School of Pharmacy

Review Article

Received date: 10/06/2015
Accepted date: 22/07/2015
Published date: 29/07/2015

***For Correspondence**

Thomas Kearney, University of California, San Francisco, UCSF Box 1369, San Francisco, CA 94143, (415) 643-3201, (415) 502-6060

E-mail: pcctk@calpoison.org

Keywords: Lamotrigine, Pancytopenia, Agranulocytosis, Sepsis.

SUMMARY

What is known and objective

Drug induced pancytopenia is a serious adverse reaction that can be fatal due to the lack of early detection and treatment. A number of case-reports suggest that lamotrigine (LTG), a second-generation anticonvulsant, is associated with blood dyscrasias. [1-25] Despite multiple serious case reports, one reported fatality, and manufacturer recognition of LTG- induced haematological abnormalities upon drug initiation, current guidelines for monitoring still do not exist. Here, we report a life-threatening case of LTG- induced pancytopenia leading to sepsis and provide a literature review of case reports.

Case summary

A 25- year- old hypotensive and febrile female reported to the emergency department following a 3 week course of LTG. On admission, the patient was found to be septic with pancytopenia. The patient was transferred to the ICU and was successfully treated with fluid resuscitation, vasopressor therapy, broad-spectrum antibiotics, and granulocyte colony stimulating factor. The patient was discharged home on hospital day 6 with an alternative anticonvulsant regimen of topiramate and levetiracetam.

What is new and conclusion

We provide evidence of a temporal relationship with the initiation and discontinuation of LTG therapy that suggests LTG was a probable cause of pancytopenia that led to sepsis in this patient. Clinicians need to be aware of this serious adverse event and should be informed on the importance of performing routine haematological monitoring during the induction of LTG therapy.

WHAT IS KNOWN AND OBJECTIVE

LTG is in a class of second-generation anticonvulsants which was developed for its improved side-effect record and reduced need for monitoring [1,26]. LTG has been favoured for its claimed benefit of an improved adverse reaction profile over older anticonvulsants [27,28]. Although thought to be a safe treatment option for patients with epilepsy, there have been a number of case reports in post-marketing use of LTG and manufacturer acknowledgment suggesting that there is a risk for development of haematological abnormalities during LTG initiation [29].

We report a life-threatening case report of LTG-induced pancytopenia that led to an ICU admission and sepsis.

CASE DESCRIPTION AND CRITICAL APPRAISAL

A 25-year-old white woman presented to the emergency department (ED) of a local hospital with a two-week history of persistent fever, productive cough, vomiting, malaise, and headache. The patient reported having a small wound on her right finger that led to swelling and pain upon contact with a piece of rotten fruit. On presentation, her vital signs included temperature 38.3°C, blood pressure 81/46 mmHg, heart rate 105 beats/min, respiratory rate 24 breaths/min, and O_2 saturation 100%. On physical exam, she was lethargic, dehydrated with dry mucus membranes, but awake and oriented. Her skin examination showed right finger cellulitis with bloody discharge, and the rest of exam was normal.

Her past medical history was significant for a 13-year history of absence and juvenile myoclonic seizures with no prior history of infection. Three weeks before her presentation, she episodes of myoclonus. At that time, the patient was on levetiracetam (LEV) 1000 mg orally twice daily and no other concurrent medications. On this visit, the patient's LEV was increased (2,500 mg daily) and was also started on lamotrigine (LTG) with the following titration schedule: 25 mg orally twice daily on week 1, 50 mg twice daily on week 2, 75 mg twice daily on week 3, and 100 mg twice daily on week 4. At the time of admission she was on week 3 of was seen by her neurologist for daily the titration regimen and taking LTG 75 mg twice daily and LEV 2,500 mg daily. She admitted to smoking marijuana daily but denied drug or alcohol use.

