Case Report

Similar Effects of Tramadol and Venlafaxine in Major Depressive Disorder

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Abstract: The analgesic tramadol has many characteristics in common with the antidepressant venlafaxine. The drugs are structurally similar, share both serotonergic and noradrenergic properties, and undergo a similar metabolic fate. In this study, a patient, who developed significant depression following cessation of tramadol after several years of therapy, is described. Her depression was then treated with venlafaxine with excellent response. It appears that tramadol may have provided a prophylactic antidepressant effect in this patient. Because of its similarities to venlafaxine, tramadol may possibly exert a degree of antidepressant effect in certain patients, particularly those with chronic pain.

Key Words: depression, pain control, tramadol, venlafaxine

Tramadol is a centrally acting analgesic that activates the μm-opioid receptor and possibly has GABA-ergic properties. It also enhances the action of serotonin and norepinephrine by interference with their reuptake and release mechanisms.[2] As such, in addition to pain control, the drug may potentially improve mood. A study of 5-HT_{2A} related behavior in mice[3] and a case report[4] suggest that tramadol may also be beneficial in the treatment of obsessive compulsive disorder (OCD).

Serotonin syndrome has occurred with combinations of tramadol and other agents which inhibit serotonin reuptake, including fluoxetine, paroxetine, venlafaxine, and mirtazepine.[5–7] Tramadol has been shown to induce some antidepressant-type effects in mice, which appeared to be related to tramadol's noradrenergic activity,[8] and it has been reportedly effective in augmenting treatment in 12 patients with major depressive disorder who had a partial response to selective serotonin reuptake inhibitors.[9] A 64-year-old man with OCD and depression refractory to several antidepressants demonstrated response to treatment with tramadol monotherapy.[10] Described here is a patient with major depressive disorder who appeared to have a similar positive response to tramadol and to venlafaxine.

Case Report

In 1989, Ms. A., a 41-year-old-female with no personal or family history of mental illness and no significant medical problems underwent a laminectomy for a herniated lumbar disc. Subsequently, she had chronic low back pain. By the year 2000, she was under treatment with tramadol 50 mg twice daily as needed, which controlled her pain well. In 2003, she began having mild intermittent feelings of sadness but not enough for her to think that she required treatment.

In mid-2005, Ms. A (then 57 years old) was found to have elevated liver enzymes without any identifiable liver disease. For this reason, her physician discontinued the tramadol and with time, her liver enzymes returned to normal. He began treating her with tizanidine 4 mg up to three times daily, as needed, which controlled her pain reasonably well, with her discomfort usually resulting in a rating of less than two on a ten point pain scale. However, within a few weeks of discontinuation of tramadol, she developed significant depression with anhedonia, feelings of helplessness, lack of energy, and insomnia.

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Key Points

- Tramadol is a centrally acting μm-opioid receptor agonist analgesic, which also enhances the action of serotonin and norepinephrine.
- Tramadol and venlafaxine are structurally similar and undergo a similar metabolic fate.
- Tramadol may exert a degree of antidepressant effect in some patients.
- Venlafaxine may be beneficial for the treatment of pain in certain individuals.

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She deteriorated to the point that she became suicidal and required hospitalization for one week. Her admitting diagnosis was major depressive disorder.

She was started on venlafaxine and the dosage titrated to 150 mg daily, with good response over a two to three week period. She subsequently continued to take the medication for several months, during which she did well. Her pain remained well-controlled with tizanidine. She then felt that she no longer needed an antidepressant and asked to stop taking it. The venlafaxine was tapered over a one-week period and then discontinued. Within a few weeks, she again developed significant depression with symptoms similar to those she experienced before. Venlafaxine treatment was resumed, resulting in a good response to the medication, which she continues to take at this time.

Discussion

Ms. A.'s rapid progression of depression concomitant with discontinuation of tramadol suggests that tramadol may have been providing a protective antidepressant effect in this patient. Tramadol is a racemic mixture of two enantiomers, (+)-tramadol and (−)-tramadol. Although the (+)-enantiomer is preferentially an inhibitor of serotonin reuptake, the (−)-enantiomer is a potent inhibitor of noradrenaline reuptake,[11] so both enantiomers could theoretically help alleviate depression. The (+)-tramadol enantiomer, and to a lesser degree, the (−)-enantiomer display opioid agonist properties. This μm-opioid agonist activity may also conceivably play a role in mood improvement, as case reports have described treatment of patients with refractory major depression with the μm-opiate agonists oxycodone and oxymorphone and the partial agonist buprenorphrine.[12,13] It has been proposed that the pathophysiology of depression in a subgroup of patients may be unrelated to abnormalities of central monoaminergic systems, but rather, results from dysfunction of the endogenous opioid system.[13] This hypothesis is consistent with the finding that the brains of depressed suicide victims show up to a nine-fold increase in the number of endogenous opioid receptors over age- and sex-matched controls postmortem, suggesting that opioid upregulation may be occurring in some treatment refractory populations because of a deficit of endogenous opioid neurotransmitter availability.[14]

The response of Ms. A.'s depression to venlafaxine was likewise favorable. There are a number of similarities between venlafaxine (which is also a racemic compound) and tramadol. Like tramadol, venlafaxine has been beneficial as a treatment for various pain syndromes.[15–17] Both venlafaxine and tramadol are associated with nausea, headache, and dizziness as prominent side effects. With metabolism, both drugs yield pharmacologically active *O*-desmethyl metabolites.[18,19] Structural similarities between the two drugs are striking and include a methoxyphenyl, a N,N-dimethylamino, and a hydroxycyclohexyl group found in each compound. These groups may assume near superimposable intermolecular orientations (depending on which enantiomers and conformations are compared). Thus venlafaxine and tramadol molecules may present comparable topographic displays for recognition by common receptor sites.[20] It is of interest that the genesis of venlafaxine as an antidepressant evolved from investigations of the structurally related analgesic ciramadol.[21]

Conclusion

Tramadol and venlafaxine are structurally similar racemic compounds, share both serotonergic and noradrenergic properties, and undergo a similar metabolic fate. Just as venlafaxine may be helpful with chronic pain in some individuals, tramadol may possibly exert a degree of antidepressant effect in certain patients, particularly those with chronic pain. Although its inhibition of serotonin and norepinephrine may be less potent than venlafaxine, tramadol deserves further clinical investigation of this potential usage.

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Differences of habit and language are nothing at all if our aims are identical and our hearts are open.

—J. K. Rowling, Harry Potter and the Goblet of Fire