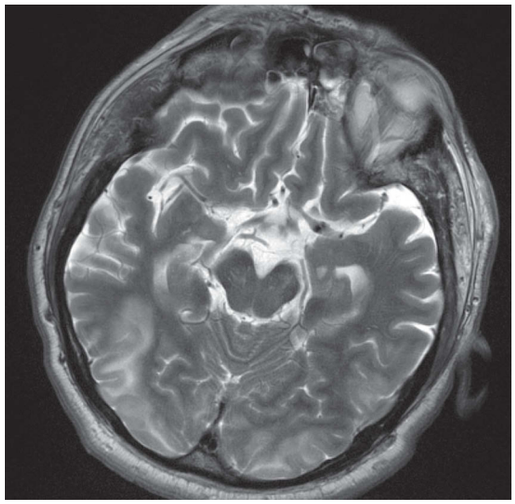

Figure 1 T2 axial MRI scan conducted at the beginning of the condition, showing hyperintense images in both occipital lobes, more marked on the right side.

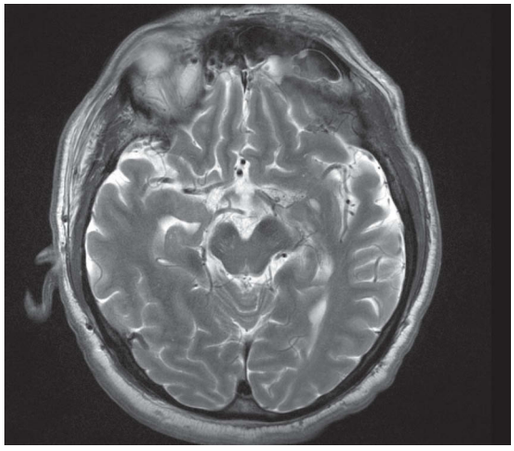

Figure 2 T2 axial MRI scan, showing resolution of the previous image alterations.

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Convulsive status epilepticus associated with a tramadol overdose

Crisis epiléptica convulsiva relacionada con sobredosis de tramadol

Dear Editor:

We describe the case of a 15-year-old male without previous history of epilepsy who presented tonic-clonic seizures during the day, followed by refractory convulsive status epilepticus (CSE). The family and perinatal history contained no relevant data. At age 9 he was diagnosed with osteoid osteoma. As he was not a candidate for surgical intervention, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was started; normally, naproxen treatment was sufficient to relieve the pain. Two weeks before admission, he presented an exacerbation of pain that showed no response to NSAIDs and led to tramadol treatment being started. After an oral dose of 25mg, he suffered complex verbal auditory hallucinations involving commands and suggestions, paranoid delusions and finally confusion psychosis. The symptoms were resolved within 24h without medical intervention. His mother stopped the administration of tramadol, but on

the day of hospital admission the patient took a dose of 500mg; subsequently he began to suffer generalised tonic-clonic seizures, without recovery of consciousness between seizures.

He was taken to a primary care centre and was given glucose and thiamine, in accordance with international guidelines. He was also given intravenous diazepam (20mg) and a loading dose of 15 mg/kg of phenytoin, with no response. Subsequently, the patient was transferred to the National Neurology and Neurosurgery Institute, where he was intubated and an infusion of sodium pentothal at a dose of 3.5 mg/kg/h was started, after an initial, intravenous load of 250mg. This treatment managed to clinically control the evidence of epileptic activity. Arterial blood gases showed: pH 7.35; PaO2, 150 mmHg; PaCO2, 38 mmHg; HCO3, 24mmol/l; SatO2, 98.4% The determination of blood chemistry showed: sodium, 140mmol/l; potassium, 4.1mmol/l; chlorine, 101mmol/l; creatinine, 1.2 mg/dl. Blood count was normal. Due to the severe circumstances, the baseline electroencephalogram (EEG) was obtained under the effect of sodium pentothal and showed a pattern of flare suppression of 3-5s duration, with irregular spike-wave complexes in the right frontal region. Subsequently, electrical silence was obtained after adjusting the dose of sodium pentothal to 5mg/kg/h. A lumbar puncture obtained a cerebrospinal fluid (CSF) opening pressure of 210mmH2O; the final pressure was 60mmH2O. Cytochemical analysis showed: leukocytes, 0/µl; glucose, 56mg/dl; protein, 32mg/dl. Serum determinations of amphetamine (normal, 1,000ng/ml), cocaine (normal, 300ng/ml), cannabis (normal, 50ng/ml) and total opium (normal, 2,000ng/ml) were all negative. Serum determination of tramadol is not available at our institution and was therefore not performed. A magnetic resonance imaging scan of the brain was carried out, including sequences weighted in T1, T2, FLAIR and diffusion, as well magnetic resonance angiography, all of which were normal. The EEG remained isoelectric for 3 days; after this period, the administration of sodium pentothal was suspended, prior to initiating magnesium valproate treatment. The residual effect of the barbiturate remained for 5 days and there was a gradual recovery of consciousness. Mean serum concentration of magnesium valproate was 112µg/ml (75-125µg/ml). The patient was discharged 30 days later with minor alterations associated with the mild neuropathy of a critically ill patient. Three months later, the neurological examination was normal.

