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CASE REPORT
Heart failure

Methylephedrine-induced heart failure in a habitual user of paediatric cough syrup: a case report

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Background For relief of cold symptoms, methylephedrine is considered to be safer than ephedrine, particularly when used at the predetermined dose. It is often present in various over-the-counter (OTC) drugs for cold, including paediatric cough syrups.

Case summary A 52-year-old man presented with worsening dyspnoea and anorexia for 2 weeks. He was a night shift worker and had been habitually taking large doses of methylephedrine-containing paediatric cough syrup for 20 years for sleep averting. On admission, his chest X-ray revealed pulmonary congestion and electrocardiogram showed sinus tachycardia with left-axis deviation. Echocardiography revealed diffuse hypokinesis with a reduced ejection fraction (EF) of 25%. The B-type natriuretic peptide level was elevated to 1092 ng/L. Even after treatment with low-dose dobutamine and furosemide in intensive care unit, right-heart catheterization demonstrated a 'wet and cold' profile. Coronary angiography revealed normal coronary arteries. Pathological examination by endomyocardial biopsy revealed cardiomyocyte hypertrophy with moderate interstitial and replacement fibrosis. In addition, cardiac magnetic resonance imaging revealed diffuse hypokinesis with mid-wall late gadolinium enhancement, which suggested fibrosis. Discontinuation of the cough syrup and optimal medical treatment with an angiotensin-converting enzyme inhibitor and a β blocker resulted in improvement in the heart failure symptoms to New York Class Association Class II. The EF also improved to 50% at 4 months after discharge.

Discussion Methylephedrine is considered to have adrenergic effects; it has milder side effects on the cardiovascular system than ephedrine. However, the long-lasting excessive intake of methylephedrine, even through OTC paediatric cough syrups, has the potential to cause heart failure.

Keywords Heart failure • Methylephedrine • Left ventricular dysfunction • Over-the-counter drugs • Case report

Learning points

- Long-lasting excessive intake of methylephedrine, even through over-the-counter (OTC) paediatric cough syrups, has a potential to cause heart failure.
- A detailed medical review about the intake of habitual drugs, including OTC, is needed to identify the causes of heart failure.

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Introduction

Ephedrine is a sympathomimetic drug that stimulates α and β receptors in sympathetic nerve terminals. Reportedly, this drug has adverse effects on the cardiovascular system[1] and can cause vasospasm,[2] ischaemic stroke,[3] and myocardial dysfunction.[4,5]

Methylephedrine is another sympathomimetic drug and is considered to be safer than ephedrine, especially when administered at the predetermined dose. Therefore, methylephedrine is often contained in various over-the-counter (OTC) drugs for cold, including paediatric cough syrups, with only few cases of adverse cardiovascular events reported to date.[6] Here, we describe a case of heart failure that resulted from the habitual intake of methylephedrine-containing paediatric cough syrup in an adult man who had used the medication for sleep disorders due to night shift work.

Timeline

Time	Events
About 20 years ago	Patient started habitual use of methylephedrine-containing paediatric over-the-counter cough syrup
Two weeks prior to presentation	Heart failure symptoms with worsening dyspnoea and anorexia developed
Emergency room admission	Blood pressure and heart rate were 146/98 mmHg and heart rate was 104 b.p.m., respectively
	Decompensated heart failure with reduced left ventricular ejection fraction (EF) of 25%
	B-type natriuretic peptide was elevated to 1092 ng/L
	Discontinuation of the cough syrup after hospitalization
	Treatment with low-dose dobutamine (2 μg/kg/min) and furosemide was started
Day 2	Enalapril and spironolactone started
Day 4	Cardiac rehabilitation initiated
Day 5	Carvedilol started
Day 8	Right-sided heart catheterization revealed 'wet and cold' profile
Day 12	Cardiac magnetic resonance imaging demonstrated diffuse hypokinesis with mid-wall late gadolinium enhancement
Five weeks	Discharged home
	Medication with 5 mg/day enalapril, 20 mg/day carvedilol, and 25 mg/day spironolactone
Four months	New York Class Association Class II. EF was 50%

Case presentation

A 52-year-old man presented at our hospital with worsening dyspnoea and anorexia for 2 weeks. A detailed medical interview revealed that he was a night shift worker and that he had been habitually taking 3–4 bottles (90–120 mL) of methylephedrine-containing paediatric OTC cough syrup daily for 20 years. The syrup contained methylephedrine (40 mg), acetaminophen (450 mg), caffeine (50 mg), chlorpheniramine (5 mg), and dihydrocodeine (16 mg) per bottle. The recommended dose of the syrup was 7.5 mL/day for paediatric use.

