Systemic Hypertension Induced by *Harpagophytum procumbens* (devil's claw): A Case Report

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Long-term intake of vasopressor and/or sodium-retaining substances such as oral contraceptives, licorice, carbenoxolone, vasoconstrictive nasal drops, cocaine, amphetamines, glucocorticosteroids and mineralocorticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), erythropoietin, and cyclosporine has been widely documented to induce hypertension in normotensive patients and to increase blood pressure (BP) in treated hypertensive patients.[1]

A correct diagnostic approach to patients with systemic hypertension should include a detailed medical history, in particular habitual self-administration of substances with documented hypertensive effects.[2] This topic is of paramount relevance in the management of hypertensive patients, because of the increasing use of drugs and substances affecting BP in the general population. About one quarter of the elderly population in the United States has been shown to regularly take NSAIDs.[3] Furthermore, dissatisfaction with conventional medications leads to a growing fraction of the population to assume herbal supplements as complementary cures for a variety of pathologies.[4]

The majority of patients consider herbal preparations as safe options for medical treatment. A large body of evidence, however, contrasts this view, as habitual consumption of herbal supplements has been shown to be associated with general and cardiovascular adverse effects, including hypertension.[5]

We present the case of a healthy normotensive woman who developed grade 2 symptomatic hypertension during self-administration of *Harpagophytum procumbens*. This compound, commonly known as devil's claw, contains an iridoid glycoside, harpagoside, which has been found to exert anti-inflammatory activity.[6] To the best of our knowledge, this is the first documented case of hypertension associated with *H procumbens* administration in humans.

CASE REPORT

A 62-year-old healthy women with no significant medical history or history of hypertension (normal office BP values for at least three measurements during the previous 6 months) presented to her general practitioner with complaints of headache and dizziness for the past 2 days. On presentation, her BP was 175/100 mm Hg and heart rate was 70 beats per minute. Physical examination disclosed no abnormalities other than a mild mid-systolic murmur on the second right intercostal space. Upon prompting, the patient admitted that in the previous 2 weeks she had been taking 2 caplets per day of a preparation containing *H procumbens* (250 mg per caplet), a natural anti-inflammatory agent, for symptomatic hand osteoarthritis. She denied the use of other medications, stimulants, illicit drugs, and other herbal or dietary supplements. Within a few days, the patient underwent a comprehensive workup including repeated office BP measurements (range: 155–170 mm Hg systolic, 90–100 mm Hg diastolic), standard blood and urine examinations, electrocardiography, Doppler echocardiography (all within normal limits), and ambulatory BP monitoring (ABPM) showing an average 24-hour BP of 147/90 mm Hg, with preserved nocturnal systolic and diastolic BP fall (>10%). *H procumbens* was immediately discontinued. Office BP gradually fell in the subsequent 2 weeks and symptoms (headache and dizziness) disappeared. A second ABPM, performed 2 weeks after *H procumbens* withdrawal, showed a fully normalized BP (average systolic/diastolic BP 124/72 mm Hg). Notably, persistence of normal BP was documented by self- and office measurements regularly taken at least once a week in the subsequent 6-month follow-up period.

DISCUSSION

To our knowledge, the patient described above represents the first report of systemic hypertension associated with *H procumbens* administration. The patient had no history of hypertension, and withdrawal of *H procumbens* was followed by normalization of in-office and out-of-office BP values within 2 weeks. Of note, the patient was found to be free of signs of subclinical organ damage such as microalbuminuria and electrocardiographic or echocardiographic left ventricular hypertrophy. The lack of evidence of subclinical hypertensive target organ damage, in combination with normal ambulatory BP values documented after *H procumbens* withdrawal, excludes preexisting masked hypertension (ie, normal office and elevated out-of-office BP), a condition often associated with subclinical cardiovascular alterations and a risk factor for the development of sustained hypertension. Hypertension was still present after 1 week of *H procumbens* withdrawal, possibly as a result of the persistent inhibition of endogenous prostaglandins synthesis.[6]

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H procumbens has historically been used as an herbal medicine for a variety of conditions (fevers, allergies, dyspepsia, fluid retention and edema, appetite stimulation). Currently, it is mostly used as an anti-inflammatory and analgesic agent for osteoarthritis.[7] This was the case of the patient of the present report, who was assuming the compound as anti-inflammatory and analgesic agent for her hand osteoarthritis in alternative to NSAIDs.

