



Case Report

Lacosamide as add-on treatment of focal symptomatic epilepsy in a patient with alcoholic liver cirrhosis



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ABSTRACT

The occurrence of epileptic seizures in the presence of hepatic disease is not uncommon in clinical practice. Selecting an appropriate AED for patients affected by liver failure who have new-onset epileptic seizures can be challenging. We describe a 64-year-old man affected by liver cirrhosis. The patient developed partial epilepsy with secondary generalization because of an intracerebral hemorrhage in the left parieto-occipital regions. After the neurosurgery procedure, seizures reappeared and were initially managed with levetiracetam. After one month, the patient experienced clusters of seizures while on stable treatment with levetiracetam. Pregabalin as add-on was not tolerated; therefore, he received a low dose of phenobarbital as add-on treatment. The patient developed hepatic encephalopathy. Phenobarbital was immediately stopped, and oral lacosamide was added. A rapid recovery of encephalopathy with a 6-month seizure freedom was obtained. The patient died 6 months later because of progressive impairment of liver function. Lacosamide may represent an alternative to other AEDs in patients with liver failure; however, further prospective evaluation of its efficacy and safety in this clinical setting is needed.

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1. Introduction

Selecting an appropriate antiepileptic drug (AED) for patients affected by liver dysfunction and new-onset epileptic seizures can be challenging since first-line AEDs may contribute to worsen encephalopathy and result in hepatotoxicity. Efficacy, tolerability, and toxicity represent the main factors influencing the choice of an AED, mainly when specific comorbidity may affect epilepsy [1]. Since the liver and kidney represent the main organs involved in the elimination of most drugs, their dysfunction may highly influence the pharmacokinetics of AEDs [2]. In the past two decades, the introduction of newer AEDs with a better pharmacokinetic profile than traditional AEDs has improved the management of these patients [2].

Lacosamide (LCM), (R)-2-acetamido-N-benzyl-3-methoxypropionamide, is a new AED with selective enhancement of sodium channel inactivation. Lacosamide is well absorbed after oral administration (100%) [2], food does not affect the rate or the extent of the absorption, and the binding to plasma protein is minimal (less than 15%) [3]. Lacosamide is primarily eliminated from the systemic circulation by

renal excretion and biotransformation. After oral or intravenous intake, 95% of LCM is recovered in the urine and <0.5% in the feces. The major compounds found in the urine include unchanged drug (40%), about 30% as the inactive O-desmethyl metabolite, and a structurally unknown polar fraction (about 20%). The metabolites do not show pharmacologic activity. Metabolism is through the CYP450 2C19 without any significant drug interaction. In the presence of mild to moderate (Child A and B) liver disease, no dose adjustment is usually recommended [2]. Elimination and toxicity in the presence of severe hepatic failure (Child C) have not been studied [2]. Therefore, LCM may represent a valid alternative AED when previous treatment failed, and the remaining AEDs should be cautiously utilized in patients with hepatic impairment [2].

2. Report of the case

A 64-year-old man affected by moderate alcoholic liver cirrhosis (MELD score: 14; Child–Pugh Class B) experienced focal seizures with secondary generalization characterized by ascending paraesthesias followed by hypoesthesia and jerks of the right limbs. No prior history of alcohol-related seizures was obtained. Brain MRI showed an intracerebral hemorrhage in the left parietal–occipital regions. Sodium and ammonia levels were within normal range. After the neurosurgery procedure, seizures recurred and were initially managed with levetiracetam (LEV) (up to 3000 mg/day). Because of seizure reappearance,

