A dangerous duo?

A combination of common diet drugs (fen-phen) may lead to heart valve disease

Derek R. Boughner, MD, PhD

Résumé

LA CLINIQUE MAYO A SIGNALÉ que des cardiopathies monovalvulaires ou multivalvulaires semblent faire leur apparition chez un groupe de 24 femmes de moins de 50 ans qui prenaient une combinaison d'anorexiants prescrits fréquemment (fenfluramine et phentermine) pour perdre du poids. Chez 5 patientes, le problème a été assez sérieux pour nécessiter une intervention chirurgicale aux valvules. Les résultats échocardiographiques et histologiques chez les patientes en question ressemblaient aux anomalies structurelles constatées dans des cas de cardiopathies causées par un syndrome carcinoïde. Les 2 médicaments en cause modifient le métabolisme de la sérotonine, et les chercheurs supposent que les 2 médicaments pris ensemble produisaient un effet synergique. Il faudrait éviter cette thérapie combinée jusqu'à ce que la situation soit clarifiée.

A recent article in the *New England Journal of Medicine* reporting the development of unusual valvular heart disease in women taking combined diet-drug therapy is cause for concern.[1] The editors of the *New England Journal of Medicine* lifted the usual news embargo on the article 7 weeks before publication, an approach taken only when they believe a report may have immediate significance for public health. The agents involved were fenfluramine and phentermine, prescribed in combination ("fen-phen"). Both drugs are approved individually for use as appetite suppressants, and both are associated rarely with the development of pulmonary hypertension,[1,2] but other serious cardiovascular effects have not been documented before now.

All 24 patients in the reported case series were women, most of them younger than 50 years of age, who had been taking the fen-phen combination for 1 to 2 years. Single or multivalvular heart disease of an unusual type was identified during surgery (in 5 cases) or echocardiographically (in the remaining 19 cases), and all cases came to light through clinical presentation rather than as part of a patient study. The possibility of an association between the drugs and the valve lesions observed was raised individually by the consulting physicians at the Mayo Clinic and a nearby health centre. Heart valve disease can ordinarily be grouped into 4 categories — congenital, rheumatic, myxomatous and degenerative; other rare patterns attract attention.

In this case, the valves appeared thickened, with reduced leaflet or cusp motion, implying rigidity. The extent and pattern of involvement was not consistent with the usual disorders. Chordal tethering and shortening was also noted for the atrioventricular valves. Overall, the echocardiographic features were similar to those seen in carcinoid syndrome.[3] The pathologic findings in the 5 patients who underwent valvular heart surgery were of particular interest. All 5 were treated for severe mitral regurgitation, and 1 also underwent aortic valve replacement and tricuspid valve repair. Histopathologic examination of the explanted valves revealed a plaque-like process identical to the lesions observed in patients with valvular heart disease caused by ergotamine ingestion or carcinoid.

The latter rare disorder has been associated with heart valve disease for many

Editorial

Éditorial

Dr. Boughner is Professor of Medicine and Medical Biophysics and Director of the Heart Valve Research Laboratory, Robarts Research Laboratory, University of Western Ontario, London, Ont.

Can Med Assoc J 1997;157:705-6

years.[4] Metastatic ileocecal carcinoid tumours can produce tricuspid regurgitation and, occasionally, tricuspid stenosis. Pulmonary stenosis is also common, and mild involvement of the mitral valve is sometimes seen. In contrast, when the carcinoid is bronchial in origin, the cardiac lesions produced are predominantly left heart rather than right heart. In both cases, thick, whitish "carcinoid plaques" develop on the valve surfaces and gradually thicken and tether the structures.[5] The plaques are composed of smooth muscle cells (myofibroblasts) embedded in a stroma of reticulum fibres and acid mucopolysaccharides. There are no elastic fibres and few collagen fibres present, and the smooth muscle cells have the appearance of myointimal cells. The pathogenesis of these plaques in carcinoid syndrome remains obscure. Investigators have postulated that, in the case of the ileocecal tumours, the responsible agent is inactivated in the lung, resulting in the primarily right-sided lesions. Serotonin, secreted by the tumour, is the most likely culprit and provides a possible link to the diet drugs. Fenfluramine alters serotonin metabolism in the brain, promoting the rapid release of serotonin and inhibiting its reuptake, and phentermine interferes with its pulmonary clearance. A synergistic effect between the 2 drugs was suggested by the authors of the case series, but serotonin levels were not measured in any of the 24 patients. Therefore, serotonin is not proven to be the etiologic agent in heart valve disease caused by carcinoid syndrome or ergotamine ingestion or by fen-phen, but logic suggests that this area be investigated further.

The public health concern involves the apparently widespread use of these 2 drugs, both of which were approved and released nearly 2 decades ago. Clinical reports indicate that each individual drug, taken alone, is suitably safe, although both are occasionally associated with the development of pulmonary hypertension. In the article in the *New England Journal of Medicine*, pulmonary hypertension was identified in 25% of the 24 patients, but it was unclear whether pulmonary hypertension was primary or secondary to the valve lesions.

The affected valves were mitral, aortic and tricuspid valves, with a preponderance of left-sided involvement necessitating surgical intervention. If only the tricuspid valves were involved, as is usually the case in the carcinoid syndrome, the problem might not be as serious, since normal tricuspid valves commonly leak to a minor extent and even significant tricuspid regurgitation can be well tolerated. The same is not true for mitral and aortic valves, as evidenced by the need for high-risk valve surgery in 20% of the reported cases. In the remaining patients, medical management was appropriate, but there was no clear evidence that discontinuing the drugs resulted in reversal of the valve lesions. However, the follow-up period was too short to draw any firm conclusions.

The Mayo Clinic is planning a more definitive case–control study to clarify the possible association and the relative incidence of this type of problem. The initial report is a cautionary note to be appended to the potential side effects of these widely used anorectic agents. During patient follow-up, careful auscultation should be carried out to detect new murmurs and echocardiographic monitoring should be considered. Although there is evidence that each drug, taken alone, is suitably safe, it is appropriate to avoid their combined use for the time being. We will await with interest further clarification of this potentially significant problem.

References

1. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine–phentermine. *N Engl J Med* 1997;337(9). In press. Obtained July 13, 1997, from the Web site of the Mayo Clinic.

2. McMurray J, Bloomfield P, Miller HC. Irreversible pulmonary hypertension after treatment with fenfluramine. *BMJ* 1986;292:239-40.

3. Pellikka PA, Tajik AJ, Khandheria BK, Seward JB, Callahan JA, Pitot HC, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. *Circulation* 1993;87:1188-96.

4. Thorson A, Biorck G, Bjorkman G. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects) peripheral vasomotor symptoms, bronchoconstriction and an unusual type of cyanosis: a clinical and pathologic syndrome. *Am Heart J* 1954;47:795-9.

5. Strickman NE, Rossi PA, Massumkhani GA, Hall RJ. Carcinoid heart disease: a clinical, pathologic and therapeutic update. *Curr Probl Cardiol* 1982;6(11):1-42.

Reprint requests to: *Dr. Derek R. Boughner, Director, Heart Valve Research Laboratory, Robarts Research Laboratory, 100 Perth Dr., PO Box 5015, London ON N6A 5K8; fax 519 434-3278*