CASE REPORT

Challenges in a large mixed drug overdose patient

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SUMMARY

A 39-year-old homeless man was found confused and incoherent after ingesting an estimated total of 200 tablets of various medications. He presented to the emergency department with delirium, tachycardia, clonus and hyperthermia of 38.0°C. His condition worsened rapidly with his temperature rising to 39.9°C despite active cooling. The patient was subsequently sedated, intubated, paralysed and admitted to the intensive care unit, where he remained for 38 days. His initial presentation of a large mixed drug overdose manifested as serotonin syndrome, which had a protracted course complicated by ethanol withdrawal. He eventually stabilised and was transferred to the general ward, and was subsequently discharged from hospital on day 47 with continuing psychiatric care. This case demonstrates the challenges and considerations in diagnosis and management of large mixed drug overdoses where multiple toxidromes overlap.

medications that the patient had access to and were found on his toxicology screening had serotonergic qualities to varying degrees (table 1). A working diagnosis of serotonin syndrome was made clinically based on Hunter's criteria,⁴ and in consultation with the local poison centre. The patient was also treated for concurrent alcohol withdrawal given a Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar)⁵ score of 24.

INVESTIGATIONS

As part of initial investigations in the emergency department, a serum toxicology screen was done which was negative for acetaminophen, salicylates, acetone, ethanol, isopropyl alcohol, methanol, ethylene glycol, benzodiazepines and tricyclics but positive for barbiturates (primidone). A comprehensive urine toxicological analysis was positive for benzodiazepines, barbiturates, olanzapine, primidone, quetiapine, bupropion and citalopram.

BACKGROUND

It is estimated that deliberate self-poisoning accounts for 170 000 presentations to UK hospitals every year.¹ Of emergency department presentations for self-harm, 82–95% of these are from medication overdose or self-poisoning.² Owing to the wide number of causative agents and their interactions, it can be extremely challenging to diagnose and treat multiple and overlapping toxidromes. Detailed evaluation and timely treatment in the emergency department and intensive care unit (ICU) are critical to the care of patients with large mixed drug overdoses.³

CASE PRESENTATION

A 39-year-old man presented to our emergency department via ambulance after being found incoherent at his residential shelter from an unknown overdose. He was last seen at his baseline the day before. Paramedics estimated that over 200 pills were missing from his recent prescriptions comprising: bupropion, escitalopram, olanzapine, phenytoin, primidone and quetiapine. He denied any alcohol or other substance use.

On arrival, he was tachycardic (109 bpm) and had a temperature of 38.0°C. He was confused and agitated, and had some difficulty responding to questions. He was initially given oral-activated charcoal, intravenous saline and intravenous diazepam for agitation. Over the subsequent hour, the patient's condition declined rapidly with increasingly altered mental status (agitation, confusion), autonomic system excitation (diaphoresis, hyperthermia, tachycardia) and neuromuscular excitation (myoclonus, hyper-reflexia, tremors, muscle rigidity). The

DIFFERENTIAL DIAGNOSIS

Serotonin syndrome is very difficult to diagnose with large mixed drug overdoses. Careful consideration of various medications is needed to diagnose serotonin syndrome, particularly as symptoms are overlapped by other syndromes. Given the mixture of drugs ingested and clinical presentation, we were concerned about other possible diagnoses, particularly neuroleptic malignant syndrome (NMS) caused by excessive dopamine blockade,⁶ anticholinergic syndrome, malignant hyperthermia and infection.

Serotonin syndrome is a clinical diagnosis with specific neurological signs, the most important being generalised hyper-reflexia which occurs in moderate-to-severe cases and is seen rarely in any other condition.⁷ Commonly, there is sustained clonus at the ankle and ocular clonus, and lower limbs have a greater degree of hyper-reflexia than the upper limbs. While NMS can present with similar altered mental status and autonomic dysfunction, it has characteristic clinical associations including bradykinesia, lead pipe rigidity and other extrapyramidal features.⁷

Measurement of blood 5-HT levels is not helpful as it is the local concentration at nerve terminals that causes the physiological effects.⁸ Strictly, the diagnosis of serotonin syndrome requires that other possible diagnoses are ruled out. In this case, our patient's clinical presentation met Hunter's criteria for serotonin syndrome.⁴

