Serotonin Syndrome with Rhabdomyolysis: A Case Report and Recommended Prevention

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ABSTRACT

Serotonin syndrome is a severe but preventable adverse drug reaction. This syndrome is rare and usually underrecognized. It is resulted from the excessive serotonin receptor stimulation, mostly by combination of serotonergic agents. The clinical triads are altered mental status, autonomic dysfunction and neuromuscular abnormalities. Occasionally, severe cases of serotonin syndrome are complicated by rhabdomyolysis and other potentially life-threatening conditions. In this report, we describe a 22-year-old man presenting with serotonin syndrome and rhabdomyolysis from serotonergic drug interaction. In addition, recommendation of preventive strategies is included.

Keywords: Serotonin syndrome; Neuroleptic malignant syndrome; Rhabdomyolysis

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CASE REPORT

A 22-year-old man with a history of bipolar disorder for 6 months was treated with lithium carbonate 300 mg/day and paroxetine 40 mg/day. He had poor drug compliance and his last pills were three days before admission. He had had a watery diarrhea for three weeks and went to a district hospital. From there he received fluoxetine 20 mg, sertraline 50 mg, amitryptyline 10 mg, atenolol 50 mg, norfloxacin 400 mg. Two hours after taking the medications he had dizziness, agitation, worsening of his diarrhea as well as intermittent painful muscle spasm; hence, he immediately came to Siriraj Hospital. On physical examination, the vital signs were blood pressure 187/117 mmHg, heart rate 150 beats/minute, respiratory rate of 24 per minute, and a temperature of 36.5°C. The patient had profound sweating, shivering, intermittent painful muscle spasm, and generalized hyperreflexia. Other neurological signs were normal. Laboratory data were significant for elevated white blood cell count (30,500 cells/mm^3), hematocrit (56.6%), creatine kinase (14,350 U/L), aspartate aminotransferase (132 U/L), and uric acid (10.4 mg/dL). His psychotropic drugs were discontinued. Intravenous fluid was started and he was monitored for his vital signs as well as urine output.

Within several hours the patient felt substantially improved and his vital signs returned to normal levels. On the following day he fully recovered, his diarrhea disappeared and creatine kinase decreased to 7,272 U/L, 3,845 U/L and 1,714 U/L on the second, third and fourth day of admission, respectively. He was discharged with complete recovery on day 5 after admission.

DISCUSSION

In this case, the diagnosis of serotonin syndrome was made on the history of exposure to serotonergic agents and on clinical grounds. The patient had the clinical triad of serotonin syndrome which were mental (dizziness and agitation), autonomic (hypertension, tachycardia, diaphoresis and diarrhea) and neuromuscular manifestations (painful muscle contraction and hyperreflexia). His symptoms occurred suddenly (2 hours) after drug ingestion and he recovered rapidly (over several hours) after drug discontinuation. The complication of serotonin syndrome in this case was rhabdomyolysis which was an uncommon manifestation. The cause of this syndrome in the patient was the combination of the selective serotonin reuptake inhibitors (SSRIs), lithium and tricyclic antidepressant.

Serotonin syndrome is an iatrogenic condition characterized by a sudden onset of mental changes, autonomic dysfunction and neuromuscular abnormalities.[1-6] The early cases of this syndrome were: the patients received L-tryptophan and a monoamine oxidase inhibitors (MAOI). In more recent cases the patients took tricyclic antidepressants (TCAs) with MAOI. With the advent of the SSRIs, there have been a number of reports of this syndrome in more recent literature. Serotonin syndrome usually occurs when two or more serotonergic agents which are used in combination; however, the cases have been reported after a single agent therapy.[7-11]

Serotonin syndrome is the result of the excess of serotonin causing overstimulation of serotonin (5-HT) receptors, especially the 5-HT1A receptor. Currently, there are seven major types of 5-HT receptors including the 5-HT1 (subtypes A, B, C, D, E, F), 5-HT2 (subtypes A, B, C), 5-HT3 to 5-HT7.[12] A stimulation of 5-HT1A-receptors results in repetitive behaviors such as chewing, licking, myoclonus, hyperreflexia, and mental status changes.[13] A stimulation of the 5-HT2-receptors contributes to platelet aggregation, vasoconstriction resulting in the increases in blood pressure and heart rate, and behavioral as well as cognitive changes. In addition, an activation of the 5-HT2-receptors may cause broncho-

TABLE 1. The mechanisms of serotonin syndrome and causative medications.[1,2]

