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Selected Topics: Toxicology

HYPERTENSIVE URGENCY: AN UNDESIRABLE COMPLICATION OF A "MALE PERFORMANCE" HERBAL PRODUCT

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☐ **Abstract—Background: Hypertensive urgency is a clinical scenario that may be associated with herbal supplement use and that requires special consideration with regard to emergency department management. Case Report: A 49-year-old man presented to the emergency department with palpitations and severely elevated blood pressure without evidence of end organ dysfunction. Hypertension failed to be controlled with multiple doses of oral clonidine and intravenous labetalol. The patient later admitted to using an herbal supplement containing yohimbine, a selective α2-adrenoreceptor antagonist specifically linked to cases of refractory hypertension. Why Should an Emergency Physician be Aware of This?: Between 17–35% of the U.S. adult population may use herbal supplements on a sporadic or regular basis; pharmacologically active agents in herbal supplements may affect both a patient's presentation and response to treatment. Most patients do not mention over-the-counter and herbal products in their medication profile unless specifically asked, and therefore it is important for emergency physicians to be aware of the pharmacologic effects of herbal supplements in the evaluation and treatment of refractory severe hypertension.**

☐ **Keywords—herbal supplement; hypertensive urgency; yohimbine**

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INTRODUCTION

Yohimbine, also referred to as yohimbe, is derived from the bark of the West African tree *Pausinystalia yohimbe*, traditionally consumed as a tea for purposes of increased sexual energy (1). Still in widespread use, yohimbine reached its peak popularity in 2013, when retail sales topped $67 million (2). In 2017, yohimbine ranked in the top 15 herbal supplements sold in the United States, with sales of $19.9 million (3). Although widely available over-the-counter, multiple studies have called its safety into question.

CASE REPORT

A 49-year-old man presented to the emergency department (ED) via ambulance for complaints of palpitations and severely elevated blood pressure measurements taken by the occupational health nurse at his workplace. He had been moving furniture in an office when symptoms of a "fluttering" sensation in his chest, anxiety, and lightheadedness caused him to discontinue activity and present to the health unit. His blood pressure was measured as 280/160 mm Hg, and the nurse contacted emergency medical services for assistance. The paramedic upon arrival recorded a blood pressure of 280/142 mm Hg with a heart rate of 113 beats/min; the patient reported a mild frontal headache (1 out of 10 in severity) and a sensation of pounding in his chest but denied chest pain

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or pressure, shortness of breath, visual changes, or nausea. He was administered nitroglycerin 0.4 mg sublingually. Upon arrival to the ED the patient still reported a pounding sensation in his chest as well as anxiety, with an initial blood pressure recorded as 284/118 mm Hg and a heart rate of 88 beats/min. He was afebrile with oxygen saturation of 98% on room air. He took no medications; he stated he had not been seen by a physician for more than 10 years but remembered being told in the past that he had "borderline hypertension." He denied the use of tobacco, caffeine, stimulants, or illicit substances.

During the physical examination he was alert and conversant, his pupils were equal and reactive but fundi were poorly visualized, and his heart sounds were notable for occasional extrasystoles corresponding to premature ventricular contractions on cardiac monitor. His lungs were clear, his abdomen was soft without masses, and his extremities were well perfused, without edema.

The initial evaluation included an electrocardiogram that showed tall R waves in aVL and precordial leads consistent with left ventricular hypertrophy as well as frequent premature ventricular contractions, but no ischemic ST or T changes. Laboratory studies revealed normal renal function, mild hypokalemia (3.1 mmol/L), and a troponin <0.03 mg/dL. He was administered oral clonidine 0.3 mg and oral potassium chloride 40 meq. Repeat blood pressure was recorded as 253/127 mm Hg; he reported feeling lightheaded but appeared comfortable. He was administered labetalol 20 mg intravenously, and 10 min later his blood pressure was recorded as 217/126 mm Hg. Multiple repeated doses of clonidine and labetalol did not bring the diastolic blood pressure below 125 mm Hg or the systolic blood pressure below 210 mm Hg. Although he remained relatively asymptomatic without evidence for end organ damage, the severe and refractory nature of his hypertension prompted more aggressive treatment measures; nitroprusside infusion was initiated at 0.5 μg/kg/min. His blood pressure fell to 181/103 mm Hg and he was admitted to an intensive care unit.

On repeated questioning the patient admitted using an over-the-counter herbal compound, 1 or 2 capsules once or twice daily to improve his energy level and "get his nature"; he had taken 2 capsules the morning of presentation to the ED. Although he did not have the actual product available for analysis, the supplement's ingredients were researched online by name and were reported to contain yohimbe bark extract 62.5 mg and yohimbine alkaloid 5 mg per capsule. The product was described as a "sexual health formula for men to fuel enhanced blood flow." Of note, although the product's website recommended consultation with a health professional before use, there were no specific warnings about potential hypertensive or other cardiovascular effects.

On arrival to the intensive care unit, his blood pressure was recorded as 150/96 mm Hg and he was rapidly weaned off nitroprusside. Hypertension management was initiated with oral lisinopril 40 mg. His blood pressure in the hospital remained <160 systolic and ventricular ectopy resolved with correction of hypokalemia. Serial sampling of troponin levels remained negative; he underwent renal ultrasound which revealed no abnormalities. Urine toxicology screen was negative for opiates, amphetamines, cocaine, phencyclidine, and cannabinoids. No toxicologic screen for serum yohimbine level was obtained. The patient was counseled against the use of yohimbine and discharged the following day; his blood pressure at discharge was 152/76 mm Hg.

