



Hyperthermia and Rigidity Following Overdose of an Unknown Drug; A Case Report and Literature Review

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ABSTRACT

Drug induced hyperthermia is a rare presentation which can rapidly lead to gross metabolic abnormality and death. These presentations are further complicated by the wide range of potentially causative agents. We present a case of rigidity and hyperthermia, following overdose of an initially unknown substance leading to challenging management decisions in the Emergency Department. This case was later identified as Serotonin Syndrome. The patient presented with trismus which was managed with rapid sequence induction of anaesthesia to allow airway protection. On extubation a significant degree of laryngeal oedema complicated weaning, a possible complication of Serotonin Syndrome not previously described in the literature. We discuss the pathophysiology of Serotonin Syndrome, important differentials and practical considerations in managing hypertonicity of unknown origin in a young person.

Keywords: Serotonin syndrome; Overdose; Hyperthermia; Hypertonicity.

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Introduction

Serotonin Syndrome (SS) is a life-threatening condition that typically presents with neuromuscular hyperactivity, autonomic hyperactivity and neurocognitive symptoms. This syndrome is thought to be triggered by stimulation of post synaptic 5HT_{1A} and 5HT_{2A} receptors found

in both the central and peripheral nervous systems [1]. Incidence appears to be increasing, reflective of increased prescription of pro-serotonergic agents, but cases where symptoms are mild may not be identified as diagnostic practice varies [2]. Whilst most patients are between 22 and 50 years old, SS has been described in all age groups. There appears to be a slight female predominance (male to female

ratio is 1:1.7). Selective serotonin reuptake inhibitors in particular are involved in a substantial proportion of UK overdoses. In 2013 the UK National Poisons Information Service (NPIS) found citalopram and fluoxetine to be the most common substances discussed in telephone queries [3].

Case Report

A previously well 17-year-old woman taking no regular medication was found collapsed by her family at home. She left a note apologising for letting them down. She was brought to the Emergency Department by ambulance. During transfer she became combative and suffered three short tonic-clonic seizures, which terminated with a total of 15mg rectal diazepam. On arrival, she was unresponsive with a GCS of 8 (E4V1M3), tachycardic, tachypnoeic, hypertensive and had an invasive temperature of 40.1°C, despite receiving paracetamol in transit. In addition, she was found to have increased muscular tone (board-like rigidity). Airway assessment demonstrated trismus and bilateral nasopharyngeal airway devices were inserted. High flow oxygen and intravenous (IV) fluid resuscitation were given. Evaporative cooling was applied using damp towels and a fan. The initial arterial blood gas revealed a pH of 7.00, pO₂ 26.3 kPa, pCO₂ 9.4 kPa, base excess of -13.8mmol/L and lactate of 8.2mmol/l.

Due to the severity of the hypertonicity, the unknown nature of the precipitant and the need for reliable muscle relaxation to achieve a definitive airway, dantrolene 180mg IV was given. Conditions for induction were further optimised by alerting the anaesthetic team and retrieving the difficult intubation equipment. Initial medical therapy had little effect on the hypertonicity, which resolved following successful rapid sequence induction of anaesthesia with 200mg propofol, 2mg midazolam and 100mg rocuronium IV. Prior to transfer chlorpromazine 12.5mg IV was given.

A computed tomography (CT) scan of the patient's brain revealed no abnormality and she was then transferred to the Intensive Care Unit (ICU). Roughly 4 hours after the patient was found collapsed her paracetamol level was found to be 35mg/L. Despite paracetamol having been administered in the ambulance this was felt to reflect a potential paracetamol overdose and an IV N-acetylcysteine infusion was prescribed. The initial creatinine kinase level was 813 U.I⁻¹ and 8.4% bicarbonate was administered in addition to fluid resuscitation.

Within 24-48 hours patient's metabolic abnormality was corrected. ICU care was complicated by ventilator associated pneumonia and an unexpected degree of laryngeal oedema. She was successfully extubated on day 13. During this time, empty medication packets were found hidden in the patient's room equivalent to 3.15g of venlafaxine (approximately 40 mg/kg), 150mg of loratidine, 1.6g

of ibuprofen and 5.5g of paracetamol (approximately 78mg per kg). In total the patient spent 17 days in hospital allowing continued speech and language therapy. She was then discharged to a psychiatric inpatient unit for further assessment and made a complete recovery.

