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Case Report

Lamotrigine-induced fulminant hepatic failure: an unusual presentation

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ABSTRACT

Lamotrigine (LTG) is indicated for the management of seizures either alone or in combination with other anticonvulsant agents. Adverse effects with it are usually mild. Less than 1% of subjects show deranged liver function tests during long therapy. Fulminant hepatic failure with LTG is an unusual presentation. We report a fatal case of hepatic failure with LTG monotherapy in a 22-year-old male patient suffering from a seizure disorder. Cases of LTG induced hepatotoxicity should be carefully monitored, particularly serious case of fulminant hepatic failure which should be adequately assessed and reported to determine their exact incidence.

Keywords: Lamotrigine, Hepatic failure

INTRODUCTION

A seizure is a transient episode of uncontrollable motor activity, focal or generalized usually accompanied by clouding or loss of consciousness. Around 50 million people worldwide are affected by it.[1] Lamotrigine (LTG) is a phenyltriazine and belongs to an anticonvulsant class of its own. It is indicated for the management of partial and generalized seizures either alone or in combination with other anticonvulsant agents. The adverse effects reported with the use of LTG are mild and include somnolence, fatigue, nervousness, dizziness, and rash in 10-90% cases. Eosinophilia, facial edema, lymphadenopathy, and atypical lymphocytosis can also occur. Elevated transaminases or hepatitis is reported as a rare side effect (<1%). LTG prescribing information has a black box warning about life-threatening skin reactions, including Stevens–Johnson Syndrome, drug rash with eosinophilia and systemic symptoms syndrome and toxic epidermal necrolysis, hepatotoxicity.[2]

LTG-induced rash and hepatotoxicity is a hypersensitivity reaction to the drug protein complex. This hypersensitivity reaction presents as diffuse maculopapular rash, followed in a few days by high fever, nausea and vomiting.[3] The rash can develop into a systemic hypersensitivity reaction and multiorgan failure or simply associated with jaundice and hepatitis. Risk factors for an increased incidence of rashes are patients who are currently on or those who have recently

discontinued sodium valproate, young age, high starting dose, and rapid dose escalation.[2,3] LTG induced hepatotoxicity is usually rapidly reversible within 1-2 weeks of the drug being stopped. Prolonged exposure after the appearance of symptoms may escalate the injury to result in irreversible, rapidly progressive liver failure.[4] Hepatic encephalopathy begins with a period of delirium that gradually evolves into stupor, then coma and may ultimately lead to death.[4]

Here, we report a case of a patient who was on LTG therapy for 2 months for seizure disorder and had a fulminant hepatic failure with a fatal outcome.

CASE REPORT

A 22-year-old male patient with history of seizure disorder was on treatment with sodium valproate 500 mg BD for 3 years but because of uncontrolled seizures he was shifted to tab. LTG 50 mg BD, 2 months back by a private practitioner. The liver function tests (LFTs) were normal at the time LTG therapy was instituted which was, however, not documented.

He was prescribed LTG initially 50 mg BD for 1-week which was titrated up to 100 mg BD. He developed generalized red maculopapular eruptions after 1-week of increment in dose for which patient took topical treatment from a private practitioner. Following this he developed yellowish discoloration of the sclera, urine, clay colored stool for 30-35 days and gradually progressive deterioration in sensorium for 5-7 days. He was brought to the hospital in the unconscious state and was having diffuse maculopapular rashes. Pulse rate and blood pressure were 140/mins regular and 110/70 mmHg, respectively. Eye examination revealed icterus and exposure keratitis. Bilateral coarse crepitations were audible. Biochemical investigations revealed derangement in LFTs, blood urea, and serum sodium (Table 1).

Ultrasound abdomen showed no abnormality. Non-contrast computed tomography head was also normal. Serology for hepatitis-B and hepatitis-C were negative. Based on clinical signs suggestive of hepatic encephalopathy Grade 4, coagulopathy and hyperbilirubinemia, a diagnosis of fulminant hepatic failure was made. LTG was withheld immediately. Patient was kept in ICU and put on ventilatory support in adjunct to other supportive treatment for hepatic failure. Nasogastric tube was placed to permit the safe administration of nutrients and medications. Patient was administered injection ceftriaxone, injection mannitol, injection pantoprazole, tablet rifaximin, and injection metrogyl, injection vitamin K, syrup lactulose, dextrose fluid, and fresh frozen plasma. Close monitoring of vital functions and biochemical parameters was done. Patient's relatives were advised for liver transplantation, but they refused the treatment. Hence, the patient was managed conservatively. Clinical status of the patient did not show any improvement even on 3rd day of admission. Biochemical parameters like serum glutamic oxaloacetic transaminase/serum glutamic

Table 1: Investigations.

Parameters	19/2	20/2	21/2
Hb (g/dl)	13.2	12.2	12.4
TLC	15000/mm^3	16000/mm^3	16000/mm^3
DLC (P/L/M/E/B)	93/5/1/1	80/16/2/2	80/16/2/2
Platelets count	2.5 lacs	2.5 lacs	2.4 lacs
Total bilirubin (mg/dl)	16.4	16.2	16.0
Direct bilirubin (mg/dl)	15.4	15.2	15.0
Indirect bilirubin (mg/dl)	1.0	1.0	1.0
Prothrombin time	77.7	22.2	26.6
INR	8.25	2.22	1.88
SGOT (U/L)	1410		521
SGPT (U/L)	521		270
S. ALP (U/L)			225
S. proteins (g/dl)	6.2		
A/G	1.3		
Blood urea (mg%)	53	57	48
Blood glucose (mg%)	84	82	49
S. K^+ (mEq/l)		3.1	3.9
S. Na^+ (mEq/l)	127	150	138

Hb: Hemoglobin, TLC: Total leukocyte count, DLC: Differential leukocyte count, P: Polymorphonuclear leukocyte, L: Lymphocyte, M: Monocyte, E: Eosinophil, B: Basophil, INR: International normalized ratio, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, S. ALP: Serum alkaline phosphatase, A/G: Albumin/Globulin ratio, S. K^+: Serum potassium, S. Na^+: Serum sodium

pyruvic transaminase showed some improvement, but on 4th day of admission patient succumbed to his illness.