In the ED, she was immediately started on intravenous (IV) fluid resuscitation and received a total of 6 litters of normal saline with improvement in her blood pressure, but became oedematous and was given 20 mg of IV furosemide to manage her fluid overload. Vasopressor therapy was initiated with norepinephrine and titrated to a mean arterial pressure of 65 mmHg. Additionally, LTG and LEV were discontinued. Blood cultures were sent and she was started on empiric antibiotic therapy with ceftriaxone and vancomycin for a presumptive diagnosis of pneumonia versus cellulitis. The patient was admitted to the intensive care unit (ICU) and remained hypoxic and tachycardia.

Initial laboratory tests revealed pancytopenia as evidenced by a haemoglobin of 8.9 g/dl [reference range 12-16 g/dL], hematocrit 25.3 % [36-47%], white blood cell count (WBC) 0.8 x10^{3}/uL [4.8-10.8 10^{3}/uL], absolute neutrophil count (ANC) 0.0 x 10^{3} cells/uL [1.9-8.0 10^{3}/uL], and platelets 82 x 10^{3}/uL [130-400 10^{3}/uL]. The progression of her WBC, ANC, and platelet counts are illustrated in **Figure 1**. Blood counts prior to LTG therapy never revealed a past history of blood dyscrasias. Her chemistry panel also showed multiple electrolyte imbalances: sodium 129 mmol/l , potassium 2.9 mmol/l, chloride 95 mmol/L, bicarbonate 23 mmol/l , BUN 8 mg/dl , creatinine 1.1 mg/dl , glucose 152 mg/dl, calcium 7 mg/dl, magnesium 1.4 mg/dl, and phosphorus 1.2 mg/dl. Her lactate was 2.2 mmol/l [0.5-2.2 mmol/L], and C-reactive protein (CRP) was 29.23 mg/dl [0.0-0.7 mg/dL]. Liver function tests were normal with aspartate aminotransferase (AST) 21 U/L [10-38 u/L] and slightly elevated alanine aminotransferase (ALT) 74 U/L [0-34 u/L]. Urine toxicology screen was negative for amphetamine, benzodiazepine, cocaine and opiates, but was positive for cannabinoid.

