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Dexfenfluramine and heart-valve regurgitation in Chinese patients with type 2 diabetes

II型糖尿病華人患者服用dexfenfluramine與心瓣血液回流的關係

Objective. To assess whether valvular lesions are associated with the use of dexfenfluramine in Chinese patients with type 2 diabetes.

Design. Case-control study.

Patients and methods. Thirty-six obese Chinese patients with type 2 diabetes and a history of dexfenfluramine use during the period January 1992 and September 1997 were recruited into the study, while another 43 age- and sex-matched Chinese patients with type 2 diabetes were recruited as controls. The mean age for the cases was 44.1 years (standard deviation, 11.2 years; median, 42.5 years; range, 20-64 years). The 43 control subjects were age- and sex-matched, and had a mean age of 48.5 years (standard deviation, 10.9 years; median, 51.0 years; range, 16-63 years; P>0.05). The male-to-female ratio was confirmed as similar between the two groups (10:26 versus 12:31; P>0.05). All patients were clinically free from cardiovascular disease. Patients with a history of underlying valvular disease from any cause were excluded from the study. All patients underwent echocardiographic assessment, and the presence of any valvular lesions was documented.

Results. The mean duration of dexfenfluramine use by the cases was 21.8 weeks (standard deviation, 29.0 weeks; median, 18.0 weeks; range, 1-160 weeks). Subjects with a history of dexfenfluramine use had higher rates of significant aortic regurgitation, tricuspid regurgitation of any severity, and of any valvular regurgitation, compared to controls (11.1% versus 0%, P<0.05; 30.6% versus 4.7%, P<0.01; and 61.1% versus 34.9%, P<0.05, respectively). Logistic stepwise regression analysis to predict the risk of valvular lesion was conducted, with age, sex, history of dexfenfluramine use, body mass index, waist-hip ratio, blood pressure, fasting plasma glucose, lipid profile, and duration of diabetes as independent variables. A history of dexfenfluramine use was the only significant parameter entered into the model (significant aortic regurgitation: β=9.19, standard error=46.6, P<0.05; any tricuspid regurgitation: β=2.76, standard error=10.8, P<0.05).

Conclusion. In Chinese patients with type 2 diabetes, a history of dexfenfluramine use is associated with heart-valve regurgitation, particularly aortic regurgitation.

目的：評估在II型糖尿病華人患者中，瓣膜損傷是否與服用dexfenfluramine有關。

設計：病例對照研究。

患者與方法：本研究所選的對象均為II型糖尿病的華人患者。研究病例組為36位肥胖的病患者，均在1992年1月至1997年9月期間服用dexfenfluramine。我們另選43位患者為對照病例，年齡和性別與研究病例組相似。研究病例組平均年齡為44.1歲(標準差：11.2歲；中位數：42.5歲；分佈域：20至64歲)。43個對照病例患者的年齡和性別與研究病例組相似，平均年齡為48.5歲(標準差：10.9歲；中位數：51.0歲；分佈域：16至63歲；P>0.05)。兩組男女比例接近(研究病例組為10：26，對照組為12：31；P>0.05)。本研究所選患者均無心血管疾病，亦無曾患任何潛在性瓣膜疾病的紀錄。所有患者都接受超聲心動描記法評估，任何瓣膜損傷均有紀錄。

結果：研究病例組服用dexfenfluramine的平均用藥時間為21.8週(標準差：29.0週；中位數：18.0週；分佈域：1至160週)。曾服用dexfenfluramine的患者，出現以下各類

Key words:
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型血液回流的比率均高於對照組患者：嚴重主動脈血液回流 (11.1%比0%；P<0.05)、不同嚴重程度的三尖瓣血液回流 (30.6%比4.7%；P<0.01)，以及任何瓣膜性血液回流(61.1%比34.9%；P<0.05)。我們以對數級進迴歸分析預測出現瓣膜損傷的機會，用作為自變量的項目包括年齡、性別、dexfenfluramine的用藥史、體質指數、腰臀圍比值、血壓、空腹血糖值、血脂肪水平、患糖尿病時間長短。Dexfenfluramine用藥史是本研究中，迴歸分析模型唯一的有效參數(嚴重主動脈血液回流：β=9.19，標準誤差 =46.6 ， P<0.05；所有三尖瓣血液回流：β=2.76 ，標準誤差 =10.8 ， P<0.05)。

結論：在II型糖尿病華人患者中，dexfenfluramine用藥史與出現心臟瓣膜血液回流是相關的，其中以主動脈血液回流的關係最為密切。

Introduction

Obesity is now regarded as a chronic disease rather than a social stigma, and anti-obesity agents are increasingly used. Accumulated evidence has shown anti-obesity medications, such as fenfluramine, to have harmful effects and these agents have been banned from the market. However, drugs containing similar ingredients are still currently available over-the-counter in Hong Kong.