H procumbens is a perennial herb from the Kalahari region of Southern Africa belonging to the Pedaliaceae family. It is also known as harpago, devil's claw, grapple plant, and wood spider. Major chemical components of *H procumbens* include iridoid glycosides, sugars, triterpenoids, phytosterol, and aromatic acids. The anti-inflammatory activity of this herbal product has been related to harpagoside, a monoterpene glycoside. Harpagoside inhibits inflammation by interacting with both cyclo-oxygenase (COX) and lipoxygenase-mediated pathways of arachidonic acid cascade as well as with cytokine release. Recent literature data have shown that harpagoside inhibits COX-2 via nuclear factor kappa B expression;[8] this effect is of major relevance in BP homeostasis. A large body of evidence has demonstrated that COX-2 inhibition by both nonselective and selective NSAIDs significantly increases BP in normotensive and hypertensive individuals. The hypothesized mechanisms for the pressor effect include: (1) reduced vasodilation and natriuresis caused by suppression of vasodilator prostaglandins, (2) reduced aldosterone clearance, and (3) increased production of vasoconstrictor prostaglandins (thromboxane A and leukotrienes).[9]

In a prospective, randomized, double-blind, double-dummy trial including 88 patients, Chrubasik and colleagues[10] compared the efficacy and tolerability of a 6-week course of *Harpagoside* and rofecoxib (a selective synthetic COX-2 inhibitor) for low back pain treatment. The authors found no significant intergroup differences in efficacy and tolerability, a result that has been ascribed to similar mechanisms of action of both active compounds.

It is worth noting that an excess of thrombotic cardiovascular events and new-onset hypertension during rofecoxib treatment, as compared with naproxen, has been reported in a large prospective study.[11] Different from synthetic COX-2 inhibitors, occurrence of cardiovascular events has not been reported for *Harpagoside,* although available literature focusing on adverse effects associated with *H procumbens* treatment is scant. A systematic review by Vlachojannis and colleagues[12] on the safety of *H procumbens* preparations for osteoarthritic and low back pain including 28 clinical trials reported a similar incidence of side effects during *H procumbens* treatment and placebo, with minor adverse events, mostly of gastrointestinal nature, reported in around 3% of patients.

A number of adverse drug interactions have been occasionally described for *H procumbens*. They include an increased risk of gastrointestinal bleeding, hypoglycemia, and arrhythmias when *H procumbens* is associated with NSAIDs and anticoagulants, hypoglycemic medications, anti-arrhythmic agents, or digoxin, respectively. Little information is available about BP effects of *H procumbens* in humans. An experimental study conducted by Circosta and colleagues[13] in conscious normotensive rats demonstrated that a crude methanolic extract of *H procumbens* induced a dose-dependent reduction in arterial BP and heart rate. This finding was not confirmed in subsequent animal and human studies. A review based on five electronic literature databases summarizing the adverse cardiovascular and pressure effects of herbal medicines did not include *H procumbens* among the substances that cause hypertension.[14] More recently, Jalili and colleagues[15] reviewed 56 articles published from 1991 to 2011 focusing on the association between herbal products and hypertension; the authors were able to identify 29 papers providing reliable information about the hypertensive effects of herbal agents. In this updated review, the list of herbal products associated with hypertension (including as many as 16 substances such as arnica, bitter orange, blue cohosh, dong quai, ephedra, ginkgo, ginseng, guarana, licorice, pennyroyal oil, Scotch broom, senna, southern bayberry, St John's wort, and yohimbine) did not include *H procumbens*.

The present report adds a new piece of information to recent literature[16] by documenting the association between subchronic use (>2 weeks) of a product containing *H procumbens* and new-onset moderate systemic hypertension in a healthy postmenopausal woman.

CONCLUSIONS

More safety data on herbal medicinal products are highly needed, as well as surveillance and clinical research on this important topic, in order to limit the occurrence of serious adverse effects related to the growing use of self-medications. In this perspective, a careful medical history in hypertensive patients should include specific questioning concerning the use of herbal products. Finally, more extensive literature on the risk related to self-administration of herbal products is of paramount importance for reducing the burden of side effects related to these alternative forms of medical care.

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