Introduction

Obesity is a major health problem in most developed countries around the world. It is estimated that there are approximately 76 million obese people in the United States, thus making 1 in every 3 people obese (1). Furthermore, obesity has been labeled the second leading cause of preventable death (the first being smoking) in the United States, contributing to 300,000 deaths annually (1). Health problems associated with obesity primarily involve the cardiovascular system, such as hypertension, hypercholestrolemia, stroke, and myocardial infarction. Physicians are accordingly motivated to help their patients lose weight in order to minimize the impact of obesity on their health. Consequently, many diets, regimens, herbs, and drugs have been introduced to help in this common endeavor, however none have been as potent as the combination drug therapy commonly known as "fen-phen".

Two landmark studies

Fen-phen is a combination of fenfluramine or dexfenfluramine (fenfluramine's d-isomer) and phentermine, all of which have been individually approved by the Food and Drug Administration (FDA) as appetite suppressants for short-term use in the medical management of obesity. Fenfluramine is a serotonergic agonist that performs its action of appetite suppression via the activation of serotonergic pathways in the brain, thus giving one the sensation of fullness. Fenfluramine and dexfenfluramine promote the rapid release of serotonin, inhibit its reuptake, and may have receptor-agonist activity, thus making serotonin more susceptible to metabolism and breakdown (2). Phentermine, on the other hand, is a noradrenergic agent that interferes with the pulmonary clearance of serotonin and also helps in appetite suppression (2). Although the individual efforts of either of these two drugs have not been very successful in combating obesity, a 1992 study demonstrated that long-term combination therapy of fenfluramine hydrochloride and phentermine hydrochloride proved successful in weight management (3). Subsequently, although the FDA had not yet approved the combination, many physicians established overnight fen-phen treatment programs with the promise of a long-term cure for obese individuals. By 1996 the total number of prescriptions for this new "cure" had exceeded 18 million (4).

Nonetheless, it has recently appeared that physicians, the media, and even the scientific community have acted hastily in their open-armed acceptance of this so-called cure for obesity. All of these communities failed to recognize that the 1992 study had not fully assessed the long-term side effects of fen-phen treatment. One commonly known side effect of fenfluramine, dexfenfluramine and phentermine treatment alone has been known to be pulmonary hypertension (5). It is believed that these drugs may either have a vasoconstrictive action via serotonin or may alter the degree of depolarization of pulmonary vascular smooth muscle (5). The groundbreaking 1992 study by Weintraub concluded that in combination these drugs might be just as effective as either drug alone, with the added advantages of the need for lower doses of each agent and perhaps fewer side effects. However, what the study failed to identify is that patients, especially women,

who have been on fen-phen treatment for approximately a year or more may be at an increased risk for developing valvular heart disease.

In another landmark study led by Dr. Connolly at the Mayo Clinic and printed in the New England Journal of Medicine on August 28, 1997, it was concluded that fen-phen treatment might be associated with valvular heart disease (6). In this study, twenty-four women of fairly young age (almost all below 50 years old) who previously had no history of cardiac disease were evaluated at approximately one year after the initiation of fen-phen therapy. All twenty-four women presented with unusual valvular morphology and regurgitation involving both right and left-sided heart valves upon echocardiography. Eight of these women also presented with pulmonary hypertension. The study further reported that surgical intervention was required in as many as five of these patients. Histopathological findings in these five surgically treated patients included plaques on the leaflets and chordal structures while valve architecture remained intact. These features are identical to those seen in carcinoid or ergotamine-induced valvular disease.

Serotonin may be common link and cause of fen-phen related valvular heart disease

Carcinoid tumors have been associated with valvular heart disease for many years (7). Valvular disease in these patients is believed to be due to the release of serotonin into the bloodstream by the tumor. Supporting evidence for serotonin induced valvulopathy is due to the fact that serotonin agonist drugs, such as ergotamine, are also believed to induce valvular heart disease (8). Finally, oral tryptophan, a precursor to serotonin, has also been associated with an increased risk for valvular disease in patients (8). Hence, the etiology behind fen-phen caused valvular heart disease is believed to be an increased level of serotonin in the bloodstream, which by mechanisms that have not yet been elucidated, results in plaque-like deposits on valvular leaflets and chordal structures. Although serotonin levels were not measured in the 24 patients in Connolly's study, this hypothesis has been the most plausible theory put forth to date regarding fen-phen induced valvular heart disease.

Disbelief of new study

Many, however, did not believe that Connolly's study was conclusive evidence for terminating fen-phen from the market, primarily because of a number of flaws in the design of the study as well as no previously reported evidence of valvular heart disease in patients on fen-phen therapy. For example, Connolly's study did not employ a control group or a case-control study, thus no definitive statements could be made about fen-phen therapy directly causing valvular heart disease. Also in Connolly's study neither direct inspection nor histopathological evaluation was carried out in 19 of the 24 patients, only the five patients that underwent surgery were identified with plaques on leaflets and chordal structures. Nonetheless, Connolly's study did raise awareness among the scientific community of the possible risks associated with fen-phen treatment.