At presentation inflammatory markers were somewhat raised, with a white cell count of 16.0x10⁹/L and neutrophil count of 11.4x10⁹/L. Potassium levels were normal throughout, despite a mild acute kidney injury with a urea of 5.3mmol/L and a creatinine of 105umol/L. Creatinine kinase levels continued to rise in the first 24 hours peaking at 14,083 U.I⁻¹. Salicylate levels were undetectable. Liver function tests were normal. CT head was normal. No QT prolongation was identified on ECG.

Discussion

Hyperthermia and rigidity are key features of SS, malignant hyperpyrexia (MH) and neuroleptic malignant syndrome (NMS). Differentiating these conditions is challenging when the trigger is unclear. MH is an autosomal dominant genetic condition. In MH a mutation in Ryanodine receptors, which are found in calcium channels, causes uncontrolled release of calcium ions when exposed to certain drugs. Triggers include depolarising muscle relaxants (suxamethonium) and volatile anaesthetic agents (halothane, desflurane, sevoflurane, isoflurane) [4]. These agents have typically been restricted to in-hospital use, however methoxyflurane is increasingly used in the pre-hospital and outpatient setting as Pentrox[®] for analgesia. Unfortunately, previous exposure to triggers without complication does not rule out the disease. In MH increased uncoupling of oxidative phosphorylation produces tetany, excessive carbon dioxide production, hyperthermia, tachycardia, anaerobic metabolism, acidosis, muscle breakdown and hyperkalaemia. Dantrolene, a skeletal muscle relaxant that acts on calcium channels, is the treatment of choice in MH and may need to be continued for 72 hours to prevent recurrence [5]. With early detection and treatment, the mortality rate of MH has fallen to less than 5% [4].

NMS is an idiopathic drug reaction that can occur at any time during anti-dopaminergic therapy but most commonly develops within 10 days of treatment [6]. Drug levels are often normal. Typical features are hyperthermia, altered mental status and skeletal muscle rigidity. Autonomic dysfunction may present as tachycardia, hypotension or hypertension, or diaphoresis. In severe cases where diagnostic certainty is high bromocriptine, a dopamine agonist, can be used to treat NMS. SS has many potential causes (Table 1). The cause may be high or low dose monotherapy, or serotonergic agents used in combination. Features include tremor, myoclonus, ataxia, hyper-reflexia (neuromuscular hyperactivity), hyperthermia, sweating, tachycardia,

Table 1. Serotonergic agents which may trigger serotonin syndrome.

Class	Drugs
Antidepressants	Selective serotonin reuptake inhibitors (SSRI), Monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA), serotonin norepinephrine re-uptake inhibitors (SNRI),
Opioids	Tramadol, pethidine, fentanyl, pentazocine, buprenorphine oxycodone, hydrocodone
Sympathomimetic	MDMA, amphetamines, methamphetamine, cocaine
Herbs	St John's Wort, ginseng, nutmeg

nausea (autonomic hyperactivity) and agitation, confusion, hallucinations, seizures and coma (neurocognitive symptoms). Hypertonicity, clonus and QT interval prolongation are signs of life threatening disease. SS is a clinical diagnosis and the Hunter Serotonin Toxicity Criteria (HSTC) can be used to aid identification (Table 2) [7]. There is no correlation between the symptoms and serum serotonin concentration.

Serotonin (5-hydroxy tryptamine or 5HT) is formed by the decarboxylation and hydroxylation of the essential amino acid tryptophan and is metabolized by monoamine oxidase-A (MAO-A) into 5-hydroxyindoleacetic acid. About 90% of serotonin is found in the enterochromaffin cells

within the gastrointestinal tract where it is used to regulate gastrointestinal motility [8]. The remaining 10% is synthesised centrally in serotonergic neurons and helps with mood, sleep, appetite, learning and memory. Platelets store serotonin and release it when activated causing vasoconstriction.