On admission, the patient's blood pressure was 146/98 mmHg and heart rate was 104 b.p.m. His chest X-ray revealed pulmonary congestion and electrocardiogram showed sinus tachycardia with left-axis deviation. Echocardiography demonstrated diffuse hypokinesis of the left ventricle with a reduced ejection fraction (EF) of 25% and an increased left ventricular (LV) end-diastolic diameter at 67 mm (*Figure 1A* and Supplementary material online, *Videos S1–S3*). Laboratory examination revealed elevated B-type natriuretic peptide [BNP, 1092 ng/L (normal range: <18.6 ng/L)] and liver enzyme levels, which suggested liver congestion. The cough syrup was immediately discontinued after hospitalization. Although his vital signs were relatively stable, we diagnosed his status as decompensated heart failure and low-dose dobutamine infusion was started for low cardiac output symptoms. Even after treatment with low-dose dobutamine and furosemide in intensive care unit, right-heart catheterization demonstrated a 'wet and cold' profile, with a pulmonary capillary wedge pressure of 22 mmHg, mean pulmonary artery pressure of 29 mmHg, and cardiac index of 1.89 L/min/m^2. Although the patient's coronary angiography revealed normal coronary arteries, his left ventriculography revealed severe diffuse hypokinesis with mild mitral regurgitation (*Figure 2A and B* and Supplementary material online, *Video S4*). Pathological examination by right ventricular endomyocardial biopsy revealed cardiomyocyte hypertrophy with moderate interstitial and replacement fibrosis and absence of secondary cardiomyopathies and myocarditis (*Figure 3A and B*). In addition, cardiac magnetic resonance imaging revealed diffuse hypokinesis with mid-wall late gadolinium enhancement, which suggested fibrosis (*Figure 4*).

Discontinuation of ingesting the cough syrup and optimal medical treatment (OMT) with an angiotensin-converting enzyme inhibitor and a β blocker improved the heart failure symptoms to New York Class Association Class II at 4 months after discharge. The patient's EF was also improved to 50%, and LV reverse remodelling was achieved (*Figure 1B* and Supplementary material online, *Videos S5–S7*). In addition, his BNP level decreased and was within the normal range (<5.8 ng/L).

Discussion

Ephedrine-containing 'ephedra' is widely known as a weight-reducing substance and is used for enhancing exercise capacity. However, it reportedly has a potential to cause adverse cardiac events. The adrenergic effects of ephedrine can induce coronary spasm or shorten the refractory periods in the myocardium. Because several patients

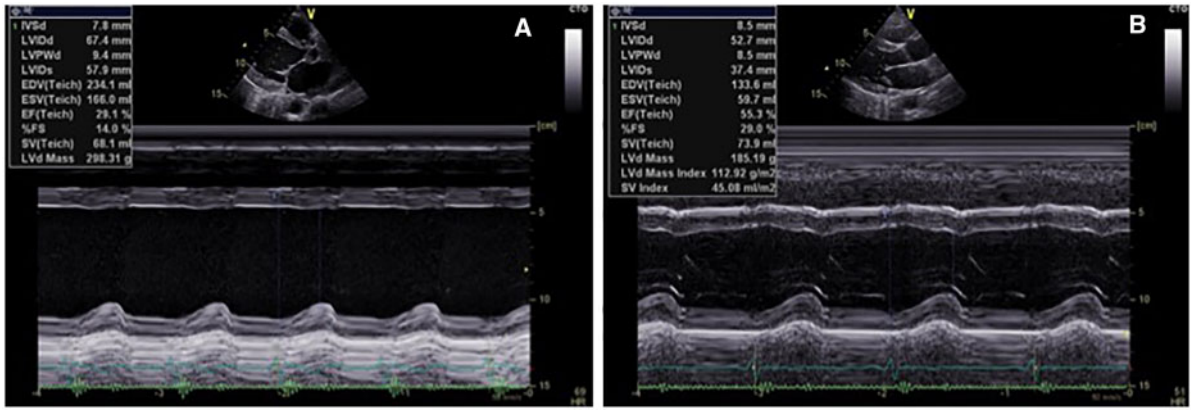

Figure 1 (*A*) On admission, echocardiography with M-mode showed diffuse hypokinesis of the left ventricle, and the left ventricular end-diastolic diameter was enlarged at 67 mm. (*B*) Four months after discharge, the ejection fraction was improved to 50%, and left ventricular reverse remodelling was achieved.

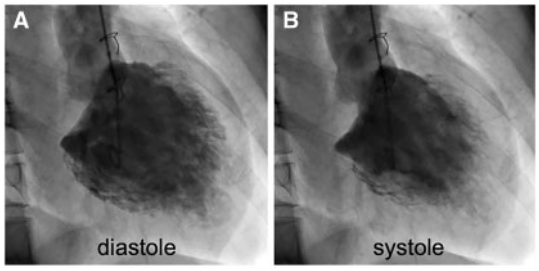

Figure 2 Left ventriculogram of the patient during (*A*) diastole and (*B*) systole showed severe diffuse hypokinesis.

who used supplements containing ephedra have reported arrhythmia,[7] stroke,[3] or myocardial infarction,[8] its use was restricted by US Food and Drug Administration. Methylephedrine also has adrenergic effects; however, its effects on the central nervous system and blood pressure are milder than those of ephedrine. Adrenergic effects, especially the β2 adrenoreceptor-stimulating effect, are antitussive in nature. Therefore, methylephedrine is commonly used in cough medicines, including OTC paediatric cough syrups. In the present study, the patient had been habitually taking OTC paediatric cough syrup as a revitalizer for a long time. Even considering body size, the patient had been taking obvious high-dose methylephedrine-containing paediatric cough syrup. We decided the cough syrup was related to heart failure or LV dysfunction, and it was discontinued after hospitalization. In general, hospitalized patients with heart failure experience a reduction in their body weight during the hospitalization period. Although the body weight of the patient in the present study reduced during the decongestion process within the first few days, it increased by 1.2 kg during hospitalization and after decongestion. Therefore, we concluded that the methylephedrine-induced weight loss was reversed and the body weight increased, although the patient was hospitalized for heart failure.

