

# Prolonged serotonin toxicity with proserotonergic drugs in the intensive care unit

Luke E Torre, Rajiv Menon and Bradley M Power

The serotonin syndrome was extensively reviewed in 1991 by Sternbach.<sup>1</sup> The clinical signs and symptoms had been reported since the 1960s and were seen mainly with use of monoamine oxidase inhibitors (MAOIs) and L-tryptophan. Since then, its incidence has increased owing to the plethora of new proserotonergic agents available to treat both psychiatric and non-psychiatric conditions.<sup>2</sup> In addition, illicit drugs with proserotonergic effects have become more prevalent.<sup>3</sup> In critical care, serotonin toxicity is seen mainly in the setting of overdose with multiple proserotonergic agents. Its clinical course is well recognised, with most patients requiring observation alone. A proportion require supportive care with mechanical ventilation and administration of benzodiazepines in critical care environments, usually for less than 48 hours.<sup>4,5</sup>

The pharmacodynamics of some of the agents involved suggest that prolonged serotonin toxicity is theoretically possible, but to our knowledge it has not been reported previously. We describe three patients with prolonged serotonin toxicity after overdose with proserotonergic agents and discuss the mechanisms, predictive factors and critical care management of this condition.

## Clinical records

### Patient 1

A 21-year-old woman with a history of depression, post-traumatic stress disorder and borderline personality disorder was brought to the emergency department (ED) 2 hours after a large polypharmacy overdose, including (estimated doses): tramadol (3 g), quetiapine (15 g), escitalopram (560 mg), mirtazapine (315 mg), fluoxetine (1.1 g), risperidone (120 mg) and lithium (slow release, 13 g). Other agents not known to cause serotonin toxicity were also ingested.

On arrival in the ED, the patient was drowsy (Glasgow Coma Score [GCS], 10/15), with tachycardia (heart rate, 130 beats per min), hypertension (blood pressure, 165/90 mmHg) but no fever (temperature, 36.1°C). Within 15 minutes, she developed increasing rigidity, and the GCS fell to 5/15, necessitating intubation for airway protection. This was performed after intravenous administration of midazolam (5 mg) and suxamethonium (100 mg). After intubation, activated charcoal (50 g) was given via a nasogastric tube, a morphine and midazolam infusion was begun, and the patient was admitted to the intensive care unit.

## ABSTRACT

Serotonin toxicity secondary to drug therapy, interaction or overdose is an increasing phenomenon worldwide. A proportion of patients require admission to an intensive care unit, but the treatment needed is usually supportive and of short duration. Prolonged ICU admission to control ongoing or long-lasting serotonin toxicity has not been reported previously.

We describe three patients with prolonged serotonin toxicity, lasting 12–18 days. Symptoms of toxicity were easily demonstrable in each and were refractory to currently recommended therapies.

We review the pharmacological mechanisms that led to prolonged serotonin toxicity in these patients. Predictors for prolonged serotonin toxicity include involvement of irreversible monoamine oxidase inhibitors (MAOIs) or slow-release preparations resistant to the effects of activated charcoal (eg, lithium). We also discuss the implications of prolonged toxicity for critical care management, to maintain optimal patient outcomes.

Crit Care Resusc 2009; 11: 272–275

Electrocardiography (ECG) initially showed sinus tachycardia with widespread T-wave inversion in the anterior and inferior leads; this resolved over 24 hours. The QRS and QT intervals were not prolonged at any time, while the QTc was only mildly prolonged in the first 24 hours (maximum, 475 ms). The serum concentration of lithium on Day 3 of admission was below the therapeutic range.

During the ICU admission, the patient had fevers, rigidity and clonus which were treated with a midazolam infusion. A single dose of cyproheptadine (12 mg enterally), and regular olanzapine, had no appreciable effect.

By Day 6, there were no clinical signs of rigidity and clonus, and the patient was extubated and transferred to an observation ward. However, these symptoms recurred within 12 hours and persisted despite treatment with oral diazepam. The patient was reintubated and readmitted to the ICU.

She was extubated on Day 9, but serotonin toxicity symptoms did not resolve completely until Day 12, when she was discharged.

**Patient 2**

A 49-year-old man with bipolar affective disorder had been treated with lithium and phenelzine for 2 years. Ten days before he presented to the ED, his psychiatrist had replaced phenelzine with tranylcypromine. For the next 2 days, the patient was slightly drowsy, and thereafter he became increasingly agitated, tremulous and confused. He was brought to the ED by his wife.

He was noted to be delusional, with a GCS of 14, tachycardia (heart rate, 123 beats per min), fever (temperature, 38.1°C), and blood pressure in the reference range. He had muscle rigidity, hyperreflexia and clonus in his legs. His serum lithium concentration was in the therapeutic range. He was diagnosed with serotonin toxicity secondary to MAOI interaction. On the basis of the history given by his wife, an overdose was not suspected, and activated charcoal was not given.

