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[Case Report]

# SEROTONIN SYNDROME CAUSED BY MINIMUM DOSES OF SSRIS IN A PATIENT WITH SPINAL CORD INJURY

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**Abstract**: There have been only a few reports of serotonin syndrome developing after mono-therapy with a selective serotonin reuptake inhibitor (SSRI). We report a case of serotonin syndrome caused by long-term therapy with fluvoxamine prior to treatment with paroxetine. An 18-year-old man with spinal cord injury (SCI) at thoracic level 2-3 presented with onset of serotonin syndrome after taking fluvoxamine (50 mg per day) for 8 weeks prior to treatment with paroxetine (10 mg per day) for 6 days. He had confusion, agitation, severe headache, tachycardia (124 beats/minute), hypertension (165/118 mmHg), high fever (39.1°C), and myoclonus. All of the symptoms disappeared within 24 hours after discontinuation of administration of paroxetine. This is an interesting case of serotonin syndrome that developed after minimum doses of single therapy with an SSRI in a patient with SCI.

**Key words**: Fluvoxamine, Paroxetine, Serotonin syndrome, Spinal cord injury

## INTRODUCTION

Many patients with spinal cord injury (SCI) experience depressive feelings because they cannot accept their illness and they feel hopeless for their future.[1)] Selective serotonin reuptake inhibitors (SSRIs), new antidepressant agents, are recommended for treatment of depression because they have fewer side effects than those of tricyclic antidepressants (TCAs). However, different combinations of drugs that can affect the serotonergic system, such as TCAs, SSRIs and monoamine oxidase (MAO) inhibitors, induce severe toxicity referred to as "serotonin syn-

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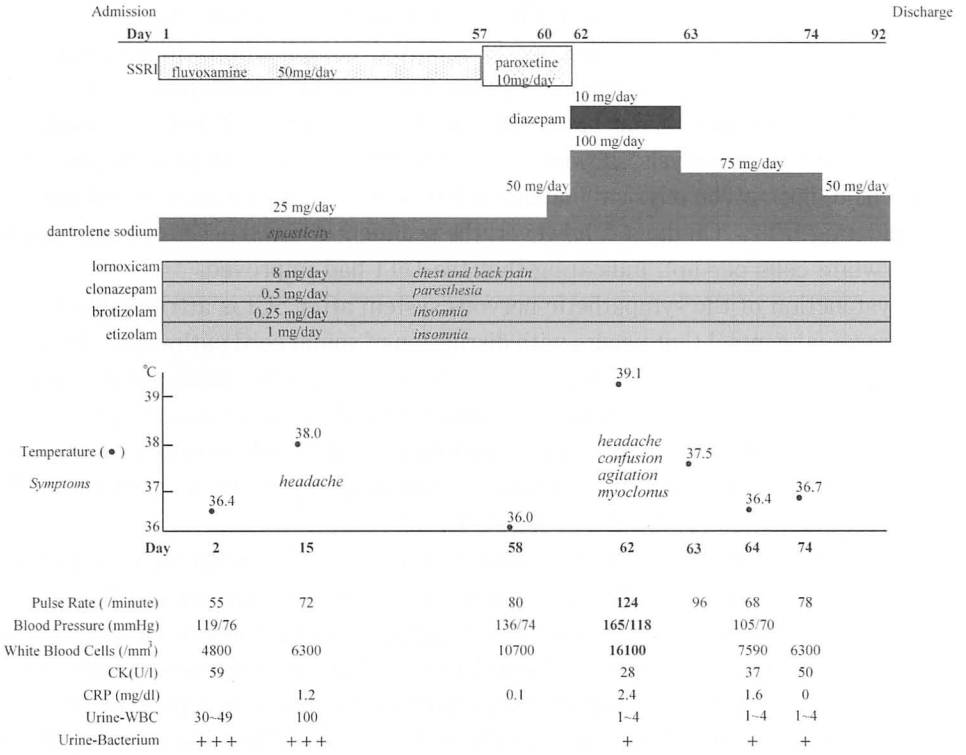
drome".[2] In Japan, two SSRIs, fluvoxamine and paroxetine, have been commercially available since 2000. The usual doses of fluvoxamine and paroxetine used in Japan are 50-150 and 10-40 mg/day, respectively. To our knowledge, there are only two reports[3,4] of serotonin syndrome induced by mono-therapy with SSRIs. Our patient had damage to the spinal cord at thoracic 2 and 3 (T2-3) levels caused by a motor vehicle accident and his depression was treated with fluvoxamine at the usual dose (50 mg per day) for 8 weeks. Six days after switching to paroxetine, he had an abrupt onset of serotonin syndrome. We discuss briefly why such low doses of SSRIs induced serotonin syndrome in our patient with SCI.