Mechanisms	Associated medications
Increased substrate supply	L-tryptophan, 5-hydroxytryptophan
Increased serotonin release	Amphetamine and derivatives, cocaine, reserpine, tetrabenazine, levodopa, MAOIs
Reduced reuptake of serotonin	SSRIs, trazodone, nefazadone, venlafazine, TCAs, bupropion, dextromethorphan, tramadol, meperidine, sibutamine, cocaine, amphetamine and derivatives
Inhibition of serotonin metabolism	MAOIs
Postsynaptic receptor stimulation	Buspirone, sumatriptan, zolmitriptan, naratriptan, rizatriptan, lithium, carbamazepine

spasm and incoordination because of its presence in the lung and the cerebellum.[1] Moreover, a stimulation of the 5-HT3 receptors causes diarrhea, nausea and abdominal pain.[14] No single receptor appears to be responsible for the development of the serotonin syndrome and several neurotransmitter systems may be implicated. Serotonin syndrome can occur by several mechanisms, triggered by medications as shown in Table 1. Additionally, pharmacokinetic reactions can also cause the syndrome. For example, fluoxetine and paroxetine are potent inhibitors of cytochrome (CYP) 2D6, being administered they increase their potential to invoke toxic serum levels of other serotonergic medications metabolized through this system.[1]

A diagnosis of the syndrome is based on clinical judgement. Typically, it consists of a triad of symptoms, i.e., mental, autonomic and neuromuscular manifestations. It usually has a sudden onset of less than 24 hours after the introduction of a serotonergic agent (50% within two hours; 75% within 24 hours).[5,15] Mental symptoms, including confusion, elevated mood, coma or semicoma, agitation, nervousness and insomnia, are observed in approximately 40% of the patients.[15,16] Autonomic symptoms are fever (26.8%), diaphoresis (48.8%), tachycardia (44%), mydriasis (19.5%), nausea/vomiting (26.8%), diarrhea (9.7%) and low or high blood pressure (5-35%).[5] Neuromuscular symptoms are seen in 50% of the patients, e.g., myoclonus, tremors, chills, rigidity, hyperreflexia, impaired co-ordination, mydriasis, and akathisia.[15] Life threatening complications can occur in severe cases. The complications are disseminated intravascular coagulation, leucopenia, thrombocytopenia, seizure, multi-organ failure, rhabdomyolysis, hyperkalemia, renal failure as well as acidosis and respiratory failure.[1-4,17-19]

Laboratory tests are not useful in the diagnosis of serotonin syndrome. Drug levels are often within acceptable limits. Elevations in white blood cells, creatine kinase levels, and liver enzymes are possible in some cases.[1-3]

Serotonin syndrome is generally self-limited, resolving rapidly after the discontinuation of causative agents. Seventy percent of cases recover within 24 hours; however, 40% may require ICU admission, and 25% may need intubation. The mortality rate is 2.5%.[15]

There are several differential diagnoses with serotonin syndrome. The principal one is neuroleptic malignant syndrome (NMS) because these two disorders share common manifestations and patients taking SSRIs are also frequently on neuroleptics.[1-6] The clinical differences of these two syndromes are shown in Table 2.

The treatment of serotonin syndrome begins with immediate withdrawal of the causative medication. The treatment is primarily supportive such as intravenous hydration, reduction of muscle contraction (by benzodiazepine) and careful monitoring of autonomic instability as well as other threatening complications.[1,3] Beta-blockers with 5-HT1A-receptor blocking properties (propanolol and pindolol) can reverse some of the neuromuscular and autonomic complications and are particularly useful in controlling tachycardia and hypertension.[1,21] Nonspecific 5-HT2 blockers, including methysergide, cyproheptadine and phenothiazines, appear to be safe and may be effective.[3,5,18,22]

How to prevent serotonin syndrome

Prevention of serotonin syndrome is crucial, as it is one of an iatrogenic diseases that can be prevented.[1] The strategies to help preventing serotonin syndrome and its complications include the following:

1. Patients must be educated to avoid self-medication.

2. The use of MAOIs in combination with TCAs, SSRIs, and sumatriptan is contraindicated. After discontinuing SSRIs, it is crucial to wait at least two weeks before initiating an MAOI. The only exception to this rule

TABLE 2. Demonstrates clinical differences between NMS and serotonin syndrome.[1-4,6,20]