The patient's presentation (autonomic instability, agitation, tremor) could also be consistent with concomitant alcohol withdrawal, where he had no ethanol on serum toxicology. He had a previous diagnosis of an alcohol use disorder, as well as a

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Table 1 Medications discovered on toxicological analysis in our patient and their serotonergic properties

Medication	Class of medication	Context of use in our patient	Serotonergic properties	Half-life (range in hours) ¹³
Bupropion	NDRI	Patient had been prescribed; found on urine toxicology screening	Bupropion has been noted in previous case studies to independently precipitate serotonin syndrome. ¹⁴	9.6–20.9
Escitalopram	SSRI	Patient had been prescribed; found on urine toxicology screening	Rare but previously described in the literature to independently precipitate serotonin syndrome ¹⁵	22–32
Olanzapine	Atypical antipsychotic	Patient had been prescribed; found on urine toxicology screening	Olanzapine is an antagonist of the serotonin 5-HT ₂ and 5-HT ₃ receptors, which could potentiate biased activation of 5-HT _{1A} receptors and precipitate serotonin syndrome. ¹⁶	21–54
Phenytoin	Anticonvulsant	Patient had been prescribed; found on urine toxicology screening	No cases of phenytoin-induced serotonin syndrome were identified in the literature.	6–60
Primidone	Anticonvulsant	Patient had been prescribed; found on urine and serum toxicology screening	Primidone has previously been found to increase serotonin levels in the human body. ¹⁷	3.3–22.4
Quetiapine	Atypical antipsychotic	Patient had been prescribed; found on urine toxicology screening	Previously demonstrated to precipitate serotonin syndrome in conjunction with citalopram (also identified in our patient). The supposed aetiology is quetiapine-induced supersensitivity of 5-HT _{1A} receptors. ¹⁸	3–9

NDRI, norepinephrine-dopamine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

CIWA-Ar score of 24 on presentation. Alcohol withdrawal consists of the key clinical findings of: anxiety, tremor, headache, disorientation, agitation, delirium, hallucinations, diaphoresis, insomnia, nausea/vomiting, hyper-reflexia, tachycardia, hypertension, seizures, low-grade fever and hyperventilation.⁹

TREATMENT

Following clinical diagnosis, the patient was treated in the emergency department for serotonin syndrome with aggressive supportive care. He was originally given intravenous diazepam 5–10 mg every 30 min. He was monitored continuously on telemetry for any cardiac dysrhythmias. An original 1 L intravenous bolus of normal saline was given, followed by 1 L of cold normal saline with the intent to control the patient's hyperthermia. Owing to the inability to lower his rising temperature with supportive measures and active cooling (ice packs placed on the neck, axilla and groin, as well as a cooling blanket), the patient required deep sedation, paralysis and intubation for airway protection. He was subsequently started on intravenous midazolam 2–4 mg every 30 min, and transferred to the ICU for hyperthermic protocol. He was also treated with a dose of cyproheptadine (12 mg, then 4 mg every 4 hours via nasogastric tube, to a maximum of 32 mg/day), a benign intervention which may have an effect on shortening length of stay but is not proven to change outcomes in serotonin syndrome.¹⁰

OUTCOME AND FOLLOW-UP

The patient had a protracted ICU course complicated by ventilator-associated pneumonia, line sepsis, dysrhythmias, refractory hyperthermia and delirium. The patient did not develop significant rhabdomyolysis, renal failure or coagulation abnormalities, all serious complications of serotonin syndrome.⁷ Despite receiving cyproheptadine on admission to the ICU, there was no clinical effect on his serotonergic symptoms. The patient continued to be agitated, despite aggressive treatment with benzodiazepines. He was kept on an intravenous midazolam infusion (up to 30 mg/hour) that took 30 days to wean off. There was a question of the patient metabolising midazolam more readily through his CYP-450 pathway, and lorazepam was added as it is not metabolised through this enzymatic pathway.¹¹ It was only on day 28 of admission after starting high-dose diazepam (40 mg orally every 4 hours) that the patient had a

significant improvement in his agitation and his clonus only abated on day 30 of admission.

