Serotonin syndrome due to an overdose of moclobemide?

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ABSTRACT

Serotonin syndrome, a triad of autonomic instability, altered mental status and neuromuscular abnormalities, is usually attributed to serotonergic overdoses. Moclobemide is a new selective monoamine oxidase inhibitor (MAOI) that generally causes mild, self-limited gastrointestinal and central nervous system effects after ingestion. We present a case of serotonin syndrome that occurred after moclobemide overdose, and discuss the recognition and treatment of this important condition. Serotonin syndrome may become increasingly common because of the liberal use of selective serotonin reuptake inhibitors, new MAOIs and other agents such as codeine and meperidine, which have the potential for harmful interaction.

Key words: serotonin; serotonin syndrome; monoamine oxidase inhibitor; moclobemide; codeine; Fiorinal; overdose; ingestion

RÉSUMÉ

Le syndrome sérotoninergique, une triade formée de symptômes neuro-végétatifs, cognitifs et neuro-musculaires, est habituellement attribuable à des intoxications sérotoninergiques. Le moclobémide est un nouvel inhibiteur sélectif de la monoamine-oxydase (IMAO) qui a généralement des effets indésirables bénins et spontanément résolutifs au niveau du tractus gastro-intestinal et du système nerveux central après l'ingestion. Nous présentons un cas de syndrome sérotoninergique découlant d'un surdosage au moclobémide et discutons de l'identification et du traitement de cette atteinte importante. Le syndrome sérotoninergique pourrait devenir de plus en plus courant avec l'usage répandu des inhibiteurs sélectifs du recaptage de la sérotonine, des nouveaux IMAO et autres agents comme la codéine et la mépéridine qui peuvent être la source d'interactions nocives.

Introduction

Serotonin syndrome, the result of a serotoninergic hyperstimulation, is characterized by the classic triad of altered mental status, autonomic dysfunction and neuromuscular abnormalities. Findings include agitation, coma, hyperthermia, tachycardia, tremor, rigidity, and seizures. Complications include disseminated intravascular coagulopathy, cardiac dysrhythmias, rhabdomyolysis, renal failure, seizures, coma and death.[1,2] This syndrome is generally attributed to overdoses of selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRI and SNRI), or of agents like monoamine oxidase inhibitors (MAOIs) that reduce serotonin metabolism.[1,3–7] There are reports of serotonin syndrome occurring after overdoses of a single serotoninergic agent (usually an SSRI) and more rarely, after a single dose of an SSRI.[4,5,8,9] Serotonin syndrome has also occurred after combined overdoses involving serotoninergic agents

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and selective MAOIs,[1,3,10–12] but not after selective MAOIs alone. We report a case of serotonin syndrome that occurred after a primary overdose of moclobemide, a newer, selective, reversible MAOI.

Case report

A 36-year-old female was brought to the emergency department (ED) by paramedics after being found unresponsive by her boyfriend. Her past medical history included depression, a previous multi-drug overdose, hypothyroidism, hypertension, anemia, and a recent bout of otitis media. There was no history of illicit drug use. Her medications included moclobemide, Fiorinal (ASA, caffeine, codeine and butalbital), ibuprofen, amoxicillin, naproxen, alprazolam and a "thyroid pill," but only 2 pill bottles were found, both with moclobemide labels. The older bottle was empty and the newer one half-empty.

Little initial history was available, other than that she may have had a fight with her family and had possibly taken an overdose. We later determined that she had been involved in a physical alteration with her father the night before, and had phoned her mother, indicating that she had completed her will and written "a letter." Her boyfriend subsequently found her unresponsive in the washroom, and emergency medical services paramedics were summoned.

On arrival in the ED, she was unresponsive, with a Glasgow Coma score of 3. Her blood pressure was 150/80 mm Hg, the pulse rate was 132 beats/min, respirations were 36 breaths/min, and her body temperature was 39.7ºC. The serum glucose level was normal. There was no evidence of trauma, rash or injection drug use; however, she was flushed and diaphoretic. Her pupils were fixed and dilated, with bilateral rotational nystagmus. Findings on cardiac and respiratory examinations were otherwise normal. There was marked trismus such that the oropharynx could not be visualized. Her neck was stiff, as was the rest of her body, and the neurologic examination revealed increased tone and hyperreflexia throughout, with greater tone in the lower extremities. Plantar reflexes were upgoing bilaterally. Although she was initially in a rigid neutral position, subsequent decerebrate posturing of both arms developed. Throughout, she appeared to have mild generalized seizure activity.