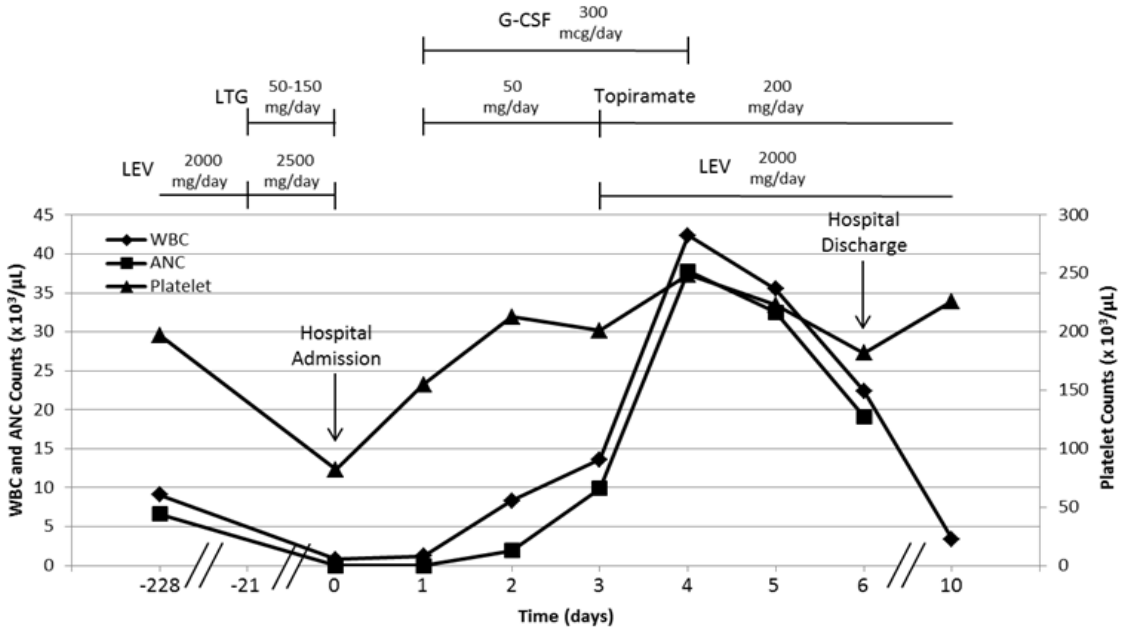

Figure 1. White blood cell (WBC), absolute neutrophil count (ANC), and platelet count at 19 months pre-admission until 10 days post-admission. Lamotrigine (LTG) initiated 3 weeks prior to admission on an escalating dose regimen, week 1 = 50 mg/day, week 2 = 100 mg/day, week 3 = 150 mg/day. LEV= levetiracetam; G-CSF = granulocyte colony stimulating factor

In the ICU, the patient remained hypotensive and febrile. She had central line placed and required norepinephrine for two days and was weaned off gradually as her BP improved. Her electrolytes were repleted and laboratory results during the ICU course showed negative blood/urine cultures and negative serologies for HIV, Hep B, Hep C, and TB. The pathologist's review of the blood smear was reported as "pancytopenia with severe leukopenia, neutropenia and normocytic anemia which could be consistent with drug induced agranulocytosis".

The patient was treated with granulocyte colony stimulating factor (G-CSF) 300 micrograms subcutaneously daily for four doses from hospital day 1 to 4. The patient was also initiated on topiramate 25 mg orally twice daily in the ED, but had a seizure on hospital day 3. The decision was made to increase the topiramate to 100 mg orally twice daily and re-start LEV 1000 mg orally twice daily. The patient remained seizure free for the remainder of the hospital stay.

On day four of the patient's hospital course, the patient's WBC, ANC and platelets peaked at 42.4 $x10^3$/uL, 37.6 $x10^3$/uL and 249 $x10^3$/uL respectively. By day six, the patient's WBC, ANC and platelets trended down to 22.4 $x10^3$/uL and 19.1 $x10^3$/uL and 182 $x10^3$/uL respectively (see **Figure 1**). The patient was discharged to home on topiramate 100 mg orally twice daily and LEV 1000 mg orally twice daily. Ten days after discharge, the patient had a follow-up visit with an outpatient physician and laboratory results revealed a WBC 3.4 $x10^3$/uL.

The mechanism by which LTG-induced blood dyscrasias occur is unknown [25]. After conducting a thorough literature search for English articles using PubMed from January 1940 to December 2012 and the Cochrane Library from January 1960 to December 2012, we identified 30 cases with a spectrum of blood dyscrasias associated with LTG that varied, and included neutropenia, thrombocytopenia, leukopenia, anemia, pancytopenia, and agranulocytosis. **Table 1** provides a summary of case reports of LTG-induced blood dyscrasias from our literature review [1-25]. **Table 2** provides the occurrence of adverse reactions reported by the manufacturer in the prescribing information for the drug, Lamictal. It is noteworthy that the incidence of pancytopenia was not listed by the manufacturer, although leukopenia was described as "infrequent" and other hematologic and lymphatic system adverse reactions described as "rare" [30].