The patient was treated with a midazolam infusion overnight while in the ED; this was continued on his transfer to the ICU. However, his symptoms worsened, with increasing aggression and deteriorating respiratory function. On Day 3, he was intubated and mechanical ventilation was begun.

Despite the addition of cyproheptadine (4 mg 4-hourly) to his treatment on Days 7–21, serotonergic symptoms persisted. Clonus and rigidity were noted as late as Day 18 of the admission. Extubation on Day 15 failed because of the patient's aggression, confusion and ongoing signs of serotonin excess, and a tracheostomy was subsequently placed. This was removed on Day 25, and he was discharged from the ICU the next day.

**Patient 3**

A 24-year-old man with a history of major depression presented to the ED after being found by friends lying on the floor unconscious with twitching movements. They reported that he had drunk alcohol and taken at least one ecstasy tablet in the preceding 24 hours. He was believed to be receiving lithium and quetiapine treatment for the depression.

On initial examination, he had a GCS of 3, tachycardia (heart rate, 145 beats per min), tachypnoea (respiratory rate, 46 breaths per min), hypertension (blood pressure, 155/75 mmHg), but was afebrile (temperature, 37.3°C). He had diaphoresis, bilateral nystagmus, dilated pupils, myoclonic jerks, rigidity, hyperreflexia and clonus.

He was intubated for airway protection after administration of propofol (200 mg), fentanyl (100 µg) and suxamethonium (100 mg). Activated charcoal was not given. ECG showed sinus tachycardia with no prolongation of the QRS, QT or QTc intervals. His serum concentration of creatine kinase peaked at 3450 U/L. Serum lithium concentration was not measured.

A midazolam infusion was begun, and the patient was admitted to the ICU. Serotonergic symptoms were still present on Day 3, at which time his mother discovered phenelzine in his refrigerator. It was confirmed with his psychiatrist that his regular medications were lithium and phenelzine.

Therapy with high-dose benzodiazepines was continued, but serotonergic symptoms of rigidity, hyperreflexia and clonus were regularly noted until Day 16. Cyproheptadine was not given. He was extubated on Day 16 and discharged from the ICU on Day 18.

**Discussion**

These three cases illustrate the occurrence of prolonged serotonin toxicity after ingestion or overdose of proserotonergic agents. The cases differed in cause but shared a prolonged duration of toxicity, far in excess of the duration previously reported. For example, a symptom duration of 4 days was reported after ingestion of multiple proserotonergic agents,<sup>6</sup> and 5 days in a case of interaction with linezolid.<sup>7</sup> An audit of all drug overdoses in our institution in 2008 revealed an average ICU length of stay of 41 hours. Here, we review the mechanisms underlying each of our three cases.

Lithium has been previously implicated in serotonin toxicity.<sup>8,9</sup> Its mechanism of action is complex and not completely understood,<sup>10</sup> but it is known to increase serotonin levels in the cerebrospinal fluid by inducing serotonin synthesis.<sup>10,11</sup> In Patient 1, slow-release lithium in combination with the multitude of proserotonergic agents ingested at particularly high doses accounted for the prolonged toxicity. Activated charcoal has no effect on lithium absorption from the gastrointestinal tract, and haemodialysis to remove lithium was not indicated as the lithium ingested was in a slow-release form, and the patient's plasma lithium level was subtherapeutic.

The use of non-selective, irreversible MAOIs for the treatment of psychiatric illness has been limited by drug interactions. Two main classes of drug interaction cause concern — hypertensive crisis and serotonin toxicity.

**Hypertensive crisis** typically occurs when patients taking MAOIs ingest dietary amines, which are found in high concentrations in pickled fish, red wine and soft cheeses. Ingested amines are usually inactivated by monoamine oxidase (MAO) in the gastrointestinal tract, but this is inhibited by MAOI therapy, allowing the amines to be absorbed and to circulate to the central nervous system. There, they directly increase synthesis and release of monoamines such as noradrenaline and dopamine. In combination with the already present central MAO inhibition, this leads to the symptoms and signs of hypertensive crisis.