The patient presented to the ED 10 days later complaining of lip and tongue swelling of 2 days' duration; he had discontinued lisinopril the day before and denied use of other medications, stimulants, or herbal products. His blood pressure was recorded as 172/96 mm Hg. There was mild swelling of the upper lip but no airway compromise. He denied chest pain or shortness of breath. He was observed for several hours, with subjective improvement in symptoms; he was advised to discontinue lisinopril and to begin blood pressure therapy with metoprolol 50 mg daily. The patient was lost to subsequent follow-up.

DISCUSSION

Yohimbine, a selective α2-adrenoreceptor antagonist, is an indole alkaloid derived from the bark of the Pausinystalia yohimbe tree (4). As a α2-antagonist, yohimbine's inhibition of central α2-adrenoreceptors leads to an increase in sympathetic tone, including an increase in blood pressure. This effect has been seen at doses as low as 0.125 mg/kg (8.75 mg in a 70-kg adult) and appears to be dose-dependent (5). Oral yohimbine is absorbed quickly, reaching peak concentration within an hour of ingestion, and while its elimination half-life is also <1 h, the presence of active metabolites that persist after initial hepatic metabolism suggest that it may have a longer duration of effect (5).

Early use as a pharmacologic tool in studying autonomic regulation included animal studies that observed an increase in sexual behavior, which led to its use for erectile dysfunction as well as dysautonomic hypotension (6). Its effectiveness for sexual dysfunction has not been sufficiently proven to warrant German Commission E approval, with expressed concern for excessive risks for hypertension and tachycardia (1).

Decades of Poison Center data suggest that yohimbine is far from benign. The National Poison Data System used by U.S. Poison Control Centers tracks medical outcomes using severity codes, with "minor effect" for cases with

Table 1. Commonly Used Herbal Products that May Cause or Exacerbate Hypertension

Bitter orange (synephrine)
Blue cohosh
Dong quai
Ginseng
Guarana (caffeine)
Licorice
Ma huang (ephedra)
St. John's wort
Yohimbine

minimal, fully resolving symptoms; "moderate effect" for non–life-threatening but more prolonged or systemic symptoms; and "major effect" for life-threatening symptoms or those leading to long-term disability (7). In a 10-year comparison to other botanical products before the ban on ephedra in 2004, cases with known yohimbine ingestion had the highest rate of moderate or major adverse effects (417 cases), even when compared with ephedra-containing products—by comparison, 267 cases (7). A subsequent retrospective study found that approximately 30% of yohimbine cases had moderate or major effects (8). The most recent data show a slight decrease in the rate of moderate or major effects from yohimbine, with 140 cases in 2017 (41 moderate and 1 major adverse effect) (9). Multiple authors have called for U.S. Food and Drug Administration review of yohimbine's safety (7,8,10).

Yohimbine is one of several herbal products linked to hypertension (4). As these products are considered dietary supplements under the Dietary Supplement Health and Education Act of 1994, they are not required by the U.S. Food and Drug Administration to undergo safety or efficacy testing before reaching the consumer market, nor is standardization a guarantee that the product has the precise amount of pharmacologically active ingredient as labeled (11). Several herbal products containing yohimbine are available over-the-counter and are marketed primarily for weight loss, energy, and sexual enhancement. Several cases in the literature have linked yohimbine to adverse outcomes, including hypertensive urgency, cardiomyopathy, and death (12–14). The amount of yohimbine ingested in these cases is unknown because the concentration of yohimbine in herbal supplements varies and patients reported ingesting vague amounts, like "multiple pills" (12). Toxicologic screening for yohimbine is not routine, even in cases of 2 deaths in which blood concentrations were measured. There is no standard formula for extrapolating the oral dose from the yohimbine blood concentration, and therefore a lethal oral dose has not been established (14).

This case of hypertensive urgency that was refractory to initial therapy shows both an adverse effect of yohimbine as well as its interaction with conventional medication. Treatment with clonidine, an α2-agonist, failed to lower the patient's blood pressure, most likely because of yohimbine's action as an antagonist of the same α2 receptor. Our patient apparently had pre-existing hypertension that was exacerbated by his use of yohimbine. Experimental studies have shown both an alteration in the balance of α-adrenoreceptors and an increased responsiveness to the hypertensive effects of yohimbine in patients with pre-existing hypertension (15). Clonidine failure in the setting of yohimbine use has been previously described, in which case repeated doses of 5–20 mg of intravenous labetalol proved effective (10). This was not the case for our patient, who failed management with intravenous labetalol but whose blood pressures normalized after administration of nitroprusside, perhaps suggesting the utility of directly acting vasodilators in refractory cases. Table 1 summarizes commonly used herbal products associated with hypertension (6,16,17).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

A significant proportion of the U.S. adult population, estimates ranging from 17–35%, use herbal supplements for a wide array of indications (16–18). Most patients do not mention over-the-counter products in their medication profile unless specifically asked (16). Herbal supplements may affect both a patient's presentation and their response to treatment. Emergency physicians should ask specifically about herb and supplement use when taking a medication history because patients might not consider these to be medications or may not wish to divulge the condition they are aiming to self-treat by their use of supplements. Refractory hypertension is a clinical scenario associated with herbal supplement use, and this case illustrates unique considerations with regard to emergency management.

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