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Serotonin syndrome due to association of venlafaxine, maprotiline and reboxetine

Venlafaxine is a powerful antidepressant from the age of selective serotonin reuptake post-inhibitors, with a dual serotonergic (5HT) and noradrenergic (NA) action. It has been associated to serotonin syndrome (SS) in some isolated cases, when introduced immediately after abrupt discontinuation of fenelzine [2] or fluoxetine [1] or even when administered alone at low doses [3]. However, we did not know the association of SS with maprotiline or reboxetine when administered separately or combined with venlafaxine. We next present a case of this triple combination with a resultant SS.

1. Case

A 50-year-old man, with antecedents of hepatopathy and alcohol dependence. He was receiving ambulatory treatment with venlafaxine 300 mg/d, ludiomil 150 mg/d, reboxetine 8 mg/d, vitamin B complex and intramuscular *S*-adenosilmetionine. He was admitted in our Psychiatry Unit after having gone to the hospital emergency service with a clinic of negativism and perplexity, which was evaluated as a somatic syndrome, a complication of the depressive disorder for which he had been receiving treatment, of several days of progressive evolution. The psychopathological exploration revealed a confusion state, semi perplexity, oppositionist negativism, and semi stuporous mutism. In the physical exploration, there was non-parkinsonic generalized rigidity, alternating with psychomotor agitation, tremor in superior extremities, profuse diaphoresis, hyperreflexia with very elevated symmetrical osteotendinous reflexes, with flexor cutaneous. The blood pressure oscillated between 140/105 and 125/80 mmHg. The axilar temperature was 37.4 °C. Cardiac and respiratory frequency with light alterations. Analysis: leukocytosis of 16.900 with neutrophilia (70%), CK = 964 U/l, and thyroid hormones with TSH = 4.58 μUl/ml and T4L = 1.22 ng/dl, with no more interesting findings. Negative determination of drug abuse in urine. Negative serologies. Thorax X-ray: elevation of right diaphragm; ECG and cranial magnetic resonance with no findings. As he manifested serotonergic clinic, all the previous psychopharmacological treatment was retired, introducing endovenous fluid therapy and diazepam in slow perfusion. The syndrome resolved within the following days, with a complete recovery and no sequels.

2. Our comment

An antidepressant therapeutic strategy with a clear serotonergic and noradrenergic enhancement was chosen. Venlafaxine is a relatively weak inhibitor of CYP2D6 isoenzime, but reboxetine inhibits it more, so there is also pharmacokinetic interaction. From the pharmacodynamic perspective, the 5HT neuron postsynaptic action through somatodendritic alpha 1 receptors is excitatory and makes NA act as an accelerator that stimulates 5HT liberation. Enhancing venlafaxine also inhibits dopamine reuptake, contributing to the confussional syndrome presented by the patient.

Despite its importance, SS is not properly taken into account many times and not recognizing it on time can potentially be very serious.

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Dental pain during repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation (rTMS) is being proposed as a non-invasive treatment with few side effects in patients with major depressive disorders [1,3,4,7]. The most common side effect of rTMS is the provocation of epileptic seizures [5,6], less frequently induction of migraine attacks, tension type headache or tinnitus [2] is reported. Stimulation over frontal areas can be uncomfortable for some subjects, due to local irritation of muscles and nerves underlying the stimulation coil [5]. The discomfort is related to the intensity and frequency of the stimulation [5]. Side effects at more distant locations are rarely reported.

A 57-year-old female patient with a 2-year history of major depressive disorder meeting ICD-10 criteria actually presented with a moderate depressive episode. In addition to psychopharmacotherapy (mirtazapine and lithium), rTMS treatment of the left dorsolateral prefrontal cortex was applied. The patient reported a pulsating, local dental twinge in the region of the upper left jaw correlated with the rTMS treatment. During the inter train interval the dental pain disappeared, but emerged again during the next train of stimuli. The intensity of pain gradually diminished during the course of treatment. The pain was found to be dependent on the stimulus intensity and remained despite repositioning the coil a few centimetres. In contrast, direct rTMS of the upper left jaw caused no pain. The physical examination of the oral region revealed no pathologies excepting a small amalgam restoration of the left upper second molar.

It remains unclear, which central or peripheral nerve structures might be involved in the generation of these pain sensations. Pain projected to the teeth via local irritation of the superficial temporal portion of the trigeminal nerve by the pulsating magnetic fields and projection via the *N. buccalis* into the dental region seems, to our mind, the most likely explanation for this phenomenon. A central pain origin, caused by irritation of the sensory cortex is considered to be less likely. In a patient with the sulcus centralis located more frontal than usual, stimulation of primary sensory areas is possible. However, this should cause sensations on the contralateral side and, so far, such sensations have not been reported. The amalgam inlay was intact and direct stimulation of the upper left jaw did not induce any pain in the dental region of the upper left jaw. Therefore, irritation of the local dental nerves by rTMS seems to be unlikely.

Our case showed that dental pain was a disturbing side effect of rTMS. Such side effects could be a reason for patients to cancel rTMS treatment. However, initial dental pain during rTMS may be tolerated by patients, if there was appropriate information provided prior to rTMS application. This case should draw more attention to possible side effects of rTMS. Accordingly, we recommend that patients be comprehensively informed about all possible side effects, infrequent or otherwise, related to rTMS therapy.

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