

Isolated Fluvoxamine Poisoning Presenting with Hypertonia and Seizures: A Case Report

K. DESHPANDE

Department of Critical Care Medicine, Flinders Medical Centre, Adelaide, SOUTH AUSTRALIA

ABSTRACT

Pharmacological management of depressed patients has often relied upon the use of agents that are toxic when taken in large quantities. The recent introduction of selective serotonin reuptake inhibitors (SSRIs) has represented a major advance in the management of depression. While a 'serotonin syndrome' may develop if these drugs are taken in association with other agents, these drugs are believed to have minimal toxicity when taken as an isolated overdose.

A case of fluvoxamine poisoning presenting with hypertonicity and seizures is described, highlighting the fact that the SSRI's may not be harmless when taken in isolation, particularly when taken in large amounts. (Critical Care and Resuscitation 2002; 4: 177-180)

Key words: Fluvoxamine, seizures, hypertonicity, serotonin syndrome

The morbidity and mortality caused by tricyclic antidepressant and nonselective monoamine oxidase inhibitor overdosage are well recognised. The introduction of selective serotonin reuptake inhibitors (SSRIs) in the management of depressed patients has been heralded as a new phase in psychotherapy, with the added advantage of an associated reduced risk of morbidity and mortality when taken as an overdose.

While a 'serotonin syndrome' may be provoked when a SSRI is taken in association with another serotonin receptor agonist or monoamine oxidase inhibitor, an isolated overdose is thought to be relatively harmless.¹

A case is reported of a woman who presented with hypertonia and seizures following an overdose of fluvoxamine.

CASE REPORT

A 21 year old woman with a past history of depression, obsessive compulsive disorder and anorexia nervosa presented to the emergency department 30 minutes after the ingestion of 6000 mg of fluvoxamine. A routine serum drug screen including paracetamol, acetylsalicylate and ethyl alcohol was negative. She had

no access to any other medications and denied taking any other agents.

She presented with a Glasgow coma score of 15, blood pressure of 110/70 mmHg, pulse 106 beats per minute and a temperature of 37.3°C. During an attempt to insert an intravenous cannulae she suddenly complained of dizziness, developed mydriasis and intermittent myoclonic jerks which were followed by a grand mal seizure. After a brief post-ictal period a further grand mal seizure occurred. Intravenous diazepam 2.5 mg, suxamethonium 100 mg and thiopentone 100 mg were administered. The patient was intubated, mechanically ventilated and admitted to the department of critical care medicine. As she remained hypertonic with upgoing plantar reflexes, intravenous propofol 1% was used to maintain sedation.

The initial post intubation blood gas (F_IO₂ 100%) revealed a pH of 7.38, HCO₃⁻ 19.7 mmol/L, PCO₂ 36.1 mmHg, PO₂ 538 mmHg and a lactate of 6.3 mmol/L. The laboratory investigations revealed a plasma sodium of 147 mmol/L, potassium of 3.6 mmol/L, anion gap 25 mEq/L creatinine of 0.063 mmol/L, creatine kinase 94 U/L, lactate dehydrogenase 233 U/L white cell count of 7.7 x 10⁹/L, with the remaining electrolytes, liver funct-

Correspondence to: Dr. K. Deshpande, Department of Critical Care Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042

ion tests, platelet count, INR and APTT being within normal limits. An ECG was performed which demonstrated generalised nonspecific T wave flattening and T wave inversion in the inferior leads (Figure 1).

A nasogastric tube was inserted and 100 g of activated charcoal was administered. The next morning, approximately 15 hours after her admission, the propofol was discontinued. At this stage she was drowsy but cooperative and was extubated. Her blood pressure was 115/60, pulse 98 beats per minute and temperature was 36.8°C. She was hyperreflexic with an increased tone in all limbs although her plantar reflexes now were normal. The post extubation blood gas (breathing oxygen through nasal cannulae at 4 L per minute) revealed a pH of 7.39, HCO_3^- 23.7 mmol/L, PCO_2 39.7 mmHg, PO_2 154 mmHg and a lactate of 1.9 mmol/L. The laboratory investigations revealed a plasma sodium of 143 mmol/L, potassium of 3.1 mmol/L, anion gap 9 mEq/L creatinine of 0.048 mmol/L, creatine kinase 63 U/L, lactate dehydrogenase 136 U/L with the remaining electrolytes and liver function tests being within normal limits. Later that day she was discharged to the ward for further management.

