Clinical Case Report

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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 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Interventions and outcomes: LTG, amantadine, and VPA were withdrawn, the remaining 2 drugs, benzhexol and compound preparation (flupentixol and melitracen), were continued to use, and the patient improved in 2.5 months after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.[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.[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.[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.[4] Various systemic and neurologic side effects of LTG, such as spasticity, ataxia, nystagmus, and tremor, have also been reported.[4] Reutens et al[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 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

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All interventions given were part of normal health care and therefore ethics approval was not required in this study. However, informed consent was obtained from the patient.

The authors have no conflicts of interest to disclose.

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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 as a security guard according to his wife. There was no recurrence of the upper limbs tremor at 6 months follow-up.

3. Discussion

In this case, we have reported an unusual patient with upper limbs resting-type tremor induced by VPA and LTG, which improved after discontinuation of the culprit drugs. This confirms the initial diagnosis of drug-induced tremor. This case is unusual in 2 regards: firstly, his tremor is disabling and not mild; secondly, this case is the first documented case of resting-type tremor which is different from postural and action tremor caused by LTG with VPA reported in 1993.[5]

Indeed, the patient had been treated initially with VPA and LTG due to epilepsy, approximately 1.5 years later, the patient developed resting-type tremor with high amplitude of the arms and gradually worsened. Therefore, amantadine was added because of upper limbs tremor for 4 months, and compound preparation (flupentixol and melitracen) was also added at that time due to psychosomatic disease with anxiety, but upper limbs tremor did not improve within 2 months.

Firstly, to establish the causal relationship between medication (VPA and LTG) and tremor, we applied WHO Uppsala Monitoring Centre criteria,[6] the result showed that this adverse reaction had "probable" relationship with medication administration. Meanwhile, we assessed severity of this adverse reaction according to the Common Terminology Criteria for Adverse Events[7] in grades 1 to 5 (mild to lethal), the grade of the patient was 4 (disabling).

Secondly, we searched the literature of adverse reactions about tremor and extrapyramidal reaction on VPA, LTG, and amantadine. The results showed: Lautin et al[8] firstly reported a case of tremor with VPA in 1979; Reutens et al[5] reported that 3 patients presented disabling postural and action tremor after LTG with VPA, and their symptoms disappeared after reducing dosage of LTG or VPA. In addition, mild tremor was also observed in patients of VPA monotherapy and VPA-LTG combination.[3,9,10] Pathophysiologic mechanisms of extrapyramidal adverse reaction of VPA remains unknown, although a transient imbalance between functionally reciprocal subgroups of GABA pathways leading to remediable dopamine inhibition might be hypothesized.[11] Another study showed that the number of dopaminergic cells in the substantia nigra was reduced after treatment with VPA in mice.[12] Meanwhile, pharmacokinetic interaction of VPA inhibiting LTG metabolism,[13] pharmacodynamic interaction between VPA and LTG, and individual susceptibility such as chronic hepatitis B may have played a part in extrapyramidal adverse reaction of VPA and LTG.[5] However, amantadine is indicated in the treatment of drug-induced extrapyramidal reactions, and amantadine-induced tremor was not found by literature review.

To our knowledge, we have not found case report of upper limbs disabling tremor induced by VPA, LTG, and amantadine administrated together. In summary, we believe it is not possible to say with certainty if upper limbs tremor of the patient developed as a sole consequence of any one from VPA, LTG, and amantadine or as a consequence of possible synergistic effect of his medications. However, we speculate that simultaneous use of VPA and LTG is a possible culprit cause due to their long-term use of 2 years and antagonism of dopamine. Amantadine is not considered as a main culprit drug in a large part due to its effects on dopamine neurons and short-term use, especially 4 months after developing upper limbs tremor.

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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