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A case of discontinuation syndrome following the discontinuation of low-dose mirtazapine therapy in malignant lymphoma

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ABSTRACT

We report the case of a 69-year-old woman with malignant lymphoma who suffered from major depressive disorder. A low dose of mirtazapine (15 mg/day) brought about dramatic improvement in her mental status. However, after discontinuation of the mirtazapine, anxiety, restlessness, irritability, nausea, insomnia, imbalance and sensory disturbances occurred. When mirtazapine therapy was restarted, these symptoms resolved completely. These findings suggest that discontinuing even a low dose of mirtazapine might result in discontinuation syndrome, particularly in patients in poor physical condition. To the best of our knowledge, this is the first report describing a discontinuation syndrome due to the discontinuation of a low dose of mirtazapine.

Keywords: depression; discontinuation syndrome; mirtazapine; malignant lymphoma

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INTRODUCTION

The interruption of treatment with an antidepressant medication sometimes results in antidepressant discontinuation syndrome. Symptoms of antidepressant discontinuation syndrome can include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal. For all approved antidepressant agents, there have been case reports or warnings from the manufacturers of such reactions occurring in response to either abrupt discontinuation or medication tapering [1]. These medications include selective serotonin reuptake inhibitors (SSRIs) [2], tricyclic antidepressants [3], monoamine oxidase inhibitors (MAOIs) [4], venlafaxine [5], mirtazapine [6], and duloxetine [7]. Mirtazapine is a popular agent for treating depression in cancer patients [8], and it is considered an essential drug by the International Association for Hospice and Palliative Care. It has been reported that discontinuation of a high dose (60 mg/day) of mirtazapine could result in discontinuation syndrome. We recently encountered a case with malignant lymphoma who experienced discontinuation syndrome due to the discontinuation of even a low dose of mirtazapine.

CASE PRESENTATION

Ms. A, a 69-year-old inpatient with malignant lymphoma (stage IVA) was diagnosed with major depressive disorder according to DSM-IV-TR. Her performance status was 3 [symptomatic, > 50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours)]. She complained of depressive mood, anxiety and insomnia. Her depressive symptoms emerged 2 weeks after she was diagnosed. Her total Hamilton Depression Rating Scale 17 item version (HAMD-17)

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score was 20. She was treated with rituximab plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy for malignant lymphoma and etizolam (1.5 mg/day) for her depressive mood, insomnia and anxiety. Her depressive state gradually worsened. Her HAMD-17 score was 32 at 2 weeks after etizolam treatment initiation. Thus, mirtazapine (15 mg/day) and supportive psychotherapy were initiated 4 weeks after her depressive symptoms emerged, without changing her chemotherapy regimen. Her insomnia improved dramatically and her depressive symptoms also improved promptly, within a week. Her HAMD-17 score was 7. She stopped taking mirtazapine on her own following endoscopic examination because she felt she was oversedated, 7 days after mirtazapine treatment initiation, and continued taking only etizolam. She quickly experienced anxiety, restlessness, irritability, nausea, insomnia, imbalance and sensory disturbances, with electricshock like sensations, predominantly prickling sesnations, in the lower extremities, within 48 hours after mirtazapine discontinuation. Mirtazapine treatment was restarted at the same dose without changing the patient's other medications. Her symptoms completely resolved within 24 hours of mirtazapine treatment resumption. She continues to receive mirtazapine 15 mg.

DISCUSSION

We presented a case of discontinuation syndrome due to discontinuation of a low dose of mirtazapine. There are two other reports of withdrawal syndrome due to the discontinuation of mirtazapine, one in a 28-year-old male patient and one in a 25-year-old female patient who discontinued treatment with mirtazapine 60 mg [6, 9]. Both were young patients without physical diseases. On the other hand, the patient in the present study was elderly and in poor physical condition. Therefore, it is possible that age and physical condition might be factors affecting the emergence of discontinuation syndrome. Mirtazapine is metabolized by the cytochrome P450 (CYP) isozymes 2D6 and 3A4. However, vincristine inhibits CYP2D6 and CTP3A4. Accordingly, it is reasonable to assume that the withdrawal syndrome that was seen following the discontinuation of mirtazapine 15 mg/day was due to an increase in the mirtazapine concentration because of the inhibition of CYP3A4 by vincristine. In other words, the patient's mirtazapine concentrations might be higher than expected. Although the precise mechanism of the discontinuation syndrome is unknown, this pharmacokinetic interaction could be a factor. Another possibility is that when mirtazapine therapy is stopped, the 5HT2, 5HT3 and H1 receptors are no longer occupied, and synaptic serotonin is suddenly decreased, which may induce withdrawal symptoms such as anxiety, insomnia, and nausea. In any case, clinicians should exercise caution when tapering or stopping mirtazapine therapy, even low-dose therapy, particularly in patients who are elderly, in poor physical condition, or using vincristine. Incorporating a 7.5 mg treatment step might prevent the emergence of withdrawal syndrome in such cases.

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