

Case Report

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Acute Liver Injury during Co-treatment with Levetiracetam and Temozolomide

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ABSTRACT

Drug-induced liver injury (DILI) accounts for approximately 10 percent of all cases of acute hepatitis. The patterns of acute injury include any form of hepatic injury, but the most common problems are cholestasis, hepatocellular damage, or a mixed type. DILI is often reversible, and discontinuation of the offending agent usually results in a complete recovery; however, some cases may lead to chronic liver injury, cirrhosis, and even death. Temozolomide (TMZ) is an alkylating, anti-neoplastic agent used for the treatment of refractory anaplastic astrocytoma, newly-diagnosed Glioblastoma multiforme (GBM) and metastatic melanoma. Levetiracetam (LEV) is an established second-generation antiepileptic drug and is most commonly approved as adjunctive treatment of partial-onset seizures with or without secondary generalization. When administered separately each of these drugs is considered to be relatively safe and only few cases of severe liver injury can be found throughout the literature; however, LEV and TMZ are commonly used together in the treatment of brain malignancies. We report three patients who presented with jaundice during treatment with TMZ and LEV, and propose a mechanism for liver sensitization by LEV for TMZ-induced injury.

KEYWORDS: Levetiracetam; Temozolomide; Liver injury; MGMT; Glioblastoma multiform.

ABBREVIATIONS: LEV: Levetiracetam; TMZ: Temozolomide; MGMT: O-6-methylguanine-DNA methyltransferase; DILI: Drug-induced liver injury; MRI: Magnetic Resonance Imaging; INR: International Normalized Ratio; TB: Total Bilirubin; LFTs: Liver function tests; ALL: Acute Lymphocytic Leukemia.

INTRODUCTION

Drug-induced liver injury (DILI) accounts for 2-5% hospitalizations due to jaundice, and 10% of all cases of hepatitis in adults. However, the last can reach even more than 40% in elderly patients. The overall incidence of drug hepatotoxicity ranges between 1/10,000 to 1/100,000¹⁻³ and it is the most common cause of acute liver failure in developed countries.^{4,5}

Antiepileptic drugs are frequently used for secondary prevention of seizures in patients with brain malignancy. LEV has a novel structure and unique mechanisms of action. Unlike other anti-epileptic drugs, it inhibits calcium release from intra-neuronal stores.⁶ It is commonly used due to its low incidence of adverse events⁷ and low risk of drug interactions, which attributed to its limited hepatic metabolism and minimal effect on protein binding of other drugs.⁸ Moreover, it lacks cytochrome P450 isoenzyme-inducing potential and is not associated with clinically significant pharmacokinetic interactions with other drugs.⁶ Therefore,

it is not surprising that only few case-reports depict significant hepatotoxicity as a result of treatment with LEV.⁹

TMZ is an orally administered alkylating agent which used for the treatment of GBM and was demonstrated to prolong overall survival when added to radiotherapy.¹⁰ The anti-neoplastic effect of TMZ is attributed to the methylation of a guanine group in DNA. The resulting O6-methylguanine mispairs with thymine upon DNA replication, and therefore arrests the cell cycle.¹¹ There are a few cases reported in the literature describing TMZ induced liver injury.¹² The fact that TMZ metabolizes mainly by spontaneous hydrolysis in the plasma to active metabolites and non-significantly by the liver¹³ implies that the chances for pharmacokinetic interaction are low. Yet, a pharmacodynamic interaction cannot be excluded. Nonetheless, hepatic toxicity of this commonly used drug combination has not been previously reported. Here we present three patients with brain malignancy that were treated with TMZ and LEV and developed severe liver injury and suggest a potential mechanism responsible for this toxicity.

