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CASE REPORT

Diagnosis of serotonin syndrome in the intensive care population: a case report

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Abstract

ICU admission due to serotonin syndrome (SS) is well described in the literature. However, development of SS during ICU admission has not been reported to date. We present a patient in whom SS was suspected during ICU admission. SS may be induced by either increased serotonergic activity or by lowering the cerebral serotonin sensitivity threshold. SS is not easily recognized, especially in ICU populations because it can easily be confused with clinical deterioration or other drug-related toxidromes. SS is a potentially fatal clinical syndrome, which requires rapid diagnosis and timely treatment. This case demonstrates the need to consider SS in the differential diagnosis of ICU patients with unexplained hyperthermia and signs of autonomic dysregulation, who are treated with serotonergic active medication.

Introduction

Serotonin syndrome (SS) is a potentially life-threatening condition caused by absolute or relative serotonergic overstimulation in the central nervous system. SS may be induced by either increased serotonergic activity or by lowering the cerebral serotonin sensitivity threshold.[1] Diagnosing SS depends on clinical observation since laboratory analysis and imaging do not provide the specific information needed for this condition. Symptoms can vary widely, but include changes in mental status and behaviour, motor system changes and autonomic instability, including hyperthermia.[2] SS symptoms show overlap with symptoms found in neuroleptic malignant syndrome (NMS), sepsis and delirium. Diagnosing serotonin syndrome during an intensive care unit (ICU) admission is even more challenging, because crucial symptoms may be lacking (e.g. absence of muscle rigidity and hyperreflexia in cases of critical illness polyneuromyopathy) or mistaken for clinical deterioration. Correct and timely diagnosis followed by rapid treatment, however, is crucial, since a significant proportion of SS cases (17%) lead to a worse outcome, with a mortality rate of up to 0.2%.[3] SS is mostly seen as a result of inadvertent interactions between serotonin-active drugs and/or intentional self-poisoning.[4,5] We describe a patient who was suspected of SS during ICU admission, whilst continuing a medication regime that included citalopram and amitriptyline.

Case report

A fifty-five year old somnolent male was admitted to the Department of Internal Medicine of a large academic teaching hospital in the Netherlands. The patient was admitted with a suspected recurrent gastrointestinal perforation and intentional opioid overdose. The patient's psychiatric history revealed long-term alcohol abuse, generalized anxiety disorder, recurrent depressive disorder, auto-mutilation and several attempts of intentional self-poisoning. His medical history indicated circular colonic ulcers (due to abuse of non-steroidal anti-inflammatory drugs), insulin dependent diabetes mellitus, hypertension and asthma. Earlier in the same year, the patient had been admitted to the ICU on two separate occasions, due to severe community acquired pneumonia (CAP) and abdominal sepsis as a result of gastrointestinal perforation.

Medications upon admission consisted of amlodipine 10 milligrams once daily, metoprolol 50 milligrams twice daily, pantoprazol 40 milligrams twice daily, citalopram 20 milligrams three times daily, amitriptyline 50 milligrams three times daily, oxazepam 10 milligrams twice daily, ferrous fumarate 200 milligrams three times daily, vitamin B complex forte once daily, morphine 10 milligrams four times daily and novo rapid. No allergies were reported.

Prior to ICU admission, the patient was treated with naloxone, resulting in mild recovery of his somnolent status. Psychotropic drugs were continued, based on the pre-admission dosing