There are a few case reports on ephedrine-induced cardiac dysfunction;[4,5] however, the relationship between ephedrine and cardiac dysfunction has not been fully elucidated. The possible underlining mechanisms of ephedrine-induced cardiac dysfunction include myocardial injury due to elevated levels of catecholamine or free radicals.[5] In the present study, endomyocardial biopsy revealed cardiomyocyte hypertrophy with moderate interstitial and replacement fibrosis, which is consistent with the findings of myocardial injury caused by continuous catecholamine stimulation. A few animal studies have demonstrated that ephedrine cardiotoxicity was enhanced by the addition of caffeine. Nyska *et al.*[9] have suggested that myocardial ischaemia followed by myofibre necrosis was induced more intensively by the combined exposure of ephedrine and caffeine. Therefore, the pathological changes in the myocardium may be caused not only by the methylephedrine but also by the caffeine present in the cough syrup.

Fortunately, the patient's LV systolic dysfunction was reversible, and his heart failure symptoms improved after discontinuation of the cough syrup and OMT. However, the long-lasting excessive intake of methylephedrine must be considered, even through OTC paediatric cough syrups, as a potential cause of LV dysfunction. A detailed medical review about the intake of habitual drugs, including OTC medications, is needed to identify the cause of heart failure or LV dysfunction.

Lead author biography

Moeko Suzuki graduated from Ehime University School of Medicine in 2016. Then, she began her clinical carrier as a Resident Doctor at Uwajima City Hospital. After completing her residency programme, she decided to specialize in cardiology at Ehime University Hospital in 2018. With a keen interest in cardiology, she is currently a clinical fellow of cardiology at Ehime Prefectural

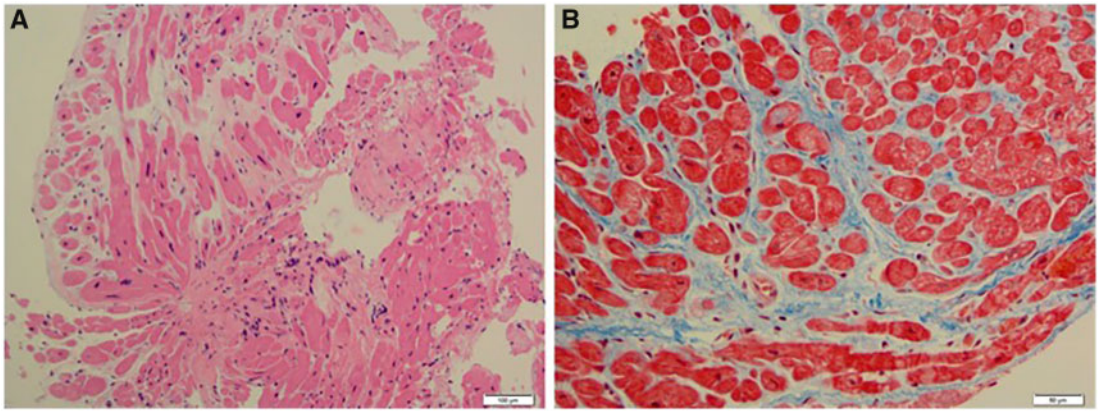

Figure 3 Pathological examination with (*A*) haematoxylin and eosin staining and (*B*) Masson's trichrome staining showed cardiomyocyte hypertrophy with moderate interstitial and replacement fibrosis.

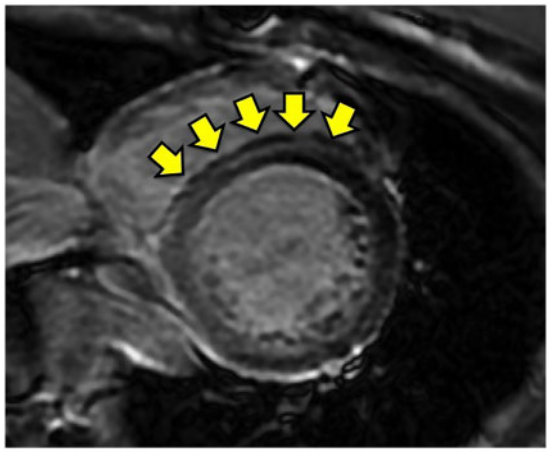

Figure 4 Cardiac magnetic resonance imaging showed mid-wall late gadolinium enhancement, which suggested fibrosis.

Imabari Hospital, Ehime, Japan. Her research interests focus on cardiovascular imaging and heart failure.

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 author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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