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pregabalin was firstly added (up to 150 mg bid), but pregabalin was quickly withdrawn for lack of tolerability (excessive daytime somnolence). After one month, the patient experienced focal seizures with secondary generalization while on stable treatment with levetiracetam (3000 mg/day); therefore, he was evaluated in the emergency ward and received phenobarbital (50 mg/day) as add-on treatment. After 24 h, the patient became stuporous, and mental status fluctuated. Metabolic encephalopathy was confirmed by EEG showing generalized polymorphic slowing, diffuse triphasic sharp waves, and left temporal–parietal PLEDs (Fig. 1A). Blood ammonia level was 168 $\mu\text{mol/L}$ (normal range: 30–85), phenobarbital level was 9 $\mu\text{g/mL}$ (normal range: 15–40), and aspartate aminotransferase and alanine aminotransferase were slightly altered but substantially unchanged when compared with previous values. Fluid therapy was instituted. Phenobarbital was immediately stopped, and a single oral loading dose of LCM (200 mg), followed approximately 12 h later by 100 mg twice daily up to 200 mg twice a day maintenance dose, was started. By the third day of LCM therapy, the patient became more responsive, and blood ammonia level was in the reference range. One week later, EEG showed sporadic interictal sharp waves in temporal–parietal–occipital regions and normal background activity (Fig. 1B). After six months, the patient was still seizure-free at follow-up. After this follow-up, the hepatic failure progressively worsened (MELD score: 20; Child–Pugh Class C); therefore, we slowly reduced lacosamide to 200 mg daily in order to avoid possible hepatic toxicity due to the probable increase of the area under the curve [2]. Transjugular intrahepatic portosystemic shunt (TIPS) was performed to treat portal hypertension and previous esophageal bleeding. The patient remained seizure-free, but he was also added to the liver transplant waiting list. Nevertheless, he died six months later.

3. Discussion

The use of AEDs in the presence of hepatic failure is complex and requires great familiarity with the pharmacokinetics of these agents [4]. This report showed the common difficulties encountered when hepatically metabolized standard antiseizure medications such as phenobarbital are prescribed for patients affected by alcoholic liver cirrhosis. The pharmacokinetics of elimination of many classical AEDs becomes unpredictable, and the threshold for developing or detecting central nervous system side effects diminishes. These problems may contribute to worsening encephalopathy. LEV is considered as a valid treatment for patients affected by liver dysfunction and epilepsy, though a dose reduction may be needed in patients with severe liver cirrhosis [5]. We found only a previous case report describing an acute liver failure in a young patient affected by an unspecified epileptic disorder. This subject was previously treated with LEV and LCM, and the liver dysfunction appeared after the increase of LEV dose during a convulsive status epilepticus (CSE) [6]. Although liver biopsy confirmed a toxic origin of hepatic failure, specific clinical details are lacking (other treatments, CSE outcome, EEG and MRI findings, LEV and/or LCM withdrawal); therefore even if possible, this report does not allow the conclusion to be made that LEV treatment induced the acute liver failure [6].

PGB was also considered in our patient because it is not metabolized by the liver and is excreted renally. It has negligible binding to plasma proteins and does not have any significant drug–drug interactions [7]. The pharmacokinetic properties of PGB are favorable, but it provoked a significant sleepiness in our patient when added to LEV, leading to PGB discontinuation. A low dose of phenobarbital

