Case study

Serotonin syndrome after initiation of pregabalin on a stable regimen of antidepressant medication

ABSTRACT

Aims: Serotonin syndrome is a potentially life-threatening drug interaction caused by excess serotonin in the central nervous system (CNS) and/or peripheral nervous system leading to cognitive, autonomic and somatic effects ranging from barely perceptible to fatal. A number of drugs and drug interactions cause serotonin syndrome, however, the exact mechanisms often remain elusive.
Presentation of Case: In the following case, serotonin syndrome was caused by the addition of pregabalin in a patient with recurrent major depressive disorder and concurrent medication with paroxetine and trazodone.
Discussion: This case illustrates the risk of psychotropic polypharmacy leading to an increased vulnerability towards Serotonin Syndrome.
Conclusion: Pregabalin with its serotonergic action has a liability to cause Serotonin Syndrome. This should especially be kept in mind in patients with psychotropic polypharmacy.

Keywords: Serotonin syndrome, pregabalin, paroxetine, trazodone

1. INTRODUCTION

Serotonin syndrome (SS) is a potentially life-threatening drug interaction caused by excess serotonin in the CNS and/or peripheral nervous system. As a consequence, excess serotonin causes cognitive alteration, ranging from headache to hypomania, agitation, confusion, hallucination and coma, autonomic dysregulation with shivering, sweating, hyperthermia, tachycardia, hypertension, nausea, and diarrhea, as well as somatic, in particular neurological effects such as tremor, hyperreflexia and myoclonus (1). The presenting symptomatology varies from barely perceptible, then often not acknowledged, to fatal.

Serotonin syndrome can occur from a variety of pharmacological conditions: inhibition of serotonin reuptake, decreased serotonin metabolism, increased serotonin synthesis and release, and activation of serotonergic receptors (2). Another mechanism increasing the risk for SS is the Cytochrome P450 system, in particular, inhibition of CYP450 2D6 (3). Clinically, SS is often caused by an overdose of single serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs), however, more frequently occur from drug-drug interactions of several concomitant serotonergic agents prevailing. In particular, monoamine oxidase inhibitors (MAOI) have been associated with this syndrome alongside other antidepressants such as tricyclic antidepressants (TCA), serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), bupropion, trazodone and mirtazapine, opioids with frequent reports on tramadolol, CNS stimulants, serotonin1-agonists such as triptans, herbs, in particular hypericum (St. John's wort), and others such as valproate, lithium, and atypical antipsychotics.

Pathophysiologically, it was originally suspected that the 5HT1a receptor was primarily associated with this syndrome, later the 5HT2a receptor site has been identified as contributing system. At last, increased norepinephrine levels were documented in SS (4).

Furthermore, various neurotransmitters have been implicated in the emergence of the SS, including the N-Methyl-D-Aspartate (NMDA) - receptor, namely, antagonists at this receptor site such as Gamma-Amino-Butyric Acid (GABA) and dopamine (5).

2. PRESENTATION OF CASE

Mrs. E. is a 44-year-old patient with a recurrent major depressive disorder, posttraumatic stress disorder (PTSD) after an assault by her ex-partner, a combined personality disorder, opiate dependence currently on methadone maintenance and chronical medically unexplained symptoms since 2013 with multilocular pain symptoms, nausea, obstipation and chronic fatigue, indicating a somatization disorder.

She was on weekend leave from psychiatric hospital treatment where she was an inpatient due to increasing depressive symptoms and prolonged pain symptoms, when she experienced a change in mental status with disturbance of consciousness and cognition, as well as tremor and myoclonus of the upper and lower extremities, headache and diaphoresis. With further aggravation of symptoms the following day, she was urgently transferred to the University Hospital Zurich for further evaluation and management. The primary diagnostic assessment showed an inconspicuous cranial CT- scan, renal failure with decreased GFR (44ml/min), increased inflammatory parameters (C- reactive protein 66mg/l), elevation of Ammonia 40umol/l, upper and lower extremity clonus, resting tremor of the hands and sedation. At time of admission the patient was on a stable psychotropic regimen of paroxetine 50mg, trazodone 50mg, bupropion XR 450mg, paliperidone 6mg and methadone 7.5mg. Due to multiple physical complaints with varied pain symptoms, therapy with pregabalin was initiated and gradually increased within the weeks before, reaching 750mg on the day of admission. During the first night of hospitalization, Mrs. E. presented with a single episode of acute dyspnea and arterial hypoxemia and had to be transferred to resuscitation room for further acute management. No pathological changes were seen in her chest X-ray and after oral administration of 125mg methylprednisolone, oxygen application via face mask and initiating intravenous administration of 2.2g amoxicillin/clavulanic acid due to suspected infectious disease, hypoxemia resolved and the patient was transferred back to the regular floor. The hemodynamic profile remained stable all the time.

The reported cognitive dysfunction and clinical presentation being highly suggestive of a serotonin syndrome, trazodone and bupropion were halted, paroxetine was cut down to 10mg and pregabalin reduced to 700mg. Within the next 48 hours, the mental disturbances and neuromuscular symptoms went into remission and the patient could be transferred back to psychiatric hospital.

3. DISCUSSION

In this case, SS was triggered by the concomitant administration of pregabalin in addition to a stable regimen of paroxetine, trazodone, bupropion, and paliperidone.

Gabapentin as an analogue of pregabalin has been shown to increase serotonin levels in the CNS (6). Only one case report has described SS in the context of pregabalin treatment as a preoperative co-administration to oxycodone therapy (7). It demonstrated that pregabalin as an agent increasing the whole blood serotonin concentration in therapeutic dose ranges, was associated with an increased risk of SS development in combination with oxycodone treatment. It is known that opioids exert not only an effect on opioid receptors, but also play a role in neuronal serotonin reuptake acting as a weak serotonin reuptake inhibitor (8, 9), thus being involved in serotonin toxicity reactions (10). In our case the patient was on a stable methadone maintenance treatment which might have been an additional provoking factor for SS development in presence of high dosage pregabalin treatment in combination with other serotonergic agents. Also initial renal failure and decreased GFR with the renal pathway being the primary route of pregabalin clearance might have contributed to pregabalin accumulation and increased serotonin toxicity.

This case illustrates the requirement of a heightened awareness in the presence of psychotropic polypharmacy leading to an increased vulnerability towards SS syndrome.

SS involves a spectrum of clinical findings presenting with the typical triad of SS features: 1) mental status changes 2) autonomic dysfunction 3) neuromuscular excitability (1).

The diagnosis is made on the basis of clinical symptoms using the Hunter criteria (11). To fulfill these diagnostic criteria, a serotonergic agent has to be present plus one of the following clinical findings: spontaneous clonus; inducible clonus plus agitation; ocular clonus plus agitation; tremor plus hyperreflexia; hypertonia plus temperature >38℃ plus ocular or inducible clonus. In Mrs. E's case the diagnostic criteria were met with occurrence of a spontaneous clonus under serotonergic polypharmacy. Thoracic rigidity associated with SS might have been a predisposing factor to the outlined episode of hypoventilation and hypoxemia.

4. CONCLUSION

In summary, this is another case report illustrating SS in the context of addition and titration of pregabalin in addition to a stable psychotropic regimen with serotonergic agents, in our case paroxetine, trazodone, bupropion, paliperidone, and methadone. Although this patient has already been predisposed to SS due to psychotropic polypharmacy administered prior to the development of SS, the addition of pregabalin with its serotonergic action triggered the onset of this syndrome. To date, pregabalin has not often been associated with SS, however, should be kept in mind for its liability to cause SS.

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