ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**(1), 1–5
https://doi.org/10.1093/ehjcr/ytac023

CASE REPORT
Arrhythmias / Electrophysiology

Taken to heart—arrhythmic potential of heart-leaf sida, a banned ephedrine alkaloid: a case report

Evaline Cheng [1], Ruth Hsiao[2], Zenaida Feliciano[3,4], Jaime Betancourt[5,6], and Janet K. Han [3,4]*

[1]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA; [2]Department of Medicine, Division of Cardiology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA; [3]Department of Medicine, Cardiac Arrhythmia Center, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA; [4]Department of Medicine, Cardiac Arrhythmia Center, VA Greater Los Angeles Healthcare System, 11301 Wilshire Blvd 111E, Los Angeles, CA 90073, USA; [5]Department of Medicine, Division of Pulmonary and Critical Care Medicine, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA; and [6]Department of Medicine, Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

Received 24 August 2021; first decision 21 September 2021; accepted 31 December 2021; online publish-ahead-of-print 19 January 2022

Background Ephedra and ephedrine alkaloids were commonly used in herbal supplements before being prohibited by the European Commission and US Food and Drug Administration. However, ongoing, unknowing use by consumers can lead to potential adverse cardiovascular effects, such as arrhythmias.

Case summary A 65-year-old-man with a history of idiopathic pulmonary fibrosis status post-right single lung transplant was admitted for dizziness and resting tachycardia. Electrocardiogram showed a narrow complex, long R-P tachycardia with upright P-waves in lead V_1. An initial workup suggested an arrhythmia associated with the consumption of an herbal supplement containing heart-leaf sida, a banned botanical ephedrine alkaloid. After the supplement was discontinued, the patient's heart rate abruptly decreased without other intervention. Electrocardiogram showed a change in P-wave morphology in lead V_1 from upright to biphasic (+/−) after conversion to normal sinus rhythm. Thus, a diagnosis of atrial tachycardia originating at or near the donor right superior pulmonary vein was favoured.

Discussion Atrial tachycardia can be precipitated by the proarrhythmic effects of ephedrine alkaloids, especially in patients with underlying risk factors and susceptible atrial anatomical substrate post-lung transplantation. Despite being banned by the European Union and the USA, ephedrine alkaloids continue to be used in over-the-counter herbal supplements and may go undetected by consumers. Ongoing vigilance for ephedrine alkaloids, more rigorous regulation, and active patient education can help reduce potential cardiovascular adverse events.

Keywords Herbal supplements • Narrow complex tachycardia • Atrial tachycardia • Ephedrine alkaloids • Heart-leaf sida • Case report

ESC Curriculum 5.1 Palpitations • 5.5 Supraventricular tachycardia

* Corresponding author. Tel: 310 268 3750, Email: janet.han@va.gov
Handling Editor: David Niederseer
Peer-reviewers: Robert Schönbauer; Christoph Clemens Kaufmann
Compliance Editor: Rayhan Noah Saiani
Supplementary Material Editor: Damien Farhad Nur Salekin

Learning points

- Ephedra and ephedrine alkaloids continue to be used in over-the-counter herbal supplements despite ephedrine bans by the European Commission and US Food and Drug Administration.
- Atrial tachycardia is a potential arrhythmic side effect of ephedrine alkaloids, especially in patients with underlying risk factors and susceptible atrial anatomical substrate.

Introduction

Herbal supplements are commonly used and easily available worldwide. While one in five people report usage of herbal supplements, about 70% of patients do not disclose this use to their physicians.[1,2] The unknowing consumption of Ephedra and ephedrine alkaloids, a banned ingredient in the European Union (E.U.) and USA, can lead to adverse cardiovascular effects such as hypertension, arrhythmias, and acute myocardial infarction.[3–5] We describe such use and subsequent associated arrhythmia in a 65-year-old man. This case highlights the clinical challenges of recognizing the consumption of ephedrine alkaloids and emphasizes the need for increased vigilance to help reduce cardiovascular adverse events.