regimen. Additional investigations showed no signs of gastrointestinal perforation. Worsening of the hypoxaemia, however, despite maximal oxygen therapy, required ICU admission for the third time in one year. After endotracheal intubation, mechanical ventilation was initiated. The chest X-ray showed consolidation of the left lower lobe. Recurrent CAP was suspected and treatment with ceftriaxone 2 grams once daily and ciprofloxacin 400 milligrams twice daily was initiated. During the first week of his ICU stay, the patient suffered from refractory bronchospasm, requiring muscle relaxation and permissive hypercapnia. The patient then showed signs of intrapulmonary shunting and a computed tomographic (CT) scan of the pulmonary arteries was made, showing a massive pulmonary embolism in the right pulmonary artery. The prophylactic dose of dalteparin was increased to a therapeutic one. After two weeks of respiratory support, the patient's clinical condition improved. As a result of severe muscle weakness, a percutaneous tracheostomy was performed. Despite low inflammatory markers ($8*10^6$ leukocytes /ml and C-reactive protein (CRP) 30 mmol/l), the patient developed a persistent fever up to 40 degrees Celsius, in combination with refractory hypertension, tachycardia, agitation and anxiety. Biochemical analysis showed a hyponatremia (131 mmol/L), most probably caused by the syndrome of inappropriate antidiuretic hormone secretion. Three weeks after ICU admission, the patient experienced an episode of clonic seizures. A CT scan of the brain revealed no abnormalities. Delirium, NMS, SS, anticholinergic syndrome (ACS) and viral meningitis were considered in the differential diagnosis. The Naranjo scale was used to estimate the probability of an adverse drug reaction (ADR) due to serotonin-active drugs. The Naranjo scale is a ten-item questionnaire designed for determining the likelihood of whether an ADR is actually due to the drug rather than the result of other clinical factors. Probability is assigned via a score termed definite (>9 points), probable (5-8 points), possible (1-4 points) or doubtful (0 points).[6] The Naranjo score in our case was 5 points, which does not actually prove the patient's clinical condition was caused by an adverse reaction of a combination of citalopram and amitriptyline, but made a SS very likely. Citalopram was withdrawn, the amitriptyline dose was gradually tapered off and oxazepam 50 mg three times daily was initiated. Serum concentrations of amitriptyline, nortriptyline, citalopram and desmethylcitalopram were low (21 µg/ml, <10 µg/ml, 15 µg/ml and < 10 µg/ml respectively). No other serotonergic medication was initiated during ICU admission. Twenty-four hours after withdrawal of citalopram, the patient's agitation and anxiety diminished significantly. Hypertension, tachycardia and hyperthermia declined progressively, and returned to normal within the next six days. Seven days after the first suspicion of SS, the patient had completely recovered and could be transferred back to the Department of Internal Medicine.

Discussion

Serotonin syndrome is a complexity of symptoms which is probably caused by changes in the sensitivity of the serotonin receptor system in the brain stem and spinal cord.[1] SS is mostly caused by a combination of serotonin-active drugs, resulting in serotonergic overstimulation (*table 1*).[4-15] However, case reports of selective serotonin reuptake inhibitor (SSRI) poisoning, have indicated that severe toxicity can occur and deaths have been reported following massive single ingestions, although this is exceedingly rare.[4,16-18] The exact incidence of SS is unknown due to a of lack of good quality studies. Mackay et al., estimated the incidence of SS for nefazodone at 0.4 per 1000 users, SS is therefore marked as an uncommon disorder.[19] Eighty-five percent of general physicians are not aware of its existence. In addition, in the absence of specific laboratory tests and imaging characteristics, SS can only be diagnosed by clinical observation and might therefore be easily overlooked.[19] The incidence of SS may become more significant with the increasing prescription of antidepressants in general and SSRIs in particular.[20]

The main indication for prescribing SSRIs is major depression. SSRIs are, in addition, frequently prescribed for anxiety disorders, eating disorders, chronic pain, posttraumatic stress disorder and depersonalization disorder.[21] Serotonin-active drugs are not regularly prescribed in the ICU department. Intensivists have therefore little experience with the serious side effects of these drugs. In addition, diagnosing SS in an ICU population is hampered by the clinical condition of the patient, for instance, absence of muscle rigidity and hyperreflexia in

Table 1. Serotonin-active drugs.

Class	Drugs
Antidepressants	MAOIs (e.g. tranylcypromine, moclobemide), TCAs (e.g. amitriptyline, nortriptyline), SSRIs (e.g. citalopram, paroxetine), SNRIs (duloxetine, venlafaxine), bupropion, nefazodone, trazodone, lithium
Antipsychotics	risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone
Opioids	tramadol, pethidine, fentanyl, pentazocine, buprenorphine, oxycodone, hydrocodone, meperidine
CNS stimulants	phentermine, diethylpropion, amphetamine, sibutramine, methylphenidate, methamphetamine, cocaine
Antimigraines	triptans (e.g. sumatriptan, rizatriptan, zolmitriptan)
Psychedelics	MDMA, MDA, 5-Methoxy-diisopropyltryptamine, LSD, (S)-ketamine
Anti-emetics	ondansetron, granisetron, metoclopramide, erythromycin
Miscellaneous	L-Dopa, valproate, buspirone, linezolid, dextromethorphan, chlorpheniramine, ritonavir