CASE REPORTS

Case 1

A 60-year-old man was admitted to our hospital because of jaundice, weakness, pale stools, and dark urine. His past medical history included GBM diagnosed 6 months previously, which presented with seizures. He underwent brain biopsy and was treated with a short course of TMZ (150 mg of TMZ per day, calculated based on body surface area of 2.2 m²). After 42 days of treatment, he developed a tonic-clonic seizure, for which he was treated with LEV. His Liver function tests (LFTs) were normal.

Initial assessment revealed a marked jaundice without confusion or somnolence. Laboratory tests revealed total bilirubin (TB) 322 mol/L, alanine aminotransferase (ALT) 375 U/L (normal range NR 0-40 U/L), aspartate aminotransferase (AST) 222 U/L (NR 0-35 U/L), alkaline phosphatase (ALP) 411 U/L (NR 40-130 U/L), gamma-glutamyl transpeptidase (GGT) 709 U/L (NR 8-61 U/L), and prothrombin time 36.6 sec (NR 25-40 seconds), INR 1.0 (NR 1-1.4 ratio). Antinuclear antibodies (ANA), antimitochondrial antibodies (AMA) and serum complement (C3, C4) were all negative or normal. Viral serology for hepatitis A, B, and C, EBV, and CMV were negative as well. Serum level of ceruloplasmin was normal. An abdominal ultrasound revealed normal liver size with no evidence of focal lesion, no evidence of gallbladder or bile duct stones, and no evidence of ascites. Duplex examination revealed normal flow in the hepatic and portal veins. A cerebral CT scan demonstrated multiple ring enhancing lesions with no change from previous test.

The proposed diagnosis was drug induced liver injury (DILI). TMZ and LEV were discontinued and treatment with

hydrocortisone (100 mg tid) was started. The patient's state of liver failure continued to deteriorate for the next few days (total bilirubin 321 mol/L). However, 4 days after discontinuation of TMZ and LEV, LFTs began to improve and 6 weeks later, they returned to the normal range.

It should be noted that the patient was also treated with herbal remedies (*Lineum usitatissimum*, *Fumariaceae*, *Curcuma longa*, and *Silybum marianum*), of which none were found to cause a liver injury in literature review.

Case 2

A 63-year-old woman presented with jaundice of 3 days duration. She did not have any additional complaints. Three months previously she had been diagnosed by brain biopsy with an astrocytoma, which had presented with speech disturbances and right hand weakness in addition to sight disorder in the right temporal visual field. She had been treated with TMZ (135 mg per day calculated based on body surface area of 1.82 m²) and LEV for the last 5 weeks. A week before admission, a treatment with fluconazole was initiated due to oral thrush. Blood tests taken one month before admission revealed normal LFTs.

On admission physical examination revealed a markedly icteric woman without confusion or somnolence. Laboratory blood tests disclosed the following results: TB 486 mol/L, ALT 2,682 U/L (NR 0-40 U/L), AST 1,162 U/L (NR 0-35 U/L), ALP 1,159 U/L (NR 40-130 U/L), GGT 1,191 U/L (NR 8-61 U/L), PTT 25.1 sec (NR 25-40 seconds) and INR was 1.03 (NR 1-1.4 ratio). A triphasic CT scan of the liver was normal. ANA, AMA and C3 C4 were all negative. Viral serology for hepatitis A, B, and C, EBV, and CMV were negative for acute infection. Serum ceruloplasmin was normal.

The proposed diagnosis was DILI, and TMZ and LEV were stopped, and 5 days after discontinuation of TMZ and LEV, LFTs improved though they did not return to the normal range (TB 577 mol/L three weeks later), the patient underwent liver biopsy with the evidence of cholestatic injury and bile duct damage due to the used drugs, after few days her conditions were deteriorated and the patient succumbed.