Timeline

Time	Events
Presentation at clinic	Patient presented with several months of dizziness and new onset resting tachycardia. Electrocardiogram (ECG) showed narrow complex long R-P tachycardia.
Hospital Day 1	Patient disclosed the use of an over-the-counter herbal supplement for several months. Herbal supplement was found to contain heart-leaf sida and was discontinued.
Hospital Day 2	Resting heart rate abruptly decreased. Electrocardiogram showed sinus rhythm. Based on change in P-wave morphology after conversion to sinus rhythm, patient was diagnosed with atrial tachycardia.
Hospital Day 3	Patient remained in sinus rhythm and was discharged home.
Follow-up at 1 week	No recurrence of symptoms or tachycardia. He remained off the herbal supplement.
Follow-up at 1 month	No recurrence of arrhythmias on 14-day ECG patch.

Case presentation

A 65-year-old Caucasian man with a history of idiopathic pulmonary fibrosis status post-right single lung transplant 14 months prior and sick sinus syndrome with a permanent dual-chamber pacemaker 6 years prior presented at a cardiology clinic with several months of dizziness and persistent resting tachycardia around 120 beats per minute (b.p.m.) with a home pulse oximeter. He denied fever, chest pain, dyspnoea, or prior episodes of palpitations. Beyond his immunosuppression (cyclosporine, mycophenolate mofetil, prednisone) and prophylaxis (trimethoprim-sulfamethoxazole, valganciclovir), his medications included atorvastatin 40 mg daily, tiotropium 2.5 mcg-olodaterol 2.5 mcg inhaled daily, furosemide 60 mg daily. Upon detailed medication reconciliation, he also reported taking an over-the-counter herbal supplement, marketed for 'natural stress relief', for several months, which had not been disclosed to prior clinicians.

Pacemaker interrogation (Medtronic, Minneapolis, MN, USA) demonstrated supraventricular tachycardia (SVT) at 120 b.p.m. Electrocardiogram (ECG) showed a narrow complex, long R-P tachycardia (NCT) with upright P-waves in leads V_1 and I and biphasic (+/−) P-waves in inferior leads (*Figure 1A*). Based on P-wave morphology and vector, differential diagnosis of this long R-P NCT included atrial tachycardia (AT) originating from the native high crista terminalis or donor tissue right superior pulmonary vein (RSPV) vs. sinus tachycardia with the abnormal P-wave morphology from post-lung transplant cardiac rotation. Potential underlying precipitants included transplant rejection, medication toxicity, and toxic-metabolic triggers like infection or hyperthyroidism.

The patient was admitted for evaluation and telemetry monitoring. Vital signs on admission included: heart rate 117 b.p.m., blood pressure 138/83 mmHg, respiratory rate of 18, and oxygen saturation 95% on room air. Physical examination was notable for tachycardia, normal heart sounds without murmurs, and lung sounds clear to auscultation bilaterally. Routine labs for toxic-metabolic disturbances did not show acute findings. Chest X-ray was negative for acute pulmonary processes such as transplant rejection, although rotation of his heart post-lung transplant was noted (*Figure 2*). Upon further history-taking, the patient revealed that starting the herbal supplement coincided with his timeline of symptoms. Further investigation of the herbal supplement revealed a combination of over 130 ingredients, including whole plant heart-leaf sida in unlisted dose (*Figure 3*). Heart-leaf sida, or *Sida cordifolia*, is a botanical source of ephedrine alkaloids, which was banned by the US Food and Drug Administration (FDA) in 2004. The herbal supplement, specifically heart-leaf sida, was the suspected cause of tachycardia, and it was discontinued.

Within 24-h of stopping the herbal supplement, the patient's heart rate abruptly decreased without atrioventricular nodal blocking agents or other interventions (*Figure 4*), suggesting an SVT related to herbal supplement ingestion. Subsequent ECG in normal sinus rhythm (NSR) at 87 b.p.m. demonstrated a biphasic (+/−) P-wave in leads V_1 and V_2 with continued abnormal P-

