Serotonin Syndrome with a Combination of Fluoxetine and Lithium

氟西汀與鈹的結合療法引致的血清素症候群

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Abstract

A rare presentation of the serotonin syndrome occurred following the use of a fairly common combination of the antidepressant fluoxetine, a selective serotonin reuptake inhibitor, and lithium carbonate, a mood-stabiliser. The syndrome is characterised by a sudden onset of mental state changes, autonomic instability, and increased neuromuscular activity. Recovery occurred after discontinuation of the drug combination. The mood symptoms were subsequently treated with an atypical antipsychotic. Fatalties and complications may be associated with the serotonin syndrome. A detailed medication history, awareness of the syndrome, and early recognition are crucial for effective management.

Key words: Antidepressive agents; Drug interactions; Mental disorders; Serotonin uptake inhibitors

Introduction

Serotonin syndrome is a potentially fatal condition that presents with psychiatric and neurologic symptoms arising from a hyperserotonergic state. The serotonin elevation has a dose-effect on the severity of serotonergic symptoms.¹ The syndrome was initially identified in animal studies; the first human cases were reported in the 50s.²,³ The serotonin syndrome is described as a clinical triad of mental state disturbances, autonomic hyperactivity, and neuromuscular abnormalities (Table)⁴ but these features are not always consistently present in every patient.

There is still a lack of awareness and recognition of the syndrome mainly because of its rarity. A PubMed search revealed 3 case reports of serotonin syndrome with the fluoxetine / lithium combination.⁵⁻⁷ In a fourth case report the serotonin syndrome was precipitated by dextromethorphan abuse in a patient treated with fluoxetine and lithium.⁸ All these cases involved Caucasian patients and the 2 cases published in English were female patients, one a 36-year-old and the other a 61-year-old.⁵⁻⁷ We report a case in a male Chinese patient who developed the serotonin syndrome while on treatment with fluoxetine and lithium carbonate, in

Table. The serotonin syndrome clinical triad.

<table>
<thead>
<tr>
<th>Mental status changes</th>
<th>Confusion / disorientation</th>
<th>Agitation / irritability</th>
<th>Unconsciousness / coma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic hyperactivity</td>
<td>Fever</td>
<td>Diaphoresis</td>
<td>Sinus tachycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
<td>Mydriasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachypnoea</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular abnormalities</td>
<td>Myoclonic jerks</td>
<td>Hyperreflexia</td>
<td>Muscle rigidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restlessness, hyperactivity</td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ataxia or incoordination</td>
<td>Clonus</td>
</tr>
</tbody>
</table>
order to highlight the syndrome’s features and demonstrate how it may mimic several other conditions.

Case Report

A 53-year-old male presented in December 2006 to a psychiatric hospital with a 3-week history of low mood, poor sleep and appetite, weight loss, and thoughts that his life was meaningless and empty. He also reported auditory hallucinations and persecutory ideas that were mood-congruent. There was no psychiatric history or history of medical or surgical illnesses. There was no history of illicit substance or alcohol use and no history of self-medication. There were no significant findings on physical examination and his baseline haematology, renal and thyroid function tests were within normal limits. He was diagnosed with a first episode of a major depressive disorder, moderate with psychotic features.9

He was started on dothiepin (75 mg at night) and sodium valproate (400 mg at night). His condition worsened and he became withdrawn and uncommunicative and developed further loss of appetite. After 2 days, the sodium valproate was stopped and replaced with lithium carbonate (400 mg at night) that was increased to 600 mg the following day. On the fifth day, the dothiepin was stopped and the treating team added fluoxetine 20 mg per day to the lithium carbonate.

By the next day he was found to be slightly stiff with tremors. He was disorientated, confused, and restless. His blood pressure, which had been within the normal range, increased to 140/100 mm Hg and his pulse rate was 90 beats per minute. His mood was still depressed, and he became increasingly irritable. The confusion and restlessness persisted. He was nursed intensively with supervision of his activities of daily living and monitoring of mental state and vital parameters. Over the next 3 days his blood pressure fluctuated between 130/80 and 180/100 mm Hg. He spiked a fever of 38.5°C and was sweating and restless. Muscle rigidity was noted, accompanied by hyperreflexia, clonus, and occasional twitching of his limbs.

Repeated haematology and biochemistry, urine tests and serial creatinine kinase levels were normal and the serum lithium was within normal limits (< 0.5 mEq/L). There was no evidence of a septic cause. An electrocardiogram and chest X-ray were normal. Brain magnetic resonance imaging revealed no organic or structural abnormalities. By the fourth day, the differential diagnoses being considered included serotonin syndrome and catatonia. The former was considered the most likely based on the clustering of signs and symptoms, medication used and the chronological sequence of events and duration. All the medications were stopped and he was continuously monitored and given supportive measures such as hydration. His condition stabilised rapidly over the next 5 days but his mood was increasingly depressed and he was still experiencing auditory hallucinations, so he was started on low doses of an atypical antipsychotic (olanzapine). There was no recurrence of any physical symptoms and his mood eventually improved with appropriate dose titration.

