Disabling tremor induced by long-term use of sodium valproate and lamotrigine

Case report

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Abstract

Rationale: Sodium valproate (VPA) and lamotrigine (LTG) are widely used antiepileptic drugs, disabling postural, and action tremors after using LTG with VPA were reported in 1993. However, in this study, we describe a patient in whom disabling resting-type tremor induced by 2-year use of VPA and LTG.

Patient concerns: A 50-year-old man was referred to the department of neurology because of involuntary upper limbs resting-type tremor with high amplitude that had begun 6 months previously and progressively worsened, and he could not work on the day of visit. Furthermore, he had been treated with VPA, LTG, and benzhexol for 2 years as he suffered from twitch of eyelids and facial region, and amantadine, monolithic compound preparation (flupentixol and melitracen) were added in the last 2 months because of tremor and anxiety. However, the treatment had no benefit on improving involuntary movements of the patient.

Diagnoses: Drug-induced disabling tremor was diagnosed.

Interventions and outcomes: LTG, amantadine, and VPA were withdrawn, the remaining 2 drugs, benzhexol and compound preparation (flupentixol and melitracen), were continued to use, and the patient improved in 2.5 months after discontinuation of 3 drugs. There was no recurrence at 6 months follow-up.

Lessons: Considering the wide and long-term utilization of VPA and LTG, healthcare providers should be aware of them as a possible cause of tremor. When necessary, an attempt of discontinuing the suspected drugs should be made to confirm the diagnosis, instead of symptomatic treatment, especially when the adverse event was severe and fatal.

Abbreviations: LTG = lamotrigine, VPA = sodium valproate.

Keywords: disabling tremor, lamotrigine, long-term use, sodium valproate

1. Introduction

Epilepsy is a common neurological disorder characterized by episodic convulsions associated with transient confusion. More than 50 million people worldwide are affected by epilepsy.\textsuperscript{[1]} It is not only a medical problem, but also an important public health and social problem. Epilepsy is listed as one of the significant neurological and mental diseases requiring prevention and treatment. Although many patients will remain seizure free on the first or second drug, combinations are usually prescribed in those unresponsive to monotherapy.\textsuperscript{[2]} Sodium valproate (VPA) is the most widely used antiepileptic drug worldwide, and lamotrigine (LTG) is a novel antiepileptic agent. A study shows that VPA-LTG comedication exhibits a favorable pharmacodynamic interaction in patients with refractory partial epilepsy.\textsuperscript{[3]}

Generally, VPA is well tolerated, and the most commonly occurring adverse reactions are gastrointestinal disturbances, others are neurologic abnormality, such as ataxia, tremor, sedation, drowsiness, and confusion.\textsuperscript{[4]} Various systemic and neurologic side effects of LTG, such as spasticity, ataxia, nystagmus, and tremor, have also been reported.\textsuperscript{[4]} Reutens et al\textsuperscript{[5]} reported disabling postural and action tremors after LTG with VPA in 1993. However, the study on disabling resting-type tremor secondary to simultaneous administration of the 2 medicines has not been reported. To our knowledge, this is the first report about disabling resting-type tremor caused by VPA and LTG.

2. Case report

A 50-year-old man, weighing 75 kg, was referred to the department of neurology because of involuntary upper limbs resting-type tremor with high amplitude that had begun 6 months previously and progressively worsened, and he could not work on the day of visit. Furthermore, he had been treated with VPA, LTG, and benzhexol for 2 years as he suffered from twitch of eyelids and...
facial region, and amantadine, monolithic compound preparation (flupentixol and melitracen) were added in the last 2 months because of tremor and anxiety. However, the treatment had no benefit on improving involuntary movements of the patient. In lower-grade hospital, the patient had been diagnosed as epilepsy due to twitch of eyelids and facial region, VPA and LTG had been initially given 2 years ago. There was no family history of any neurological disease and clinical features in favor of Wilson disease, he denied hypertension, diabetes mellitus, injury history, and history of drug allergy other than chronic hepatitis B of 30 years. After admission, he was conscious, temperature 36.4°C, pulse was 94 times/min, regular, and blood pressure was 129/91 mm Hg. Neurological examination showed involuntary upper limbs tremor, high muscle tension of extremities, and twitch of eyelids and facial region, the rest of the neurological examination was normal. On further evaluation, routine blood test and other tests such as liver function, kidney function, urine analysis, and random blood glucose were normal. Magnetic resonance imaging of brain, electroencephalography, and neuropsychological examination did not reveal any abnormality.

Disabling tremor induced by drugs was initially diagnosed based on the chronic worsening process, an exposure history of many drugs acting on the central nervous system, and the exclusion of known causes of secondary tremor by above clinical and laboratory evaluation. In treatment, LTG (100 mg qd) and amantadine (100 mg bid) were discontinued immediately; dosage of VPA was gradually reduced (sodium valproate sustained-release tablet: 1000 mg bid for 4 days, subsequently, 500 mg bid for 5 days) and was ceased after 9 days. In other words, within 9 days all of LTG, amantadine, and VPA were withdrawn. The degree of upper limbs tremor was not increased, but somewhat reduced. With that, remaining therapy was benzhexol for 2 mg tid, flupentixol, and melitracen (flupentixol 0.5 mg and melitracen 10 mg) for 1 piece, bid (8 AM and noon). At follow-up examination 2.5 months after stopping above 3 drugs, his upper limbs tremor had apparently improved, and twitch of eyelids and facial region also improved except mouth. In addition, his mental state improved compared to 2.5 months ago, and he could work.

4. Conclusion
This case demonstrates that the long-term use of VPA and LTG can lead to disabling tremor. Considering the wide and long-term utilization of VPA and LTG, healthcare providers should be aware of them as a possible cause of tremor. When necessary, an attempt of discontinuing the suspected drugs should be made to confirm the diagnosis, instead of symptomatic treatment, especially when the adverse event was severe and fatal.

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