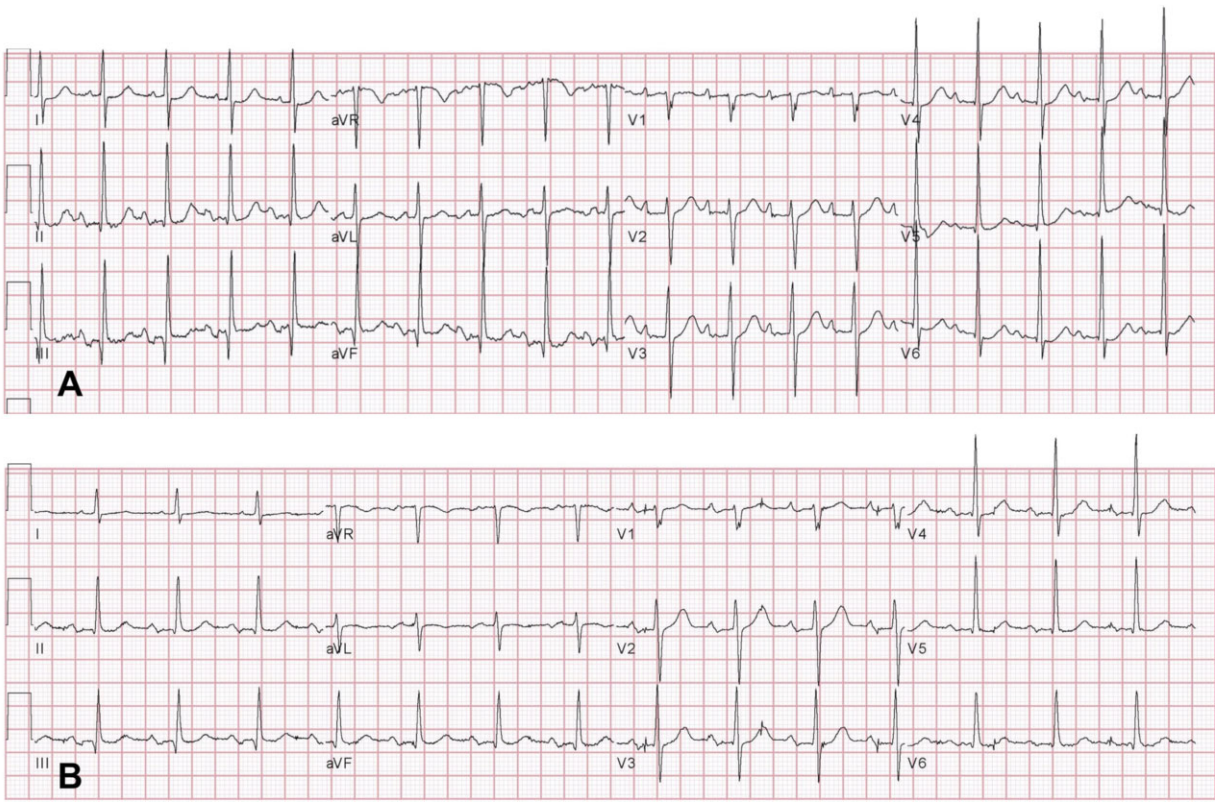

Figure 1 (*A*) Initial electrocardiogram showed narrow complex, long R-P tachycardia, 117 b.p.m. with upright P-waves in lead V_1 and biphasic (+/−) P-waves in inferior leads. (*B*) Without the supplement, electrocardiogram showed normal sinus rhythm (NSR) at 87 b.p.m. with biphasic (+/−) P-wave in lead V_1. The change in P-wave morphology in lead V_1 while on the supplement from upright to biphasic (+/−) off the supplement favours an atrial tachycardia originating at or near the donor right superior pulmonary vein.

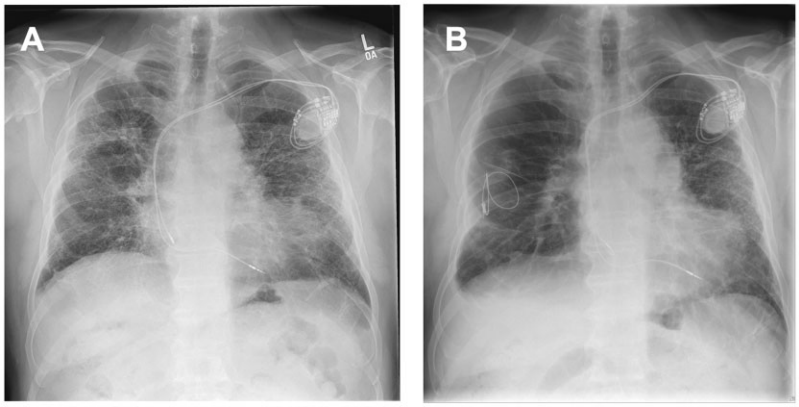

Figure 2 (*A*) Chest X-ray pre-lung transplantation. (*B*) Chest X-ray post-lung transplantation showed rotation of the heart within the thorax.