Patient Characteristics	LTG daily dose at presentation	Blood Dyscrasia	Onset	Outcome	Reference
25/F	200 mg	L,N,T	8 weeks	Return to BL in 1 week	1
35/F	50 mg	L,N	10 days	Critical Course, ICU admission, Recovered in 14 days	2
3.5/F	1.7mg/kg/day	L,N,T	Unknown	Death due to status epilepticus at age of 5 years	3
48/F	100 mg	P	10 Days	AHS, recovered in 1 week	4
11/F	50 mg	L,N,A	2 weeks	Return to BL in 1 week	5
40/F	50 mg	L,N,T	4 weeks	Return to BL 53 days after discontinuation	6
35/M	200 mg	ANM	2 months	Return to BL in 2 months	7
17/M	175 mg	ANM	2 months	Return to BL in 1 month	7
23/F	50 mg	N	4 weeks	Return to BL in 2 weeks	8
62/F	50 mg	N	4 days	Return to BL in 3 days	9
10/M	2mg/kg/day	L,N,T	4 weeks	Return to BL in 4 weeks	10
45/F	200 mg	L,T	2 months	Return to BL in 20 days	11
4/M	250 mg	P	3 weeks	Critical course with fever, pancytopenia, recovered in 2 weeks	12
30/F	100 mg	L,N,A	6 weeks	Return to BL in 1 week	13
8/M	100 mg	P	2 weeks	Critical course pancytopenia, multiple petechial and oral bleeding, recovered after 1 weeks	14
24/F	50 mg	L	6 weeks	Return to BL in 1 week	15
20/M	100 mg	L,N,A	6 weeks	Return to BL in 1 week (required G-CSF)	16
19/F	25 mg	N,A	2 weeks	Return to BL in 1 week	16

27/M	100 mg	N,A	4 weeks	Return to BL in 3 days	16
40/F	50 mg	P	2 weeks	Fulminant hepatitis, AHS return to BL in 10 weeks	17
59/F	250 mg	L,N,A	14 weeks	Return to BL in 10 days	18
50/F	300 mg	L,N	2 months	Return to BL in a few weeks	19
76/M	150 mg	L,N	4 months	Return to BL in 3 days	20
46/F	100 mg	L,T	1 year	Return to BL in 2 weeks	21
65/M	100 mg	L,T	2 months	Return to BL in 2 weeks	21
28/F	Unknown	P	2 years	Recovered after stopping time is not available	22
32/F	200 mg	ANM	3 months	HB: 2.8, required blood transfusion	23
50/F	50 mg	P	2 weeks	AHS, recovered in 1 week	24
21/F	50 mg	N	2 weeks	Recovered in 6 weeks	25
36/F	150 mg	N	4 weeks	Recovered in 4 weeks	25
L: Leukopenia, N: Neutropenia, P: Pancytopenia, T: Thrombocytopenia, ANM: Anemia, A: Agranulocytosis M: Male,					
F: female, LTG: Lamotrigine, AHS: Anticonvulsant Hypersensitivity Syndrome, VPA: Valproic Acid, BL: Baseline					

Table 2. Adverse Events and Side Effects Reported by the Manufacturers of the Drug Lamotrigine

Body System	Percentage of Patients
Central Nervous System (dizziness, ataxia, somnolence, incoordination, insomnia, tremor, depression, anxiety, convulsion, irritability, speech disorder, concentration disturbance, dry mouth)	25
Gastrointestinal (nausea, vomiting, diarrhea, dyspepsia, constipation, anorexia)	14.59
Respiratory (rhinitis, pharyngitis, increased cough)	4.98
Dermatological (rash, pruritus)	1.78
General (headache, flu syndrome, fever, abdominal pain, neck pain, seizure exacerbation, infection, chest pain, back pain)	7.83
Musculoskeletal (arthralgia)	0.18
Visual (diplopia, blurred vision, vision abnormality)	13.89
Urogenital –females only; N= 386 (dysmenorrhea, vaginitis, amenorrhea)	4.66
Metabolic (weight loss)	0.44
1. The percentages were derived from the reports of adverse reactions which were aggregated from all clinical trials in adults listed in the manufacturer product information (N= 1124).	

Most of the hematologic reactions associated with LTG occur during the initial stage of treatment, between one and four months [1,25]. In all reported cases, discontinuation of LTG or dose reduction, with or without supportive care, lead to complete recovery [1,19, 20, 29, 31]. Failure to discontinue the drug during development of haematological abnormalities can be fatal. There is one fatal case report of a 40 year old woman who developed agranulocytosis after starting therapy that included LTG in combination with other psychotropic medications [25]. It was suspected that the fatality of that case was a direct result of a delayed response to discontinue the patient's LTG and other psychotropic medications upon recognition of agranulocytosis.