Case 3

A 32-year-old man was hospitalized due to jaundice and weakness. Four months previously a diagnosis of GBM was made at brain biopsy, which had presented expressed in speech disorder and sense disturbances in his left hand that lasted several minutes. Past medical history was positive for Acute Lymphocytic Leukemia (ALL) from which he recovered following chemotherapy and radiation. During the first 14 days of treatment with TMZ (130 mg per day calculated based on body surface area of 1.76) he developed a tonic-clonic seizure. LEV was then given in combination with TMZ. His Liver function tests (LFTs) at the initiation of treatment were normal.

Initial assessment revealed a markedly icteric man without confusion or somnolence. Results on admission were TB 252 mol/L, ALT 425 U/L (NR 0-40 U/L), AST 125 U/L (NR 0-35 U/L), ALP 89 U/L (NR 40-130 U/L), GGT 134 U/L (NR 8-61 U/L), PTT 13.1 sec (NR 25-40 seconds), and INR 1.23 (NR 1-1.4 ratio).

An abdominal ultrasound revealed normal liver size with no evidence of focal lesion, no evidence of gallbladder or bile duct stones, and no evidence of ascites. Further investigation included abdominal CT supported these findings. ANA, AMA and C3 C4 were all negative or normal respectively. Viral serology for hepatitis A, B and C, EBV, and CMV were negative for acute infection. Serum ceruloplasmin was normal.

A Magnetic Resonance Imaging (MRI) revealed post surgical changes involving the right hemicalvarium. An enhanced mass posterior to the surgical bed and in continuity with the posterior horn of the right lateral ventricle was noted with no difference from previous examination.

The proposed diagnosis was DILI. Treatment with LEV was halted, the patient continued to receive TMZ, and the dose of dexamethazone was elevated from 4 mg to 10 mg a day. On follow-up examination 4 months later, no recurrent liver injury was noted.

DISCUSSION

LEV is an antiepileptic drug that is often used to prevent seizures in patients with brain malignancy due to its low incidence of drug-drug interactions and hepatotoxicity. Moreover, since LEV is excreted by the kidney, no adjustment is required in patients with hepatic impairment. A literature search for TMZ hepatotoxicity revealed only three case reports of sustained cholestasis. An additional 16 cases of cholestatic hepatitis or cholestasis associated with TMZ were identified in the FDA spontaneous reporting system between 2007 and 2010.¹⁴ In addition, reactivation of hepatitis B in a silent carrier can occur under TMZ treatment.¹⁵ Tests for antigens to hepatitis B were negative in our three patients, as mentioned above.

The diagnosis of DILI in our three patients was based on the temporal relationship between TMZ and LEV administration. Hepatic injury was observed in 5-12 weeks following the

initiation of the combination treatment in our patients. Furthermore, recovery from hepatic injury was also related temporally to discontinuation of the drugs, with improvement in all three cases 4-5 days after discontinuation of these medications. Thus, despite the low frequency of liver injury with each drug given alone, the occurrence of liver injury in these three patients raised the possibility of synergism between these two drugs in inducing the liver damage and led us to look for possible explanation for such toxic synergism for the liver. Nevertheless, a casual relationship cannot be inferred from this association. It should be noted that liver biopsies were not taken from these three patients due to the clear impression of DILI, as mentioned above. Biopsy would have amounted to an invasive procedure that was not expected to change patient management, particularly in the light of their significant CNS malignancies.

In order to quantitatively assess the potential for drug interaction between LEV and TMZ in each case, we calculated the drug interaction probability score (DIPS, Table 1).¹⁶ Scores range from -9 to 11, where values below 2 correlate with doubtful interaction. The scores calculated for the cases depicted here range between 2 and 3, which correlate with a possible interaction.