Initial management included cardiac monitoring, intravenous administration of normal saline, oxygen administration and insertion of a nasopharyngeal airway. She was intubated with 15 mg of midazolam and 100 mg of succinylcholine. At this point, the differential diagnosis included central nervous system infection, metabolic or endocrine disturbance, neuroleptic malignant syndrome (NMS), sympathomimetic overdose or an intracranial event.

Laboratory findings were as follows: hemoglobin level 134 g/L; leukocyte count 13.7×10^9; serum sodium 143 mmol/L, potassium 4 mmol/L, chloride 110 mmol/L, bicarbonate 20.8 mmol/L, glucose 6.5 mmol/L, creatinine 88 µmol/L, urea nitrogen 6.7 mmol/L urea, and creatine kinase (CK) 775 U/L. Her thyroid-stimulating hormone (thyrotropine) and free thyroxine were 0.24 mU/L and 14.5 pmol/L respectively. The remainder of her chemistry profile, including liver function test results, and serum bilirubin, calcium, magnesium and albumin, were all within the normal range, and serum osmolality was 302 mmol/kg. Arterial blood gas measurements, on oxygen, revealed a pH of 7.26, P_{CO_2} of 47.1 mm Hg, P_{O_2} of 242.7 mm Hg, HCO_3 of 19.7 mmol/L and oxygen saturation of 99.4%. Initial toxicology screening was negative for ethanol, salicylate and acetaminophen, but subsequent drug screening, obtained after benzodiazepine treatment for her seizures, was positive for barbiturates, benzodiazepines, cannabinoids and opiates. Gas chromatography confirmed the presence of butalbital, benzodiazepine metabolites, moclobemide and codeine.

Repeated doses of benzodiazepines were given to control seizures and 1 g of phenytoin was administered. Because of hyperthermia and probable rhabdomyolysis, the patient was paralyzed with vecuronium. She was hydrated with normal saline. A nasogastric tube and a Foley catheter were inserted, and 2 g of ceftriaxone intravenously, and 100 mg of thiamine were given prophylactically. Results of chest radiography and computed tomography of the head were normal. The initial electrocardiogram showed only sinus tachycardia, but slight QT prolongation was noted the next day. Blood cultures were subsequently reported as negative.

The patient was transferred to the intensive care unit (ICU) with a diagnosis of serotonin syndrome or NMS. She was given further sedation, as well as bromocriptine for 24 hours, after which she was weaned from the ventilator and extubated. She was transferred to the Psychiatric Unit after 2 days in the ICU. In follow-up, she admitted to taking excessive amounts of moclobemide, Fiorinal, alprazolam and, possibly, amoxil, naproxen and ibuprofen.

Discussion

Serotonin syndrome results from an increase in serotoninergic neurotransmission and excessive stimulation of serotonin 5-HT (5-hydroxytryptamine) receptors. Sternbach[13] suggests that 3 criteria must be fulfilled in order to make the diagnosis.[1,9] First, the symptoms should occur in the setting of a recent addition or increase in dose of a serotomimetic

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agent. Second, other causes, such as infection, metabolic or endocrine disturbances, substance abuse or withdrawal, and recent neuroleptic use should be excluded. Finally, patients should display at least 3 of the following: fever, mental status or behavioural changes, neuromuscular dysfunction (e.g., incoordination, tremor, hyperreflexia, rigidity or myoclonus, which is classically greater in the lower extremities), autonomic instability (e.g., diaphoresis, tachycardia, hyper- or hypotention, mydriasis or hyperthermia) or diarrhea.

To summarize, the diagnosis of serotonin syndrome is based upon characteristic clinical findings, appropriate drug use and the exclusion of other possible causes.

There is significant overlap between serotonin syndrome and NMS, which results from a dopamine deficiency related to the antidopamimetic effects of antipsychotic medications. Both syndromes result in altered mentation, autonomic instability, hyperpyrexia and elevated CK levels. NMS, however, usually includes a history of exposure to high potency neuroleptics or withdrawal of dopamine agonists, and involves lead pipe rigidity rather than clonus, myoclonus or hyperreflexia. Finally, patients with NMS tend not to have mydriasis.[2,9,14] Based on the clinical findings described and the absence of dopamine antagonist use, this patient's presentation was more in keeping with serotonin syndrome.

