

## Late Side-Effects of Valproate and Lamotrigine

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### ABSTRACT

Lamotrigine (LTG) is a generally well-tolerated antiepileptic drug with broad-spectrum efficacy in several forms of partial and generalized epilepsy. Adverse effects of lamotrigine are usually associated with introduction and titration. This risk increases in children and in the co-medication with valproate. Herein, we report four patients with late adverse-effects, under the co-medication valproate and LTG, not related to drug introduction or titration. This study demonstrates that late side-effects without apparent etiology in children, adolescents and adults in chronic use of LTG, especially when associated to VPA, led to a diagnostic investigation, sometimes invasive. It must be emphasized that, due to the excellent seizure control, the authors opted for drug decrease instead of drug withdrawal, as previously done. Studies on late adverse effects are scarce, but physicians must be aware of these risks.

**Key words:** lamotrigine, side-effects, epilepsy, anti-epileptic drugs.

### RESUMO

#### *Efeitos adversos tardios no uso de valproate e lamotrigina*

Lamotrigina (LTG) é uma droga antiepiléptica bem tolerada com eficácia em diferentes formas de epilepsia, parcial e generalizada. Os efeitos adversos da lamotrigina estão freqüentemente associados com a sua introdução e a sua titulação. Este risco encontra-se aumentado em crianças e quando a LTG é usada em associação com o valproato. Nós relatamos quatro pacientes que apresentaram efeitos adversos tardios com a co-administração de LTG e valproato, não relacionados à introdução ou o escalonamento das drogas antiepilépticas. Este estudo demonstra que efeitos adversos tardios sem etiologia aparente nas crianças, adolescentes e adultos em uso crônico de LTG, especialmente quando associados ao valproato, levou à investigação diagnóstica, por vezes invasiva. Os autores enfatizam que, devido ao bom controle de crises, os autores optaram pela redução da dose ao invés da suspensão da medicação, como previamente realizado. Embora os estudos sobre efeitos adversos tardios das drogas antiepilépticas sejam escassos, os clínicos devem estar cientes deste risco.

**Unitermos:** lamotrigine, efeitos adversos, epilepsia, drogas antiepilépticas.

### INTRODUCTION

Lamotrigine (LTG) is a newer anti-epileptic drug (AED), well-tolerated by children and adults<sup>1</sup> with a wide-spectrum efficacy, in either monotherapy or polytherapy.<sup>2,3</sup> Its mechanism of action is determined by its action blocking Na<sup>+</sup> channels<sup>4</sup> and a possible action on NMDA receptors.<sup>4,5</sup>

The pharmacokinetic profile of LTG demonstrates good absorption after oral administration, a linear relation between dose and plasma concentrations, ~55% protein binding, and an elimination half-life of 25-30 h with monotherapy.<sup>6</sup> The elimination half-life is reduced to ~15 h during combination therapy with hepatic enzyme-inducing AEDs [e.g., carbamazepine (CBZ), phenytoin

(PHT)]<sup>7-10</sup> and more than doubled to ~60 h when combined with valproate (VPA) a microsomal enzyme inhibitor.<sup>7,8</sup>

Tolerability and long-term safety studies have shown a relatively low incidence of neurotoxicity (e.g., asthenia, dizziness, somnolence, ataxia, trembling) in add-on studies and when compared with CBZ and PHT in monotherapy trials.<sup>6-11</sup> Several studies have reported a tendency to improve mental function, especially in children.<sup>12-16</sup>

The most common adverse effect leading to discontinuation of LTG is rash, which was severe enough to require discontinuation in 3% of adults in early clinical trials.<sup>17</sup> This risk increases in children and with the co-medication VPA-LTG.

There is scarce data on long-term late adverse effects on tissues or organs or on cognitive function. Herein, we report four patients with late adverse-effects, under the co-medication VPA-LTG, not related to drug introduction or titration.

## CASE REPORT

**CASE 1.** A 6 year-old girl, with partial epilepsy characterized by partial motor seizures, occurring predominantly during sleep with onset at 2 years and 6 months. EEG revealed epileptiform discharges over the centroparietal region. MRI displayed a polymicrogyria over the right opercular region. The child evolved with refractory epilepsy and medical control was obtained with association of LTG to VPA and nitrazepam. LTG was slowly introduced, according to Guberman et al. guidelines.<sup>1</sup> Nine months after the last dose adjustment, the child presented sporadic episodes of vomiting every 15 days. A pediatrician ruled out infection or other acute causes, such as metabolic disturbances. At the same time, the patient started presenting trembling and dizziness. One month later, the patient evolved with a sudden opsoclonus, ataxia, vomiting, headache and vertigo. Ancillary exams were conducted including lumbar puncture, CT and MRI in order to rule out infection or tumors. A slow decrease of LTG dose of 50 mg led to remission of these signs and symptoms without worsening of seizures.