Since Connolly et al[1] first reported a series of 24 patients with valvular heart disease who had been treated with the appetite-suppressant drugs, phentermine and fenfluramine, several studies have suggested a higher risk of heart-valve regurgitation in patients taking fenfluramine, dexfenfluramine, alone or in combination.[2,3] These investigations have been confined to Caucasians and similar information in Asians is limited. The current study aimed to investigate valvular lesions associated with the use of dexfenfluramine in Chinese patients with type 2 diabetes.

Patients and methods

All patients being seen for follow-up by the Prince of Wales Hospital (PWH) with type 2 diabetes and with a history of taking dexfenfluramine (Adifax; Servier, France) between January 1992 and September 1997 (when the drug was withdrawn from the market in Hong Kong) were contacted and invited to participate. Thirty-six obese Chinese patients with type 2 diabetes were recruited into the study. Ten (27.8%) were men and 26 (72.2%) were women. Mean age was 44.1 years (standard deviation [SD], 11.2 years; median, 42.5 years; range, 20-64 years). A further group of 43 age- and sex-matched Chinese patients with type 2 diabetes were recruited as controls. Their mean age was 48.5 years (SD, 10.9 years; median, 51.0 years; range, 16-63 years; P>0.05; men:women=12:31; P>0.05). All subjects were clinically free from cardiovascular disease. Subjects with a history of underlying valvular disease due to any cause were excluded from the study. The VDRL test was not completed, and autoimmune markers were not measured. Subjects with a previously diagnosed heart murmur but no evident valvular lesion on subsequent echocardiography were included in the study.

Co-existing type 2 diabetes in an obese patient is one of the major indications for considering anti-obesity drug therapy.[4] The present study was confined to patients with type 2 diabetes because this group comprised almost all patients attending the PWH at the time of the study who were prescribed dexfenfluramine. Further, there was no evidence to suggest that the effect of dexfenfluramine on valvular lesions was different in diabetic and non-diabetic patients.

Echocardiography

Transthoracic echocardiography (Sequoia 512; Acuson, California, US) assessments were performed for all subjects by the same cardiologist, blinded as to whether patients had or had not used dexfenfluramine. Heart-valve regurgitation was visually rated as normal, trace regurgitation, or mild, moderate, or severe regurgitation.[5,6] The US Food and Drug Administration criteria for aortic regurgitation (AR) of mild or greater severity, and mitral regurgitation of moderate or greater severity were used to determine the presence or absence of significant valvular regurgitation. Tricuspid regurgitation (TR) of moderate or greater severity was also regarded as significant regurgitation.[7,8]

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 8.0; SPSS Inc., Chicago, US) software on an IBM-compatible computer. Results were expressed as a mean and SD or as a percentage, as appropriate. Analysis of variance, and the Chi squared test were used for between group comparisons where appropriate. The age- and sex-adjusted partial correlation coefficient between duration of dexfenfluramine intake and presence of valvular regurgitation was calculated. Logistic stepwise regression analysis was performed to predict the risk of valvular lesion, with age, sex, history of dexfenfluramine use (1=yes, 0=no), body mass index (BMI), waist-hip ratio, blood pressure, fasting plasma glucose, lipid profile, and duration of diabetes as independent variables. A P value of less than 0.05 (2-tailed) was considered significant.

Results

The clinical characteristics of the 79 patients are summarised in the Table. The control group were less obese (BMI, 33.6±3.7 kg/m^2 versus 26.0±4.0 kg/m^2; P<0.001) and had higher blood pressure than the cases. The mean duration of dexfenfluramine use in the cases was 21.8 weeks (SD, 29.0 weeks; median, 18.0 weeks; range, 1-160 weeks). Dexfenfluramine had been discontinued before echocardiography

Table. Clinical characteristics of patients with type 2 diabetes in relation to dexfenfluramine use (n=79)

	Total (n=79)	Dexfenfluramine use (n=36)	No dexfenfluramine use (n=43)
*Clinical characteristics**			
Age (years)	46.5±11.2	44.1±11.2	48.5±10.9
Males (%)	31.6	34.9	27.8
Body mass index (kg/m^2)	29.5±5.4	33.6±3.7	26.0±4.0†
Waist-hip ratio	0.96±0.17	0.93±0.06	0.98±0.22
Systolic blood pressure (mm Hg)	140±24	125±20	153±19†
Diastolic blood pressure (mm Hg)	86±12	81±11	90±11†
Fasting plasma glucose (mmol/L)	8.9±2.7	9.4±3.2	8.5±2.2
Glycated haemoglobin (%)	7.74±1.80	7.54±1.82	7.91±1.79
Cholesterol (mmol/L)	5.4±1.0	5.3±0.9	5.6±1.1
Triglyceride (mmol/L)	2.1±1.6	1.8±1.0	2.4±2.0
High-density lipoprotein (mmol/L)	1.3±0.3	1.2±0.3	1.3±0.3
Low-density lipoprotein (mmol/L)	3.3±0.9	3.3±0.8	3.3±0.9
Duration of diabetes (years)	6.6±4.8	7.5±3.7	5.9±5.4
Duration of dexfenfluramine (weeks)	-	21.8±29.0	-
*Echocardiographic findings**			
Significant aortic regurgitation	4 (5.1)	4 (11.1)	0‡
Significant mitral regurgitation	0	0	0
Significant tricuspid regurgitation	0	0	0
Any aortic regurgitation	17 (21.5)	8 (22.2)	9 (20.9)
Any mitral regurgitation	20 (25.3)	9 (25.0)	11 (25.6)
Any tricuspid regurgitation	13 (16.5)	11 (30.6)	2 (4.7)§
Any regurgitation	37 (46.8)	22 (61.1)	15 (34.9)‡
Aortic valve thickening	3 (3.8)	1 (2.8)	2 (4.7)
Mitral valve thickening	2 (2.5)	1 (2.8)	1 (2.3)
Ejection fraction (%)	66.8±8.4	64.3±9.5	68.9±6.9‡
Diastolic dysfunction	11 (13.9)	4 (11.1)	7 (16.3)
Left ventricular hypertrophy	5 (6.3)	3 (8.3)	2 (4.7)

