CASE REPORT

Previously undiagnosed serotonin toxicity: From pre-anaesthetic assessment to postoperative management — a case report

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Abstract

Serotonin syndrome (SS), also known as serotonin toxicity, is a life-threatening condition induced by certain drugs that affect serotonin metabolism. We report a case of SS, induced by a combination of three drugs encountered in a patient with a previously suspected allergy to metoclopramide and pitofenone discovered as an "anaesthetic incident". In the immediate postoperative period, following the administration of antiemetic and analgesic treatment, the patient presented generalized myoclonus and intense abdominal pain. The diagnosis of SS was established using the Hunter Criteria. After the discontinuation of potentially triggering medication and anticonvulsant therapy, the patient was discharged from the ICU with complete resolution within six days. Given the increased use in clinical practice of drugs that may interfere with serotonin metabolism, the rising prevalence of mental health disorders and the increasing use of illicit drugs, it is essential for anaesthetists to be aware of the potential for SS occurrence.

Keywords: Serotonin Syndrome. Anaesthesia. Awareness.

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Introduction

Serotonin syndrome (SS) is a drug-induced condition usually caused by a combination of substances which interfere with serotonin metabolism or act as a direct serotonin receptor agonists. SS is observed across a full range of age groups, with a growing incidence secondary to increased clinical use of SS trigger drugs. Due to its clinical polymorphism, the true incidence of SS is unknown, the condition is under-recognised and under-reported by physicians.[1]

Clinically, SS consists of a combination of mental status changes, neuromuscular hyperactivity and autonomic hyperactivity. Symptoms can range from mild and nonspecific to severe symptoms that include hyperthermia, seizures, stiffness, coma, and death.[1,2]

Given the widespread use of serotonergic medications, it is important for anaesthetists to identify high-risk patients and effectively manage peri-operative cases of SS.

Case Report

Written consent was obtained from the patient for publishing this case report.

The patient was a 36-year-old female with a BMI of 23.43, scheduled for a diagnostic hysteroscopy at the Emergency Hospital Targu Mures, Romania on 22.06.2020 after an episode of hypogastric pain and prolonged metrorrhagia. The patient had a prior surgical history for endometriosis, and bilateral ureteral stents for urolithiasis. During the pre-anaesthetic assessment, the patient reported a history of allergy to metoclopramide and pitofenone described as an "anaesthetic incident" in her previous surgery. The patient was unable to mention how the allergy manifested and these events were not recorded in her medical files.

On the day of surgery, a complete blood count was performed, which showed secondary anaemia (haemoglobin 8.50 g/L and a haematocrit of 29%) in the absence of other pathological findings.

The procedure was performed using a size 3 laryngeal mask airway. Pre-oxygenation was followed by anaesthetic induction with: lidocaine 1 mg/kg, propofol 2 mg/kg and fentanyl 0.2μg/kg. Anaesthesia was maintained with an oxygen, and air admixture (50%:50%) and Sevoflurane. Intraoperatively, mechanical ventilation maintained an end-tidal carbon dioxide of 30-35 mmHg. The patient's haemodynamic profile remained stable throughout the 30 minutes operation. Postoperative pain management comprised of analgesics as acetaminophen 1g, metamizole 1g, tramadol 100 mg and granisetron 1 mg for nausea/vomiting prophylaxis. Urine output was 150 ml.

The patient was admitted to the postoperative care unit with the total reversal of anaesthesia, (GCS 15 points, Aldrete score 8 points immediately following surgery and 10 points one hour after surgery) haemodynamically stable and spontaneous respirations with supplemental oxygen.

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Two hours after anaesthetic recovery, the patient presented generalized myoclonus, intense abdominal pain, headache, nausea and photosensitivity. There was no altered state of consciousness, no focal neurological deficit and no motor or sensory deficit.

The current episode was interpreted as a SS that occurred in response to co-administration of tramadol, granisetron and fentanyl. The collateral history from the patient's mother revealed that the patient had experienced similar symptoms after her previous surgeries, which lasted more than 24 hours.

Supportive therapy was started with the discontinuation of any triggering agents, intravenous fluids, oxygen on a non-rebreather mask, diazepam 10 mg intravenously and propofol 50 mg. The neurological examination revealed hyperreflexia, positive Romberg sign and a positive Babinski sign bilaterally. Anticonvulsant therapy was initiated with 2 mg of midazolam at the onset of seizure activity, 4 mg/day of clonazepam and 100 mg/day of hydrocortisone hemisuccinate, with successful alleviation of symptoms. Laboratory findings revealed normal serum levels for creatine kinase (31 U/L), procalcitonin and C-reactive protein, but D-dimer (295 ng/ml) and prothrombin time (13.80 sec.) were increased. Myoclonic seizures subsided but reappeared during the evening, requiring continuous administration of propofol at a rate of 0.5 mg/kg/h.

