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OBSERVATION

Serotonin Toxicity Associated with *Garcinia cambogia* Over-the-counter Supplement

Annette M. Lopez · Joshua Kornegay · Robert G. Hendrickson

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Introduction

Garcinia cambogia, also known as the Malabar tamarind, is a plant that is commonly used in India and Southeast Asia for its sour taste and as a food-bulking agent [1]. The plant contains hydroxycitric acid (HCA) and has recently become a popular ingredient in over-the-counter supplements designed for weight loss and weight management [2]. Most of these supplements contain from 20 to 60 % HCA.

There is limited evidence that HCA may increase serotonin concentrations and thereby increase the risk of serotonin toxicity. HCA analogs increase serotonin concentrations within the brains of rats [1, 3], and randomized human studies have found elevations in free serum serotonin concentrations after the administration of HCA derivatives [4].

We report a case of suspected serotonin toxicity in the presence of therapeutic dosing of serotonin reuptake inhibitors (SSRIs) when combined with a nutritional supplement containing *G. cambogia* and hydroxycitric acid.

Case Presentation

A 35-year-old woman was in her normal state of health when she developed stuttering speech and profuse sweating. She arrived to the emergency department via ambulance, and her vital signs were notable for hypertension (169/100 mmHg) and tachycardia (102 beats per min). Initial physical exam revealed an anxious appearing, diaphoretic female with a stuttering, but non-aphasic, speech pattern. She was tachycardiac (120 beats per min), and her neurologic examination demonstrated spontaneous ankle clonus in the lower extremities as well as bilateral ocular clonus. She had inducible clonus of her mandible resulting in rhythmic jaw motions and stuttering. She was hyperreflexic (3+ patellar reflexes) and tremulous. Pertinent additional findings included sinus tachycardia on her electrocardiogram, leukocytosis (22 K/mm^3), hypokalemia (3.2 mmol/L), and a normal head CT. The patient's urine immunoassay (Syva EMIT) was positive for cannabinoids and oxycodone, both of which were prescribed to her by her primary provider for a chronic pain syndrome. The patient provided this information freely on history and denied any other substance use.

The patient's medication history was significant for having consistently taken a *G. cambogia* supplement daily for the last 2–3 months for weight loss. The product label listed the following as active ingredients: *G. cambogia* (fruit rind) extract (60 % HCA) 1,000 mg, chromium 200 μg, potassium 50 μg, and calcium 50 μg. The serving size was listed as two capsules, and the patient confirmed her dose at two capsules three times a day. She reports that she had been stable on escitalopram (20 mg) for over 1 year, but 1 month ago and approximately 1–2 months after starting to take *G. cambogia*, the patient developed a tremor, flushing, and diaphoresis. She was diagnosed with serotonin toxicity, and the escitalopram was discontinued. At that time, she did not report her *G. cambogia* intake to her doctor and had always taken the supplement in the presence of escitalopram. She was allowed 2 weeks without escitalopram or any other antidepressant, and then, sertraline 50 mg daily was started approximately 1.5 weeks prior to this admission. The patient reportedly was compliant in taking these medications: baclofen, gabapentin, omeprazole, oxycodone, silodosin, solifenacin, and diphenhydramine.

A. M. Lopez · J. Kornegay · R. G. Hendrickson (✉)
Department of Emergency Medicine, Oregon Health and Sciences University, SW Sam Jackson Park Road, CSB-550, Portland, OR 97239, USA
e-mail: hendriro@ohsu.edu

A. M. Lopez · R. G. Hendrickson
Oregon Poison Center, 3181 SW Sam Jackson Park Road, CSB-550, Portland, OR 97239, USA

In the emergency department, she was treated with IV lorazepam and 8 mg of oral cyproheptadine for presumed serotonin toxicity. After these interventions, the patient had significant improvement of her symptoms and was admitted for further care and monitoring.

The following morning, she was evaluated by the toxicology service. She had recurrence of some of her lower extremity and jaw clonus 8–12 h after her dose of cyproheptadine. The family at bedside also reported that the patient experienced multiple visual hallucinations overnight. She was again treated with 8 mg oral cyproheptadine, and her symptoms improved.

Discussion

G. cambogia has become a popular over-the-counter supplement used for weight loss, reportedly due to the effects of its active ingredient, HCA. Animal research has suggested that HCA has appetite-suppressant qualities via the production of hepatic glycogen and subsequent activation of the glucoreceptors which generate feelings of satiation. HCA may also inhibit de novo fat synthesis by competitive inhibition of adenosine triphosphate citrate (*pro-3S*) lyase, the required enzyme needed for fat synthesis, responsible for generating acetyl coA from citrate [4–6].