Our patient had features of pancytopenia with anemia, leucopenia and thrombocytopenia which have been previously reported as possibly associated with LTG use [4,31]. However, some of these cases were associated with a hypersensitivity reaction and generalized rash [4,32]. There are other reports of an atypical LTG- induced drug reaction and purpura observed 2 months after initiation of therapy [33]. Our patient did not have any skin manifestations suggestive of a hypersensitivity reaction apart from the cellulitis in her arm.

An objective causality assessment using the Naranjo scale yielded a score of 7, indicating a probable adverse drug reaction in our case. We suspected LTG-induced haematological abnormalities in our patient because of the close temporal relationship between the initiation of LTG and the onset of symptoms, improvement with LTG discontinuation, pathologist's review of blood smear, results of appropriate laboratory tests ruling out other pathologies, re-challenge with levetiracetam without LTG not resulting in pancytopenia, and the normalization of blood counts after discharge. Some case reports demonstrated that LTG induced leukopenia persisted even after stopping other anti-epileptic drugs and increasing the dose of LTG [15]. Others have re-challenged their patients with LTG after a potential episode of LTG-induced neutropenia which resulted in the recurrence of neutropenia demonstrating a strong causality association [8]. A re- challenge with LTG was not performed in our patient.

The possibility of other aetiologies or contributing factors for this patient's pancytopenia cannot be definitively ruled out. Improvement of blood counts coincidental with a de-challenge of LTG is not definitive proof of causation. Our patient was ill for approximately two weeks with a possible viral illness or bacterial infection, which could have been a potential etiology for her neutropenia [34]. However, our patient improved after stopping LTG and she had significant bone marrow suppression and pancytopenia within two weeks of LTG therapy. Additionally, we are unaware of any published cases of an association between marijuana use and pancytopenia. Furthermore, our patient admitted to chronic daily use of marijuana suggesting this to be an unlikely cause of this patient's presentation.

WHAT IS NEW AND CONCLUSION

This report provides further evidence of a causal link between LTG and pancytopenia. We have not found similar reports of patients developing severe sepsis following lamotrigine initiation. There are no current recommendations in the manufacturer's package insert for complete blood count monitoring during LTG therapy. Clinicians need to be aware of this serious adverse event and should be informed on the importance of performing routine haematological monitoring during the induction of LTG therapy.

CONFLICT OF INTEREST STATEMENT

Authors reported no conflicts of interest.

