

[CASE REPORT]

Successful Treatment of Symptomatic Epilepsy with Oral Valproic Acid and Levetiracetam in a Patient with Short-bowel Syndrome

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Abstract:

Valproic acid (VPA) and levetiracetam (LEV) are used in epilepsy treatment. However, their use to treat short-bowel syndrome has not been reported. We herein report a 68-year-old man who was hospitalized for symptomatic epilepsy following cerebral infarction. He had a history of superior mesenteric arterial occlusion, and only 30 cm of his jejunum was intact. VPA and LEV were administered, and good blood levels were achieved at clinical doses. This suggests that the gastrointestinal tract absorption of LEV and VPA is good even in patients with short-bowel syndrome and a 30-cm jejunum.

Key words: valproic acid, levetiracetam, short-bowel syndrome, epilepsy

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Introduction

Drug therapy may be difficult when a significant portion of the small intestine is resected, as in patients with a short and small bowel. Drug absorption from the gastrointestinal tract is altered in these patients; however, this effect is variable in patients and differs by drug (1-3).

Symptomatic epilepsy is defined as seizures associated with acute central nervous system disorders, such as metabolic, toxic, organic, infectious, and inflammatory disorders. In patients with cerebrovascular disorders, symptomatic epilepsy is defined as the occurrence of an epileptic seizure within seven days of the development of a cerebrovascular disorder. If seizures persist, patients should be treated according to the status of epilepsy. Seizures are likely to recur; in such cases, antiepileptic drugs should be administered (4). Valproic acid (VPA) and levetiracetam (LEV) are antiepileptic drugs. VPA acts via the γ -aminobutyric acid (GABA)_A and glutamate receptors and is used as the first-choice drug for generalized tonic-clonic seizures and absence seizures. LEV acts through synaptic vesicle protein 2A and is used as

the first-choice drug for partial seizures (5).

The drug information sheets for VPA and LEV state that the former is absorbed from the stomach to the lower digestive tract (stomach, duodenum, small intestine, and large intestine), and the latter is considered to be absorbed from the proximal small intestine, distal small intestine, and ascending colon. However, the exact site of absorption is unknown, and no report has described the use of VPA and LEV in patients with short-bowel syndrome.

We herein report a patient with only 30 cm of the jejunum intact due to superior mesenteric arterial occlusion who received VPA and LEV treatment.

Case Report

A 68-year-old Japanese man was admitted to our hospital for the treatment of convulsive seizures. He was admitted to another hospital for seizures in 2018. He was diagnosed with symptomatic epilepsy due to a left-hemispheric cerebral infarction; he received diazepam and LEV intravenously, after which his seizures disappeared. Two days later, he was transferred to our hospital. In 2017, he was treated

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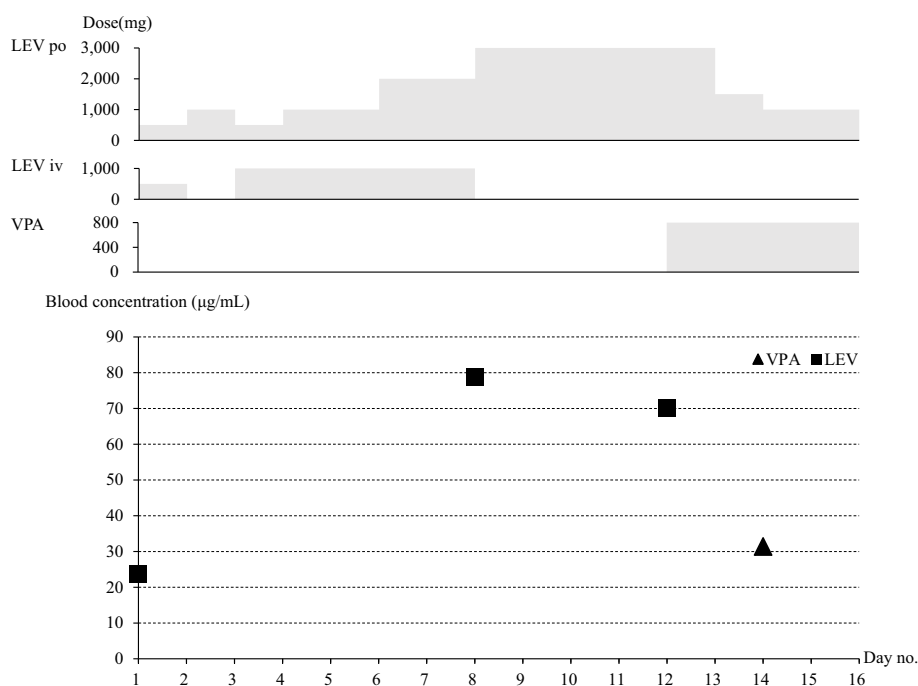


