Serotonin Syndrome Induced by Combined Use of Mirtazapine and Olanzapine Complicated with Rhabdomyolysis, Acute Renal Failure, and Acute Pulmonary Edema—A Case Report

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Abstract

Purpose: Serotonin syndrome is a potentially life-threatening complication of serotonergic agents. Although mirtazapine is a relatively safe antidepressant and has a comparatively low incidence of side effects, it still could induce serotonin syndrome.

Case Report: We described a 34-year-old man with schizophrenic disorder who presented with acute consciousness disturbance, extremely high fever, rigidity, and spontaneous clonus in lower limbs. Two days before entry, oral mirtazapine was added to his regular medication of olanzapine. The serotonin-related symptoms resolved soon after withdrawal of mirtazapine and olanzapine combined with treatment with intravenous benzodiazepine and oral cyproheptadine. However, the clinical course was complicated by rhabdomyolysis, acute renal failure, and acute pulmonary edema. After receiving mechanical ventilation, hemodialysis, and appropriate supportive treatment, his general condition recovered and he was discharged without any neurological sequelae.

Conclusion: With the increasing use of serotonergic agents, awareness of serotonin syndrome is important. Early diagnosis and timely discontinuation of the offending agent(s) are imperative to prevent morbidity and mortality.

Key Words: antidepressant, mirtazapine, olanzapine, rhabdomyolysis, serotonin syndrome

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INTRODUCTION

Serotonin syndrome is a potentially fatal adverse drug reaction of serotonergic medications. Knowledge of serotonin syndrome may help in the early recognition of this syndrome, allowing for timely intervention to resolve it[(1)]. The spectrum of serotonin syndrome, which encompasses manifestations of excessive intrasynaptic serotonin, ranges from minor symptoms to death. The classic triad symptoms of serotonin syndrome consist of alteration of mental status, neuromuscular hyperactivity, and autonomic instability, but not all of these findings are

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consistently present in all patients with this syndrome[2]. Serotonin syndrome should be considered in patients taking serotonergic medications who presented with altered mental status.

The list of serotonergic agents causing serotonin syndrome is long. It is reported with single or combined use of selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, norepinephrine dopamine reuptake inhibitors, monoamine oxidase inhibitors, opioids, and tricyclic antidepressants, which leads to excess intrasynaptic serotonin[3]. On the contrary, mirtazapine, a different kind of antidepressant, does not significantly increase serotonin concentration[4]. It is a potent antagonist of central alpha 2-adrenergic autoreceptor and an antagonist of postsynaptic 5-HT2 and 5-HT3 receptors[5]. It is therefore classified as a noradrenergic and specific serotonergic antidepressant. Mirtazapine has a comparatively low incidence of side effects, such as drowsiness, sedation, increased appetite, and weight gain[5-7]. Although mirtazapine is a relatively safe antidepressant, there are still sporadic case reports of mirtazapine-induced serotonin syndrome due to either monotherapy or combined therapy with other serotonergic agents[8-15]. To the best of our knowledge, there has been no report of mirtazapine-induced serotonin syndrome in Taiwan. We herein describe a case of serotonin syndrome due to combined therapy with mirtazapine and olanzapine.

CASE REPORT

A 34-year-old man presented to the emergency room with acute consciousness disturbance. According to his family, he had a history of schizophrenic disorder for over ten years, for which he took oral olanzapine 5 mg once per day. Two days before entry, oral mirtazapine 30 mg once per day was added to the regimen. He was comatose on arrival with a blood pressure of 61/31mm Hg, a pulse rate of 145 beats per minute, a respiratory rate of 18 per minute, and a body temperature of 42.2°C. Profound sweating, rigidity of four limbs, and frequent spontaneous clonus in lower limbs were observed. The electrocardiogram showed sinus tachycardia. The non-contrast brain computed tomography scan was not remarkable. The hemogram showed a hemoglobin of 11.4 g/dL, a white blood cell count of 8.59×10^9/L with 88.9% neutrophils, and a platelet count of 159×10^9/L. A significant elevation of serum creatine kinase (46814 [62-287] U/L) was found with presence of myoglobin in the urine. The serum aspartate transaminase was 759 (8-38) U/L, the alanine transaminase 115 (4-44) U/L, blood urea nitrogen 31.9 (5-23) mg/dL, and creatinine 1.9 (0.5-1.3) mg/dL. The serum concentrations of sodium and potassium were within normal limits.

