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Case Reports

Valvular Heart Disease Caused By Chinese Preprietary Slimming Medicine Adulterated With Fenfluramine

K ***Chang***, TWL ***Mak***, L ***Kwong***, KT ***So***

Abstract Anorectic drugs containing fenfluramine and dexfenfluramine have been classified as 'off-label' drugs in Hong Kong for several years. In this study, we report a case of valvular heart disease found in a teenager who had been taking Chinese proprietary medicine as a weight reducing agent for six months. Fenfluramine was identified in the diet pills. Two other herbal proprietary slimming products adulterated with fenfluramine and affecting several hundred people were subsequently discovered.

Key words Appetite depressants; Chinese medicine; Fenfluramine; Heart valve diseases

Introduction

Anorectic drugs containing fenfluramine, dexfenfluramine and phentermine have been utilised in recent years as appetite suppressants in the treatment of obesity. Fenfluramine, dexfenfluramine and the pharmacological combination with phentermine, known as fen-phen, were withdrawn from the United States (U.S.) market in 1997 due to the reported associations with pulmonary hypertension and valvular heart disease.[1] Anorectic drugs containing these products were subsequently banned in Hong Kong. Following the ban, there has been only one reported case of valvular disorder complicating fen-phen in Hong Kong, that of a 39-year-old woman.[2] Here, we present the case of an adolescent female diagnosed to have valvular heart disease after taking Chinese proprietary medicine. The 'off-label' product, fenfluramine, was subsequently identified in the diet pills. To our knowledge, this is the first local case in the paediatric population.

Department of Paediatrics & Adolescence, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China

K **Chang** （張傑） *MBBS, MRCPCH(UK)*
L **Kwong** （鄺玲） *MBBS, FHKAM(Paed)*
KT **So** （蘇鈞堂） *MBBS, FHKAM(Paed)*

Department of Clinical Pathology, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, N.T., Hong Kong, China
TWL **Mak** （麥永禮） *MBChB, FHKAM(Pathology)*

Correspondence to: Dr K **Chang**

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Case Report

The 17-year-old was in good health until the time of presentation, when she complained of precordial discomfort and shortness of breath of two months' duration. Precordial discomfort was non-specific in nature. It occurred daily, was unrelated to exercise, lasted for approximately one hour and subsided spontaneously. Palpitations were not experienced. The patient sometimes complained of accompanying shortness of breath. She had lost 7 kg over a period of one year and had developed oligomennorrhea 4 months prior to hospitalisation.

She started dieting two years ago. Initially she dieted by decreasing food intake. Without achieving the desired result, she began to use a Chinese proprietary product, "*Seven Days Seven Fairy Maidens Forever-Youth Immunity Capsule*" (七仙七日常駐青免疫膠囊) (Figures 1a & 1b) purchased from a pharmacy in Shenzhen, China. Although the product claimed to be purely herbal in nature, the patient stopped taking it after six months later because of frequent precordial discomfort and dizziness. She then switched to two other slimming products for 2 months.

Figure 1 Anorectic drug package in (a) Chinese and (b) English.

On physical examination she appeared fatigued. Her body mass index was 16.4 and her resting heart rate was 55 beats per minute with regular rhythm. Blood pressure was normal and there was no lanugo hair. Initial cardiac examination revealed no abnormalities and the rest of the physical examination was unremarkable. Throughout the period of hospitalisation, she complained of recurrent precordial discomfort. Sublingual glyceryl trinitrate did not relieve the discomfort and electrocardiogram was normal during the periods of discomfort. Cardiac enzymes and chest X-ray were normal. Echocardiogram showed mild mitral and aortic valve regurgitation. The mitral valves were slightly thickened. Ventricular ejection fraction was 37%. There was no pulmonary hypertension. Holter and Treadmill studies were normal. Fenfluramine, a banned anorectic drug, was subsequently identified in "*Seven Days Seven Fairy Maidens Forever-Youth Immunity Capsule*" by toxicology studies (REMEDi HS Drug Profiling System; BioRad Laboratories; Hercules, CA, USA).

Anorexia nervosa could not be established after psychiatric consultation. During the three-week hospital stay, her caloric intake was raised and her body weight increased by 10%. Somatic complaints resolved gradually. The importance and nature of prophylactic treatment for prevention of bacterial endocarditis prophylaxis prior to any invasive procedure was explained. A six-month follow-up echocardiogram showed resolution of the cardiac lesions.

Discussion

Fenfluramine (fen), dexfenfluramine (dex) and phentermine were approved by the United States Food and Drug Administration (FDA) as appetite suppressants for short-term (i.e. a few weeks) management of obesity in 1973, 1996 and 1959 respectively.[3] Safety beyond one year of use was not established. Fenfluramine and dexfenfluramine act by affecting the metabolism of serotonin in the brain.[4] Phentermine is a noradrenergic central nervous system stimulant. Combinations of fenfluramine and phentermine were used in the hope that weight reduction might be achieved with lower dosage and fewer side effects.[5] Approximately 14 million prescriptions have been written for either fenfluramine or dexfenfluramine since 1995.[6] Several million Americans have been exposed to these drugs. In August 1997, researchers at the Mayo Clinic and Mayo Foundation reported 24 cases of rare valvular disease in women who took the fenfluramine-phentermine combination therapy.[7] Another 28 cases were reported simultaneously by physicians from the FDA.[3] Subsequently more than 100 additional provider-initiated case reports were received by the FDA. As a result, the manufacturers withdrew fenfluramine and dexfenfluramine from the market in September 1997.[1] Phentermine, when given alone, has not been implicated in the pathogenesis of valvular heart disease.[3]