wave morphology in the limb and precordial leads attributed to post-lung transplant cardiac rotation or transplant atrial anastomosis (*Figure 1B*). Given the abrupt resolution of the NCT and change in P-wave morphology in lead V_1 from upright to biphasic (+/−) after conversion to NSR, a diagnosis of AT originating at or near the donor RSPV was favoured.[6] Since the AT resolved with herbal supplement discontinuation, electrophysiology study (EPS) was deferred.

One week later, the patient was seen for follow-up and denied recurrence of symptoms. A 14-day ECG patch (Zio, iRhythm Technologies, San Francisco, CA, USA) at 1 month follow-up subsequently showed sinus rhythm at an average 94 b.p.m. with

first-degree atrioventricular block and <1% atrial premature contractions.

Discussion

In 2004, the US FDA banned dietary supplements containing ephedrine alkaloids, such as ephedrine, pseudoephedrine, and norephedrine, due to unreasonable risk of illness or injury.[3] By 2013, the European Food and Safety Authority Panel on Food Additives and Nutrient Sources also concluded that ephedrine alkaloids in supplements posed a significant safety concern, and a similar *Ephedra* ban within the E.U. was imposed by the European Commission in 2015.[4,5] Ephedrine alkaloids were previously sold widely for weight loss, energy, and athletic performance and still used in traditional Asian medicine. Common botanical sources include *Ephedra* species and *Sida cordifolia*, otherwise known as 'heart-leaf sida' due to the plant's heart-shaped leaves.[3] With molecular similarity to catecholamines, ephedrine alkaloids have significant alpha- and beta-adrenergic activity and enhance the release of endogenous catecholamines, contributing to hypertension, vasoconstriction, and tachycardia.[7] Adverse cardiovascular events including acute myocardial infarction, stroke, and lethal ventricular arrhythmias have been reported.[8]