During hospitalization, myoclonic episodes reappeared, however, their intensity was significantly reduced as compared to the day of surgery. The patient's condition gradually improved and she was discharged on day six with complete recovery.

Discussion

SS is a relatively frequent situation that can occur as a consequence of general anaesthesia or as a complication of pain management in selected cases. Diagnosis of SS is established by using the Hunter Serotonin Toxicity Criteria that requires the presence of at least one of the symptoms (Table-1). In our case, the patient presented with spontaneous clonus, tremor, and hyperreflexia.[1]

Some of these symptoms can be interpreted as pertaining to a separate pathology or as an allergic reaction related to a specific drug, which could be a source of error in pre-anaesthetic assessment. Catharina E. Van Ewijk et al in a 10-week prospective observational cohort study observed that in the ICU, 72% of patients diagnosed with delirium were on long term treatment with drugs which could trigger SS.[3]

In our case we suspected that the first interaction with a drug that produced SS was undiagnosed and presented at the pre-anaesthetic assessment as an allergy to metoclopramide.[4]

Table: The Hunter serotonin syndrome criteria.[1]

Hunter Criteria[1]	Spontaneous clonus
	Inducible clonus with agitation or diaphoresis
	Ocular clonus with agitation or diaphoresis
	Tremor and hyperreflexia or hypertonicity
	Temperature higher than 38° C and ocular or inducible clonus

Usually, severe cases are precipitated by therapeutic doses of a combination of serotonergic drugs, but a single high dose of some drugs, such as tramadol and 3, 4-methylenedioxymethamphetamine ('ecstasy') may also induce serotonin toxicity.[1,2] Some opioids inhibit the serotonin transporter (SERT), leading to elevated concentrations of plasma serotonin.[5]

Related to general anaesthesia, the drugs that are most associated with SS are opioids, generally used in the combination with other serotonergic drugs.[4] In our case, the trigger was the concomitant administration of an antiemetic drug: granisetron, and two opioids: fentanyl and tramadol. Granisetron is a 5-HT3 receptor antagonist. Tramadol acts through several mechanisms: increasing serotonin release, inhibiting SERT and the Cytochrome P450 microsomal oxidases. Fentanyl binds to serotonin 5-HT1A (Serotonin 1A receptor) and 5-HT2A receptors and produces an efflux of serotonin.[6-8]

The most serious complications of SS are disseminated intravascular coagulation (DIC), rhabdomyolysis, metabolic acidosis, renal failure, myoglobinuria and acute respiratory distress syndrome.[6] In this case, laboratory tests showed an increase in D-dimer (295 ng/ml) and a modified prothrombin time test (13.80 sec), which may suggest a slow evolution to DIC.

The fact that the patient misunderstood the events that occurred during her previous anaesthesia and that those events were overlooked and not reported at all, made the anaesthetist avoid these drugs in her postoperative management, but without excluding other drugs from the SS risk class. Metoclopramide was excluded but granisetron was given instead, which together with tramadol and sustained by fentanyl, caused a moderate to severe form of serotonin toxicity.

The differential diagnosis of SS can be made with malignant hyperthermia and anticholinergic toxicity which are not characterized by clonus or hyperreflexia. In neuroleptic malignant syndrome, the onset of symptoms is usually slow.[7] Also, in this case, we can consider the differential diagnosis with anaphylactic shock where the

main clinical sign is haemodynamic instability with hypotension and acute airway obstruction. Anaphylactic shock was ruled out due to peri- and postoperative haemodynamic stability.[9]

In our case, the operation had diagnostic purposes, with the patient later requiring an additional surgical intervention for curative purposes. This case represents a challenge in terms of anaesthesia and requires careful aesthetic management, post-operative analgesia and antiemetic treatment. Total opioid-free intravenous anaesthesia can be performed with intravenous hypnotic and non-depolarizing muscle relaxant ± an inhalation agent.[10] For analgesia, to avoid the administration of opioids, a transversus abdominis plane block associated with the rectus sheath block can be performed as part of multimodal pain management. Also, spinal anaesthesia or combined spinal-epidural anaesthesia is a technique that can be considered both for anaesthesia and for cutting acute pain in the immediate postoperative period.

Conclusion

This case report emphasizes the importance of a thorough pre-anaesthetic assessment in order to identify those patients with a high-risk of SS, and to avoid co-administration of drugs that interact with serotonin metabolism. Future efforts should focus on increasing anaesthetists' education in the diagnosis and management of this syndrome.

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