The mainstays of treatment in SS are discontinuing causative agents and supportive care [9]. Actions are aimed at normalising the vital signs and correcting acute metabolic derangement. Agitation and seizures can be controlled by Benzodiazepines. Serotonergic antagonists such as cyproheptadine, can be used, however they may cause sedation and hypotension. Chlorpromazine is a 5HT_{2A} antagonist which can achieve receptor blockade at lower doses than its

Table 2. Clinical criteria for the identification of serotonin syndrome.

Hunter Serotonin Toxicity Criteria (HSTC)	
Patient on serotonergic agent and meets one of following criteria	
➤	Spontaneous clonus
➤	Inducible clonus PLUS agitation or diaphoresis
➤	Ocular clonus PLUS agitation or diaphoresis
➤	Tremor PLUS hyperreflexia
➤	Hypertonia PLUS temperature above 38°C PLUS ocular clonus or inducible clonus

Table 3. Conditions causing hyperthermia and muscle rigidity.

Condition	Drugs causing	Onset	Clinical features
Malignant hyperthermia (MH)	Depolarising muscle relaxants or volatile anaesthetic agents	Within minutes or 24 hours	Hyperthermia, rigidity, rise in end tidal CO ₂
Neuroleptic Malignant syndrome	Dopamine antagonist	Days to weeks	Hyperthermia, rigidity
Serotonin syndrome	Serotonin agonist	Within 24 hours	Neuromuscular hyperactivity, autonomic hyperactivity, neurocognitive changes

Table 4. Recent case reports describing serotonin syndrome and their outcomes.

Article	Number of cases	Age Group	Causative serotonergic agent	Outcomes
Patel & Galarneau 2016 [13]	2	Adolescent	Fluoxetine	Complete recovery in all
Prakash et al. 2015 [14]	12	Adult	Valproic acid, herbal products, fluoxetine, cough syrup (chlorpheniramine+ dextromethorphan), tramadol, venlafaxine, paroxetine,	Complete recovery in all
Malik & Kumar 2012 [12]	1	Adult	Escitalopram, cocaine	Complete recovery
Grenha et al. 2013 [10]	1	Paediatric	Sertraline	Complete recovery
Caamano et al. 2016 [15]	1	Elderly	Tramadol, escitalopram	Small parenchymal intracranial bleed requiring further care.

alternative cyproheptadine [5]. Dantrolene and bromocriptine are less effective in SS. Patients who are unable to protect their own airway, or who have severe muscle rigidity, should have a definitive airway placed.

SS may be more difficult to recognise in younger age groups as there is a lack of published cases from the paediatric population and a tendency for children to present in a more non-specific way [7]. Prescribing of SSRIs is increasing in children and adolescents, and the incidence of serotonin syndrome in this group appears to be increasing as a result [10]. Adolescents who make further attempts to harm themselves do so with increasing suicidal intent, increasing threat to life and with decreasing time between events [11]. This effect increases the importance of early prevention and, where possible, interventions to interrupt the cycle of self-harm. Support strategies should be used which help young people learn to cope with stressful triggers, rather than solely focusing on harmful behaviour. Hyperthermia and muscular rigidity can be present in all the above conditions

(Table 3) making diagnosis challenging when the causative agent is not known. Both dantrolene and chlorpromazine were used in this case to improve muscular rigidity. Whilst there is no level 3 or higher evidence to support their use in SS, both these agents were given in accordance with current UK NPIS Toxbase guidance. After reviewing recently published case reports, we note that patients with serotonin syndrome present in a wide variety of ways, but where recognition and management is prompt, recovery is usually complete (Table 4) [10, 12-15].

In conclusion, SS is an important medical emergency, increasingly frequent in our population, which requires rapid metabolic control. Recognition is essential. Benzodiazepines are a cost-effective method to rapidly achieve seizure control and reduce agitation. If significant rigidity continues despite initial measures, induction of anaesthesia and neuromuscular blockade are the next steps in management.

Conflicts of Interest: None declared.

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