Figure 1. Doses and trough blood concentrations of levetiracetam (LEV) and valproic acid (VPA) after admission of the patient to our hospital. The horizontal axis shows the number of days of hospitalization. The vertical axis shows the drug blood concentrations. Closed triangles and closed squares indicate the blood concentrations of VPA and LEV, respectively. LEV: levetiracetam, VPA: valproic acid, iv: intravenous, po: per os

for a cerebral infarction in our hospital. At the same time, he developed superior mesenteric arterial occlusion, requiring subtotal resection of the small intestine, ileocecal resection, and anastomosis of the jejunum and ascending colon. Thus, only 30 cm of his jejunum was intact. He received warfarin at 1.5 mg/dose every 24 hours. The patient had a medical history of retinitis pigmentosa and cerebral infarction and was suspected of having lung cancer.

First hospitalization for epilepsy

The doses and trough blood concentrations of LEV and VPA after admission to our hospital are shown in Fig. 1. On day 1 of admission to our hospital, no seizures were observed; however, LEV was continued, assuming that symptomatic epilepsy focused on the temporal lobe persisted owing to restlessness and continued monologues, making communication difficult. Intravenous administration of 500 mg LEV every 12 hours, prescribed by a previous physician, was changed to oral administration in tablet form. On day 3, diazepam and LEV were administered intravenously because of recurrent seizures. Although the symptoms disappeared, both LEV oral administration and intravenous administration were continued every 12 hours at 500 mg/dose until day 5; 10 mg diazepam suppository was administered before sleep as a preventative measure. On day 5, we received the day-1 LEV blood concentration results, showing a concentration of 23.8 µg/mL. This concentration was within the effective range achieved by intravenous administration of 500 mg/dose every 12 hours, but the absorption after oral admini-

stration was unknown. The oral dose of LEV was increased by 1,000 mg/dose every 12 hours from day 6, and intravenous administration was continued. From day 8, the oral dose was increased to 1,500 mg/dose every 12 hours, and intravenous administration was discontinued. Even in the absence of convulsive symptoms, diazepam was intravenously administered when there were prognostic symptoms of symptomatic epilepsy, such as anger and repetition of words. On day 12, although there were no seizure symptoms, prodromal symptoms persisted. VPA syrup was added at 200 mg/dose every 6 hours because seizure management was difficult with LEV alone. After day 13, there was no prodrome, so the LEV dose was reduced to 750 mg/dose every 12 hours on day 13 and then to 500 mg/dose every 12 hours on day 14. The LEV blood concentration on day 8 was 78.9 µg/mL according to the laboratory data obtained on day 14, and the VPA blood concentration was 31.4 µg/mL. On day 16, the patient was discharged on VPA at 200 mg/dose every 6 hours and LEV at 500 mg/dose every 12 hours, without any seizures. During hospitalization, there were no adverse effects other than somnolence.

Second hospitalization

Twenty-one days after discharge, the patient was readmitted for dehydration due to oral intake problems. He received warfarin at 1 mg/dose every 24 hours, VPA at 400 mg/dose every 12 hours, and LEV at 500 mg/dose every 12 hours. The doses and trough blood concentrations of LEV and VPA after re-hospitalization are shown in Fig. 2. After three