The mechanism of interaction between LEV and TMZ is not clear. As mentioned above, the anti-neoplastic effect of TMZ is attributed to the methylation of a guanine group in DNA which results in O6-methylguanine mispairs with thymine, and therefore arrests the cell cycle. However, this effect of TMZ depends on the inhibition of the O-6-methylguanine-DNA methyltransferase (MGMT) gene, a DNA-repair protein that removes alkyl groups from the O6 position of guanine, the important site of DNA alkylation.¹⁷ Moreover, it was shown that a key mechanism for resistance to TMZ is MGMT over expression.¹⁸ On the other hand, it has been hypothesized that LEV is the most potent MGMT inhibitor among several antiepileptic drugs.¹⁹ In fact, LEV was shown to cause a p53-mediated inhibition of MGMT, thereby sensitizing GBM cells to TMZ.¹⁹ Hence, it is not surprising that the combination of LEV and TMZ has been suggested to contribute to the effect of TMZ on GBM cells *in vitro*.

However, this effect of LEV can serve as two-edged sword, given the fact that low MGMT levels may expose hepatocytes to potential damage by TMZ, since MGMT plays a crucial role in the defence against the alkylating agent cytotoxicity. In

Case	Age	Gender	Disease	Duration of treatment* (months) LEV / TMZ / both	Maximal INR	Maximal TB	DIPS score**
1	60	Male	GBM	3 / 2 / 2	1.00	322	2
2	63	Female	Astrocytoma	2 / 1 / 1	1.03	486	2
3	32	Male	GBM	3 / 3 / 3	1.23	252	3

*The duration of treatment (months) before the appearance of liver injury.

**DIPS score evaluate the potential for drug interaction (between LEV and TMZ), values between 2-4 represent possible interaction.

INR: International Normalized Ratio; TB: Total Bilirubin.

Table 1: Summarizes data from the three patients presented above.

fact, it was shown in mice that diurnal variation of glucocorticoid levels modulates expression of the MGMT gene, which correlates with the risk of dacarbazine-induced hepatotoxicity.²⁰ Specifically, glucocorticoids upregulate MGMT gene expression in hepatic cells. Upregulated MGMT gene expression removes the mutagenic DNA adduct O6-alkylguanine that is produced by exposure to alkylating agents, preventing hepatic cell death by promoting recombination and repair of double-strand breaks. LEV is a potent MGMT inhibitor, acting in opposition to the effects of glucocorticosteroids. When administered in combination with TMZ, LEV may therefore enhance the risk of liver injury.

In the current cases one may raise a question as to the real cause for the liver injury, since two patients were treated with concomitant agents (herbal medications or fluconazole) that may cause such complication by themselves. However, a review of literature revealed that none of the herbal medications that patient 1 had taken (*Lineum usitatissimum*, *Fumariaceae*, *Curcumin*, and *Silybum marianum*) are known to cause a liver damage; in fact, several recent studies have shown a protective effect of these medications in states of liver injury.²¹⁻²⁴ Nevertheless, no study examined the combination of these herbal medications, thus, potential liver toxicity cannot be excluded. As to the second patient who was treated with fluconazole, although LFT abnormalities are associated with all of the azoles, these abnormalities are more likely with itraconazole and ketoconazole than with fluconazole^{25,26} and the later seems to have a lower risk of treatment discontinuation because of adverse events.²⁷ Moreover, toxicity is dosage-related, and is detected during weeks 2-6 after initiation of therapy.¹ Furthermore, most of these patients have asymptomatic elevation of serum transaminase levels, and reported cases of symptomatic hepatic injury are rare.

An additional question that should be mentioned is the rarity of liver injury with LEV and TMZ. Although we describe three patients who developed liver complication following concomitant administration of LEV and TMZ, thousands of patients taking the same treatment do not develop liver injury, suggesting additional genetic or environmental susceptibility factors. Therefore, until more validated data are available, caution should be exercised when using both medications concomitantly.

CONCLUSION

In conclusion, it appears that LEV and TMZ may have drug-to-drug interaction. Combined treatment with LEV and TMZ may enhance the risk for development DILI, in comparison to treatment with either of these drugs alone. Therefore, liver enzymes follow-up should be considered when giving LEV and TMZ concurrently until more reliable prospective data becomes available.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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