DISCUSSION

There are four different types of serotonin or 5-hydroxytryptamine (5-HT) receptors known as 5-HT₁, 5-HT₂, 5-HT₃, 5-HT₄. The 5-HT₁ receptors contain four subtypes designated 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1c} and 5-HT_{1D}, and are distinguished from the other receptor types (i.e. 5-HT₂, 5-HT₃, 5-HT₄ receptors) by their

increased (e.g. 1000 times greater) affinity for exogenously supplied serotonin. The 5-HT_{1A} receptor subtype is the most widespread of all serotonin receptors and, along with all 5-HT₁ receptors, shares a close structural similarity to the beta adrenergic receptor. Central 5-HT_{1A} agonism has anxiolytic and antidepressant effects.²

The selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram) are a group of drugs that inhibit cerebral serotonin reuptake with little affinity for adrenergic, cholinergic, dopaminergic or antihistamine receptors. The symptoms that develop after an acute SSRI overdose are minor and usually consists of sinus tachycardia, drowsiness, orolingual dyskinesia, restlessness (akathisia), tremor, nausea and vomiting.³

The SSRIs can cause a 'serotonin syndrome' particularly if they are co-administered with other psychotropic agents. This syndrome is believed to be caused by an excessive stimulation of postsynaptic serotonin receptors located in the lower brain stem (i.e. pons, medulla) and spinal cord where the serotonin 5-HT_{1A} receptor subtype predominates. The syndrome can theoretically be caused by any agent or combination of agents that produce an increase in serotonergic neurotransmission. For example,

Serotonergic drugs

- L-tryptophan (which increases 5-HT synthesis)
- tricyclic antidepressants, fluoxetine, paroxetine, sertraline, pethidine, cocaine, fenfluramine (which inhibit 5-HT uptake).

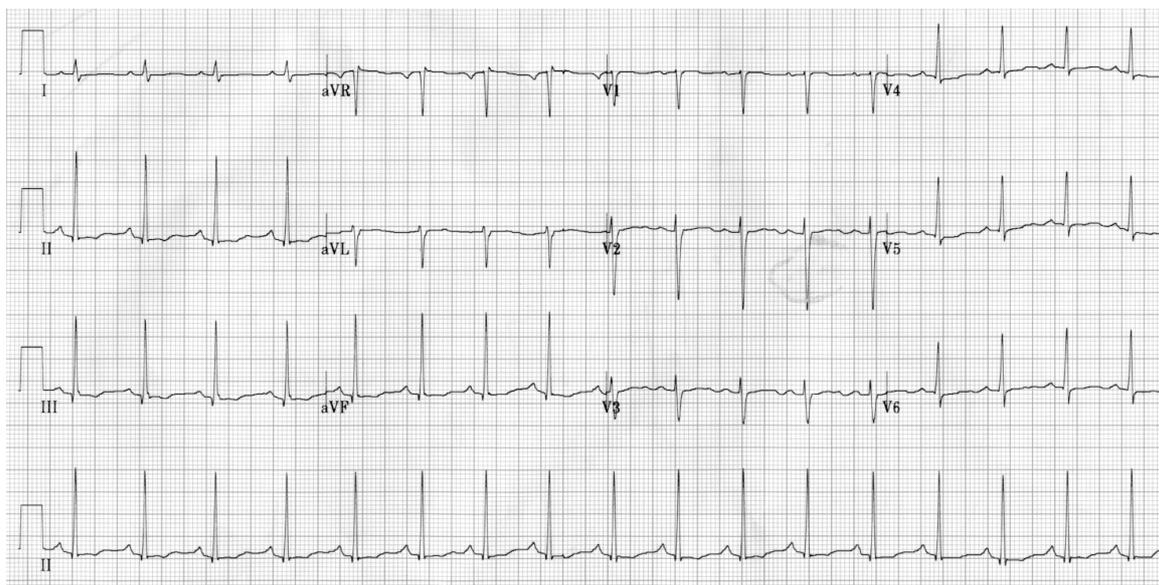


Figure 1. The 12-lead ECG on presentation showing sinus rhythm at a rate of 100 beats per minute with generalised non specific T wave flattening and T wave inversion in inferior leads.

