HOSPITAL CHRONICLES 2019, 14(1): 27–30

CASE REPORT

Sustained Serotonin Syndrome in a Resistant Depressed Patient During Maintenance Treatment

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KEY WORDS: *serotonin syndrome, major depression, fluoxetine, amitryptiline, lithium carbonate*

ABSTRACT

A 57 years old male with a history of major depression under maintenance treatment with fluoxetine, amitryptiline and lithium carbonate presented cognitive dysfunction, autonomic instability and behavioral and neuromuscular disturbances. Despite immediate cessation of fluoxetine and amitryptiline and gradual discontinuation of lithium, symptoms persisted for several days. The patient's mental status began to improve only fifteen days after discontinuation of the antidepressants and eight days after complete cessation of lithium. Since the patient had been under treatment with three serotonergic agents, a diagnosis of serotonergic syndrome was posed. The unusually delayed recovery may be attributed to sustained changes at the serotonine receptor lever, due to long-term administration of serotonergic medications.

Abbreviation List
5-HT = 5-Hydroxytryptamine
MAOIs = Monoamine Oxidase Inhibitors
NMS = Neuroleptic Malignant Syndrome
SNRIs = Serotonin-Norepinephrine Reuptake Inhibitors
SSRIs =Selective Serotonin Reuptake Inhibitors
SNRIs = Serotonin-Norepinephrine Reuptake Inhibitors
TCAs = Tricyclic Antidepressants

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Manuscript received February 12, 2019; revised manuscript received June 12, 2018; Accepted June 19, 2019

INTRODUCTION

Serotonin syndrome (SS) is a relatively rare but potentially life threatening condition caused by agents that affect serotonin (5-Hydroxytryptamine; 5-HT) metabolism or act as direct 5-HT receptor agonists or both.[1] 5-HT is a monoamine neurotransmitter synthesized from the aminoacid tryptophan. In the central nervous system it regulates functions such as mood, appetite, sexual activity, sleep and some cognitive functions. Peripherally, 5-HT promotes platelet aggregation and also affects peristalsis and vascular tone.[2,3] A large number of agents, such as antidepressants (monoamine oxidase inhibitors-MAOIs, tricyclic antidepressants-TCAs, selective serotonin reuptake inhibitors-SSRIs, serotonin-norepinephrine reuptake inhibitors-SNRIs, buspirone, St. John's wort), antibiotics (linezolid), antiemetics (ondasetron) antimigraine medications (sumatriptan), drugs of abuse (amphetamine, cocaine, LSD, ecstasy), herbal supplements, and others have been associated with SS.[1] The vast majority of antidepressants can cause SS either by direct receptor agonism (buspirone), decreased reuptake of 5-HT (SSRIs, SNRIs, TCAs) or decreased 5-HT breakdown (MAOIs).[1] Lithium is used in combination with other antidepressants and has also been implicated in the development of SS.[4,5]

The authors declare that there is no financial relationship or conflict of interest to disclose concerning this article

Several studies in animals and a limited number in humans[6,7] indicate that SS is caused by an excess 5-HT receptors stimulation[8] but the pathophysiology is not completely understood.[1] It can be produced either by a dose increase, addition of a new medication, concomitant administration of serotonergic drugs or through drug interactions.[1,8] The onset of SS typically occurs within hours after the precipitating factor(s). However, cases with delayed onset of 24 hours or more have been reported.[1,8]