**Table 1. Drugs associated with serotonin toxicity<sup>5,12</sup>**

<b>Selective serotonin reuptake inhibitors (SSRIs)</b>	<b>Analgesics</b>
Fluoxetine	Pethidine
Paroxetine	Tramadol
Sertraline	Dextromethorphan
Fluvoxamine	Fentanyl
	Buprenorphine
<b>Serotonin and noradrenaline reuptake inhibitors (SNRIs)</b>	<b>Antiemetics</b>
Venlafaxine	Metoclopramide
Citalopram	Ondansetron
Escitalopram	<b>Anticonvulsants</b>
Bupropion	Valproate
Mirtazepine	<b>Illicit drugs</b>
<b>Tricyclic antidepressants</b>	Amphetamines
<b>Monoamine oxidase inhibitors (MAOIs)</b>	Methylenedioxymethamphetamine (MDMA)
Phenelzine	Lysergic acid diethylamide (LSD)
Tranlycypromine	<b>Herbal preparations, dietary supplements</b>
Moclobemide	St John's wort
<b>Lithium</b>	Ginseng

**Serotonin toxicity:** This is seen in patients taking MAOIs in combination with other proserotonergic agents. The list of drugs implicated is extensive; common agents are shown in Table 1.

The MAO enzyme has two subtypes with different spectra of activity. MAO-A is mainly responsible for the breakdown of noradrenaline, adrenaline and serotonin, while MAO-B mainly breaks down phenylethylamine. Both break down dopamine and tyramine. The half-life of the enzyme is 13 days for central MAO and 9.5 days for hepatic MAO.<sup>13</sup> In the setting of irreversible blockade, ingestion or overdose of other proserotonergic agents causes prolonged toxicity because of the inability to degrade central serotonin and other amines. This explains the toxicity seen in Patient 3.

Both phenelzine and tranlycypromine cause irreversible MAO inhibition. Phenelzine is a substituted hydrazine that is oxidised by MAO to reactive intermediates. These irreversibly inactivate the flavin prosthetic group of MAO, causing potent inhibition of both MAO-A and MAO-B. Tranlycypromine is a non-hydrazine with a chemical structure similar to that of amphetamine, and some stimulant properties. It is predominantly an irreversible inhibitor of MAO-A, but also causes some irreversible inhibition of MAO-B. In addition, its amphetamine-like structure is believed to have direct effects on central amine receptors.<sup>14</sup>

The reason that straight substitution of one irreversible MAOI for another causes serotonin toxicity is unclear. As the

enzyme has been irreversibly blocked, a change in MAOI should theoretically have no additional effect. However, the need for precautions when substituting one irreversible MAOI for another is well known, and a 14-day washout period is classically advised, although a 1997 case series of eight patients suggested a shorter delay period may be relatively safe.<sup>15</sup> In Patient 2, it was possible that the direct central amine effects of tranlycypromine, when substituted for phenelzine, resulted in progression to serotonin toxicity.

The increasing use of linezolid in ICUs has brought the MAOIs back into the spotlight. Linezolid is a synthetic oxazolidinone antibiotic used to treat infections with antibiotic-resistant gram-positive organisms. It is also a reversible, non-selective inhibitor of MAO, and there are multiple case reports of serotonin toxicity caused by combinations of linezolid and other proserotonergics, usually selective serotonin-reuptake inhibitors (SSRIs).<sup>7,16</sup> Linezolid has a short half life of 4–5 hours, and the reversible nature of its MAO inhibition suggests it would not cause prolonged serotonin toxicity with drug interaction. There is a case report of serotonin toxicity of 9 days' duration caused by linezolid and an SSRI, but the neurological symptoms resolved within 3 days, and only hypertension took 9 days to resolve, on its own not enough to warrant a diagnosis of serotonin toxicity.<sup>17</sup>

Our case series also demonstrates the failure of treatments to significantly reverse clinical serotonin toxicity. Cyproheptadine, a 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) antagonist, was given to both Patient 1 and Patient 2 but did not significantly alter the clinical course. Olanzapine, an atypical antipsychotic with 5-HT<sub>2A</sub> antagonism, was also given to Patient 1, again with no significant effect. Benzodiazepines were useful in controlling the symptoms of toxicity, but symptoms recurred when they were discontinued.

This lack of effect was predictable. As MAO was irreversibly inhibited and resynthesis of MAO was required in Patients 2 and 3, cyproheptadine and olanzapine were unlikely to be useful. Their role would be limited to controlling symptoms that persist despite appropriate benzodiazepine therapy, rather than attempting to shorten the clinical course. We recommend not using these agents when prolonged toxicity is predicted, as they are unlikely to be effective. However, more importantly, they may decrease symptoms temporarily or inconsistently, leading to extubation failure.

Prolonged ileus was observed in our three patients. Accelerated bowel sounds and diarrhoea are classically described with serotonin toxicity. However, our patients developed ileus, as do many of the patients who require intubation and ventilation. The causes are multifactorial and include therapy with benzodiazepines, other sedatives and

## CASE REPORTS

analgesics, immobilisation, and possibly delay in feeding in anticipation of a short ICU stay and early extubation.

