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Encephalopathy secondary to lamotrigine toxicity☆

Encefalopatía secundaria a intoxicación por lamotrigina

Dear Editor:

Voluntary ingestion of drugs with suicidal intent is more frequent in patients with epilepsy or psychiatric disorders than in the general population.[1] In this way, drugs prescribed for those conditions are susceptible to cause intoxication.

Lamotrigine, a broad-spectrum antiepileptic drug (AED), is approved for treating epilepsy (both in monotherapy and in polytherapy) and also bipolar disorder, due to its action as a mood stabiliser.[1] It is widely used due to its good tolerability.[1] However, given its high toxicity index compared to other AEDs,[2] we must be familiar with its pharmacological profile and other possible adverse effects.

We present the case of a 38-year-old man with personal history of arterial hypertension and migraine. In the previous year and a half, the patient had experienced sudden episodes of loss of consciousness without prodrome or abnormal movements. A brain magnetic resonance imaging scan and long-term video-EEG revealed no pathological findings, despite the clinical events observed. However, he was receiving treatment with lamotrigine at 150 mg/12 hours, with limited treatment adherence. He presented no history of using or abusing drugs.

These episodes led to medical leave from work, and given the increasing number of events and the possibility of having to stop work permanently, the patient attempted suicide by taking lamotrigine (total dose of approximately 1000 mg). His family found him on the floor, nearly unconscious, and he was transferred to hospital.

Upon arrival, 8 hours after the last time he was seen without symptoms, he presented arterial blood pressure values of 148/70, tachycardia at 110 bpm, oxygen saturation of 95%, axillary temperature of 36.2 °C, and a blood glucose level of 182 mg/dL. The edges of the tongue were bitten and the patient presented nausea and vomiting. Neurological examination revealed somnolence, bradypsychia, and partial orientation; a Glasgow Coma Scale score of 13 points (eye opening: 3; verbal response: 4; motor response: 6); reactive, mildly miotic pupils; dysarthria with no language alterations and intelligible speech; ability to follow instructions; no visual field alterations; and vertical nystagmus in all gaze positions, with a horizontal component. He presented no limitations when performing extrinsic eye movements or involvement of other cranial nerves, and showed preserved muscular balance and sensitivity in the limbs; ataxia predominantly affecting the upper limbs; generalised hyperreflexia with spontaneous and sustained bilateral ankle clonus and bilateral Hoffman sign; bilateral flexor plantar reflex; and no neck rigidity or other sign of meningeal involvement. The patient also presented mild oppressive headache of parietal predominance. The general examination identified no other abnormalities.

Emergency studies revealed metabolic acidosis, with lactate at 8.9 mmol/L; isolated leukocytosis (21 700 cells/mm^3); normal renal and liver function; calcium and magnesium ions within normal levels; and normal urinalysis results, with negative results in the urine toxicology test. A brain CT scan and baseline EEG study yielded no pathological results, and a lumbar puncture revealed an opening pressure of 22.5 cm H_2O and cerebrospinal fluid with no alterations.

Awaiting results for the concentration of lamotrigine in the blood (sample extracted 8-12 hours after ingestion), we started fluid replacement therapy to promote renal excretion in the event of intoxication and maintained clinical and haemodynamic monitoring until the drug was eliminated. Telemetry showed no alterations in cardiac conduction or repolarisation, and an isolated episode of fever (37.8 °C) with no infectious focus. The patient progressively improved, remaining asymptomatic after 48 hours. Results for blood lamotrigine concentration were 17.2 mg/L, leading us to diagnose metabolic encephalopathy secondary to lamotrigine intoxication.