**CASE 2.** An 18 year-old female adolescent with refractory epilepsy since the age of 8 months characterized by generalized seizures – myoclonic and tonic-clonic seizures. Later, these seizures were associated to atypical absence and atonic seizures. MRI revealed a diffuse malformation of cortical development characterized by band heterotopia (*double cortex*). After several drug trials, co-administration of VPA-LTG led to partial seizure control, abolishing disabling seizures that affected daily activities. In 2003, 1 year and 3 months after the last AED adjustment, with stable doses, the patient presented involuntary movements affecting the head and neck,

characterizing tics. A LTG decrease in 25 mg led to the remission of these movements.

**CASE 3.** A 15 year-old female adolescent with epilepsy onset at the age of 4 years, which evolved with disabling seizures. EEG showed multifocal epileptiform discharges and MRI demonstrated band heterotopia. The patient evolved with refractory epilepsy and at the age of 11 years, LTG was associated to VPA with satisfactory seizure control. Two years after the last dose increase, the child presented an acute episode with *nistagmus*, ataxia, tremor and vertigo. Ancillary exams did not reveal an etiology for these signs and symptoms. Decrease of 50 mg in LTG dose led to remission of this clinical picture, without seizure worsening.

**CASE 4.** A 14 year-old male adolescent with refractory myoclonic epilepsy with onset at 1 year of age. This patient was referred at the age of 12 years with partial seizure control with a ketogenic diet that had to be withdrawn after 5 years. Interruption of this treatment led to reiterated *status epilepticus*. The patient was admitted using VPA and clonazepam. LTG was introduced according to Guberman et al. criteria.<sup>1</sup> The patient had total remission of generalized tonic-clonic events and partial control of myoclonic seizures (brief weekly events) with high doses of LTG (400 mg/day) and VPA (1.5 g/day). One year after the last adjustment of these doses, patients began presenting speech and gait difficulties. The neurologic exam showed ataxia and disabling tremor. LTG reduction (50 mg) led to remission of the cerebellar signs and symptoms.

## DISCUSSION

These four cases showed a common characteristic – a prolonged gap between the last dose adjustment and the onset of adverse effects. This period ranged from 9 months to 2 years. Other possible systemic triggering factors that could increase the blood level of LTG or VPA, or both, were ruled-out. Late side-effects without apparent etiology in children, adolescents and adults in chronic use of LTG, especially when associated to VPA, led to a diagnostic investigation, sometimes invasive, painful and stressful for both patients and their families.

The revision of La Roche and Helmers<sup>18,19</sup> demonstrated that side-effects led to drug withdrawal in 10.2% of all patients under LTG therapy (n = 3501). Rash was the main reason for treatment discontinuation. It has been postulated that side-effects may be lessened by slow introduction and titration.<sup>1,18,19</sup>

Rare studies have reported side-effects after chronic use of LTG (ex, 6 months).<sup>20</sup> The study of Mackay et al.<sup>21</sup> evaluated adverse-effects six months after LTG intro-

duction. *Rash* and Steven-Johnsons syndrome were earlier manifestations, observed during introduction. In the same study, other adverse-effects such as mood disorder, ataxia, visual blurring and diplopia were reported few months after treatment onset. Although the occurrence of these effects is rare (0.1-0.2%), it serves as a warning to possible late neurological and psychiatric signs and symptoms.

Patients described in this series presented heterogeneous signs and symptoms, such as ataxia, vertigo and headache, which are common adverse-effects.<sup>1,22</sup> On the other hand, tics, abnormal eye movements and movement disorders as observed in two patients are rare.<sup>23-25</sup> The mechanisms that cause abnormal eye movements and movement disorders are highly hypothetical. It has been postulated that AED may act on sodium channels causing such anomalies, by acting on dopaminergic metabolism with the inhibition of excitatory aminoacides (glutamine). Another hypothesis is that the increase in epileptiform discharges may cause these abnormal eye movements.<sup>26</sup> In disagreement with the latter, none of our patients had a worsening of epileptiform discharges or seizures during these events.

An important factor that must be stressed is that, due to the excellent seizure control obtained in these refractory cases, the authors opted for drug decrease instead of drug withdrawal, as usually done.<sup>27-29</sup>

## CONCLUSION

It is believed that after introduction of one AED, without dose increments, adverse-effects will not be observed. We corroborated the few cases in the literature that show serious adverse-effects with chronic use and stable doses of LTG and VPA. This must be kept in mind in order to avoid unnecessary exams. Additionally, we showed that a low dose decrease may lead to the remission of these serious adverse effects without consequences to the patient, such as seizure worsening.

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