Encephalopathy induced by levetiracetam in a young woman with normal renal function

Marina Padroni\textsuperscript{1}  
Elisa Fallica\textsuperscript{2}  
Laura Piccolo\textsuperscript{1}  
Cinzia Monetti\textsuperscript{2}

\textsuperscript{1} Department of Biological, Psychiatric and Psychological Science, Section of Neurology, University of Ferrara  
\textsuperscript{2} Neurology Unit, Department of Neuroscience and Rehabilitation, Azienda Ospedaliera Universitaria, Ferrara, Italy

Corresponding author:  
Marina Padroni  
Department of Biological, Psychiatric and Psychological Science, Section of Neurology, University of Ferrara  
Via Aldo Moro, 8  
44124 Ferrara, Italy  
E-mail: marinapadroni@gmail.com

Abstract

Levetiracetam (LEV) is an usually well-tolerated antiepileptic drug, effective in focal and generalized seizures. It has renal elimination and no hepatic metabolism. Commonly reported side effects are tiredness, sleep disturbances or psychiatric effects like aggression, anxiety and depression. Cases of LEV-induced encephalopathy have been rarely reported and especially in patients with renal impairment (1) or when LEV was added to valproate (VPA) (2, 3). In these cases, patients developed psychomotor speed impairment and decreased level of consciousness, reflecting a diffuse slowing of the EEG. Following discontinuation of LEV, they showed a gradual improvement of the state of consciousness with normalization of EEG. We describe a case of LEV-induced encephalopathy in a Caucasian woman with normal renal function, who received LEV in association with ethosuximide (ETS).

KEY WORDS: levetiracetam, encephalopathy.

Case report

A 36-year-old woman, followed elsewhere for idiopathic generalized epilepsy defined as \textit{Petit mal}, presented to our Hospital for recurrent generalized seizures. She was born full-term with spontaneous delivery and she had a normal somatopsychic development. She is right-handed. The onset of epilepsy was around puberty. Since then, she was treated with ethosuximide for absence seizures. At the age of 14, she developed generalized convulsive seizures during sleep (4-5 episodes). These were resistant to VPA but responsive to carbamazepine (CBZ) add-on. Since then, she was treated with CBZ MR 400 mg 1 tablet and an half bis in die (bid) in association with ETM 250 mg (5 ml) bid, presenting only catamermal absences. At the age of 36, during a period of physical and psychological stress, she had two generalized convulsive seizures during sleep. CBZ was replaced with PB 100 mg/die, with rapid withdrawn of CBZ in about a month. ETM was unchanged.

One month later, she was admitted to our Department for recurrent seizures (three generalized convulsive seizures on awakening). Plasma concentrations of PB and ETM were 8.4 μg/ml and 37 μg/ml respectively (just below the therapeutic range). Routine laboratories showed normal renal, liver and thyroid function tests and neurological examination was negative. PB was replaced with LEV, rapidly titrated up to 1500 mg/day. ETM was unchanged. EEG showed a good background activity and interictal generalized abnormalities (Fig. 1). She was free of seizures for three days, so she was discharged.

Two days later, she was re-admitted to our Department for recurrent seizures (three generalized convulsive seizures on awakening). Plasma concentrations of PB and ETM were 8.4 μg/ml and 37 μg/ml respectively (just below the therapeutic range). Routine laboratories showed normal renal, liver and thyroid function tests and neurological examination was negative. PB was replaced with LEV, rapidly titrated up to 1500 mg/day. ETM was unchanged. EEG showed a good background activity and interictal generalized abnormalities (Fig. 1). She was free of seizures for three days, so she was discharged.

Four days later, the persistence of clinical and EEG findings of diffuse encephalopathy associated with normal blood tests, led us to consider the possibility of drug induced encephalopathy. Therefore, we decided to suspend LEV. The withdrawal of LEV induced clinical and EEG gradual improvement (Fig. 3). ETM was unchanged, while CBZ was reintroduced and titrated.

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up to 800 mg/day. One month later, the patient reported only her usual catamenial absences. She asked for stopping ETM, that she was taken from the puberty, switching to another antiepileptic drug, to attempt to control also this type of seizures. In agreement with her, we progressively introduced topiramate (TPM). At present, the patient referred wellness and she was free of catamenial seizures, even after ETM discontinuation.

Discussion

LEV is an usually well-tolerated antiepileptic drug, effective in focal and generalized seizures. It acts on synaptic vesicle protein SV2A, preventing vesicle exocytosis and presynaptic neurotransmitter release. LEV undergoes minimum metabolism in blood via hydrolysis and is eliminated through kidneys. It has no hepatic metabolism and lacks of significant drug interactions. Despite this, cases of hepatic failure (4, 5) and VPA-induced hyperammonemic encephalopathy promoted by LEV have been reported (3). Furthermore, there are evidences that the enzyme inducing AEDs have a modest influence on the kinetics of LEV (6, 7). These results suggest that LEV is metabolized by cytochrome P450 enzymes to a greater extent than what previously hypothesized. Accumulation of drug may also occur in patients with renal failure causing a LEV-induced myoclonic encephalopathy with triphasic waves (1). Reduction in creatinine clearance may not be reflected by serum creatinine levels, especially in elderly patients, and LEV encephalopathy was also reported in an elderly woman with normal renal function (8). Other Authors (9) described a case of LEV-induced encephalopathy in a patient with normal renal function. The seizures were controlled by LEV, but the drug leaded to altered state of consciousness due to encephalopathy. LEV withdrawal determined a remarkable clinical improvement and the EEG normalization. Mahale et al. (10) reported electroencephalo-

Figure 1 - Normal EEG background activity and interictal generalized epileptiform abnormalities.

Figure 2 - Diffuse slowing of the EEG background activity and prolonged sequences of triphasic waves.

Figure 3 - Normal EEG background activity and interictal generalized epileptiform abnormalities after LEV discontinuation.
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Graphic correlates of levetiracetam-induced encephalopathy in the form of non convulsive status epilepticus (diffuse slowing of background rhythm with generalised triphasic waves that disappeared on intravenous administration of lorazepam) in a patient with preserved renal function. In this patient LEV was stopped and substituted with clobazam. Within two days, there was a gradual improvement in his mental status and a normalization of the EEG. In our patient the seizures were controlled increasing LEV, but the drug lead to global psychomotor speed impairment and generalized slowing of EEG background activity with triphasic waves. After LEV withdrawal, remarkable clinical improvement and EEG normalization were seen. We cannot explain the complete physiopathological mechanisms responsible for the observed encephalopathy. Renal and hepatic functions were normal and no enzyme inhibitors drugs were used as co-medication. A limitation of our report is the lacking of information about LEV levels in plasma, but the administered dose doesn’t seem to justify a dose-related toxicity. This case report confirms that drug induced encephalopathy should be considered an unusual side effects of LEV and it must be take into account even in young patients without liver or renal failure.

References