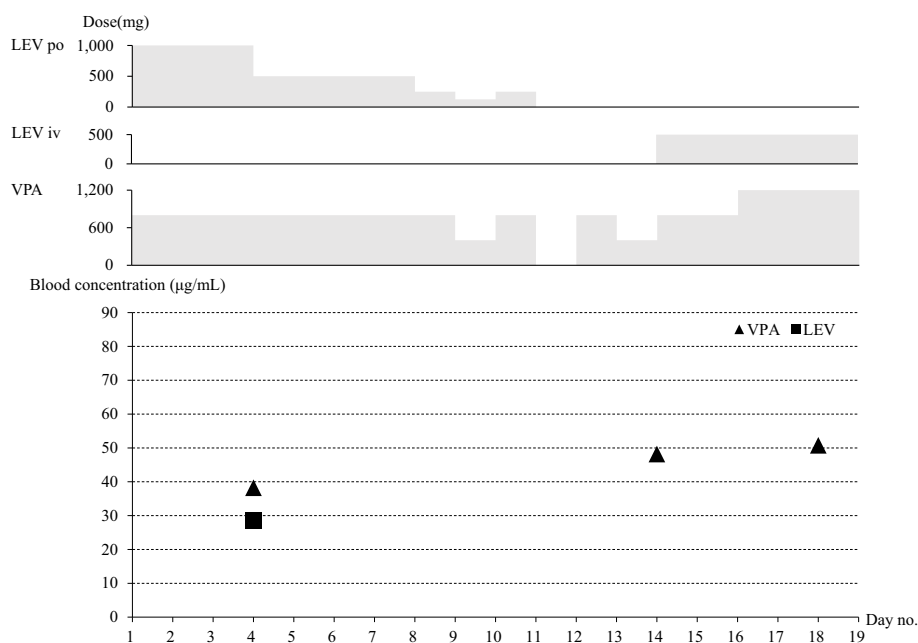


Figure 2. Doses and trough blood concentrations of levetiracetam (LEV) and valproic acid (VPA) after re-hospitalization. The horizontal axis shows the number of days of hospitalization. The vertical axis shows the drug blood concentrations. Closed triangles and closed squares indicate the blood concentrations of VPA and LEV, respectively. LEV: levetiracetam, VPA: valproic acid, iv: intravenous, po: per os

days of re-hospitalization, his dehydration was alleviated by drip treatment. Blood concentrations of VPA and LEV on day 4 were 38.3 and 28.5 $\mu\text{g/mL}$, respectively. Dehydration was suspected of being due to a loss of appetite, attributable to LEV; therefore, the LEV dose was reduced and discontinued on day 11. On day 14, a tonic seizure occurred, but the symptoms disappeared rapidly with the administration of 10 mg diazepam as a suppository and intravenous administration of 500 mg LEV. The blood concentration of VPA was 48.2 $\mu\text{g/mL}$, and the VPA dose was increased to 600 mg/dose every 12 hours; the blood concentration of VPA on day 18 was 50.8 $\mu\text{g/mL}$. The intravenous administration of LEV at 500 mg/dose every 24 hours was continued until day 18. The patient was discharged on day 19.

Discussion

We encountered a patient with short-bowel syndrome and a 30-cm residual small intestine who was administered VPA and LEV. According to studies on VPA in rats and pigs, the absorption of VPA from the stomach and duodenum to the colon is good (6, 7); however, its gastrointestinal absorption in humans is unknown. Moreover, there have been no reports of VPA use in patients with short-bowel syndrome. Regarding LEV, although it has been reported to be absorbed from the small intestine to the ascending colon (8) and used to treat short-bowel syndrome (9), there are no reports of its blood concentration measurements in patients with epilepsy on LEV with short-bowel syndrome. In our patient, good blood levels were achieved at clinical doses,

suggesting that the digestive tract absorption of LEV and VPA may be good even in patients with short-bowel syndrome.

In this case, the blood concentration of LEV was 78.9 $\mu\text{g/mL}$ when administered at an oral dose of 1,000 mg/dose every 12 hours and intravenous dose of 500 mg/dose every 12 hours, and 70.1 $\mu\text{g/mL}$ at an oral dose of 1,500 mg/dose every 12 hours alone. Although there is a correlation between the dose and blood concentration of LEV (10), there is no clear effective blood concentration range; 12-46 $\mu\text{g/mL}$ is set as the reference blood concentration (11).