- 3,4-methylenedioxyamphetamine or 'ecstasy', cocaine, dextromethorphan, pethidine, pentazocine and fenfluramine (which increase 5-HT release)

Serotonin receptor agonists

- lysergic acid diethylamide, L-dopa, psilocin, mescaline, lithium, buspirone

Monoamine oxidase inhibitors (MAOIs)

- tranylcypromine, phenelzine, moclobemide (which decrease 5-HT metabolism).^{4,5} While selegiline, as a selective MAO-B inhibitor is less likely to cause the serotonin syndrome, in toxic doses it loses its selectivity and thus is capable of inducing the serotonin syndrome.⁶

Because of the long half life of fluoxetine (e.g. 7 days) and its active metabolite norfluoxetine (18 days) as well as the prolonged effect of the irreversible MAOIs, the serotonin syndrome may occur when a precipitating drug is introduced, as long as 5 to 6 weeks after discontinuation of fluoxetine, sertraline, paroxetine or an irreversible MAOI.

The serotonin syndrome is characterised by the rapid onset of:^{4,7,8}

- a cognitive and behavioral abnormality (e.g. insomnia, dizziness, anxiety, confusion, disorientation, agitation, euphoria, delirium, hallucinations, seizures, coma),
- autonomic dysfunction (e.g. mydriasis, unreactive pupils, diaphoresis, tachycardia, hypertension, hypotension, diarrhoea, nausea, salivation, piloerection, flushing, pyrexia, hyperthermia), and or
- a neuromuscular abnormality (e.g. restlessness, tremor, shivering, hypertonicity, hyperreflexia, rigidity, myoclonus, trismus, orolingual dyskinesia, oculogyric crisis, opisthotonus, nystagmus, ataxia, dysarthria, Babinski reflex, rhabdomyolysis).

While there are many similarities between the neuroleptic malignant syndrome (NMS) and the serotonin syndrome the distinguishing features of the NMS are as follows:

1. it is caused by a central dopamine deficiency (c.f. an excess stimulation of the 5HT_{1A} receptors),
2. bromocriptine may be used to treat the NMS (bromocriptine may precipitate the serotonin syndrome),
3. there is a history of exposure to neuroleptic agents or withdrawal of dopamine agonists (rather than serotonergic agents, agonists and MAOIs),
4. there is lead pipe rigidity (rather than clonus, myoclonus or hyper-reflexia), and
5. there is an absence of mydriasis.⁹

The diagnosis of the serotonin syndrome is a clinical one as there are no tests available which are pathognomonic of the disease.¹⁰ Similar to the NMS, in severe cases there may be a leucocytosis, an elevated plasma creatine kinase (due to rhabdomyolysis) and features of renal failure, hepatic failure, acute respiratory distress syndrome and disseminated intravascular coagulation. The syndrome typically resolves within 24 hours, although confusion may last for days.

Treatment is generally symptomatic and includes, discontinuation of the causative agent, control of body temperature (which may require, in severe cases, intubation and paralysis with a nondepolarising relaxant and artificial ventilation to reduce the muscular rigidity), acid-base and fluid and electrolyte maintenance. Serotonin antagonists (e.g. up to 4 mg of cyproheptadine orally per hour,¹¹ 100 mg of chlorpromazine i.m., daily¹² and 2 mg of methysergide 12-hourly)¹³ as well as propranolol and benzodiazepines,⁴ have also been used to manage the agitation and hypertonicity, although in some cases they may have minimal beneficial effects.¹¹

While the serotonin syndrome has been previously reported after a large dose of fluvoxamine,¹⁴ this effect is believed to be rare.^{1,15} Moreover, overdoses of up to 9 g have reportedly produced minimal symptoms, although in one study of patients with fluvoxamine overdose the development of seizures occurred only in patients after doses > 1500 mg.¹⁶

The case reported herein, highlights the fact that the SSRI's may not be harmless when taken in isolation, particularly when these agents are taken as a large overdose.

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