Clinical differences	NMS	Serotonin syndrome
Precipitating factors	Sudden withdrawal of dopaminergic agents or introduction of agents that block dopamine signaling (eg, neuroleptics and antiemetics)	Combination of agents that potentially stimulate serotonin receptors such as SSRIs and MAOIs
Onset	Slower; 3-9 days following an addition of a neuroleptics	Sudden, within 24 h (in 75% of cases) following the addition of a serotonergic agent
Mental status	Stupor, alert mutism, coma	Agitation, coma
Autonomic symptoms	Hyperthermia (>38°C)	Dilated pupils, diarrhea, diaphoresis, vomiting
Neuromuscular symptoms & signs	Akinesia, extrapyramidal rigidity	Shivering, ataxia, myoclonus, hyperreflexia, ankle clonus, Barbinski sign, nystagmus
Elevation of WBC, LFT and muscle enzymes	Common	Less frequently
Recovery	Slower, days to weeks	Rapid, 70% within 24 h
Mortality	15-20%	2.5%

is in the use of fluoxetine which requires five weeks because of its long half-life. In switching from MAOIs, a 2-week drug washout period is required before starting an SSRI. Meclobemide, being the exception in this case, requires only 24-hour washout period because it reversibly inhibits MAO.

3. Avoid pharmakokinetic interaction between drugs metabolized by cytochrome P450 systems. The addition of a drug that inhibits cytochrome isoforms CYP2D6 and CYP3A4 to the therapeutic SSRI regimens can cause serotonin syndrome. Fluoxetine, paroxetine, sertraline, and nefazodone may increase other medications being substrates of this enzymatic system. Fluoxetine and paroxetine are potent inhibitors of the CYP2D6 system, hence they might increase serotonergic metabolites when combined with trazodone and nafazodone. Paroxetine and fluvoxamine inhibit the liver enzymes for the metabolism of TCAs, thus they increase the risk of serotonin syndrome. Patients being treated with SSRIs should not be prescribed meperidine, fentanyl, triptans (e.g. sumatriptans) and dextromethorphan because they can cause serotonin excess.

4. Check patient's drug compliance regularly and check all of the medications that the patient is taking including pain-killers, cough suppressants, recreational drugs, antibiotics, weight reduction agents, herbal products and antiepileptic drugs.

5. Physicians should always keep this syndrome in mind and early recognize serotonin syndrome in patients who have a sudden worsening of psychiatric or neurological illnesses following a change in medications and stop the inciting medications immediately.

CONCLUSION

Serotonin syndrome is a result of excessive serotonin receptor stimulation. It is often described as a clinical triad of mental status changes, autonomic hyperactivity and neuromuscular abnormalities. A number of drugs and drug interactions have been reported as the causes of this potentially life-threatening adverse drug-reaction. Even though the diagnosis is simply based on history and physical examination, there are several differential diagnoses. Management of the syndrome is immediate removal of the precipitating drugs and the supportive cares. In addition, as the syndrome is a predictable condition, its prevention is substantially crucial and physicians should always be aware of it.

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บทคัดย่อ

กลุ่มอาการซีโรโทนินและการสลายตัวของกล้ามเนื้อ: รายงานผู้ป่วยและการป้องกัน

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กลุ่มอาการซีโรโทนินเป็นผลข้างเคียงของยาที่รุนแรงแต่สามารถป้องกันได้ ภาวะนี้พบได้น้อยและมักไม่ได้รับการวินิจฉัยที่ถูกต้องโดยมีสาเหตุจากการที่มีการกระตุ้นตัวรับของซีโรโทนินมากเกินไป ซึ่งมักพบในผู้ป่วยที่ได้ยาที่มีผลต่อซีโรโทนินหลายตัวร่วมกัน อาการของโรคมี 3 อย่างคือ อาการทางสมอง อาการทางระบบประสาทอัตโนมัติ และอาการของระบบประสาทกล้ามเนื้อ ในบางครั้งผู้ป่วยกลุ่มอาการซีโรโทนินอาจเกิดภาวะแทรกซ้อน ได้แก่ การสลายตัวของกล้ามเนื้อและภาวะแทรกซ้อนอื่นที่อาจมีผลอันตรายถึงแก่ชีวิต บทนิพนธ์นี้ได้รายงานผู้ป่วยชายอายุ 22 ปี ที่มาด้วยกลุ่มอาการซีโรโทนินและมีการสลายตัวของกล้ามเนื้อจากปฏิกิริยาระหว่างยาที่มีผลกระตุ้นซีโรโทนิน นอกจากนั้นยังได้กล่าวถึงคำแนะนำในการป้องกันกลุ่มอาการนี้ด้วย