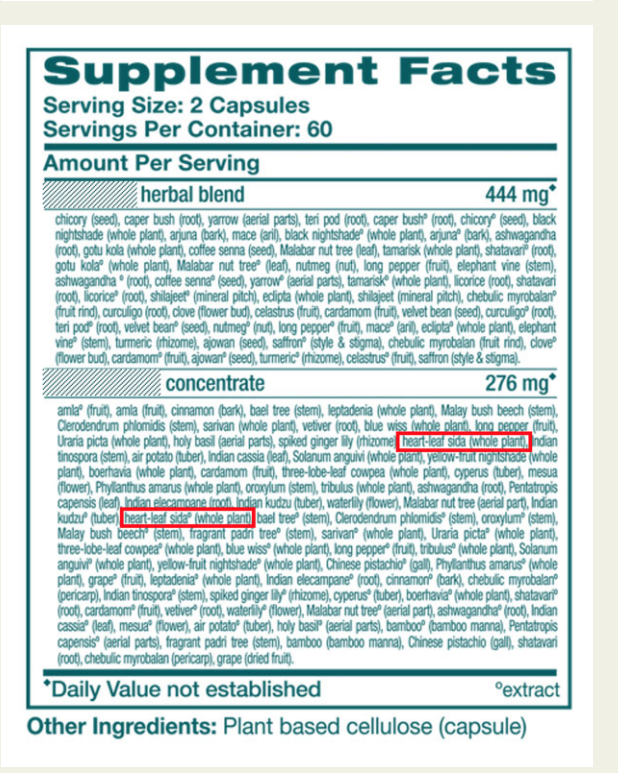
Supplement Facts
Serving Size: 2 Capsules
Servings Per Container: 60
Amount Per Serving
herbal blend 444 mg*
chicory (seed), caper bush (root), yarrow (aerial parts), teri pod (root), caper bush[a] (root), chicory[a] (seed), black nightshade (whole plant), arjuna (bark), mace (aril), black nightshade[a] (whole plant), arjuna[a] (bark), ashwagandha (root), gotu kola (whole plant), coffee senna (seed), Malabar nut tree (leaf), tamarisk (whole plant), shatavari[a] (root), gotu kola[a] (whole plant), Malabar nut tree[a] (leaf), nutmeg (nut), long pepper (fruit), elephant vine (stem), ashwagandha [a] (root), coffee senna[a] (seed), yarrow[a] (aerial parts), tamarisk[a] (whole plant), licorice (root), shatavari (root), licorice[a] (root), shilajeet[a] (mineral pitch), eclipta (whole plant), shilajeet (mineral pitch), chebulic myrobalan[a] (fruit rind), curculigo (root), clove (flower bud), celastrus (fruit), cardamom (fruit), velvet bean (seed), curculigo[a] (root), teri pod[a] (root), velvet bean[a] (seed), nutmeg[a] (nut), long pepper[a] (fruit), mace[a] (aril), eclipta[a] (whole plant), elephant vine[a] (stem), turmeric (rhizome), ajowan (seed), saffron[a] (style & stigma), chebulic myrobalan (fruit rind), clove[a] (flower bud), cardamom[a] (fruit), ajowan[a] (seed), turmeric[a] (rhizome), celastrus[a] (fruit), saffron (style & stigma).
concentrate 276 mg*
amla[a] (fruit), amla (fruit), cinnamon (bark), bael tree (stem), leptadenia (whole plant), Malay bush beech (stem), Clerodendrum phlomidis (stem), sarivan (whole plant), vetiver (root), blue wiss (whole plant), long pepper (fruit), Uraria picta (whole plant), holy basil (aerial parts), spiked ginger lily (rhizome), heart-leaf sida (whole plant), Indian tinospora (stem), air potato (tuber), Indian cassia (leaf), Solanum anguivi (whole plant), yellow-fruit nightshade (whole plant), boerhavia (whole plant), cardamom (fruit), three-lobe-leaf cowpea (whole plant), cyperus (tuber), mesua (flower), Phyllanthus amarus (whole plant), oroxylum (stem), tribulus (whole plant), ashwagandha (root), Pentatropis capensis (leaf), Indian elecampane (root), Indian kudzu (tuber), waterlily (flower), Malabar nut tree (aerial part), Indian kudzu[a] (tuber), heart-leaf sida[a] (whole plant), bael tree[a] (stem), Clerodendrum phlomidis[a] (stem), oroxylum[a] (stem), Malay bush beech[a] (stem), fragrant padri tree[a] (stem), sarivan[a] (whole plant), Uraria picta[a] (whole plant), three-lobe-leaf cowpea[a] (whole plant), blue wiss[a] (whole plant), long pepper[a] (fruit), tribulus[a] (whole plant), Solanum anguivi[a] (whole plant), yellow-fruit nightshade[a] (whole plant), Chinese pistachio[a] (gall), Phyllanthus amarus[a] (whole plant), grape[a] (fruit), leptadenia[a] (whole plant), Indian elecampane[a] (root), cinnamon[a] (bark), chebulic myrobalan[a] (pericarp), Indian tinospora[a] (stem), spiked ginger lily[a] (rhizome), cyperus[a] (tuber), boerhavia[a] (whole plant), shatavari[a] (root), cardamom[a] (fruit), vetiver[a] (root), waterlily[a] (flower), Malabar nut tree[a] (aerial part), ashwagandha[a] (root), Indian cassia[a] (leaf), mesua[a] (flower), air potato[a] (tuber), holy basil[a] (aerial parts), bamboo[a] (bamboo manna), Pentatropis capensis[a] (aerial parts), fragrant padri tree (stem), bamboo (bamboo manna), Chinese pistachio (gall), shatavari (root), chebulic myrobalan (pericarp), grape (dried fruit).
*Daily Value not established °extract
Other Ingredients: Plant based cellulose (capsule)

Figure 3 The herbal supplement included heart-leaf sida, a banned ephedrine alkaloid, and over 130 other ingredients as labelled.