Tramadol hydrochloride (tramadol) is a centrally acting synthetic analgesic chemically related to opiates. Its action involves 2 different mechanisms: binding to mu-opioid receptors by M1 metabolite and promoting the release of serotonin with mild inhibition of serotonin and noradrenalin reuptake.[1,2] The effective dose varies, depending on pain management indications, from 50 to 400mg/day. Therapeutic monitoring of plasma concentration is not necessary and therefore not widely available. Tramadol is metabolised to M1 by cytochrome P450 (CYP) and isoenzyme 2D6, and the concomitant use of inhibitors of this isoenzyme results in increased tramadol concentrations and decreased M1 concentrations. This fact is important because most of the toxicity of tramadol appears to be attributable to monoamine reuptake inhibition rather than to the effect of opioids. Reported symptoms of tramadol overdose include drowsiness, nausea, tachycardia, agitation, respiratory depression and convulsions in approximately 8% of patients.[3]

Although tramadol has been reported to cause seizures in animals and humans at therapeutic[1-3] and toxic[4] doses, it has also been found to have antiepileptic properties in at least one rat epilepsy model.[5] A case-control study in Great Britain found no increased risk of idiopathic seizures associated with the use of tramadol.[6] However, one Australian article identified tramadol as the most frequently associated cause of provoked seizures.[7] In addition, a certain number of cofactors, such as history of alcohol abuse and the use of drugs known to lower the seizure threshold, such as selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA), have been identified as risk factors for new onset seizures after the use of tramadol.[8] A study conducted on tramadol addicts found that seizures were more common in younger consumers with prolonged exposure to tramadol and with a combined use of tramadol and alcohol.[9]

The lesser-known complications of tramadol include severe serotoninergic syndrome,[10] complex auditory hallucinations[11,12] and even death.[13] In addition, the concomitant use of SSRIs and TCAs has the greatest relevance. It should be noted that some case descriptions, as well as information from the World Health Organization and the Netherlands Pharmacovigilance Centre, involve the concomitant use of NSAIDs in the occurrence of complex auditory hallucinations.[12,14] In the case described in this document, the patient was being treated with NSAIDs for chronic pain management, which may have caused the initial symptoms, such as visual hallucinations.

All seizures in relation with tramadol appear to be brief[7-9] and are described within the spectrum of tonic-clonic seizures as a main manifestation. However, myoclonic cases have also been reported in humans and rats.[5,15] Convulsive status epilepticus has not been described previously, although one case-control report recently found an apparent association between the use of tramadol and the emergence of non-convulsive SE in elderly patients.[16]

To our knowledge, this is the first description of CSE closely related to tramadol overdose. The following aspects should be borne in mind in this case: first, the absence of concomitant use of SSRIs and TCAs, as well as the use of NSAIDs; second, the presence of an episode resembling hallucinatory psychosis prior to the CSE; and finally, the rapid resolution of the CSE with standard management and the suspension of tramadol.

The risk of incidental idiopathic crises with tramadol administration is well known. Doctors should consider and be able to rule out convulsive and non-convulsive status epilepticus as a potential complication of the use of tramadol. However, tramadol is still a safe, well tolerated drug for pain management in a variety of medical conditions. The authors consider the possible existence of a relationship between tramadol and NSAIDs as a predisposing factor for

complex auditory hallucinations and CSE, which seems to be an interesting option for further research in the basic field.

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Autoimmune vestibulopathy associated with autoreactive antibodies and parotid involvement

Vestibulopatía autoinmunitaria asociada con anticuerpos autorreactivos y afección parotídea

Dear Editor:

Autoimmune vestibulopathy is a rare and treatable condition characterised by recurrent episodes of vertigo or progressive clinical signs of instability with clinical data of vestibular hypofunction.[1,2] Its early recognition makes it possible to introduce immunosuppressive treatment to stop its progression.[2,3] We present a patient with autoimmune vestibulopathy and radiological findings of parotid condition.

The patient was a 52-year-old male with no personal or family history of interest, with a progressive condition of tinnitus and hearing loss of 3 years' evolution. For the past year he had suffered unsteady gait sensation, with a tendency to veer to the right. He did not report a sensation of object rotation.

The neurological examination revealed nystagmus after head shakes, corrective saccadic movements with head turns and a decrease in dynamic visual acuity compared to static.

The complementary tests were: normal Ss, normal biochemical results, negative syphilis, normal thyroid hormones, normal vitamin B12, positive ANA, fine structure anti-Golgi, positive Ro/SSA antibodies, positive transglutaminase antibodies; the rest of the results were normal or negative. The coronal sections of cranial magnetic resonance imaging showed enlarged parotid glands with small millimetric hyperintense images that could correspond to small cysts or acini, plus a more prominent one with a lobular aspect in the right parotid gland, with a size of 1.3 cm. This finding could be related to an autoimmune disease (fig. 1).

Prednisone treatment was prescribed, yielding clinical stabilisation and partial improvement of instability and tinnitus. The treatment was suspended after 4 months due to side effects, after which the patient suffered a clinical exacerbation. Immunomodulatory treatment was reintroduced, resulting in clear clinical improvement.

Autoimmune vestibulopathy is a rare entity but it must be recognised, due to the importance of early immunosuppressive treatment.[2,3] It may be the expression of a uniquely vestibular condition or be part of the clinical context of a systemic autoimmune disease (SLE, ulcerative colitis, Cogan's syndrome). Autoantibodies against the inner ear have been described, but it was not possible to determine them in our case.[3,4] In our opinion, clinical suspicion of autoimmune vestibulopathy condition should lead to immunomodulatory treatment, possibly with steroids, to prevent clinical progression and the disability that it generates. The possibility of autoimmune vestibulopathy should be considered in cases of instability and recurrent vertigo. Early treatment is essential to prevent irreversible vestibular hypofunction.