

Diet Drug Dangers Overestimated?

Wee CC, Phillips RS, Aurigemma G, Erban S, Kriegel G, Riley M, Douglas PS. Risk for valvular heart disease among users of fenfluramine and dexfenfluramine who underwent echocardiography before use of medication. *Ann Intern Med* 1998;129:870-4.

Study Overview

Objective. To determine the risk for new or worsening valvular abnormalities among users of fenfluramine or dexfenfluramine who underwent echocardiography before they began to take these medications.

Design. Cohort study.

Setting and participants. 46 patients who used fenfluramine or dexfenfluramine for at least 14 days and had echocardiograms before therapy and after 1 January 1998 at either of two primary care practices affiliated with academic medical centers in Massachusetts.

Main outcome measures. New or worsening valvulopathy confirmed by echocardiogram and defined as progression of either aortic or mitral regurgitation by at least one degree of severity and disease that met the U.S. Food and Drug Administration (FDA) criteria (at least mild aortic regurgitation or moderate mitral regurgitation). Change in severity by one degree was defined as progression from no disease to mild disease, from mild disease to moderate disease, and from moderate disease to severe disease.

Main results. Of 873 patients identified as using fenfluramine or dexfenfluramine, 76 had echocardiography before therapy was started. Of these 76, 11 were excluded by physicians and 19 declined participation. Compared with a random sample of patients who used the medications but did not have echocardiography before therapy, study patients were older ($P < 0.001$), more likely to be hypertensive ($P = 0.04$), and more likely to have coronary heart disease ($P < 0.001$).

The 46 patients included for analysis used fenfluramine or dexfenfluramine for a mean duration of 160 days. Of these 46 patients, 2 (4.3%, 95% confidence interval [CI] = 0.6% to 14.8%) developed valvular heart disease. One patient's baseline bicuspid aortic valve and mild aortic regurgitation progressed to moderate regurgitation, and the second patient developed new moderate aortic insufficiency. Also,

several patients showed progression and regression of valvular insufficiency and thickening that did not meet FDA criteria; the clinical significance of this particular finding is uncertain.

Conclusion

Although users of fenfluramine or dexfenfluramine are at risk for valvular heart disease, the incidence may be lower than suggested by previous prevalence findings.

Commentary

New or worsening valvular heart disease developed in 4.3% of a select cohort of patients who used fenfluramine or dexfenfluramine and had undergone echocardiography before therapy. When patients with existing valvulopathy were excluded, the risk was 2.6%. In comparison, echocardiographic surveys conducted subsequent to the withdrawal of fenfluramine and dexfenfluramine from the market in 1997 suggested that the prevalence of valvular disease is 30% to 38% among users of the medications (versus only 1% in normal persons) [1,2].

The authors' focus on incidence rather than prevalence is important because the previous studies may have overestimated the association between drug use and valvulopathy because of a certain level of preexisting valve lesions. However, the findings of this study would have been strengthened by a larger cohort size, longer duration of therapy, patient randomization, and absence of possible referral bias. These limitations preclude rapid acceptance of the study's findings.

Applications for Clinical Practice

Although the magnitude of the problem of cardiac valvular incompetence associated with use of fenfluramine or dexfenfluramine may remain uncertain, this study and others confirm that the problem exists. The manufacturers' voluntary withdrawal of fenfluramine and dexfenfluramine from the market spares patients and their physicians the increased risk for valvular disease [3,4].

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References

1. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations. November 1997. MMWR Morb Mortal Wkly Rep 1997;46:1061-6.
2. 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; 337:581-8.
3. Parisi AF. Diet-drug debacle. Ann Intern Med 1998;129: 903-5.
4. Statement of the American College of Cardiology on recommendations for patients who have used anorectic drugs. 18 October 1997. Available from <http://www.acc.org/pubs/news/statement.html>.

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