Serum 5-HT concentrations do not correlate with clinical findings and no laboratory test can confirm the diagnosis.[9] Several criteria, such as those of Sternbach, Radomski and Hunter, were defined.[10,11] The diagnostic criteria suggested by Sternbach[12] are less specific and less sensitive as compared to those of Hunter.[10] On the other hand, Hunter criteria were designed specifically for patients with SSRIs overdose, not SS due to other agents.[10] In current practice the diagnosis of SS is commonly based on clinical manifestations. A triad of symptoms is considered characteristic: a. cognitive or mental status changes (e.g. agitation, confusion, delirium) b. neuromuscular abnormalities (e.g. clonus, hyperreflexia, increased muscle tone and spasms, restlessness, rhabdomyolysis, rigidity, tremor) and c. autonomic hyperactivity or instability symptoms (diaphoresis, diarrhea, fever, tachycardia, hypotension or hypertension, mydriasis).[13] Some of these manifestations are similar, to some extent, to those of other conditions, mainly neuroleptic malignant syndrome (NMS)[14] and also anticholinergic toxicity and malignant hyperthermia.[9] The differential diagnosis of these conditions is very important since a different therapeutic approach is indicated.[9]

Management of SS consists of immediate discontinuation of the offending drugs and supportive care. Benzodiazepines are used for sedation and cyproheptadine as an antidote. In most cases symptoms are improved within 24 hours.[1,9-11]

In this report, we present a clinical case with the special characteristic of unexpectedly sustained signs and symptoms of SS, following pharmacotherapy with a combination of fluoxetine, amitriptyline and lithium. We believe that such relevant data, appearing in the literature, can add further knowledge and raise awareness regarding this important syndrome.

CASE REPORT

A 57-yr-old male with a history of three major depressive episodes was on maintenance treatment with fluoxetine 40 mg, amitriptyline 75 mg, and lithium carbonate 900 mg daily. The patient was referred to the psychiatric emergency department with a suggested diagnosis of depressive state, worsening and not responding to treatment. The patient was complaining of insomnia. A mild cognitive impairment was obvious and therefore there was a difficulty in eliciting clear information regarding his history, since he was living alone. He was immediately admitted to the psychiatric unit. On admission, serum lithium levels were 1.25 meq/l (therapeutic range: 0.6-1.00 meq/l). Fluoxetine and amitriptyline were immediately discontinued and lithium was gradually withdrawn over eight days. As he also presented leg oedema, cardiologic consultation was sought, which revealed left ventricular heart failure and so the patient was put on treatment with digoxin 0.25 mg, furosemide 40 mg and captopril 12.5 mg daily. Complete blood count, chemistries, erythrocyte sedimentation rate, prothrombin time, thyroid and parathyroid function were normal. All tests for sexually-transmitted diseases –including human immunodeficiency virus infection- and malignancies were negative.

During the first three days of hospitalization, his mental status became dramatically impaired. He developed further cognitive dysfunction (confusion), autonomic instability (tachycardia, nausea, diarrhea) and behavioral and neuromuscular disturbances (tremor, myoclonus, incoordination).

Electroencephalogram revealed a slightly diffuse slowing. A mild protein increase (67 mg/dl) was found in the cerebrospinal fluid. Computer tomography and magnetic resonance imaging were normal. Serum lithium levels gradually decreased and fell to 0.1 meq/l at the end of the second week.

The patient's mental status began to improve fifteen days after discontinuation of fluoxetine and amitriptyline and eight days after cessation of lithium. At the end of the third week of hospitalization the patient was almost symptom-free. He was discharged during the fourth week of hospitalization with a regimen of topiramate (200 mg/day) and drugs for his left ventricular heart failure.

DISCUSSION

Combination of serotonergic drugs is common in the treatment of depressive syndromes and lithium is used as an adjunctive treatment in resistant depressed patients.[15] Antidepressive treatment with more than one drug might prove particularly effective, but patients are at high risk of adverse reactions, such as SS.[4,10,15] This is evidenced in the case described above. The patient in question was exposed to three different antidepressant medications and subsequently presented at the emergency psychiatric department with mild, but obvious cognitive dysfunction.

The drugs used (fluoxetine, amitriptyline and lithium), in spite of their different pharmacodynamics, have the same target and therapeutic effect and thus their action appears synergistic.