On reviewing his history, it was evident that he had serotonin syndrome. He had not received any antidepressant and an antipsychotic agents. Both fluoxetine and lithium carbonate are medications that have been associated with the serotonin syndrome and there is evidence that lithium may actually increase the risk of the syndrome when administered with serotonergic agents.10,11

Discussion

While the serotonin syndrome has traditionally been described with proserotonergic drugs, this patient’s condition was precipitated by a combination of medications that, although associated with an increased risk, is infrequently seen. A confounding issue was the use of a mood stabiliser and an antidepressant, despite practice guidelines recommending the combination of an antidepressant and an antipsychotic for a major depressive disorder with psychotic features.12

The rapid medication switches and dose escalations may have increased the risk. Common medical conditions known to increase the risk of serotonin syndrome, such as hypertension, atherosclerosis, hypercholesterolaemia, and damaged vascular or pulmonary endothelium were not present in this patient.13

The serotonin syndrome can present with a range of symptoms, both varied and non-specific, and ranges in degree from mild to severe states. This can contribute to diagnostic difficulties. Neuromuscular symptoms and clonus in a patient being treated with serotonergic drugs are highly diagnostic. These features became the Sternbach criteria following a review of a small series of cases presenting with serotonin syndrome.11
The Sternbach criteria also requires exclusion of other medical conditions and antidopaminergic drug use. More recently the Hunter Serotonin Toxicity Criteria14 has listed clinical findings with statistically significant associations with serotonin syndrome. These are primarily neuromuscular including hyperreflexia, clonus (inducible, spontaneous and ocular), myoclonus, peripheral hypertonicity, and shivering. Autonomic states listed include tachycardia, mydriasis, diaphoresis, diarrhoea, and the presence of bowel sounds. Mental state changes were agitation and delirium.14 The case reported here meets these diagnostic criteria.

The underlying pathophysiology in serotonin syndrome is enhanced serotonin neurotransmission and stimulation of central and peripheral serotonin receptors.15

The actual incidence of serotonin syndrome remains unknown. The use of combination therapy, augmentation strategies, and pharmacokinetic interactions that increase serotonergic stimulation increase the risk. A recent report linked 146 cases of serotonin syndrome with the use of selective serotonin reuptake inhibitors (SSRIs) and it reportedly occurs in 14 to 16% of people who overdose with SSRIs.16,17
Some thus refer to it as serotonin toxicity to emphasise this dose relationship and poisoning from
ingestion of the medication. The onset is usually rapid — less than an hour in cases of self-poisoning — but there are also reports of delayed onset occurring several weeks after the addition of another medication.\(^\text{18}\)

The differential diagnosis for serotonin syndrome includes the anticholinergic syndrome, neuroleptic malignant syndrome, and malignant hyperthermia. In this patient, catatonia with depression was a serious consideration. The clinical picture in those with catatonic features include: (1) motor immobility manifested as catalepsy or stupor, (2) excessive motor activity, (3) extreme negativism, (4) peculiarities of voluntary movement manifested as posturing, stereotypical movements, and (5) echolalia or echopraxia.\(^\text{9}\) The clinical presentation and the recovery on withdrawal of fluoxetine and lithium made catatonia an unlikely primary diagnosis.

The anticholinergic syndrome results from poisoning with an anticholinergic agent. The clinical presentation is somewhat similar to the serotonin syndrome in the autonomic changes of hypertension, tachycardia, tachyphoea, and hyperthermia but the patient’s skin is erythematous, hot and dry, bowel sounds are decreased and absent, and there are no neuromuscular abnormalities.\(^\text{14}\) The neuroleptic malignant syndrome is an idiopathic reaction to dopamine antagonist medication which produces bradykinesia over a few days.\(^\text{19}\) Symptoms such as altered consciousness, diaphoresis, hyperthermia, and autonomic changes are shared with the serotonin syndrome but the neuromuscular changes in neuroleptic malignant syndrome include ‘lead-pipe’ rigidity in all muscle groups with bradyreflexia. In addition, a marked elevation of creatinine kinase and leukocytosis are characteristic of the neuroleptic malignant syndrome and absent in serotonin syndrome.\(^\text{20}\) It has been suggested that both these conditions may not be specific syndromes but rather part of a non-specific generalised neurotoxic syndrome and subtypes of catatonia.\(^\text{21}\) Lastly, malignant hyperthermia is a pharmacogenetic disorder related to inhalational anaesthesia or succinylcholine use. Autonomic changes are present but the skin has a distinctive mottled appearance with rigor mortis-like rigidity and hyporeflexia.

Management of the serotonin syndrome involves immediate discontinuation of suspected medications, supportive care, control of autonomic instability and hyperthermia, control of agitation and, if needed, the use of serotonin antagonists such as cyproheptadine.\(^\text{14}\) Up to 70% of cases recover within 24 hours but symptoms may persist longer in those patients who have received drugs with long elimination half-lives or active metabolites.\(^\text{10}\) Although this patient recovered from the serotonin syndrome, fatalities and complications including disseminated intravascular coagulation, rhabdomyolysis, hypotension, and acute renal failure have been reported.\(^\text{22}\)

Physicians need to be aware of this syndrome in order to recognise it early and manage it effectively. Better prescription practices, particularly avoiding polypharmacy and recognising that those patients who need combination or augmentation strategies must be closely monitored and followed, are required.\(^\text{23}\) A thorough medication history from patients is crucial as over-the-counter medications, illicit substances, and dietary supplements have also been implicated in the serotonin syndrome.\(^\text{24}\)

References