## CASE REPORT

An 18-year-old Japanese man who had no previous medical history was involved in a motor vehicle accident. There were four young men in the car. He was not the driver. He was diagnosed as having a complete fracture dislocation at the T2-3 level with immediate and complete paraplegia. Thirteen weeks after the accident, he was admitted to our hospital. Depressive symptoms such as depressive mood and insomnia were observed. His statements to us included "I was the only one injured in the accident.", "Now I am a physically handicapped person.", and "I could not prevent the accident." We diagnosed him as depressive mood, he was treated with fluvoxamine at a dose of 50 mg per day. He was also given dantrolen to depress spasticity, a non-steroidal anti-inflammatory drug (lornoxicam) to control back pain, an anti-epileptic (clonazepam) to relieve paresthesia of bilateral legs, and sleeping medication (brotizolam and etizolam) for insomnia, as shown in Figure 1.

He started rehabilitation consisting of physical therapy and massage therapy. He was given trigger-point injections twice a week for treatment of pain with stiffness around the bilateral shoulder girdles. His gait improved after ambulation exercise. However, spasticity in his legs and chest oppression increased with recovery of muscle power. Almost every night, he was anxious about his future and became angry at the slightest provocation. At night on the 49th day, he tried to commit suicide. In addition, he had sudden attacks of somatic symptoms such as shaking, sensation of smothering, chest pain and paresthesia of his back. From these symptoms, we diagnosed him as panic disorder.[5] On the 57th day, fluvoxamine was replaced with paroxetine (10 mg/day), which has been shown to be effective for treating panic disorder.[6] On the 60th day, the spasticity and chest oppression were very severe. In the evening 6 days after the start of paroxetine treatment, he had fever (39.1°C), elevation in blood pressure (165/118 mmHg) and tachycardia (124 beats/minute), and blood chemistry findings were serious, as shown in Figure 1. Serum electrolyte values were as follows: sodium 142.5 mEq/l, potassium 4.13 mEq/l, chloride 105.7 mEq/l. Specific mental and physical changes observed were confusion, agitation, disorientation, and myoclonus. Ten mg of




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pulse Rate ( /minute) | 55 | 72 | 80 | **124** | 96 | 68 | 78 |
| Blood Pressure (mmHg) | 119/76 | | 136/74 | **165/118** | | 105/70 | |
| White Blood Cells (/mm$^3$) | 4800 | 6300 | 10700 | **16100** | | 7590 | 6300 |
| CK(U/l) | 59 | | | 28 | | 37 | 50 |
| CRP (mg/dl) | | 1.2 | 0.1 | 2.4 | | 1.6 | 0 |
| Urine-WBC | 30~49 | 100 | | 1~4 | | 1~4 | 1~4 |
| Urine-Bacterium | +++ | +++ | | + | | + | + |

Figure 1. Clinical findings and time course.
The patient was given additional medications according to his symptoms such as lornoxycam for treatment of pain, clonozepam for treatment of paresthesia, and brotizolam and etizolam for treatment of insomnia.
CK, creatine kinase; CRP, C-reactive protein.
Urine-Bacterium is expressed as number of bacteria per high power field (×400).
+, less than 10; ++, less than 200; +++, More than 200

diazepam was administered intravenously, and the dose of dantrolene was increased to 100 mg. One hour later, his temperature had decreased to 37.5°C and his pulse rate had decreased to 96 beats/minute. Within 24 hours after the last administration of paroxetine, all symptoms had disappeared. The present case was diagnosed as serotonin syndrome. The diagnosis was based on three of Sternbach's symptomatic criteria[2], that is, cognitive/behavioral changes (confusion and agitation), autonomic instability (hyperthermia and tachycardia) and neuromuscular changes (myoclonus), together with laboratory data and the disappearance of symptoms within 24 hours.