MAOIs: mono-amino-oxidase inhibitors, TCAs: tricyclic antidepressants, SSRIs: selective serotonin reuptake inhibitors, SNRIs: selective norepinephrine reuptake inhibitors, MDMA: 3,4-methylenedioxymethamphetamine (Ecstasy), MDA: 3,4-methylenedioxyamphetamine, LSD: lysergic acid diethylamine, L-dopa: levodopa.

cases of critical illness polyneuromyopathy. Underdiagnosing SS in the ICU-setting might therefore be a significant problem. In our case, the patient was prescribed a combination of high dose citalopram (an SSRI) and amitriptyline (a tricyclic antidepressant (TCA)) for severe generalized anxiety disorder. Either combining proserotonergic drugs (as in this case citalopram and amitriptyline) or adding co-medication involved in inhibiting their metabolism, may result in SS.[22] Case reports have even shown SS with monotherapy of low dose citalopram or normal dose amitriptyline.[23,24] Since serum levels of citalopram and amitriptyline were low and metabolic interacting drugs (ciprofloxacin) had been stopped long before the onset of symptoms, SS in this case was probably caused by an altered level of the cerebral serotonin sensitivity threshold. Although the most plausible diagnosis for symptoms occurring three weeks after ICU submission was SS, the differential diagnosis is much more extensive. *Table 2* shows a practical guide to help differentiate psychotropic drug-related disorders from more common ICU related syndromes (e.g. sepsis and delirium).[25-29]

We would like to point out that SS should be included in the differential diagnosis in ICU patients who use serotonergic active medication and present with unexplained hyperthermia and signs of autonomic dysregulation.

Conclusion

Diagnosing SS in ICU populations is challenging because the syndrome is relatively unknown, diagnosis depends solely on clinical observation and the clinical condition of ICU patients often means that symptoms are suppressed. The recognition

Table 2. Symptoms of psychotropic drug-related disorders and common intensive care related syndromes.

	Del.	NMS	SS	ACS	SI	MH	MG/EC	Sepsis
Autonomic disturbances								
Tachycardia	+	+	+	+	+	+	+	+
Blood pressure instability	+	+	+	-	+	-	-	-
Diaphoresis	+	+	+	-	+	+/-	+/-	+/-
Hyperthermia	-	+	+	+	+	+	+	+
Tachydyspnoea	+/-	+	+	+/-	+	+	+	+
Midriasis	+/-	+/-	+	+	+	+/-	+/-	+/-
Nausea, diarrhoea and urinary incontinence	-	+/-	+/-	-	-	+/-	-	+/-
Cognitive disturbances								
Altered mental state	+	+	+	+	+	+/-	+	+
Altered perceptive cognition	+	-	-	+	+	+/-	+	+
Altered sleep-wake rhythm	+	-	-	-	-	+/-	-	-
Confusion	+	-	+	+	+	+/-	+	-
Restlessness and agitation	+	-	+	+	+	-	+	+/-
Somatic (neuromuscular) disturbances								
Tremor	+	+	+	+	+	-	-	-
Repeated movements	+	-	-	-	-	-	-	-
Muscle rigidity	-	+	+	-	+	+	-	-
Altered coordination disorders	+	-	+	+	+	-	+	-
Hyperreflexia	-	-	+	-	-	-	+	-
Myoclonus	-	-	+	-	-	-	+/-	-
Shiver	-	-	+	-	+/-	+/-	+	+
Miscellaneous								
Sudden start	+	-	-	+	+	+	-	-
Fluctuating course	+	-	-	-	-	-	-	-
Successful treatment with ap*	+	-	-	-	-	-	-	-
Non-specific laboratory abnormalities**	-	+	+	-	-	-	-	-

+: likely manifestation, +/-: possible manifestation, -: unlikely manifestation
Del.: delirium, NMS: neuroleptic malignant syndrome, SS: serotonin syndrome, ACS: anticholinergic syndrome, MH: malignant hyperthermia, SI: sympathomimetic intoxication, MG: meningitis, EC: encephalitis.
* antipsychotic agents (e.g. haloperidol)
** increased white blood cell count, elevated creatine phosphokinase, and decreased serum bicarbonate concentration.

of SS, however, is crucial because if it goes unrecognized it can lead to elevated morbidity and mortality. Changes in pharmacodynamics and pharmacokinetics in ICU populations may probably render patients more susceptible to SS. We would like intensivists to increase their awareness of SS in patients who continue to be given serotonergic active drugs. We advise consulting a psychiatrist and a clinical pharmacist in cases where serotonin-active drugs are prescribed, to discuss the risks, benefits, continuation or withdrawal of this type of medication on an individual basis.[30,31]

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