International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 8, August 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.8.2024.36

CASE REPORT

An interesting case report of serotonin syndrome in critically ill patient admitted with benzodiazepine overdose

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Received Date: 24 June, 2024 Acceptance Date: 27 July, 2024

ABSTRACT

Serotonin syndrome (SS)/ serotonin toxicity/serotonin toxidrome may be a life-threatening condition that can develop within hours to days after starting serotonergic drugs. There is wide clinical spectrum of its severity, ranging from mild illness to very severe life-threatening illness. It is caused by the increased serotonin or 5hydroxytryptamine (5HT) activity in the central nervous system resulting in increased activation of serotonergic receptors mainly 5HT2A and 5HT2B. This usually occurs due to a serotonergic drug overdose or the simultaneous use of two or more serotonergic antidepressants. It may get precipitated even after the single dose administration of SSRI, as happened in our case. (1) The classical presentation includes hyperthermia, hyperreflexia, clonus and muscular rigidity. Some of these symptoms may be masked in a critically ill patient who is on mechanical ventilator with sedatives and muscle relaxants, making diagnosis challenging in such settings.

In this case report serotonin syndrome is diagnosed with high index of suspicion and as a diagnosis of exclusion. Patient presented to us with history of benzodiazepine and insulin overdose. After initial stabilization in first three days, he was advised Escitalopram 10 mg by psychiatrist. Patient developed very high fever of 106-degree F, the very next day. After ruling out infectious and other non-infectious causes of fever swiftly and on the basis of Hunters criteria, diagnosis of SS was established in our case.

Critical care physician is supposed to be aware of this entity and keep this diagnosis in their differential diagnosis in patients who are on SSRI and develop hyperthermia or acute mental status changes even after few hours of initiation of SSRI.

INTRODUCTION

Serotonin syndrome (SS) is first described in 1960 by Oates and Sjoerdsma (2). As such this syndrome has got low prevalence but with the increasing use of antidepressants and anxiolytics drugs, this is not rare now days as shown by a large clinic based study done by Sanjay Prakash etal. (3) Many classes of drugs can precipitate SS. This include but are not limited to selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), opiates including tramadol and fentanyl, atypical antipsychotics, antitussive agents, antibiotics, weight-reducing agents, antiemetics, antimigraine agents, and herbal drugs. [4]. SSRIs are most commonly implicated drugs associated with SS and based on the French pharmacovigilance reports, these were involved in 42.1% cases of SS. (5).Serotonin syndrome or Serotonin toxicity is a life-threatening condition if not diagnosed and treated in time. It can present as diverse clinical presentation.The classical triad of serotonin toxicity contains altered mental status, autonomic instability, and neuromuscular abnormalities. (6) Mental status changes may present as agitation, restlessness, confusion and disorientation. Autonomic instability manifests as hyperthermia, dilated unresponsive pupils, abdominal pain, profuse sweating, tachycardia, fluctuation in blood pressure and flushing. Neuromuscular hyperactivity presents as, hyperreflexia, spontaneous or inducible clonus, shivering, tremors and positive bilateral Babinski sign. In critically ill patient who is on mechanical ventilator with sedation and intermittent muscle relaxants, it is difficult to appreciate these changes, making it difficult to diagnose. There is no confirmatory laboratory testing for diagnosis of serotonin syndrome and it can be diagnosed with high clinical suspicion and the

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application of various clinical criteria proposed for its diagnosis. Chiew et al in 2021 had done an extensive review of the literature on cases of serotonin toxicity and proposed four criteria: Sternbach, Serotonin Syndrome Scale, Radomski, and Hunter for assisting in diagnosis of SS. (7) Hunters criteria is the most widely accepted criteria for its diagnosis.Sensitivity and specificity of this criteria is 84% and 97% respectively. Hunters Criteria consists of ingestion of a known serotonergic agent along with at least 1 of the following: (1) spontaneous clonus, (2) inducible clonus AND diaphoresis OR agitation, (3) ocular clonus AND diaphoresis OR agitation, (4) tremor AND hyperreflexia, (5) hypertonia AND temperature greater than 38°C AND ocular OR inducible clonus. (8) It is crucial to diagnose and suspect this disease in early phase so as to stop the offending drug immediately and start the clinical management of the syndrome.Clinical presentation varies from mild symptoms to moderate symptoms to severe life-threatening symptoms such as hyperthermia and coma as occurred in our case. Mortality is more than 50% in severe cases in first 24 hours if not treated in time. The general principles of management involve stopping the culpritdrug and administering supportive care in terms of fluid and electrolyte balance, benzodiazepine to control the agitation andcyproheptadine as antidote to control neuromuscular symptoms. (9)

