

A fatal case of severe serotonin syndrome accompanied by moclobemide and paroxetine overdose

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Abstract

Aim: To present a fatal case of serotonin syndrome accompanied by moclobemide and paroxetine overdose. **Case presentation:** A 34-year-old married woman was presented following intentional ingestion of 3.5 g moclobemide and 2.6 g paroxetine. She was drowsy, agitated, and having rigor. In 1 h she developed myoclonus and diffuse muscle rigidity prominent in lower extremities. All laboratory tests were unremarkable except hyperglycemia (160 mg/dl), sinus tachycardia (103/min), and metabolic acidosis (7.051 pH, 52 mmHg pO₂, 74.7 mmHg pCO₂, 15% HCO₃, 77% SaO₂). Despite oxygen supplementation, her respiratory acidosis got worse and the SaO₂ concentration decreased to 72%. Endotracheal intubation and paralysis were decided to control muscle hyperactivity followed by hyperthermia (max. 42.3°C) unresponsive to benzodiazepine. Even aggressive supportive treatment (mechanical ventilation, buffer replacement, cyproheptadine, and dantrolene) were applied, the patient could not recover and suffered cardiopulmonary arrest 20 h after presentation. **Conclusion:** Physicians working in the emergency departments and intensive care units, managing patients presenting with acute ingestion of selective serotonin reuptake inhibitors combined with monoamine oxidase inhibitors, should be aware of recognizing and treating serotonin syndrome. This is because many of these patients may require intensive care monitoring as well as tracheal intubation and ventilatory support.

Key Words: Moclobemide, Paroxetine, Serotonin syndrome

Introduction

Serotonin syndrome is a rare but important drug-induced complication of antidepressant therapy, which can be produced by any drug or, more commonly, by a combination of drugs that increase central serotonin neurotransmission.^[1] Five basic mechanisms can increase serotonin neurotransmission: (1) augmentation of serotonin production (l-tryptophan), (2) increase in

serotonin release (amphetamine and its derivatives, cocaine), (3) inhibition of serotonin uptake into presynaptic neuron (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], dextromethorphan, meperidine, tramadol), (4) inhibition of serotonin metabolism (moclobemide and selegiline), and (5) direct stimulation of postsynaptic receptors (buspirone). Serotonin syndrome (SS) comprises variable alterations in cognition and behavior, autonomic nervous system function, and neuromuscular activity. Although, fortunately, most patients with SS improve with supportive care alone or combined with specific drug therapy, in some most severe presentation, SS rapidly progresses to cardiac arrest, coma, seizures, or multiple organ failure.^[2-5]

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This case report describes a patient who developed life-threatening serotonin syndrome and died after voluntary ingestion of 3.5 g moclobemide and 2.6 g paroxetine for suicide.

Case history

A 34-year-old, 86-kg, married white woman presented to our academic emergency department with symptoms of confusion, agitation, and rigor at 03:00 AM. Her husband found her at home lying on the floor about 02:30 AM. He figured out that 13 tablets of 20-mg paroxetine (Paxil[®]) and 15 tablets of 300-mg moclobemide (Aurorix[®]) were missing. He did not come across any other drug or alcohol at home. The patient had no prior medications, and there was nothing significant in her medical and family history. Vital signs at presentation were as follows: 140/80 mmHg blood pressure, 100 beats/min pulse rate, 20 breaths/min respiratory rate, 38.3°C temperature, and 90% oxygen saturation. She was drowsy, disoriented, non-cooperative, sweating, and had a Glasgow Coma Score of 10 (E2M5V3). She had rapid but decreased depth of respiratory effort. Half-dilated pupils were isochoric and bilateral wandering horizontal eye movements called as "ping-pong gaze" was observed. There was muscle rigidity all over the body especially in the lower extremities. In addition, hyper-reflexia was found in deep tendon reflexes bilaterally both in the lower and upper extremities. No trauma evidence was examined and rest of the examination was unremarkable. Her capillary glucose level was 167 mg/dl. Electrocardiogram showed no evidence of arrhythmia or conduction defect but sinus tachycardia. Arterial-blood-gas (ABG) result at presentation was as follows: 7.051 pH, 52 mmHg pO₂, 74.7 mmHg pCO₂, 15% HCO₃, and 77% SaO₂, which showed metabolic acidosis. Complete blood count, electrolytes, liver, and renal function tests, urine pregnancy test, urine toxicology screen (amphetamine, benzodiazepine, opiate, barbiturate, cocaine, and phenylclidine), and brain computerized tomography were normal. Supplemental oxygen was given at 4 l/min via simple facemask. She was admitted to the medical intensive care unit of the emergency department, placed on a cardiac monitor, intravenous line and normal saline started, orogastric catheter was placed, and gastric lavage was done. After gastric lavage, 1 g/kg activated charcoal was passed down the orogastric tube. Approximately in 1 h diffused continuous muscle hyperactivity (myoclonus, tremor, and rigidity) was started. Although