DISCUSSION

LTG is known to be effective as monotherapy for the treatment of seizures disorders. Literature review reveals some cases of serious LTG induced liver toxicity[5-12] of whom 2 died.[11] The majority of the patients who developed elevated liver transaminases were concomitantly taking other liver-toxic medications like carbamazepine and valproic acid. In this case, patient was on LTG monotherapy for the control of seizures. Drug dose was titrated weekly, but rashes occurred in a week of increment in dose. This reflects hypersensitivity reaction to the drug, the exact mechanism for which is unknown.[13] The proposed mechanisms are formation of antibodies against drug metabolite-protein aggregates, possibly owing to inheritable deficiency in cellular detoxification mechanisms. Another mechanism involves the formation of toxic arene oxide metabolite by cytochrome P-450 enzymes. These metabolites are normally detoxified by the enzyme epoxide hydrolase, which may be lacking or mutated in persons that develop the reaction.[14]

In previous reports, co-medication with other anticonvulsant medications or rapid dose titration and coexisting medical conditions were risk factors. In this case, the patient denied the use of over the counter medications. Although the patient was on sodium valproate for 3 years, but this medication was stopped before starting treatment with LTG. There was no history of alcohol or substance abuse. LTG is the likely cause of fulminant hepatic failure as there was no serological evidence of viral hepatitis. The proposed treatment for fulminant hepatic failure is liver transplantation[15] which was refused by patient's relatives and this resulted in a fatal outcome.

One such death because of fulminant hepatic failure following LTG intake has been reported in British Medical Journal in which patient was on concomitant medications such as valproic acid and carbamazepine. The patient developed hypersensitivity reaction after 48 hrs of dose titration to 100 mg twice daily and death occurred 58 days after admission to hospital.[7]

The association of rash and fulminant hepatic failure with LTG in the present case is categorized as "possible," according to World Health Organization-Uppsala Monitoring Centre causality assessment scale.

CONCLUSION

LTG is known to cause hepatotoxicity. However, fulminant hepatic failure with LTG is very unusual presentation. Hence, clinician should be vigilant to look for signs of hepatic failure in patients who developed rashes. Cases of LTG-induced fulminant hepatic failure should be adequately reported for proper assessment of the incidence.

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REFERENCES

1. World Health Organisation. Factsheet: epilepsy, October 2012. Available at http://www.who.int/mediacentre/factsheets/fs999/en/. Accessed on 12 October 2014
2. GlaxoSmithKline. Lamictal Prescribing Information, May 2007. Available at https://www.gsksource.com/gskprm/htdocs/documents/LAMICTAL-PI-MG.PDF. Accessed on 12 October 2014.
3. Guberman AH, Besag FM, Brodie MJ, Dooley JM, Duchowny MS, Pellock JM, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia. 1999;40(7):985-91.
4. Cash WJ, McConville P, McDermott E, McCormick PA, Callender ME, McDougall NI. Current concepts in the assessment and treatment of hepatic encephalopathy. QJM. 2010;103(1):9-16.
5. Arnon R, DeVivo D, Defelice AR, Kazlow PG. Acute hepatic failure in a child treated with lamotrigine. Pediatr Neurol. 1998;18:251-2.
6. Fayad M, Choueiri R, Mikati M. Potential hepatotoxicity of lamotrigine. Pediatr Neurol. 2000;22(1):49-52.
7. Makin AJ, Fitt S, Williams R, Duncan JS. Fulminant hepatic failure induced by lamotrigine. BMJ. 1995;311(7000):292.
8. Mecarelli O, Pulitano P, Mingoia M, Ferretti G, Rossi M, Berloco PB, et al. Acute hepatitis associated with lamotrigine and managed with the molecular adsorbents recirculating system (Mars). Epilepsia. 2005;46(10):1687-9.
9. Overstreet K, Costanza C, Behling C, Hassanin T, Masliah E. Fatal progressive hepatic necrosis associated with lamotrigine treatment: a case report and literature review. Dig Dis Sci. 2002;47(9):1921-5.
10. Schaub JE, Williamson PJ, Barnes EW, Trewby PN. Multisystem adverse reaction to lamotrigine. Lancet. 1994;344(8920):481.
11. Moeller KE, Wei L, Jewell AD, Carver LA. Acute hepatotoxicity associated with lamotrigine. Am J Psychiatry. 2008;165(4):539-40.
12. Amante MF, Filippini AV, Cejas N, Lendoire J, Imventarza O, Parisi C. Dress syndrome and fulminant hepatic failure induced by lamotrigine. Ann Hepatol. 2009;8(1):75-7.
13. Could Lamictal cause sudden death? Ehealth Me.com. Available at http://www.ehealthme.com/ds/lamictal/sudden+death+unexplained. Accessed on 12 October 2014.
14. Leeder JS, Riley RJ, Cook VA, Spielberg SP. Human anti-cytochrome P450 antibodies in aromatic anticonvulsant-induced hypersensitivity reactions. J Pharmacol Exp Ther. 1992;263(1):360-7.
15. Gotthardt D, Riediger C, Weiss KH, Encke J, Schemmer P, Schmidt J, et al. Fulminant hepatic failure: etiology and indications for liver transplantation. Nephrol Dial Transplant. 2007;22 Suppl 8:viii5-8.

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