This case report is written to increase the awareness of this syndrome in critically ill patients. In critical care setting diagnosis is challenging as many symptoms and sign of this syndrome resembles with sepsis, there is absence of definitive diagnostic test and use of mechanical ventilator with sedation and muscle relaxants further masking many symptoms and signs.

CASE REPORT

This case report represented a case of young male of 32 years presented to our emergency department with a alleged history of ingestion of 40mg of alprazolam tablets along with unknown units of glargine insulin in a comatose condition. He is a known case of depression and was on multiple antidepressants with poor compliance. Immediately after securing the airway and initial resuscitation, he was shifted to intensive care for further management.

After three days of supportive care, patient became conscious and started comprehending to verbal commands. Weaning from the ventilator was planned. Psychiatric opinion was sought in view of depression and suicidal tendency. He was started on Escitalopram 10 mg tablet. Six to eight hours after starting this, patient developed very high fever of 106-degree Fahrenheit with autonomic instability in terms of tachycardia and hypertension along with marked tremulousness for which he had to be started on sedation and muscle relaxant again and his weaning is postponed. A detailed Work up for very high-grade fever, not responding to IV paracetamol was done.

All the cultures and procalcitonin levels were sent and later were found to be negative. With the background of starting SSRI few hours before and the sudden change in her clinical condition in terms of change in his mental status, agitation and marked tremulousness along with high fever, possibility of SS was also kept. In view of high probability, he was immediately started on Syp Cyproheptadine 12 mg stat through Ryle's tube and citalopram is stopped. Sedation and relaxant were stopped and during sedation holiday, his reflexes were checked. There was evidence of hyperreflexia along with inducible clonus and agitation during this time for which he had to be started on sedation with benzodiazepines. Diagnosis of SS was confirmed as per Hunters criteria. Patient was continued on cyproheptadine 4 mg 6 hourly through Ryle's tube. All supportive care in terms of temperature control, fluid, electrolyte and nutritional management is continued. Patient had to be given short acting benzodiazepines to control his agitation despite he is the case who earlier presented with BZD overdose. After 24 hours his all-clinical parameters improved and he was weaned off from the ventilation after 48 hours of precipitation of his SS. He was sent to ward after 6 days of his ICU stay and sent back home in fully conscious and alert state on 8th day of his admission. The aim of this case report is to increase the recognition of serotonin syndrome in critically ill patients. There are many causes of such kind of deterioration in critical care setting and diagnosis can easily be overlooked or missed.

Table 1 Lab parameters at the time of admission and follow up

Parameter	Reference range	DAY 1	DAY 3	DAY 4	DAY 5	DAY 6	DAY 8
PH	7.35-7.45	7.0	7.38	7.32	7.43	7.4	7.49
PaCO2	35-45	30	43	33	41	41.1	41.2
HCO3 - (mmHg)	22-26	10	25.4	20	27.2	25.5	32.3
Blood glucose (mg/dl)	70-100	96	108	120	134	110	146
Sodium (mmol/L)	135-155	130	135	136	138	140	138
Serum lactate (mmol/L)	0.50-1.50	3.2	1.6	2.6	2.3	1.5	0.9
Hb (gm/dl)	13.0-17.0	16.2	13.8				
WBC Total	4000-10000	18300	8530	22380	17240	13110	7450
Platelet Count (mm^3)	1.5-4.1	2.1	1.8	1.9	1.6	1.76	2.5
Urea	19.2-42.8	56	46	35	38	42	38