While the most common arrhythmia associated with ephedrine is sinus tachycardia, AT can also develop through its proarrhythmic effects. From *in vitro* studies of human cells, ephedrine was found to increase the peak currents of slowly activating potassium channels in a concentration-dependent manner.[9] These potassium channels exist in the atria, and effects of ephedrine can shorten the cardiac action potential duration to create a lower threshold for re-entry.[8,10] Although this patient did not undergo EPS to definitively localize the AT, its sudden termination and change in P-wave in lead V_1 from upright in AT to biphasic in NSR was consistent with an AT near the RSPV. In this case, the onset of the patient's palpitations approximately overlapped with the use of the herbal supplement, and its resolution also correlated with supplement discontinuation. While diurnal heart rate variation could be considered as an explanation for this trend, physiological study of heart rate variation in healthy adult subjects showed a gradual heart rate decline with sleep, rather than the abrupt decrease demonstrated in this case.[11] Following lung transplantation, patients are also more susceptible to atrial arrhythmias, which tend to occur in a bimodal distribution: 24% in the postoperative period, 2% near 6 months, and 11% after 12 months. Further, EPS within this population have revealed macro-reentry in the left atria along surgical anastomosis lines with the donor pulmonary vein, as well as focal ATs from donor pulmonary veins.[12]

The widespread use of herbal supplements represents a unique challenge for physicians. Dietary supplements are not required to

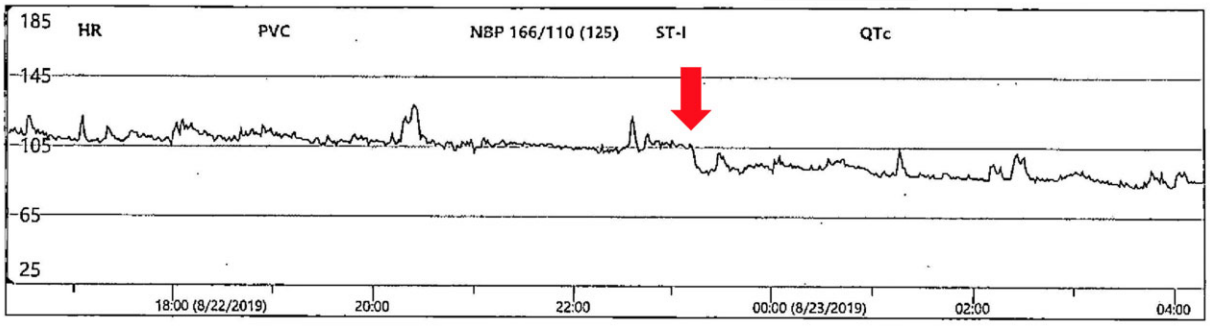

Figure 4 On telemetry, heart rate abruptly decreased within 24-h after discontinuing the herbal supplement, as highlighted by the arrow, which was suspected to be due to conversion to sinus rhythm.

provide proof of safety, purity, or strength of their ingredients.[13] Ephedrine alkaloids are often used in combination with other ingredients, further limiting the ability to discern quantities of active compounds. Beyond the potential for impurities, it is possible that one of the other ingredients in the patient's herbal supplement contributed to his AT. However, literature search for each ingredient's labelled and scientific name did not reveal associations with SVT, although ashwagandha (*Withania somnifera*) was attributed to ventricular tachycardia in one case.[14] Additionally, even small doses of ephedrine alkaloids have been associated with adverse effects, and the rapid resolution of AT after supplement discontinuation is expected with ephedrine's short serum half-life and renal excretion within 24 h.[7,8]

Despite the US FDA ban, it is concerning that a supplement containing ephedrine alkaloids was domestically available. One study of online weight loss supplements also found that 11% had ephedrine ingredients which could be a violation of the ban.[15] Further, variable naming conventions, such as 'heart-leaf sida', do not clearly identify the active ingredient, leaving patients at risk. Thus, existing bans within the E.U., USA, Canada, Australia, and New Zealand do not provide full reassurance about the availability of Ephedra and ephedrine alkaloids.[4] Physicians should actively engage with patients about their use of herbal supplements and encourage more comprehensive regulation for patient safety.