A diagnosis of serotonin syndrome with rhabdomyolysis was highly suspected on the basis of the case history and presentation. His regular medications were stopped. He received intravenous benzodiazepine, including 10 mg of diazepam and 4 mg of lorazepam, and oral cyproheptadine therapy immediately. His body temperature was reduced to 36.6°C eight hours later. But acute renal failure and acute pulmonary edema developed as complications of rhabdomyolysis. He was intubated with mechanical ventilatory support for five days and underwent two emergency hemodialysis treatments. His acute renal failure and acute pulmonary edema resolved, and he made a full recovery. He was discharged from the hospital 25 days after admission without any neurological sequelae.

DISCUSSION

Serotonin syndrome is a disorder arising from an increase in intrasynaptic serotonin. Its diagnosis is challenging because the clinical spectrum of this syndrome varies widely from benign to lethal. In our case, the extremely high body temperature and frequent clonic movements induced by serotonin syndrome led to the complications of rhabdomyolysis, acute renal failure, and acute pulmonary edema, which could be life-threatening if not treated appropriately. Clinical symptoms of serotonin syndrome usually occurs soon after initiating therapy with a serotonergic agent, increasing the dosage of current serotonergic agent, or following overdose, and up to 60% of patients presented to the hospital within six hours[16]. Our case followed the typical clinical course, with development of symptoms soon after the add-on of mirtazapine.

The first case of mirtazapine-associated serotonin syndrome was reported in 1998 by Benazzi, who described a patient treated with mirtazapine–fluoxetine

combination[8]. Since then, a few cases of mirtazapine-associated serotonin syndrome, due to either mirtazapine monotherapy or combined therapy with other drug(s), have been documented in the literature[9-15]. Table 1 gives the features of these cases. All cases, except the one reported by Duggal et al[12] and our case, occurred with mirtazapine monotherapy or combined use of mirtazapine and another serotonergic agent. The case described by Duggal et al was precipitated by the addition of olanzapine to a mirtazapine and tramadol combination[12]. On the contrary, our case developed serotonin syndrome after mirtazapine was added to olanzapine treatment. Up to now, no case of mirtazapine-associated serotonin syndrome has been reported in Taiwan, although this syndrome has been found to be associated with the use of venlafaxine[17], citalopram[18], amantadine[19], and meperidine[20].

The incidence of serotonin syndrome is expected to rise in association with the growing number of

Table 1. Clinical characteristics and outcomes of reported cases of mirtazapine-associated serotonin syndrome.

Author	Culprit medications	Symptoms	Treatment	Outcome
Benazzi F[8]	Mirtazapine and fluoxetine	Dizziness, headache, nausea, agitation, walking difficulty, tremor, insomnia	Discontinuation of mirtazapine	Complete recovery
Hernandez JL, et al[9]	Mirtazapine	Mental change, diaphoresis, fever, tachycardia, hypertension, cogwheel rigidity, tremor, myoclonus, hyperreflexia	Discontinuation of mirtazapine, supportive treatment	Significant improvement with residual mild rigidity
Demers JC, et al[10]	Mirtazapine and fluvoxamine	Restlessness, tremor, twitching, flushing, diaphoresis	Discontinuation of all medications, oral cyproheptadine and acetaminophen, supportive treatment	Complete recovery
Dimellis D[11]	Mirtazapine and venlafaxine	Mental change, fever, hypertension, diaphoresis, tremor, hyperreflexia	Discontinuation of all medications, oral lorazepam and propranolol, supportive treatment	Complete recovery
Duggal HS, et al[12]	Mirtazapine, tramadol, and olanzapine	Confusion, tachycardia, facial flushing and twitching, tremors, myoclonus, hyperreflexia, ataxia	Discontinuation of all medications	Complete recovery
Ubogu EE, et al[13]	Mirtazapine	Mental change, orobuccal dyskinesia, ataxia, tremor, cogwheel rigidity	Discontinuation of mirtazapine, supportive treatment	Significant improvement with residual mild dysarthria and rigidity
Houlihan DL[14]	Mirtazapine, tramadol, and venlafaxine	Mental change, fever, hypertension, diaphoresis, myoclonus, hyperreflexia	Discontinuation of all medications, supportive treatment	Complete recovery
DeBellis RJ, et al[15]	Linezolid, mirtazapine, and citalopram	Mental change, fever, tachycardia, hypertension, tremor	Discontinuation of linezolid	Complete recovery
Wu, et al (The present case)	Mirtazapine and olanzapine	Mental change, fever, tachycardia, hypotension, profound sweating rigidity, spontaneous lower limb clonus	Discontinuation of all medications, intravenous diazepam and lorazepam, oral cyproheptadine, supportive treatment	Complete recovery

