Phentermine

See also Anorectic drugs

GENERAL INFORMATION

Despite the withdrawal of the fenfluramines, the appetite suppressants phendimetrazine and phentermine have remained in widespread use for the treatment of obesity.

With phentermine, adverse reactions due to stimulation of the central nervous system are less than with dexamfetamine, although in one study withdrawal because of adverse reactions was as high as 16 of 177 patients (9%); 2 of 13 healthy young volunteers withdrew because of unacceptable stimulation [1].

ORGANS AND SYSTEMS

Cardiovascular

In a systematic review of 1279 patients taking fenfluramine, dexfenfluramine, or phentermine, evaluated in seven uncontrolled cohort studies, 236 (18%) and 60 (5%) had aortic and mitral regurgitation respectively [2]. Pooled data from six controlled cohort studies yielded, for aortic regurgitation, a relative risk ratio of 2.32 (95% CI = 1.79, 3.01) and an attributable rate of 4.9% and, for mitral regurgitation, a relative risk ratio of 1.55 (95% CI = 1.06, 2.25) with an attributable rate of 1.0%. Only one case of valvular heart disease was detected in 57 randomized controlled trials, but this was judged unrelated to drug therapy. The authors concluded that the risk of valvular heart disease is significantly increased by the appetite suppressants. Nevertheless, valvulopathy is much less common than suggested by previous less methodologically rigorous studies.

Spontaneous rupture of a retroperitoneal aneurysm occurred in a 70-year-old woman who had been taking phentermine hydrochloride, 30 mg/day, for about 1 month [3]. Other long-term medications included fluoxetine and amitriptyline, and she had no history of coronary artery disease, hypertension, diabetes, or complications of pregnancy. Although it is plausible that phentermine could have contributed to the ruptured aneurysm, other possibilities should be considered, particularly rupture of an anomalous retroperitoneal blood vessel.

Fatal pulmonary hypertension occurred in a 32-year-old man who had been taking phentermine in unknown doses for 4 months [4].

Combined use of fenfluramine and phentermine ("Fen-Phen") has been associated with varying degrees of valvular regurgitation and pulmonary hypertension. In 57 men and women (30 taking Fen-Phen and 27 controls matched for BMI) chamber dimensions, wall motion, diastolic function, valvular abnormalities, left ventricular ejection fraction, and pulmonary artery pressures were measured [5]. Those taking Fen-Phen were studied shortly after they stopped taking it and again 6–12 months later. The results in these subjects were then compared with the findings in 660 randomly selected cardiac patients with heart disease that was not caused by Fen-Phen. Valvular regurgitation was greatest among patients who had recently stopped taking Fen-Phen, 57% of all valves having regurgitation, 88% of which were "mild"; they also had the largest left ventricles at end diastole (5.03 cm) and systole and higher pulmonary artery pressures (29 mmHg), associated with a lower incidence (14%) of pulmonic regurgitation. The number of people with aortic regurgitation fell with time after the withdrawal of Fen-Phen. However, among those who continued to have aortic regurgitation, there was an increase in the number of those who progressed from mild to moderate regurgitation, with an associated increase in left ventricular end-diastolic and end-systolic dimensions and left ventricular ejection fraction. There was an increase in the incidence of pulmonic regurgitation with time and a fall in pulmonary artery pressure from 29 to 14 mmHg. The incidence of tricuspid and mitral regurgitation fell with time, while pulmonic and aortic regurgitation tended to increase or become more severe when present. Dilatation of the pulmonary ring, resulting from raised pulmonic pressures, with subsequent pulmonary regurgitation and reduced pulmonary artery pressures, appears to be a functional change in the hearts of these individuals with unknown long-term consequences.

Nervous system

Insomnia is one of the most common adverse reactions to phentermine. In a survey in Edinburgh, 20% of the subjects taking phentermine reported insomnia compared with 6% of those taking placebo [6].

Urinary tract

Phentermine can cause allergic interstitial nephritis [7].

- A 47-year-old mildly obese woman began a weight reduction program that included anorectic therapy with phentermine and phendimetrazine. She had normal renal function at the start of therapy. After 3 weeks of treatment she fell ill and discontinued treatment. She was subsequently found to have leukocyturia, a rash on her face and chest, and a rise in serum creatinine from 67 to 175 μmol/l (0.8–2.1 mg/dl). Renal biopsy confirmed the diagnosis of acute interstitial nephritis. She was treated with corticosteroids, and her renal function returned to normal.

LONG-TERM EFFECTS

Drug abuse

Some cases of toxic psychosis have been reported with abuse doses of phentermine [8].

DRUG ADMINISTRATION

Drug contamination

Despite the withdrawal of many appetite suppressants from the market, illegally imported "weight-reducing products" may still contain these unsafe drugs. They are promoted to the general public through the electronic media, print advertisements, and health food stores. A case of cardiac

arrhythmia caused by an illicit "weight-reducing pill" containing phentermine and chlorphenamine has been reported [9].

- A 23-year-old woman developed marked lethargy and syncope. Her initial heart rate was 100/minute and blood pressure 96/42 mmHg. There was prolongation of the QT interval and polymorphous ventricular tachycardia. Her family stated that 3 days before admission she had started taking 1 capsule/day of an illegally imported weight lowering pill. She was given intravenous magnesium sulfate and recovered uneventfully in 36 hours. A urine drug screen was positive for phentermine and chlorphenamine. Serum drug concentrations were not measured.

DRUG–DRUG INTERACTIONS

Fluoxetine

Following the withdrawal of the fenfluramines, alternative combinations have been explored as appetite suppressants. In an open study of a combination of phentermine +fluoxetine in 16 obese patients with binge-eating disorder, in the setting of cognitive behavioral therapy, there were significant reductions in weight, binge frequency, and psychological distress by the end of treatment; however, the patients regained most of the weight within 1 year [10]. At follow-up at 18 months there was still a reduction in binge eating in patients who continued maintenance treatment. The results did not support the long-term value of adding phentermine + fluoxetine to cognitive behavioral therapy for binge-eating disorder. It is worth emphasizing that it is not known whether phentermine + fluoxetine is also associated with cardiac valvulopathy. Moreover, the recognition that phentermine is a monoamine oxidase inhibitor [11] raises further concerns about its safety.

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