

Proconvulsant effects of high doses of venlafaxine in pentylenetetrazole-convulsive rats

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Abstract

Venlafaxine, an atypical antidepressant drug, has been used to treat several neurological disorders, presenting excellent efficacy and tolerability. Clinical seizures after venlafaxine treatment have occasionally been reported when the drug was used at very high doses or in combination with other medications. The aim of the present study was to investigate the convulsant effects of venlafaxine in rats under controlled laboratory conditions. Adult male Wistar rats (8 per group) receiving venlafaxine or saline at the doses of 25-150 mg/kg were subjected 30 min later to injections of pentylenetetrazole at the dose of 60 mg/kg. The animals receiving 75, 100 and 150 mg/kg venlafaxine presented increased severity of convulsion when compared to controls ($P = 0.02$, $P = 0.04$, and $P = 0.0004$, respectively). Indeed, an increased percentage of death was observed in these groups (50, 38, and 88%, respectively) when compared to the percentage of death in the controls (0%). The group receiving 150 mg/kg showed a reduction in death latency (999 ± 146 s) compared to controls (1800 ± 0 s; cut-off time). Indeed, in this group, all animals developed seizures prior to pentylenetetrazole administration. Surprisingly, the groups receiving venlafaxine at the doses of 25 and 50 mg/kg showed a tendency towards an increase in the latency to the first convulsion. These findings suggest that venlafaxine at doses of 25 and 50 mg/kg has some tendency to an anticonvulsant effect in the rat, whereas doses of 75, 100 and 150 mg/kg presented clear proconvulsant effects in rats submitted to the pentylenetetrazole injection. These findings are the first report in the literature concerning the role of venlafaxine in seizure genesis in the rat under controlled conditions.

Venlafaxine, an atypical antidepressant drug, has been used to treat several neurological disorders, including treatment-resistant depression (1), mild, moderate and severe depression, neuropathic pain (2), comorbid anxiety and depression (3), generalized anxiety, phobias, obsessive-compulsive

disorder, panic, attention-deficit/hyperactivity (4), and others. This antidepressant medication has shown excellent efficacy and tolerability (5), besides being the only antidepressant presenting therapeutic effects when used for acute treatment (6).

Several clinical studies have reported the

Key words

- Antidepressant
- Venlafaxine
- Convulsion
- Epilepsy
- Pentylenetetrazole

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occurrence of seizures after a venlafaxine overdose, but in half of these cases, multiple drug ingestion could be identified (7-11). On the other hand, premarketing data have shown that the risk of developing seizures with therapeutic venlafaxine doses seems to be remote (12,13). Thus, the aim of the present study was to determine whether venlafaxine has a proconvulsant effect in the well-known animal model of pentylenetetrazole-induced convulsion.

For this purpose we used 48 adult male Wistar rats (250-300 g) obtained from our own breeding colony, housed five to a cage with food and water available *ad libitum*, and maintained on a 12-h light/dark cycle (lights on at 7:00 am). Behavioral tests were conducted between 8:00 and 12:00 am. Five groups (N = 8) received venlafaxine hydrochloride (Effexor XR®, Wyeth Laboratory, São Paulo, SP, Brazil) dissolved in saline, *ip*, at the doses of 25, 50, 75, 100 and 150 mg/kg, respectively. The control group received saline. After 30 min, pentylenetetrazole (Sigma, St. Louis, MO, USA) was administered at the dose of 60 mg/kg, *ip*.

The following parameters were observed during the first 30 min: severity of convul-

sion, percentage of death per group, latency of death and latency to the first convulsion. Seizure was scored as follows (14): stage 0, no response; stage 1, ear and facial twitching; stage 2, convulsive twitching axially through the body; stage 3, myoclonic jerks and rearing; stage 4, rolling over onto a side position, wild running and wild jumping, and stage 5, generalized clonic-tonic convulsion. Latency to death was measured up to a cut-off time of 1800 s.

Statistical analysis for percent death per group was performed by the chi-square test. The other parameters were analyzed by the nonparametric Kruskal-Wallis test followed by the Mann-Whitney test. The level of significance was set at $P < 0.05$.

The group of animals that received venlafaxine at the doses of 75, 100 and 150 mg/kg presented increased severity of convulsion ($U = 4.0$, $P = 0.003$; for all groups) and percent death per group ($\chi^2 = 5.33$, $P = 0.02$; $\chi^2 = 3.69$, $P = 0.04$; $\chi^2 = 12.44$, $P = 0.0004$, respectively) when compared to controls. Venlafaxine significantly reduced the latency to death only at the dose of 150 mg/kg ($U = 4.0$, $P = 0.003$). Indeed, only at the latter dose did we observe a decrease of first convulsion latency. In this case, the animals developed seizures prior to pentylenetetrazole administration. Thus, this dose has a convulsant potential by itself. Surprisingly, although not significant, an increased convulsion latency was observed in the groups receiving venlafaxine at the doses of 25 and 50 mg/kg (see Table 1).

Venlafaxine is an antidepressant that blocks the reuptake of serotonin, noradrenaline and, to a lesser extent, dopamine. At low doses it acts only on serotonergic transmission, at moderate doses it acts on serotonergic and noradrenergic systems, whereas at high doses it affects serotonergic, noradrenergic and dopaminergic neurotransmission (15). These neurotransmitters play an important role in seizure genesis (16). Drugs that block serotonin and noradrenaline

Table 1. Convulsion severity, percentage of death per group, death latency and first convulsion latency in the animals treated with pentylenetetrazole and in the groups treated with pentylenetetrazole and venlafaxine at the doses of 25, 50, 75, 100 and 150 mg/kg.