LEV may cause somnolence, dizziness, and nasopharyngitis, but these adverse effects are not dose-dependent (12). However, there are also reports of elevated blood concentrations of LEV in patients with emotional deterioration, excitement, and depression (13). In the present case, somnolence and rage were suspected as adverse effects. Rage was observed before the administration of LEV and was considered to be an early symptom of convulsions. Even with the possibility of rage due to LEV administration, we selected LEV because it is well absorbed in the proximal small intestine according to the drug information sheet and there is a case report of its administration to a patient with short-bowel syndrome, as well as its lack of interaction with warfarin (8, 9). Somnolence is listed as a potential adverse effect of LEV administration. However, LEV is considered an extremely safe drug, as no adverse effects other than somnolence have been reported, even when its blood concentration markedly exceeded the clinical range.

The blood concentration of LEV was high in the present

Table. Laboratory Data.

	First hospitalization				Second hospitalization			
	day 1	day 4	day 14	day 16	day 1	day 4	day 14	day 18
BUN (mg/dL)	10.7	14.3	15.2	17.5	14.8	8.1	20.2	18.7
Cre (mg/dL)	1.09	1.29	0.99	0.95	1.16	0.95	1.11	0.97
eGFR (mL/min/1.73m ²)	52.6	43.7	58.4	61.1	49.1	61.1	51.6	59.8
AST (U/L)	28	26	22	13	19	ND	65	22
ALT (U/L)	38	32	29	18	18	ND	53	23

BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ND: no data

patient. As there is a correlation between the dose and blood concentration of LEV, there might be individual differences in blood drug concentrations, but the concentration may be particularly high in elderly individuals and patients with renal impairment (14, 15). In the present case, the patient was relatively old at 68 years old, which may have been one reason for the high blood drug levels. In patients with short-bowel syndrome, many factors, such as a short residual intestine, accelerated gastrointestinal transit, and the presence of gastrointestinal diseases, are associated with drug malabsorption. Furthermore, the absorption of drugs with a low bioavailability is particularly strongly influenced by these factors. Cefaclor and hydrochlorothiazide cause malabsorption in patients with short-bowel syndrome, which is thought to be due to the shortened intestinal transit time (16, 17). In contrast, procainamide and other drugs that are also absorbed in the large intestine have been reported to have good drug concentrations in patients with short-bowel syndrome (2). Moreover, levetiracetam is considered to be absorbed in the ascending colon from the small intestine, but its absorption in the ascending colon is prolonged compared with that in the small intestine (8). The characteristic of being absorbed in the large intestine and the difference in absorption time depending on the absorption site may have led to the high blood concentration in the present patient.

In this case, the blood collection points were all before dosing. The blood collection time for LEV was two days after the start of administration or after a change in dose, and that for VPA was three to five days after the start of administration or after a change in dose. Aside from the initial measurement, all other measurements were performed according to the guidelines in our country, Japan (18). However, in our hospital, the blood concentration measurement of LEV was outsourced, and real-time concentrations could not be obtained. Therefore, the dose determination of LEV was delayed, and it is thought that the trough value substantially exceeded the normal blood concentration range. Other factors that affect blood levels include laboratory test fluctuations and interactions. LEV is metabolized by the kidneys, whereas VPA is metabolized by the liver. There were no significant changes in the laboratory values of factors associated with the renal and hepatic functions during the administration of either drug (Table). Regarding interactions, VPA and warfarin have high protein-binding rates, which

may result in an increased anticoagulation effect. However, warfarin was administered at 1.0-1.5 mg/dose every 12 hours during hospitalization, and the prothrombin time-international normalized ratio (PT-INR) never exceeded 1.0-2.0; therefore, the influence of an interaction is considered to be minimal. No concomitant drugs interacted with LEV.

We reported the blood concentrations of LEV and VPA in a patient with epilepsy who had short-bowel syndrome with only 30 cm of the jejunum remaining due to occlusion of the superior mesenteric artery. The results showed good blood levels of both VPA and LEV at clinical doses, suggesting that patients with short-bowel syndrome may have good gastrointestinal absorption of LEV and VPA. To our knowledge, this is the first report on blood concentration measurements in epileptic patients with short-bowel syndrome taking LEV and VPA. Blood concentrations of drugs may be important to consider in order to maintain suitable plasma LEV and VPA concentrations in individuals with an impaired gastrointestinal function, as it may be difficult to predict the changes in the plasma LEV and VPA concentrations over time.

The authors state that they have no Conflict of Interest (COI).

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