Lamotrigine is a phenyltriazine derivative that acts by inhibiting voltage-gated calcium and sodium channels. It also reduces neuronal glutamate release, which affects the serotonergic pathway, inhibiting serotonin reuptake.[1]

It presents a bioavailability of 98% and reaches peak concentration (C_{max}) in the 1-3 hours after ingestion.[1] The half-life of lamotrigine is approximately 33 hours (22-36 h), with considerable variations between individuals[3]; half-life may decrease by as much as 25% in chronically treated patients as the drug induces its own metabolism.[1] During its degradation it undergoes hepatic inactivation, with the metabolite finally being excreted by the kidneys. The recommended therapeutic range for patients with epilepsy is 1-4 mg/L. However, adverse reactions are rare in patients with concentrations < 10 mg/L, and this value has been proposed as the upper bound of the therapeutic range, according to response.[3]

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The main adverse reactions affect the central nervous system and the cardiovascular system, due to the drug's action on the channels responsible for initiating and propagating the action potential in nerves and muscles. Its inhibition of serotonin reuptake would explain the risk of serotonin syndrome. Other reactions include hypersensitivity syndrome with pronounced skin involvement. These side effects have been observed at concentrations from 15.5 mg/L, but with no clear correlation between blood lamotrigine concentration and clinical toxicity. Furthermore, the concentrations observed seem to differ in patients ingesting the same amount of the drug[3]; some patients may not present toxic effects despite the overdose.[1]

The most frequent neurological presentations are decreased level of consciousness and ataxia, followed by vertigo, confusion, agitation, dysarthria, nystagmus, headache, seizures, and other findings associated with serotonin syndrome. Cardiac effects, which are less frequent, include sinus tachycardia and QRS and QTc widening, with the subsequent risk of arrhythmia.[1] Nausea, vomiting, and exanthema are also frequent.

In the case of our patient, altered level of consciousness and sustained spontaneous clonus may be considered part of a serotonin syndrome, fulfilling the Hunter criteria for this diagnosis,[4] in addition to lactic acidosis, slight fever with no apparent focus, and isolated leukocytosis, which normalised in the first 24 hours. He also presented other polymorphic neurological symptoms, particularly nystagmus, ataxia, and dysarthria. In terms of cardiac manifestations, he only presented self-limited sinus tachycardia. Although it was not witnessed, the tongue biting and the limited reactivity at baseline may have been associated with a seizure, which is consistent with the paroxysmal convulsive action of overdoses of certain AEDs.[1,3]

Our treatment was exclusively symptomatic due to the time elapsed. However, gastrointestinal decontamination is possible when patients are examined early, although previous protection of the airway is essential due to the risk of decreased level of consciousness and presence of seizures. Other treatments used are alkalinisation with sodium bicarbonate, intravenous lipid emulsions, and even haemodialysis, although published experience is limited.[1,3]

In conclusion, our case exemplifies the polymorphic presentation of lamotrigine intoxication. Due to the wide array of neurological symptoms and the association with serotonin syndrome, we consider it a good example to illustrate the adverse effects of a frequently used drug that, in the absence of suspicion, may be life-threatening.

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Primary cytomegalovirus infection in a patient with relapsing-remitting multiple sclerosis under treatment with alemtuzumab☆

Primoinfección por citomegalovirus en un paciente con esclerosis múltiple recurrente-remitente tratado con alemtuzumab

Dear Editor:

Alemtuzumab is a monoclonal antibody targeting the CD52 receptor, and is approved for treating active relapsing-remitting multiple sclerosis (RRMS). It depletes T and B cells by binding to the CD52 receptor.

Adverse effects of alemtuzumab include infections, with the most frequent being nasopharyngitis, urinary tract infection, upper respiratory tract infection, and herpesvirus infection.[1,2] Opportunistic infections after treatment have also been described, such as tuberculosis reactivation, listeria meningitis, and cerebral nocardiosis.[3] Recent studies report 2 cases of cytomegalovirus (CMV) reactivation[4] and a case of coinfection with CMV and *Pneumocystis jirovecii*.[5] Another case of CMV infection was reported in the group receiving high-dose alemtuzumab (24 mg/kg) in a phase III clinical trial.[6]

We report the case of a patient with pneumonia due to coinfection with CMV and *P. jirovecii* after the first cycle of alemtuzumab.

The patient was a 39-year-old woman who was diagnosed with RRMS in 2009. She was initially treated with interferon beta 1b, which was switched to fingolimod after 9 months due to ineffectiveness. In 2014, the patient started treatment with natalizumab due to persistent disease activity. In 2016, she presented John Cunningham virus seroconver-

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