a total of 8 mg midazolam was given intravenously, it lasted almost 20 min. The patient began shivering severely and vital signs began to deteriorate further. We decided to intubate and paralyze her to control the airway and avoid further muscle hyperactivity and rhabdomyolysis, as she had low SaO₂ despite supplemental oxygen (70–80%), hyperthermia (max. 42.3°C), hypercarbia (102–145 mmHg), and uncontrolled persistent muscle rigidity and shivering. Just before intubation ABG was at 6.852 pH, 74.7 mmHg pO₂, 37 mmHg pCO₂, 21% HCO₃, and 73% SaO₂. While she was intubated, paralysis was achieved with continuous infusion of vecuronium and sedation with intermittent doses of midazolam. Even necessary supportive care (mechanical ventilation, buffer replacement, etc.), cyproheptadine (Periactin[®]), a nonspecific serotonergic antagonist, 4 mg every 4 h via orogastric tube and dantrolene, a nonspecific muscle relaxant, 100 mg qid intravenously was given soon after consultation with a medical toxicologist. About 20 h after ED presentation the patient suffered cardiopulmonary arrest probably because of multiple organ failure and deep metabolic acidosis. Toxicology results revealed that blood levels of moclobemide and paroxetine were 26.53 and 3.09 mg/l, respectively. In addition, autopsy findings were unremarkable and support the diagnosis of serotonin syndrome as the cause of demise.

Discussion

SSRIs and monoamine oxidase inhibitors (MAOIs) are replacing TCAs with increasing frequency in USA and in Turkey.^[6] As SSRIs have selective affinity to inhibit presynaptic serotonin reuptake without significantly affecting norepinephrine or dopamine reuptake, MAOIs actual mechanism of therapeutic effects are probably related to delayed postsynaptic receptor modifications, indirect release of neurotransmitters, and inhibition of neurotransmitter reuptake. Although generally combination of SSRIs and even a single MAOI tablet under the right circumstances can cause serotonin syndrome (SS), effects of moclobemide alone has minor unwanted effects in even in massive ingestions.^[7] Symptoms attributed to SS may include restlessness, hallucinations, shivering, diaphoresis, and nausea, and physical signs include mental status changes (confusion, agitation, coma); neuromuscular dysfunction (myoclonus, rigidity, tremors, hyper-reflexia that tends to be more prominent in the lower than the upper extremities, clonus, ataxia, nystagmus, trismus); autonomic dysfunction (hyperther-

mia, mydriasis, sinus tachycardia, hypertension, dilated pupils).^[8] Although neuroleptic malignant syndrome (NMS) and SS have similar pathophysiology, distinguishing features of NMS are the history (prolonged exposure to neuroleptic agents or withdrawal of dopamine agonists), lead-pipe rigidity (rather than clonus, myoclonus, or hyperreflexia), and absence of mydriasis.^[1] There is unfortunately no confirmatory laboratory test for SS. It is associated with a good prognosis and generally regresses within 24–36 h, but severe cases of SS are life-threatening and require aggressive supportive care. There are some cases reported in the literature who experienced cardiac arrest possibly owing to diffuse muscle hyperactivity accompanied by chest wall rigidity, metabolic acidosis, multiple organ failure, and disseminated intravascular coagulation.^[5,10,11]

Emergency department care of SS comprises mainly supportive treatment (hydration, cooling, sedatives, paralytics, endotracheal intubation, and mechanical ventilation) and close monitoring and administration of antiserotonergic agents in selected patients (chlorpromazine, cyproheptadine, methysergide) until all symptoms resolve. Dantrolene should be reserved for patients with severe persistent muscle rigidity followed by hyperthermia (>41°C). All patients with SS should be admitted to the ward or intensive care unit according to its severity. In this case the cause of death was attributed to additive effects of paroxetine, whereas moclobemide resulted in SS.

Conclusion

Because many of these patients may require intensive care monitoring as well as tracheal intubation and

ventilatory support, emergency physicians and anesthesiologists working in the intensive care units managing patients with acute ingestion of SSRIs combined with MAOIs should be aware of recognizing and treating SS.

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