New reports come in; fenfluramine and dexfenfluramine are withdrawn from the market

Connolly et. Al.'s study prompted the FDA to issue a public health advisory on July 8, 1997, followed by letters from the FDA to 700,000 health-care professionals and institutions requesting information about any additional patients with similar symptoms (9). As of September 30, the FDA had received 144 individual, provider-initiated reports involving fenfluramine or dexfenfluramine, with or without phentermine, in association with valvular heart disease (10). Of these reports 113 met the requirements as mandated by the FDA for valvulopathy. Of these 113, 98% of the cases occurred among women, 2% used fenfluramine alone, 14% used dexfenfluramine alone, 79% used a combination of fenfluramine and phentermine, and 5% used a combination of all three drugs. The median age of the population was 44 years and the median duration of drug use was 9 months. It was found that 87 (77%) of the cases were symptomatic, 27 (24%) of the patients required cardiac valve replacement surgery, and 3 patients died after surgery. Thus based on the data, the FDA requested the voluntary withdrawal of fenfluramine and dexfenfluramine from the U.S. market, and on September 15, the manufacturers and the FDA announced the withdrawal of these drugs (10).

Fenfluramine may be sole culprit

The FDA only requested the withdrawal of fenfluramine and dexfenfluramine and not phentermine primarily because valvular heart disease has only been associated in previous studies in fen-phen combination therapy or dexfenfluramine monotherapy. As a result, it is believed that fenfluramine, the common element, is the most likely culprit and not phentermine (8). Griffen states that fenfluramine is most likely the sole cause for a number of reasons. First, fenfluramine promotes the release of serotonin from many tissues that store it and similar to carcinoid and ergotamine-induced valvular heart disease, serotonin is believed to be the common link in the pathology of these diseases. Secondly, phentermine has been on the U.S. market for 20 years, with no reported cases of associated valvulopathy, whereas fenfluramine, although having been on the market for the same length of time, has not been frequently prescribed. Third, a study led by Anchors has treated obese patients with phentermine and fluoxetine for more than two years with no reported incidences of pulmonary hypertension or valvular heart disease (11). And lastly, in at least one case that is known of, dexfenfluramine monotherapy has been associated with the new appearance of aortic valve insufficiency.

Recommendation to individuals with any exposure to fen-phen

As a result of all of the above findings the United States Department of Health and Human Services (DHHS) has recommended the following guidelines for individuals who have been exposed to either fenfluramine or dexfenfluramine alone or in combination with other drugs (i.e. phentermine) for any period of time:

- All persons should undergo a medical history and cardiovascular examination by their physician to determine the presence of cardiopulmonary signs or symptoms (10).

- An echocardiographic evaluation should be performed on all persons who exhibit cardiopulmonary signs (i.e. a new murmur) or symptoms (i.e. dyspnea) suggestive of valvular heart disease (10).

Thus, physicians now need to take responsibility and monitor the progress of their patients who have either been treated by them or other previous health-care professionals with fen-phen therapy.

Moral for health-care providers

As we enter the twenty-first century, obesity is believed to be one of the major obstacles for the medical community to overcome. As such, physicians and other scientists need to work to find solutions to combat this great adversary. However at the same time, health-care professionals must also be aware not to jump on the bandwagon and prescribe the "quick fix". Physicians, especially in the United States, have been trained to evaluate new drugs and therapies objectively and to not prescribe treatments before long-term studies have shown treatments to be safe and effective. However, many physicians have failed to meet this responsibility when prescribing fen-phen therapy. They have failed due to the fact that they have prescribed fen-phen to anyone interested, including the non-obese, without adequate analysis of the treatment regimen. Hence, this should serve as a lesson to all health-care professionals to properly analyze treatment programs before administering them.

REFERENCES

1. Kushner R. The treatment of obesity: a call for prudence and professionalism. Arch Intern Med. 1997;157:602-4.
2. Boughner DR. A dangerous duo? A combination of common diet drugs (fen-phen) may lead to heart valve disease. Can Med Assoc J. 1997;157:705-6.
3. Weintraub M. Long-term weight control: the National Heart, Lung, and Blood Institute funded multimodel intervention study. Clin Parmacol Ther. 1992;51:581-646.
4. Langreth R. Critics claim diet clinics misuse obesity drugs. Wall Street Journal. March 31, 1997:B8.
5. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med. 1996;335:609-16.
6. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997;337:581-8.
7. 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.
8. Griffen L. Asymptomatic mitral and aortic valve disease is seen in half of the patients taking ‘Phen-Fen’. Arch Intern Med. 1998;158:102.
9. Lumpkin MM. FDA health advisory. FDA Bulletin. 19997;27:2.

10. Centers for Disease Control and Prevention. Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: US Department of Health and Human Services interim public health recommendations, November 1997. JAMA. 1997;278:1729-31.
11. Anchors JM. Fluoxetine hydrochloride is a safer alternative to fenfluramine in the medical treatment of obesity. Arch Intern Med. 1997;157:1270.