REFERENCES

1. Ural AUet al. Leucopenia and thromocytopenia possibly associated with lamotrigine use in a patient. Epileptic Discord. 2005:7(1):33.
2. Nicholson RJ, et al. Leucopenia associated with lamotrigine. BMJ1995: 310(6978):504.
3. Delima SR, et al. Simultaneous Toxicities in a child on multiple anticonvulsants. J Child Neurol Epub.2008;23(9):1054-1057. DOI: 10.1177/0883073808314156.
4. Chang CC, et al. 30 Lamotrigine associated anticonvulsant hypersensitivity syndrome in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2006: (4):741-4.
5. De Camargo OA and Bode H Agranulocytosis associated with lamotrigine. BMJ; 1999: 318:1179.
6. Alleyne S, et al. Lamotrigine associated rash and blood dyscrasias in a methadone treatment patient with hepatitis C. Psychosomatics 2006;47(3):257-8.
7. Esfahani F and EDasheiff RM. Anemia associate)d with lamotrigine. Neurology.1997 49(1):306-7.
8. Le Drew K, et al. Lamotrigine induced neutropenia. Can J psychiatry 2005;50(4):242.
9. Damiani JT and Christensen RC. Lamotrigine-associated neutropenia in a geriatric patient. Am J Geriatr Psychiatry 2000;8:4,436.
10. Okur M, et al. Lamotrigine associated thrombocytopenia and leukopenia. J Emerg Med 2012; 42(5):584-5. DOI: 10.1016/j jemermed.2010.05.060.
11. Siniscalchi A, et al. Phenobarbital/lamotrigine coadministration–induced blood dyscrasia in a patient with epilepsy. Ann of Pharmacother 2010;44:2031-34. DOI: 10.1345/ aph.1P335.. Epub
12. Gumus H,et al. Hemophagocytic syndrome associated with high-dose lamotrigine. Pediatr Int 2007;49:672–673.
13. Solvason HB. Agranulocytsosis associated with lamotrigine. Am J Psychiatry 2000;157(10):1704.
14. Yang YC, et al. Hemophagocytic syndrome associated with antiepileptic drug. Pediatr Neurol 2004;30(5):358-60.
15. Kilbas S. Lamotrigine-induced leucopenia. Epileptic Disord .2006;8(4):317.
16. Ahn YM, et al. Three cases of Reverible agranulocytosis after treatment with lamotrigine. Psychiatry Investig 2008; 5:121-123. DOI: 10.4306/ pi.2008.5.2.121.
17. Ouellet G, et al. Fulminant hepatitis induced by lamotrigine. South Med J 2009;102(1):82-4. DOI: 10.1097/ SMJ.0b013e3181878b95.
18. Fadul Ce,et al . Epilepsia 2002; 43(2):199-200.
19. Das P, et al. Lamotrigine induced neutropenia in a woman with schizoaffective disorder. Prim Care Companion J Clin Psychiatry. 2007; 9:471-2.
20. Lambert O, et al. 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):157-9.

21. Ebrahimi HA and Zahedi MJ. Combined leucopenia and thrombocytopenia are possibly adverse events of lamotrigine. Iranian Journal of Pharmacology &Therapeutics 2010; 9(1):35–36.

22. Milojkovic N and Elnicki M. Anemia due to lamotrigine. Journal of General Internal Medicine 2004. 19(Suppl 1)1:36.

23. Haedicke C, et al. Lamotrigine versus carbamazepine in epilepsy [letter]. Lancet May; 1995;345:1302.

24. Rahman M and , Haider N. Anticonvulsant hypersensitivity syndrome from addition of lamotrigine to divalproex. Am J Psychiatry 2005;162(5):1021.

25. Normann C,et al. Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled , double blind study.J Clin Psychiatry 2002;63(4):337-44.

26. Landmerk C and Patsalos PN. Drug interaction involving the new second-and third-generation antiepileptic drugs. Expert Rev Neurother 2010;10:119-40. DOI: 10.1586/ ern.09.136.

27. French JA, et al. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2004; 62(8): 1252-60.

28. Schiller Y and Krivoy N. Safety and efficacy of lamotrigine in older adults with epilepsy and co-morbid depression. Clinical Medicine: Therapeutics; (2009);1:825-33.

29. GlaxoSmithKline Hematologic effects of various formulatons of lamictal tables 2012;.1-4.

30. Lamictal [package insert], North Carolina: GlaxoSmithKline, 2015

31. Nazer L, et al. Fatal agranulocytosis associated with psychotropic medication use. Am J Health-Syst Pharm 2012;69:863-867.

32. Ural AU, et al. Leucopenia and thrombocytopenia possibly associated with lamotrigine use in a patient. Epileptic Disord 2005;7(1):33-35

33. Amile-Lefond CM and Felgenhauer JL. Localized purpura associated with lamotrigine. Pediatric Neurol 2006;35(3):227-8

34. Husain EH, et al. Infectious etiologies of transient neutropenia in previously healthy children. The Pediatric Infectious Disease Journal 2012;31(6):575-7.DOI:10.1097/INF.0b0