The association between appetite suppressants and valvular disease varies substantially among studies. The prevalence of valvuopathy might be as high as 30% in subjects exposed to fenfluramine-phentermine and is reduced with fenfluramine or dexfenfluramine alone.[8] The relationship between the duration of therapy and incidence of valvular problems was demonstrated in the Boston Collaborative Drug Surveillance Program that conducted a population-based and nested case-control analysis of 6,532 subjects treated with dexfenfluramine, 2,371 who received fenfluramine, 862 who were treated with phentermine and 9,281 obese subjects who did not take these drugs.[9] The five-year cumulative incidence of an idiopathic valvular disorder was 0 per 10,000 among subjects who had not taken appetite suppressants or those who had take phentermine alone; 7.1 per 10,000 among those subjects that received fenfluramine or dexfenfluramine for less than 4 months and 35 per 10,000 among patients treated with fenfluramine or dexfenfluramine for 4 or more months.

Echocardiogram features of patients receiving fenfluramine are similar to those seen in rheumatic heart disease but valvular obstruction is conspicuously absent.[7] Mitral and aortic valve involvements are by far the most common. The mitral valves usually show signs of thickening. Diastolic doming of anterior mitral leaflets is relatively immobile compared with the posterior leaflets. Chordae tendinae is thickened and shortened. Mitral regurgitation is due to leaflet tethering and malcoaptation. The aortic valves may appear thickened with leaflet retraction in the absence of aortic dilatation or fibrocalcification. Pathologic features of valvular disease in association with patients receiving fenfluramine are similar to those present in malignant carcinoid heart disease.[3,7,10] The mitral leaflets and chordae appear thickened with a glistening white appearance. The histopathologic picture is a plague-like encasement of the leaflets and chordal structures with a 'stuck-on' appearance. Proliferative myofibroblasts are surrounded by an abundant extracellular matrix. The link between carcinoid heart disease and anorectic drug induced valvular disease appears to be serotonin.[7] Phentermine may contribute by interfering with pulmonary clearance of serotonin.[11]

Echocardiogram has been used to evaluate the course of valvular heart disease associated with anorectic drugs. One report evaluated 50 patients with previous exposure to fen that had at least mild mitral valve disease (76%) and/or aortic regurgitation (86%). Initial echocardiogram was obtained at approximately 190 days after drug cessation and repeated one year later. Among patients with mitral regurgitation, 45% improved, 50% remained the same and 5% deteriorated by at least one grade.[12] Potential for stabilisation or improvement of the lesions should be considered when counselling patients about the possible need for valve replacement.

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force recommended the banning of fenfluramine and dexfenfluramine in 1997.[6] The Task Force also advocated conducting full cardiac assessments in all exposed patients and repeating these 6-8 months later if no abnormalities were found. Caution is advised regarding non-prescription anorectic drugs, herbal anorectics and dietary supplements. Echocardiogram should be performed in patients presenting with heart murmur or other signs or symptoms of valvular involvement. Optimal timing of follow-up echocardiogram to determine course of valvulopathy is undetermined. Patients developing valvulopathy require bacterial endocarditis prophylaxis.

In Hong Kong, pharmaceutical products containing fen have been deregistered since January 1998.[13] Since then, there has been one case report of valvular disease in a 39-year-old woman taking fenfluramine-phentermine for 2 years.[2] Our patient is the first documented case of valvular disease associated with fenfluramine use. Retrosternal discomfort in this young woman could not be explained by the degree of valvular involvement alone. Excessive dietary restriction and psychosocial elements may also have contributed to her symptoms.

This case was reported to Hong Kong's Department of Health when fenfluramine in the herbal pill was confirmed. A hotline was set up by the Department of Health to answer inquiries from the public. Out of more than 200 calls, over 100 patients required referral to hospitals for further evaluation. In the subsequent 3 months, two other herbal proprietary slimming products adulterated with fenfluramine, affecting several hundred patients were discovered. Using medication for weight reduction is popular. As illustrated by the present case, some slimming products, even those claiming to be 'natural' or containing pure 'herbs', may also contain banned anorectic drugs. With increasing interflow between Hong Kong and China, strict control of these banned products is difficult. The desire to be thin is becoming increasingly prevalent in Hong Kong. Clinicians should be suspicious when encountering patients taking slimming products, and should record information about the product where available. Depending on presentation, the presence of valvular damage should be considered, and the patient assessed accordingly.

Conclusion

Fenfluramine and dexflenfluramine are effective but dangerous weight reducing agents. In a society obsessed by thinness, their illicit use will continue. The medical profession should be vigilant to the possibility of valvular disease in any patient who reports taking anorectic drugs. The general public should be made more aware of the dangers of these over-the-counter anorectics. Whenever a case of valvular disease caused by these banned anorectics is encountered, the Department of Health should be informed so that action can be taken and the general public can be alerted.

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