* Values are represented as a mean±SD, or No. (%)
† P<0.001
‡ P<0.05
§ P<0.01

for a mean period of 3.6 years (SD, 1.8 years; median, 4.6 years; range, 0.5-5.3 years).

The Table also summarises the echocardiographic findings for the 79 patients. Patients with a history of dexfenfluramine use had a higher rate of significant AR, any degree of TR, and any valvular regurgitation, compared to controls (11.1% versus 0%, P<0.05; 30.6% versus 4.7%, P<0.01; and 61.1% versus 34.9%, P<0.05, respectively). There was no significant valvular stenosis seen. Patients with a history of dexfenfluramine use also had a lower ejection fraction compared to controls (64.3±9.5% versus 68.9±6.9%, P<0.05). The age- and sex-adjusted partial correlation coefficient for duration of dexfenfluramine use and presence of any valvular regurgitation or significant valvular regurgitation were not significant (r= –0.243, P=0.173 and r=0.069, P=0.703, respectively).

Using logistic stepwise regression analysis to predict the risk of valvular lesion, with age, sex, history of dexfenfluramine use, BMI, waist-hip ratio, blood pressure, fasting plasma glucose, lipid profile, and duration of diabetes as independent variables, the history of dexfenfluramine use was the only significant parameter entered into the model (significant AR: β=9.19, standard error [SE]=46.6, P<0.05; any TR: β=2.76, SE=10.8, P<0.05).

Discussion

Findings from several studies in Caucasians have supported earlier reports of an association between primary pulmonary hypertension, valvular regurgitation, and the use of fenfluramine or dexfenfluramine.[2,3,9] Primary pulmonary hypertension is rare in Chinese compared to western populations.[10] The risk of pulmonary hypertension or heart-valve lesions associated with appetite suppressant use has not been documented in Chinese, though the case of a Chinese woman with unexplained multiple heart-valve changes associated with a history of fenfluramine and phentermine use was reported in a local journal in 1998.[11]

Data on pulmonary pressure were incomplete for patients in this study, so valvular status alone was considered. The severity of valvular lesion was graded visually. This is a globally accepted way to classify valvular lesions. The grading of valvular lesions was completed by the same cardiologist for all patients. Hence, there was no bias introduced by the assessment procedure. Detailed information on left ventricular dimensions was not available for all patients. Though a dilated left ventricle may affect the presence of valvular regurgitation, the overall ejection fraction was satisfactory in these patients and the number with left ventricular hypertrophy was small (n=3).

In this study, a positive association between dexfenfluramine and valvular regurgitation in Chinese patients with type 2 diabetes was found. In particular, a higher risk of significant AR was evident in patients with a history of dexfenfluramine use compared to controls. Although the former group of patients tended to be more overweight,

logistic regression analysis indicated that a history of dexfenfluramine use was the only parameter significantly associated with the presence of valvular lesions. The difference in BMI between the two groups is a limitation of this study. However, recent epidemiological studies have discounted the possibility that obesity itself causes a higher risk of heart-valve regurgitation.[12,13] Chronic rheumatic heart disease is still relatively common in our locality but is unlikely to have influenced the results of this study, since patients with or without a history of dexfenfluramine use were clinically similar apart from differences in BMI.

The subjects in this study were all Chinese patients with type 2 diabetes. The prevalence of AR in those subjects with a history of dexfenfluramine use is high (11.1%) compared to the reported prevalence in Caucasian non-diabetic subjects taking dexfenfluramine (5.4%).[2] Although visual grading of the severity of valvular lesion is globally accepted, inter-observer variation between the two studies may explain the relatively high percentage of AR in the current study. This may also partly reflect the relatively small sample size of the study. Whether diabetes per se is an additional risk factor for the development of valvular lesions associated with dexfenfluramine use remains uncertain.

Conclusion

In Chinese patients with type 2 diabetes, a history of dexfenfluramine use was associated with heart-valve regurgitation, particularly AR. Long-term surveillance of these patients is warranted in order to detect early clinical sequelae of such valvular lesions.

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