Our patient presented with symptoms that are consistent with serotonin toxicity (hypertension, tachycardia, diaphoresis, ataxia, hallucinations, muscle rigidity, tremor, spontaneous lower extremity clonus, and ocular clonus) by both the Hunter Serotonin Toxicity Criteria and the Sternbach Criteria.

The following are the patient's symptoms that are consistent with serotonin toxicity using the Hunter Serotonin Toxicity Criteria [7] in the presence of a serotonergic agent:

1. Spontaneous clonus
2. Inducible clonus and diaphoresis
3. Tremor and hyperreflexia.

The following are the patient's symptoms that are consistent with serotonin toxicity using the Sternbach criteria [8]:

1. Recent addition/increase in a known serotonergic agent (*G. cambogia* and sertraline)
2. Absence of other etiologies
3. No recent addition/increase of a neuroleptic agent
4. At least three of the following symptoms: positive (agitation, myoclonus, hyperreflexia, diaphoresis) and negative (mental status change, shivering, diarrhea, incoordination, fever).

There is limited evidence that HCA may increase endogenous serotonin concentrations. Rat studies have suggested that a novel HCA extract, Super CitriMax (HCA-SX), was capable of inhibiting the uptake of serotonin in isolated brain cortical cells in a manner similar to SSRIs [5] and that HCA-SX increases serotonin concentrations in rat brain tissue [3]. The mechanism of increased serotonin concentrations is not clear but has been hypothesized to be from the upregulation of genes that encode serotonin receptors [1]. A randomized, placebo-controlled, double-blind pilot study found that in 30 obese human subjects, there was an increase in serum serotonin concentrations of 39.8 % (initial level of 216±23.55 ng/mL, final level (8 weeks later) 302±26.74 ng/mL), compared to controls (initial level of 220±17.09 ng/mL, final level 266.3±15.31) [3, 4].

Our patient had signs and symptoms consistent with serotonin excess leading to the development of serotonin toxicity in the presence of an SSRI (escitalopram) and *G. cambogia*, followed by a resolution of symptoms once the SSRI was removed. Upon rechallenge with another SSRI (sertraline) at therapeutic doses in the continued presence of *G. cambogia*, the patient again developed symptoms consistent with serotonin toxicity. Further supporting evidence for the presence of serotonin toxicity in this case includes the improvement of symptoms upon addition of cyproheptadine at 8 mg dosing, with return of symptoms once the medication was cleared. Upon readministration of the cyproheptadine, her symptoms resolved. The delay of 1–2 months from the start of the HCA-containing product may be explained by the noted elevation over time in serum serotonin levels by participants in the pilot study conducted by Preuss et al. [4]. In this study, statistically significant differences in serotonin levels were noted between 4 and 8 weeks in the groups receiving HCA. Thus, there appears to be a delay in the buildup of intrinsic serotonin. This patient received a psychiatric consultation as part of her hospital course to help with medication recommendations. Given the severity of her symptoms, her SSRIs and *G. cambogia* supplementation were discontinued. On follow-up, the patient had not been rechallenged with SSRIs and was started on an antipsychotic (quetiapine) for adjunctive depression disorder management.

We do not have definitive proof of a cause and effect relationship between *G. cambogia* and serotonin toxicity. We were unable to obtain blood testing to exclude all other pharmaceutical causes of serotonin toxicity, and it is possible that our patient took another xenobiotic, though she denied this on direct questioning. It is possible that our patient developed serotonin toxicity from the single-agent SSRI and that *G. cambogia* is unrelated. However, she had been on a stable dose of escitalopram without symptoms for over 1 year and had only developed serotonin toxicity after the addition of *G. cambogia*. Given the unregulated nature of the nutritional supplement industry, another potential explanation for the noted effects could be adulteration or contamination of the products being used by the patient. Finally, there is a

physiological basis for her development of serotonin toxicity since *G. cambogia* increases serotonin concentrations and acts as a reuptake inhibitor.

We are not aware of previous cases of serotonin toxicity associated with *G. cambogia* use. In the largest prospective trial on *G. cambogia* that included 100 subjects, there was no difference in the rate of side effects in the study or placebo groups, and no clinical signs of serotonin excess were reported. However, this study specifically excluded subjects who were taking any prescription medications.

Conclusion

G. cambogia extracts and its hydroxycitric acid (HCA) derivatives are being used by individuals in attempts to lose weight and/or to maintain weight loss. These agents have experimental animal and human data supporting increases in the concentrations of endogenous serotonin. This case illustrates how the addition of *G. cambogia* to an SSRI regimen was associated with the development of symptoms consistent with serotonin toxicity. We postulate that serotonin toxicity in our patient was due to elevated serotonin concentrations due to the combination of *G. cambogia* and two different SSRIs.

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Conflict of Interest No conflicts to declare.

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