Other adjuvant treatments were used to help control his agitation. To assist in treating alcohol withdrawal, clonidine was added on day 9 of admission and eventually switched to dexmedetomidine due to concerns about delirium. Neither course contributed to reducing the patient's symptoms. The patient also received sedation with intravenous hydromorphone and propofol. Cisatracurium besilate was used for paralysis. On day 25 of admission, psychiatry was consulted and haloperidol (1 mg intravenous twice a day and 1–2 mg intravenous every 4 hours as needed) and valproic acid (500 mg three times a day) were added to help manage agitation and prevent seizures, respectively. The patient was stabilised after 38 days in the ICU, discharged to the general ward and finally home after 47 days of admission.

The patient has recovered completely from his symptoms. He is continuing to attend regular follow-up with a psychiatrist for major depressive disorder and is remaining sober through participating in substance use treatment.

DISCUSSION

In a large mixed drug overdose, diagnosis can be difficult to discern between the variety of medications, substances and their interactions. Our patient was diagnosed in the emergency department with serotonin syndrome, but his course in the ICU was complicated by multiple toxidromes with overlapping symptomatology.

Since its recognition in 1959, the incidence of serotonin syndrome has been rising with the increasing use of psychotropic medications. In 2005, 48 279 cases of serotonin syndrome were reported to the US Poison Control Centres, of which 118 resulted in death.¹² The clinical symptoms arise mainly from overstimulation of the serotonin 5HT_{1A} and 5HT_{2A} receptors in the central nervous system leading to the classic triad of clinical symptoms: autonomic instability, mental status changes and neuromuscular changes.⁴ Left untreated, serotonin syndrome can progress to potentially fatal rhabdomyolysis, hyperkalemia, acidosis, acute renal kidney injury, disseminated intravascular coagulopathy and death.⁷

The syndrome is treated mainly by providing supportive care for the patient including aggressive fluid replacement with a

Learning points

- ▶ Large mixed drug overdoses can manifest with multiple and overlapping toxidromes.
- ▶ Following a large mixed drug overdose, the first few hours of clinical examination are crucial for recognising toxidromes and managing aggressive supportive care.
- ▶ Serotonin syndrome can be identified using Hunter's Serotonin Toxicity criteria and specific signs include generalised hyper-reflexia (more prominent in the lower limbs), ocular clonus and sustained clonus at the ankles.
- ▶ Serotonin syndrome may be prolonged by the interaction of multiple serotonergic medications.

goal urine output of 200–300 mL/hour.⁴ Benzodiazepines can provide sedation and treatment of withdrawal symptoms, as was the case with our patient.⁹ There is limited evidence (only case reports) for the use of serotonin antagonists such as cyproheptadine in mild-to-moderate cases of serotonin syndrome.¹⁰ Moreover, cyproheptadine does not shorten the time course of serotonin syndrome¹⁰ and did not contribute significantly to the care of our patient. Chlorpromazine may be appropriate for sedation as another 5-HT₂-antagonist indicated for more severe cases of serotonin toxicity.⁷

Most patients are noted to improve their serotonergic symptoms within 24 hours of ceasing the precipitating medication,⁸ whereas our patient had persisting ankle clonus and met Hunter's criteria for diagnosing serotonin syndrome for 30 days.

Our patient's prescribed medications are not commonly associated with serotonin syndrome. It is unlikely that any single medication caused severe serotonin toxicity in our patient;⁷ we hypothesise that his rapid, severe and prolonged symptoms were due to the additive effects from multiple drugs leading to an excess of serotonin and modulation of 5-HT receptors. Several of the medications to which the patient had access have complementary serotonergic activity (table 1). Although not well understood, some individuals may also be more susceptible to serotonin excess and toxicity due to individual pharmacokinetic or pharmacodynamic effects.⁷ In addition, our patient's concomitant alcohol withdrawal made his diagnosis and treatment difficult and may have contributed to his prolonged hospital admission.

It is critically important to recognise and diagnose common toxidromes in large mixed drug overdoses. Although our patient met the criteria for the diagnosis of serotonin syndrome, no single medication from his overdose commonly precipitates serotonin excess. His clinical presentation and course were most

likely impacted by the interaction of multiple serotonergic medications and other non-serotonergic psychotropic medications, substances not detected at the time of toxicology screening, and concurrent alcohol withdrawal. The principles of care for large mixed drug overdoses are to rely on clinical assessments for diagnosis and to provide aggressive supportive treatment.

Contributors PZ wrote and edited the case report. SL managed the patient in the emergency room and supervised the writing of the report. MT and EA contributed their toxicology expertise to the management of the patient and edited the report.

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