## DISCUSSION

It is essential to eliminate alternative possibilities before setting on a diagnosis of setoronin syndrome. Alternative diagnoses include autonomic dysreflexia trig-

gered by urinary tract infection (UTI) and neuroleptic malignant syndrome.

UTI is one of the most frequently reported complications in patients with chronic SCI with neurogenic bladder dysfunction.[7] UTI induces fever and chills in such patients. On day 15, our patient also had a temperature of 38°C and headache. The sediment of urinalysis showed 3+ of bacteria and 100 white cells per high-power field (hpf). The physical findings and results of clinical tests were interpreted as indicating UTI. On day 62, however, the sediment showed a 1+ of bacteria and 1 to 4 white cells per hpf, indicating that the UTI had improved.

Dysfunction of the sympathetic nervous system after SCI is attributable to loss of supraspinal control that occurs with disruption of spinal cord pathways. Patients with SCI above thoracic level 6 cause hypotension and reflex bradycardia/cardiac arrest through autonomic dysfunction. Autonomic dysreflexia is a symptom complex characterized by a sudden exaggerated increase in blood pressure accompanied by bradycardia in response to a stimulus originating below the level of the SCI.[8] However, our patient had tachycardia (124 beats/min).

Serotonin syndrome is most frequently confused with neuroleptic malignant syndrome. Neuroleptic malignant syndrome, which is characterized by mental status changes, hyperthermia, rigidity, elevated CK, and autonomic dysfunction, is similar to serotonin syndrome. Neuroleptic malignant syndrome results from exposure to neuroleptic drugs that block dopamine receptors or deplete dopamine.[9] However, our patient did not take any dopamine receptor blocking agents, and CK level was normal.

At 6 days after switching to paroxetine from fluvoxamine, the patient developed confusion, agitation, disorientation, tremor, and myoclonic movement such as uncontrolled leg shaking. Switching to paroxetine from fluvoxamine is performed in clinic frequently. However, serotonin syndrome dose not occur usually by switching to paroxetine from fluvoxamine. Consequently, we think that specificity of our patient caused serotonin syndrome.

SSRIs such as paroxetine and fluvoxamine are metabolized by the isozyme of the hepatic microsomal cytochrome P450, CYP2D6. Lornoxicam and etizolam are substrates for CYP2C9, and brotizolam and clonazepam are substrates for CYP3A4. However, fluvoxamine is not only a substrate for metabolism by the CYP system but also an inhibitor of metabolic clearance of other drugs. Notable inhibitory interactions of fluvoxamine with CYP1A2, CYP3A4, CYP2D6 and CYP2C19 have been reported.[10]

Relationship between doses and plasma concentration of SSRIs, it is pointed out that there are nonlinear curves both paroxatine[11] and fluvoxamine.[12] In addition, there was a significant effect of the CYP2D6*10 allele on plasma paroxetine concentration at low doses.[11] In the present case and Lenzi's case, the plasma level of fluvoxamine would have been sufficiently elevated to cause onset of the syndrome during long-term therapy. Switching to paroxetine or increasing the dose of fluvoxamine could trigger the onset of serotonin syndrome. A sudden plasma

concentration rise can occur by addition of minimum dose of paroxetine. We have no information on CYP2D6 genotype of our patient. However, this case leads us to believe that our patient was a poor metabolizer of paroxetine according to low activity of CYP2D6 hereditarily.

Since an increasing number of SCI patients with depressive mood are being treated with serotomimetic agents, heightened awareness of potential drug interactions leading to the serotonin syndrome is necessary.

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