Lithium is known to interact with several cerebral proteins but it is not clear which of these interactions maintains mood stabilization. It is known to have a regulatory role on protein kinase C through action on both the inositol cycle and the glucogen synthase kinase signaling pathway.[16,17] The effect of

lithium on the second-messenger system leads to alterations in all brain neurotransmitter systems, including increased norepinephrine and 5-HT function, which could explain its antidepressant effect.[18] Furthermore, the antagonistic action of lithium at the 5-HT lA and 1B autoreceptors is well documented leading to an increase of 5-HT concentration in the synaptic cleft and increased serotonergic activity.[19]

Amitriptyline, a TCA, is well known to inhibit the reuptake of 5-HT and norepinephrine.[20] The tertiary TCAs, such as amitriptyline are more potent at the 5-HT transporter, while the secondary TCAs are more potent at the norepinephrine transporter. As the tertiary TCAs are demethylated to secondary ones, following their administration, both norepinephrine and 5-HT availability at the synaptic cleft as well as noradrenergic and serotonergic activity are increased.[21]

Fluoxetine is a SSRI, relatively selective in its 5-HT reuptake inhibition.[22] In addition, the action of both TCAs and SSRIs extends beyond the inhibition of 5-HT reuptake: presynaptic terminal, somatodendritic autoreceptors and postsynaptic 5-HT receptors are also their targets. Following long-term co-administration of these drugs, 5-HT transmission is enhanced both through increased postsynaptic receptor sensitivity -as occurs with TCAs- and reduced sensitivity of somatodendritic and terminal autoreceptors -as occurs with SSRIs.[23,24]

Our patient had been simultaneously exposed to treatment with fluoxetine, amitriptyline and lithium and this combination most probably led to increased brain 5-HT function, manifested with cognitive dysfunction.[23,24] The underlying pharmacodynamic profile of the chronic antidepressant treatment supports the suggestion that a mild SS rather than a NMS had been developed. The NMS mainly occurs with a combination of lithium and neuroleptics and rarely with serotonergic antidepressants, such as fluoxetine, although it is known that it can also induce extrapyramidal side effects through alteration of the dopaminergic transmission.[25] The diagnosis in favor of SS rather than of NMS was further supported by the appearance of the classical clinical triad of autonomic, behavioral and neuromuscular disturbances[13,14] and the normal temperature and creatine kinase activity, which are both increased in the NMS.[14] However, it must be noted that the onset of the symptoms in our patient was not typical for SS, in which it is usually abrupt. Thus, the earliest symptoms of our case were misinterpreted by the referring doctor as reflecting an exacerbation of the patient's underlying psychiatric condition. Furthermore, despite the immediate cessation of two drugs and the tapering of lithium, that were decided upon admission, the symptoms worsened and gave a full clinical picture compatible with SS during the first three days of hospitalization. The pharmacokinetic properties of antidepressants might explain this course since it is well known that fluoxetine does not require tapering off, because of its extended action after therapy discontinuation. This is mainly due to its active metabolite, norfluoxetine, an equipotent 5-HT reuptake inhibitor. Fluoxetine has an average half-life of 1 week and norfluoxetine up to 2.5 weeks.[9,26] So, it may take several weeks for the body to clear of this metabolite, after discontinuation of fluoxetine.[27] Furthermore, fluoxetine is a strong inhibitor of P4502D6 cytochrome, which normally mediates the metabolism of TCAs.[22]

This inhibition might increase up to two fold the level of amitriptyline and up to nine-fold the levels of its metabolite, nortriptyline.[28] It is clear that increased levels of active metabolites of both amitriptyline and fluoxetine exerted over a long period a net pharmacodynamic effect on the 5-HT system.

The delay of recovery, despite immediate cessation of two of the offending medication can additionally be attributed to sustained changes at the 5-HT receptor level, which, as mentioned above, occur after long-term antidepressant medication.[23,24]

As far as we know this is only reported case in which SS appeared as the result of the combined use of three serotonergic agents. Previous reports were referring to a combination of two drugs. This possibly explains the most prolonged duration of the syndrome in our patient.

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