Conclusion

Despite being banned in the E.U. and USA, ephedrine alkaloids continue to be used in over-the-counter herbal supplements. This is often under the guise of common, non-scientific names, in combination with other herbal ingredients, and in unlisted doses, such that they may go undetected by unsuspecting consumers. Ongoing vigilance for ephedrine alkaloids, more rigorous regulation, and active patient education can help reduce potential cardiovascular adverse events.

Lead author biography

Evaline Cheng, MD is a third-year internal medicine resident at the University of California Los Angeles. She completed her medical training at the University of California San Diego School of Medicine. As an upcoming general cardiology fellow at Stanford University, her clinical and research interests include preventive cardiology, cardio-oncology, and improving the delivery of cardiovascular care.

Supplementary material

Supplementary material is available at *European Heart Journal—Case Reports online*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient's next-of-kin in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

References

1. Liperoti R, Vetrano DL, Bernabei R, Onder G. Herbal medications in cardiovascular medicine. *J Am Coll Cardiol* 2017;**69**:1188–1199.
2. Garcia-Alvarez A, Egan B, De Klein S, Dima L, Maggi FM, Isoniemi M et al. Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey. *PLoS One* 2014;**9**:e92265.
3. Food and Drug Administration. Final rule declaring dietary supplements containing ephedrine alkaloids adulterated [Internet]. 2004. https://www.federalregister.gov/documents/2004/02/11/04-2912/final-rule-declaring-dietary-supplements-containing-ephedrine-alkaloids-adulterated-because-they (14 May 2021).
4. EFSA Panel on Food Additives and Nutrient Sources. Scientific opinion on safety evaluation of Ephedra species for use in food. *EFSA J* 2013;**11**. https://doi.org/10.2903/j.efsa.2013.3467.
5. European Commission. Commission Regulation (EU) 2015/403 of 11 March 2015 amending Annex III to Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards Ephedra species and Yohimbe (Pausinystalia yohimbe (K. Schum) Pierre ex Beille) [Internet]. Commission Regulation (EU) 2015/403 2015. https://eur-lex.europa.eu/eli/reg/2015/403/oj (4 August 2021).
6. Kistler PM, Chieng D, Tonchev IR, Sugumar H, Voskoboinik A, Schwartz LA et al. P-wave morphology in focal atrial tachycardia: an updated algorithm to predict site of origin. J Am Coll Cardiol EP 2021;**7**:1547–1556.
7. Andraws R, Chawla P, Brown DL. Cardiovascular effects of ephedra alkaloids: a comprehensive review. *Prog Cardiovasc Dis* 2005;**47**:217–225.
8. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000;**343**:1833–1838.
9. Jing H, Luo L, Li H, Sun J, Yi H, Wu Y et al. Ephedrine controls heart rhythms by activating cardiac Iks currents. *J Cardiovasc Pharmacol* 2010;**55**:145–152.
10. Jeevaratnam K, Chadda KR, Huang CLH, Camm AJ. Cardiac potassium channels: physiological insights for targeted therapy. *J Cardiovasc Pharmacol Ther* 2018;**23**:119–129.
11. Nakagawa M, Iwao T, Ishida S, Yonemochi H, Fujino T, Saikawa T et al. Circadian rhythm of the signal averaged electrocardiogram and its relation to heart rate variability in healthy subjects. *Heart* 1998;**79**:493–496.
12. See VY, Roberts-Thomson KC, Stevenson WG, Camp PC, Koplan BA. Atrial arrhythmias after lung transplantation. *Circ Arrhythm Electrophysiol* 2009;**2**:504–510.
13. Fontanarosa PB, Rennie D, DeAngelis CD. The need for regulation of dietary supplements: lessons from ephedra. *J Am Med Assoc* 2003;**289**:1568–1570.
14. Dwivedi S, Aggarwal A, Sharma V. Cardiotoxicity from 'safe' herbomineral formulations. *Trop Doct* 2011;**41**:113–115.
15. Lai S, Yu C, Dennehy CE, Tsourounis C, Lee KP. Online marketing of ephedra weight loss supplements. *J Altern Complement Med* 2021;**27**:796–802.