Groups (N = 8)	Convulsion severity	Death (%)	Death latency (s)	First convulsion latency (s)
Saline	3 (3-3)	0	NA ¹	55 ± 2
Venla (25 mg/kg)	3 (3-3)	12	1665 ± 135	66 ± 4
Venla (50 mg/kg)	3 (3-3.5)	12	1636 ± 164	65 ± 5
Venla (75 mg/kg)	4 (4-4.5) ⁺	50*	1137 ± 256	52 ± 5
Venla (100 mg/kg)	4 (4-4.5) ⁺	38*	1281 ± 254	52 ± 4
Venla (150 mg/kg)	4 (4-5) ⁺	88**	999 ± 146 ⁺	NA ²

Latencies to death and to first convulsion are expressed as mean ± SEM and convulsion severity as median with range in parentheses. NA¹ = not available; no animal in this group died during the cut-off time to 1800 s. NA² = not available; all animals in this group developed seizures prior to pentylenetetrazole administration. Venla = venlafaxine.

* $P < 0.05$ and ** $P < 0.01$ (chi-square test).

⁺ $P < 0.01$ (Kruskal-Wallis test followed by the Mann-Whitney test).

reuptake seem to have anticonvulsant effects (16). Thus, this effect can explain the slight increase in convulsion latency observed at the doses of 25 and 50 mg/kg, but is not sufficient to account for an anticonvulsant property.

Because the proconvulsant effects of venlafaxine occurred in the rat only at high doses, the possibility is raised that they were due to a dopaminergic effect. Several studies have shown an important role of the dopaminergic system in seizure genesis. Dopaminergic receptor activation produced differential effects depending on the receptor subtype that was activated. The D₁ receptor family agonist generally enhances cortical excitability and favors the emergence of epileptogenic activity. In contrast, the D₂ receptor family agonist has more variable effects on cortical excitability and the expression of epileptiform discharges. Whilst it may be an oversimplification to characterize D₁ and D₂ receptors as mediating pro- and anticonvulsant influences in all experimental epilepsy syndromes, there is good reason to believe that stimulating D₁ and D₂ receptors is harmful and beneficial to man, respectively (17).

From a therapeutic viewpoint, D₂ receptor-blocking neuroleptics have a long history of epilepsy as a side effect, and the putative antiparkinsonian D₁ agonist induces fits in dopamine-depleted primates, which is predictive of its proconvulsant action in human patients (17).

Thus, we may speculate that the blockade of reuptake of dopamine by venlafaxine can exacerbate the D₁ postsynaptic dopaminergic receptor effects, thereby promoting a proconvulsant effect.

However, the proconvulsant effects of venlafaxine can also be attributed to other still unknown mechanisms of action of high doses of the drug.

In humans, the minimum effective dose of venlafaxine is 75 mg/day (1.07 mg/kg for a 70 kg patient), and the maximum dose is 375 mg/day (5.4 mg/kg). The manufacturer

(Effexor®) recommends starting at doses of 75 mg/day. This dose may be increased to 150 mg/day, depending on the patient's ability to tolerate the drug and the need for a further clinical effect. Patients receiving 300-375 mg/day showed the most treatment-related adverse effects. Therefore, the usual dose range is 75-200 mg/day, which appears to be adequate and desirable for most patients (18). There are several views concerning the proconvulsant effects of venlafaxine, but in these studies, other drugs were administered concomitantly, or venlafaxine was administered at a very high dose. Conway and Nelson (7) reported seizure occurrence in a patient receiving long-term bupropion, lithium and venlafaxine when submitted to electroconvulsive therapy. On the other hand, Bernardo and colleagues (19) found that combined venlafaxine and electroconvulsive therapy appears to be safe when used in depressive subjects. Schlienger et al. (8) also reported seizures in a patient who received venlafaxine and trimipramine, both at therapeutic doses. In this case, these authors speculated about the pharmacodynamic and pharmacokinetic interaction between these drugs involving the CYP2D6 isoenzyme. Ripple and colleagues (9) related the death of an alcoholic subject to developed seizure activity while being treated with tramadol, venlafaxine, trazodone and quetiapine. No metabolites were found, such as acetate, acetone, lactate and pyruvate, that would be characteristically found in a person with alcohol withdrawal syndrome. Thus, the authors suggested possible iatrogenic seizures. Indeed, Zhalkovsky et al. (10) reported a case of seizures in a 22-year-old Hispanic man who took 3 g of venlafaxine. The patient presented tonic-clonic activity and elevation of creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH). After 13 days, venlafaxine was restarted at 37.5 mg orally twice daily. The patient tolerated the return to venlafaxine without recurrence of seizures or elevation of CPK and LDH. In

another case (11), a patient took 26 venlafaxine tablets (50 mg each) and had a single episode of generalized seizure, but no further sequelae.

The present study is the first report in the literature concerning the role of venlafaxine in laboratory animal seizure genesis under controlled conditions. Redrobe and colleagues (20) demonstrated an antidepressant effect of venlafaxine in rats at doses of 8-64 mg/kg in the forced swimming test, an animal model of depression. In the elevated plus-maze and staircase task, two animal models of anxiety, venlafaxine seems to be effective at the doses of 10-50 mg/kg (Santos

Junior JG, Do Monte FHM, Russi M and Lanziotti VMNB, unpublished results). Thus, the proconvulsant effects of venlafaxine observed in the present study were related only to high doses of the drug. In the rat, the therapeutic and proconvulsant doses of venlafaxine seem to be almost within the same range, and a number of kinetic or dynamic factors influence the increased risk of convulsion. On this basis, considering the proconvulsant effects of venlafaxine as a possible side effect in humans and laboratory animals, some caution is needed when prescribing this drug.

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