serotonergic agents on the market and the increasing use of these agents in clinical practice. However, the incidence of serotonin syndrome is likely to be underestimated because this syndrome may be misdiagnosed as another disorder if the attending physicians do not have this entity in mind. An earlier study found that over 85% of general practitioners were unaware of serotonin syndrome[1]. Clinical diagnostic criteria have been developed, including the Sternbach criteria[21], the Radomski criteria[22], and the Hunter serotonin toxicity criteria[23]. Among them, the Sternbach criteria, despite less specific, is useful for early recognition of serotonin syndrome, whereas the Hunter serotonin toxicity criteria are much more specific for features that only relate to serotonin toxicity[24]. The clinical presentation of our case, including mental status change, spontaneous clonus in lower limbs, diaphoresis, elevated temperature, tachycardia, and rigidity, fulfilled the Sternbach and the Hunter criteria and were compatible with severe serotonin syndrome according to the Radomski criteria.

The disorder most often confused with serotonin syndrome is neuroleptic malignant syndrome because they share similar clinical features, such as fever, extrapyramidal symptoms, and impaired consciousness. A detailed medication history, careful observation of clinical signs, and neurological examination can often help clinicians differentiate between these situations without much difficulty. First, serotonin syndrome is triggered by medications with serotonergic activity, whereas neuroleptic malignant syndrome is caused by medications with dopamine blocking properties. Second, the time courses of these two syndromes are different. The onset of serotonin syndrome is faster and its duration is shorter as compared to neuroleptic malignant syndrome.

Nevertheless, patients with either syndrome, as in our case, often have a history of psychiatric illness and report current use of psychiatric medications. Medication histories that are positive for both serotonergic agents and dopamine antagonists make it difficult to distinguish between serotonin syndrome and neuroleptic malignant syndrome. In this diagnostic dilemma, a laboratory profile of a low serum iron level, coupled with elevations in creatine kinase, liver function tests, and white blood cell count, might be more indicative of neuroleptic malignant syndrome[25].

Because we did not test serum iron level in our case, we could not make any differential diagnosis based on the laboratory results. However, a diagnosis of serotonin syndrome was more appropriate for our case because his symptoms started just two days after mirtazapine was added to long-term olanzapine treatment. Some might argue that the elevation of serum level of olanzapine due to pharmacokinetic interaction between mirtazapine and olanzapine could have precipitated neuroleptic malignant syndrome. We considered that this possibility was low because the effect of mirtazapine on the steady-state plasma concentration of olanzapine is negligible[26].

Although discontinuation of the causative agent(s) and supportive measures of fluid replacement, fever reduction, and as-needed support of cardiac, respiratory, and renal function are the mainstays in the treatment of both syndromes[25], the differentiation between the two syndromes still has important therapeutic implications. Bromocriptine, a dopamine agonist that is frequently used in the treatment of neuroleptic malignant syndrome, has been reported to be associated with serotonin syndrome[27]. If serotonin syndrome is misdiagnosed as neuroleptic malignant syndrome, bromocriptine use may worsen serotonergic signs[28].

CONCLUSION

With the increasing use of serotonergic agents in clinical practice, serotonin syndrome will be more often encountered. Awareness of this potentially life-threatening syndrome is important to physicians, especially who prescribe serotonergic agents and who are involved in the critical care medicine and emergency medicine. A detailed review of medication history along with careful observation of clinical presentation should prompt the diagnosis of serotonin syndrome. Early identification of this syndrome, timely discontinuation of the offending agent(s), and adequate supportive treatment can prevent morbidity and mortality.

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