The question arises whether ileus contributed to the duration of serotonin toxicity. In Patients 2 and 3, the answer is undoubtedly no. Neither patient overdosed on medication, and the half lives of the drugs involved were short, with rapid absorption from the gastrointestinal tract. However, in Patient 1, the answer is less definite. She took a massive dose of proserotonergic agents, including slow-release lithium; she did receive a single dose of activated charcoal.

Intensive care management of prolonged serotonin toxicity is significantly different from management of classic short-lived toxicity. Stress ulcer prophylaxis with a proton-pump inhibitor or H<sub>2</sub> antagonist is indicated in intubated patients with prolonged toxicity.<sup>18</sup> Enteral feeding and aperients should also be begun early, whereas they are often withheld in classic toxicity on the assumption of early extubation. Prophylaxis against venous thromboembolism is likely to be necessary and should be carefully considered, along with the most appropriate method for each patient. Care of pressure areas needs to be maintained, and catheter-related bloodstream infection becomes a significant risk because of the longer ICU stay.

A tracheostomy was performed in Patient 2 because of the failed attempt at extubation and need for prolonged ventilation. We envisage tracheostomy having very limited application in patients with serotonin toxicity, as it does not reduce the duration of benzodiazepine therapy for symptom control. It may have a role in expediting discharge from the ICU and protection of upper airway structures.

### Conclusion

Serotonin toxicity arising from overdose, medication interaction or ingestion of illicit drugs is becoming more common in Australia. Intensive care specialists need to be familiar with the pharmacology of proserotonergic agents and the management of serotonin toxicity. In addition, they need to be able to identify the small subset of patients who are likely to develop prolonged toxicity and to understand the pathophysiology in order to modify intensive care management and continue to ensure the best possible patient outcomes.

### Author details

Luke E Torre, Senior Registrar<sup>1</sup>

Rajiv Menon, Resident Medical Officer<sup>2</sup>

Bradley M Power, Intensive Care Specialist<sup>2</sup>

1 Intensive Care Unit, Sir Charles Gairdner Hospital, Perth, WA.

2 Intensive Care Unit, Joondalup Health Campus, Perth, WA.

Correspondence: antlet@bigpond.com

### References

- 1 Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; 148: 705-13.
- 2 Isbister GK, Bowe SJ, Dawson A, Whyte IM. Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; 42: 277-85.
- 3 Australian Institute of Health and Welfare. 2007 National Drug Strategy household survey: first results. Drug Statistics Series No. 20. Canberra: AIHW, 2008. (Cat. no. PHE 98.)
- 4 Prator BC. Serotonin syndrome. *J Neurosci Nurs* 2006; 38: 102-5.
- 5 Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; 352: 1112-20.
- 6 McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother* 2001; 35: 870-3.
- 7 Bergeron L, Boule M, Perreault S. Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* 2005; 39: 956-61.
- 8 Kores B, Lader MH. Irreversible lithium neurotoxicity: an overview. *Clin Neuropharmacol* 1997; 20: 283-99.
- 9 Adan-Manes J, Novalbos J, López-Rodríguez R, et al. Lithium and venlafaxine interaction: a case of serotonin syndrome. *J Clin Pharm Ther* 2006; 31: 397-400.
- 10 Lenox RH, Hahn CG. Overview of the mechanism of action of lithium in the brain: fifty-year update. *J Clin Psychiatry* 2000; 61 Suppl 9: 5-15.
- 11 Perez-Cruet J, Tagliamonte A, Tagliamonte P, Gessa GL. Stimulation of serotonin synthesis by lithium. *J Pharmacol Exp Ther* 1971; 178: 325-30.
- 12 Isenberg D, Wong SC, Curtis JA. Serotonin syndrome triggered by a single dose of suboxone. *Am J Emerg Med* 2008; 26: 840.e3-5.
- 13 Dix BA, Lambooy JP. Brain monoamine oxidase and replacement of its coenzyme flavin in rats. *J Nutr* 1981; 111: 1397-402.
- 14 Lees F, Burke CW. Tranylcypromine. *Lancet* 1963; 1: 13-6.
- 15 Szuba MP, Hornig-Rohan M, Amsterdam JD. Rapid conversion from one monoamine oxidase inhibitor to another. *J Clin Psychiatry* 1997; 58: 307-10.
- 16 Huang V, Gortney JS. Risk of serotonin syndrome with concomitant administration of linezolid and serotonin agonists. *Pharmacotherapy* 2006; 26: 1784-93.
- 17 Hachem RY, Hicks K, Huen A, Raad I. Myelosuppression and serotonin syndrome associated with concurrent use of linezolid and selective serotonin reuptake inhibitors in bone marrow transplant recipients. *Clin Infect Dis* 2003; 37: e8-11.
- 18 Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med* 1998; 338: 791-7. □