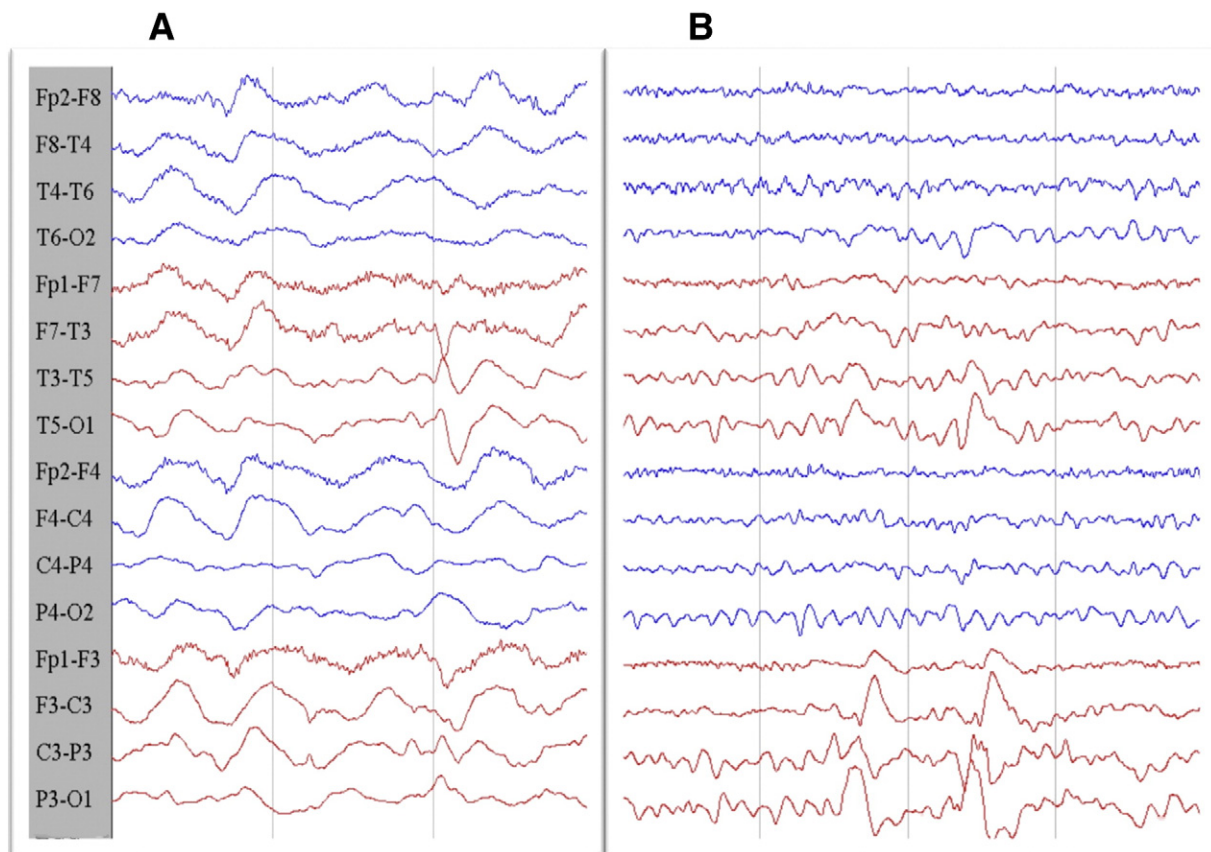


Fig. 1. Phenobarbital addition induced a widespread abnormal EEG slowing associated with diffuse triphasic sharp waves and left temporal–parietal paroxysms (A). One week later, phenobarbital withdrawal and lacosamide addition induced a prompt recovery of vigilance level, and EEG (B) showed rare interictal sharp waves in temporal–parietal–occipital regions and normal background activity. Each vertical column is 1 s of recording time.

induced an unpredictable hepatic encephalopathy as demonstrated by mental status fluctuations associated with EEG slowing and triphasic sharp waves. Phenobarbital withdrawal and LCM addition induced a prompt recovery of hepatic encephalopathy and seizure freedom. Lacosamide was chosen as an alternative to other AEDs because of its favorable pharmacokinetic properties. Lacosamide may offer some advantages in the treatment of epilepsy in patients with liver failure. Lacosamide is rapidly and completely absorbed after oral administration. Its bioavailability is not affected by food, and its pharmacokinetics are linear and time-invariant. It has a 13-hour half-life, and a steady state is achieved after 2 days of twice-daily dosing. In addition, LCM has properties that make it unlikely to produce clinically significant drug–drug interactions in patients with liver cirrhosis. The major metabolic pathway is enzymatic hydrolysis, producing an inactive O-desmethyl metabolite, but more than 40% of the dose is excreted unchanged in the urine [2,3]. In addition, the 12 months of seizure freedom obtained after LCM addition represented a significant improvement of quality of life in a patient affected by alcoholic cirrhosis with a poor prognosis.

Although a single case report does not allow any generalization, we can state that LCM may represent a valid alternative when LEV and PGB are ineffective or not tolerated in patients with moderate to severe liver

dysfunction. However, further prospective evaluation of its effectiveness and safety in this clinical setting is needed.

Conflict of interests

No conflict of interest.

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