Title

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CLINICAL VIGNETTE

Prolonged Amnestic Symptoms after Overdose of 5-hydroxytryptophan (5-HTP) *Griffonia simplicifolia* Seed Extract

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A 39-year-old male with past history of post traumatic stress disorder, marijuana use, and anxiety was brought to the Emergency Department (ED) by ambulance after unintentional overdose of 5-hydroxytryptophan (5-HTP) *Griffonia simplicifolia* seed extract. The patient ingested the supplement for its purported anxiolytic properties. Packaging directions were to take 1/16 tsp (182mg) of supplement. Notably, there were 5,495 servings per container in a small handheld package (13 x 4 x 18cm) with no serving measurement device provided. Before reading the instructions, the patient ingested ~1/2 teaspoon (1456mg) of the supplement, which was eight times the recommended dosage. The patient experienced a rapid onset of nausea and vomiting, with later flushing, diaphoresis, and myalgias. He had two episodes of diarrhea with incontinence. His wife, noting him to exhibit "psychosis and paranoid behavior," called 911.

On arrival to the ED the patient was diaphoretic, agitated, and disoriented to person, place, and time. Initial vital signs were: temperature 37.2°C, pulse 79 beats/min, blood pressure 131/89 mm Hg, respiratory rate 16 breaths/min, and oxygen saturation 98% on room air. The physical exam was otherwise unremarkable, including a non-focal neurological exam without clonus. The patient received a total of 3mg intravenous (IV) lorazepam for his agitation. He also received 4mg IV ondansetron for ongoing nausea and 3 liters of normal saline. The case was discussed with the poison control center, which recommended supportive care.

Laboratory values were notable for a white blood cell count of 15.61 k/uL with 89% neutrophilia. Chemistry and liver function panels were otherwise unremarkable. Ethanol, acetaminophen, and salicylate levels were undetectable. A qualitative urine toxicology panel (screening for opiates, benzodiazepines, amphetamines, cocaine, buprenorphine, oxycodone, methadone, and cannabinoids) was positive only for cannabinoids, which the patient had been using at regular low doses for years without a recent change in consumption. A non-contrast computed tomography (CT) scan of the brain revealed no acute intra-cranial findings, and an electrocardiogram showed sinus bradycardia rate 59 beats per minute.

After 12 hours of observation in the emergency department, the patient became oriented to self and year but remained disoriented to month, location, and situation. He had no recall of recent biographical events such as a recent residential move, or the age or school grade of his daughter. He was therefore admitted to the inpatient medicine service, where he showed gradual improvement of mental status, though with prolonged amnestic symptoms. For example, he was unable to recall any events leading up to hospitalization or why he was hospitalized. He scored 19/30 on the Montreal Cognitive Assessment (MoCA), with 0/5 points for delayed recall, 0/2 points for repetition, and 2/6 points for orientation. On hospital day four, after continued gradual improvement in memory, he was discharged home, though he continued to have long-term memory complaints.

Discussion

5-hydroxytryptophan (5-HTP) is the immediate biochemical precursor to serotonin.[1] It is often derived from and marketed as the herbal supplement *Griffonia simplicifolia* seed extract, and is found easily online or in health stores. It is used for purported anti-depressant and anxiolytic properties,[2] but reliable human studies and reports on side effects are lacking. Previously described side effects are typical of serotonergic agonism, including serotonin syndrome.[3,4]

Serotonin syndrome is a dose-dependent and predictable response to elevated serotonin that has effects both on the peripheral and central nervous systems. It encompasses a broad spectrum of disease from the mild to the life-threatening, though amnestic symptoms are not considered part of the syndrome.[5] Early signs and symptoms stem from autonomic hyperactivity and include vomiting, diarrhea, flushing, diaphoresis, tachycardia and tremor. Hyperactive muscle tone, often manifested as hyperreflexia and clonus (more pronounced in lower rather than upper extremities) are characteristic features of serotonin syndrome. However, signs of autonomic disturbance like hypertension, hyperthermia, mydriasis, and hyperactive bowel sounds can also be exhibited. The most severe cases demonstrate agitated delirium and muscle hyperactivity/ rigidity with resulting severe hyperthermia, sometimes >41 °C. When untreated, complications such as rhabdomyolysis, acute kidney injury, seizures, and disseminated intravascular coagulopathy may occur. The mainstay of treatment is supportive care aimed at hyperthermia and its complications, including sedation with benzodiazepines to suppress muscular hyperactivity. If benzodiazepines are not effective, paralysis and intubation may be necessary.[5] Although definitive evidence is lacking, cyproheptadine, a 5-HT_{2A} receptor antagonist, is often

used in moderate to severe cases to blunt the serotonergic response.[6] However, use is often limited in severe toxicities due to its lack of a parenteral preparation.

Notably, this patient had many non-specific features of serotonergic toxicity such as flushing, diarrhea, diaphoresis, and agitation. His lack of clonus, however, was inconsistent, as were his profound and persistent amnestic symptoms, which are not a recognized component of the serotonin syndrome. However, as has been noted in ingestions involving neurotransmitter derangements, there is an interplay between underlying psychiatric disease and the acute ingestion. For example, the use of hallucinogens can precipitate first episodes of psychosis or worsen baseline disease.[7-9]

It remains unclear if this case represents a single atypical presentation of serotonergic toxicity, or an idiosyncratic reaction to a supplement mediated by other neurochemical and psychiatric factors. As dietary supplements are largely unregulated, one cannot reliably trust the accuracy of the label or purity of the product, as an unidentified agent could cause the effects. Commercially available supplements may not accurately label product concentrations, or may even contain contaminants. One study of commercially available ginseng, noted measured concentrations of actual ginsenosides ranged between 0 and 300 percent of product labeling.[10] Other adulterants such as thyroid hormone, adrenal steroids, indomethacin, DES, and warfarin have also been discovered[11,12] in dietary supplements.

This case highlights several key points. As herbal supplements gain popularity we may see an increasing number of new clinical effects not previously described, or atypical presentations of known syndromes. Unstandardized compounding may also put patients at risk for taking more than recommended doses of supplements such as in this case where a small package contained over 5,000 doses and provided no means of measuring recommended doses. With these unknown factors, the astute clinician should always consider appropriate and aggressive supportive care, to be a cornerstone in the treatment of toxicologic emergencies.

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