Moclobemide and serotonin syndrome

Moclobemide is a selective, reversible MAO-A (monoamine oxidase type A) inhibitor that is considered much safer than traditional MAOIs. Moclobemide overdose produces mild to moderate CNS and gastrointestinal effects, such as drowsiness, disorientation, nausea and, on occasion, agitation, tachycardia and mild hypertension.[10,15,16] While our literature review found no apparent cases of serotonin syndrome following moclobemide ingestion alone, it is well established that moclobemide can cause serotonin syndrome when combined with other serotoninergic medications, particularly SSRIs, SNRIs and tricyclic antidepressants.[1,3,10,12,16,17] Serotonin syndrome would also be more likely if moclobemide was combined with agents known to cause serotonin syndrome, including meperidine, lithium, L-tryptophan, dextromethorphan, L-dopa (levodopa), 3,4-methylenedioxymethamphetamine (known as MDMA, or "ecstasy") and cocaine.[1–3,15,18]

The patient's history and the empty pill containers suggest that the primary toxin in this case was a large dose of moclobemide. In large doses, this agent probably loses its selectivity and reversibility, becoming more like older, irreversible MAOIs, and greatly increasing the levels of serotonin.[17] An analogy may be made to the selective MAOI-B inhibitor Selegiline (l-deprenyl), which preferentially inhibits monoamine oxidase in the brain, thereby reducing the risk of a systemic serotonin surge. At higher doses, however, Selegiline loses its selectivity and has been implicated as a cause of serotonin syndrome.[2,15]

In the case described, history and toxicologic screening suggested that our patient co-ingested some or all of the following: alprazolam, Fiorinal, and possibly nonsteroidal anti-inflammatories and amoxicillin. The presence of cannabinoid in the initial screen is insignificant, since it only indicates previous exposure and was not confirmed on subsequent gas chromatography. The possible Fiornal ingestion may be significant, since the codeine contained in this form of Fiorinal may aggravate moclobemide-related serotonin syndrome.

Treatment

The treatment of serotonin syndrome remains controversial, since much of the published literature is anecdotal. There is no specific antidote, and management is primarily supportive. Most cases resolve in 24 to 36 hours with rehydration, cooling and discontinuation of serotoninergic medications. Many authors recommend benzodiazepines to reduce excessive sympathetic outflow and control seizures.[2,5,8,19] These agents may also limit muscle contraction and reduce hyperthermia, myoclonus and rhabdomyolysis. Paralysis and mechanical ventilation should be considered in severe cases. In the event of an extreme blood pressure or pulse rise, theoretical arguments have been made for the use of beta-blockers such as propranolol, which have negative chronotropic effects and act as non-specific 5-HT antagonists.[8] Case reports suggest limited success with beta-blockers.[2,7,18]

Case reports suggest that cyproheptadine, a first generation histamine-1 receptor blocker with non-specific 5-HT antagonist properties, is effective in mild to moderate cases of serotonin syndrome, and that the non-specific 5-HT receptor antagonists methysergide and chlorpromazine may be helpful.[1,4,5,8,11,14,20] Unfortunately, cyproheptadine does not have a parenteral formulation; therefore it is less useful in severe cases and in patients who have received activated charcoal. Chlorpromazine, available parenterally, has been used with some success but might increase the risk of hypotension, dystonic reactions, NMS and seizures.[19]

Bromocriptine, a dopamine receptor agonist, and dantrolene, which inhibits calcium efflux from the sarcoplasmic reticulum into muscle, have been recommended for the treatment of NMS-related hyperthermia and rigidity.[21] These agents may, however, increase serotonin levels and precipitate or aggravate serotonin syndrome.[2,20]

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Conclusion

Serotonin syndrome is an uncommon but potentially life-threatening condition most often seen in patients presenting to the ED after serotonergic overdose. With the increasing use of newer antidepressants and the prevalence of serotoninergic drugs in the community, emergency physicians should be familiar with serotonin syndrome and consider it in patients presenting with the appropriate symptom complex.

Competing interests: None declared.

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