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S. Creatinine	0.66-1.25	1.8	1.3	1.0	1.1	0.9	0.8
S.Na*	135-155	130	135	136	138	140	138
S.K*	3.5-5.5	3.3	3.8	4.1	4.3	3.6	4.1
PT (INR)	12.4-14.8/0.89-1.13	1.1		1.2		0.9	
S. BIL Total	0.2-1.3	2.2		1.1		1.2	
S. BIL Direct	0.0-0.4	0.0		0.0		0.0	
S. BIL IN Direct	0.0-1.1	2.2		1.1		1.2	
SGOT	17-59	48		110		46	
SGPT	21-72	82		134		47	
S. ALK Phosphatase /SGGT	38-126	56		84		59	
S. Protein	6.3-8.2	7.2		6.9		7.1	
S. Albumin	3.5-5.0	3.8		3.0		3.5	
S. Globulin	2.0-4.1	2.7		2.7		2.6	
PCT (ng/ml)	<0.5	1.4		0.067		0.021	
NT Pro- BNP (pg/ml)	<125	67		110			
Fever Panel	Negative			NEGATIVE			
S. CPK	22-334 IU/L			674		108	56

DISCUSSION

Serotonin syndrome is a life-threatening condition characterised by excessive accumulation of serotonin into the synaptic cleft causing motor dysfunction leading to increased tremors, hyper reflexia and clonus. As per the article published by Charles H brown, it was suggested that 85% of physicians were unaware of SS as a clinical entity, especially those who are not prescribing SSRI routinely. (4)

In our case this young male presented with benzodiazepine and insulin overdose and during the course of his illness was prescribed SSRI (Escitalopram 10 mg) by the psychiatrist. The very next day of prescribing this drug, patient developed high grade fever of 106 F. Emergence of new high fever in critically ill patients after 3 days of his admission needs to be thoroughly evaluated for nosocomial infections like CLABSI, CAUTI and VAP. All the cultures and procalcitonin were sent which later found to be negative. Sudden onset of very high fever (106), no response of IV paracetamol and marked diaphoresis and autonomic instability in terms of tachycardia, tachypnoea and fluctuation in BP in a sedated and paralyzed patients pointed towards the diagnosis of SS especially in context of starting Escitalopram a day before. To establish the diagnosis of SS, we applied the Hunters serotonin toxicity criteria. The clinical manifestation of hyperthermia, autonomic instability, rigidity, tremors, hyper reflexia and agitation along with recent use of SSRI established the diagnosis of SS after excluding other causes of fever in critical care setting. Our case report signifies the importance of identify it even after the single use of Escitalopram tablet. Escitalopram is considered as a safest SSRI because it is a highly selective serotonin reuptake inhibitor with weak CYP450 inhibitory activity but still it may cause precipitation of SS as happened in our case too. Escitalopram is metabolized by CYP3A4, 2C19, and CYP2D6 and genetic vulnerability and gene polymorphisms may be a causative factor in development of SS with a normal therapeutic dose. (10,11). Similar case reports are also described in literature also with new start of SSRI in any predisposed individuals. (1)

Precipitation and identification of such a life-threatening syndrome because of a small single tablet in critically ill patient sometimes is very challenging and intriguing. Management of the syndrome is supportive but it is extremely important to discontinue the offending drug to treat the patient effectively. As per the literature management of serotonin toxicity comprises removal of offending agents, controlling agitation with GABA agonists such as benzodiazepines, aggressive temperature management with cooling blankets and administration of 5-HT antagonists such as Cyproheptadine. Cyproheptadine is an antihistamine with non-specific serotonin antagonism at the 5-HT1A and 5-HT2A receptors. Though Its efficacy has not been clearly established in literature but it should be considered for seriously ill patients with autonomic instability. Dose of cyproheptadine ranges from 8 mg to 16 mg orally or via naso-gastric tube, to be repeated hourly, every 2 h, or every 4 h as desired. (12, 13). In cases of severe toxicity, sometime airway protection and placement of definitive airway might be required. However our patient developed this syndrome while he was on ventilator and getting treated for BZD overdose. Our case report signifies that it is utmost important to educate the critical care specialist about this syndrome as the polypharmacy and addition of any serotonergic drug should be done very cautiously. It is also equally important that prefer not to start these drugs in patients who are on mechanical ventilator and vasopressor support till the time they become stable and are off from life supportive treatment.

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