Appetite suppressants and pulmonary hypertension

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Introductory article
Appetite-suppressant drugs and the risk of primary pulmonary hypertension

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Background. Recently in France, primary pulmonary hypertension developed in a cluster of patients exposed to derivatives of fenfluramine in appetite suppressants (anorectic agents), which are used for weight control. We investigated the potential role of anorectic agents and other suspected risk factors for primary pulmonary hypertension. Methods. In a case-control study, we assessed 95 patients with primary pulmonary hypertension from 35 centers in France, Belgium, the United Kingdom, and the Netherlands and 355 controls recruited from general practices and matched to the patients' sex and age. Results. The use of anorectic drugs (mainly derivatives of fenfluramine) was associated with an increased risk of primary pulmonary hypertension (odds ratio with any anorexic-drug use, 6.3; 95 percent confidence interval, 3.0 to 13.2). For the use of anorexic agents in the preceding year, the odds ratio was 10.1 (95 percent confidence interval, 3.4 to 29.9). When anorectic drugs were used for a total of more than three months, the odds ratio was 23.1 (95 percent confidence interval, 6.9 to 77.7). We also confirmed an association with several previously identified risk factors: a family history of pulmonary hypertension, infection with the human immunodeficiency virus, cirrhosis, and use of cocaine or intravenous drugs. Conclusions. The use of anorectic drugs was associated with the development of primary pulmonary hypertension. Active surveillance for this disease should be considered, particularly since the use of anorectic drugs is expected to increase in the near future. (N Engl J Med 1996;335:609-16)
been isolated case reports which strongly indicated that anorexigen intake can be associated causally with PPH. Usually such association can be claimed when a patient develops unexplained pulmonary hypertension in close temporal relation to anorexigen use and when no other drugs are involved. Analysis of the data collected for the primary pulmonary hypertension registry of the US National Institutes of Health showed that approximately 12% of all their patients with PPH had a history of anorexigen use, and Brenot et al found that, among their 125 cases of PPH, 14% had a history of anorexigen use (25% of all their female patients). Based on these data, it is not likely that anorexigen use is currently the overwhelming cause of PPH, but if anorexigen use continues to increase, it is likely to become an increasingly important cause of PPH.

For the prospective International Primary Pulmonary Hypertension Study (IPPHS) Group, 35 centres in France, Belgium, the Netherlands, and the UK agreed to participate and to report cases of PPH diagnosed between September 1992 and September 1994. A total of 95 patients with PPH were identified, 64 of whom had been reported by French centres. Definite use of anorexigenes had been reported by 30 of the 95 patients with PPH but by only 26 of 355 controls. Although the study was international in design, the data largely represented the French experience. Perhaps the most striking finding of the IPPHS was that roughly 12% of the patients with PPH had taken anorexigenes for 12 months or longer (compared with 0.6% in the control group).

Anorexigenes and PPH: the historical context

Several medical centres in Switzerland, Austria, and Germany registered an increased incidence of severe pulmonary hypertension beginning in 1967. Roughly 18 months after the anorexigen Mencol (aminorex fumarate) had been released in these three countries; by 1970 150 cases of PPH associated with anorexige use had been reported. The 1985 review by Gurtner followed 71 anorexigen users in the study and found that among their 125 cases of PPH, 64 of whom were identified, 64 of whom had been reported by French centres. Definite use of anorexigenes had been reported by 30 of the 95 patients with PPH but by only 26 of 355 controls. Although the study was international in design, the data largely represented the French experience. Perhaps the most striking finding of the IPPHS was that roughly 12% of the patients with PPH had taken anorexigenes for 12 months or longer (compared with 0.6% in the control group).

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Phentermine hydrochloride

Amphetamine

Aminorex

5-Hydroxytryptamine (5-HT)

Dexfenfluramine hydrochloride

Fluoxetine hydrochloride

Sertraline hydrochloride

Figure 2. Chemical structures of 5-hydroxytryptamine (5-HT, serotonin) and 5-HT-releasing appetite suppressants or antidepressants.

HT persisted in those patients who had received lung transplantation. If this finding of raised levels of 5-HT in patients with PPH can be confirmed in other populations with PPH, it would be tempting to speculate that agents which alter the metabolism of 5-HT could be trigger factors for PPH (figs 3 and 4).

It is clear from experimental data that 5-HT does, indeed, cause pulmonary vasoconstriction and produces both hyperplasia and hypertrophy of isolated cultured pulmonary artery smooth muscle cells. The proliferative effect of 5-HT is apparently transduced through the 5-HT2 receptor. However, the relationship between alteration in 5-HT metabolism and PPH is probably more complex, as evidenced by the absence of reports of a relationship between the chronic intake of antidepressants such as fluoxetine hydrochloride (a very widely used drug) and PPH. However, in our centre we have recently diagnosed PPH in a woman who had not taken anorexigens but had been treated for her depression with sertraline hydrochloride (unpublished observation).

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Genetic disposition + Trigger factor

Primary pulmonary hypertension

High blood flow

Anorexigens

Other

Platelet mast cells

Pulmonary vascular cell growth

Pulmonary vasoconstriction

Appetite suppressants

a) amphetamine-like

b) 5-HT related

5-HT
Anorexigen-associated pulmonary hypertension and obesity: risk-benefit ratio

It should be clear from the above that anorexigens can cause pulmonary hypertension. It should also be appreciated that many patients are looking for a pharmacological solution to their obesity problem. In the USA dieting and weight management are a multibillion dollar industry. Hundreds of new diet pill clinics have opened during the last year. Presently we have no good understanding of the relationship between body weight and pulmonary hypertension – apart from the well known association of the obesity/hyperventilation/poly-cythemia syndrome and pulmonary hypertension.

Gurtner, summarising his experience of 71 patients with presumed anorexigen-induced PPH, found that 50% of the patients had used aminorex while being only mildly overweight (110% of ideal body weight). While anywhere from 400 to 1000 additional new cases of PPH per year, the normal incidence of PPH is about 1.2 cases per one million population/year, the risk of developing PPH for non-overweight users of fenfluramine has been estimated at 28 per million/year, and that for overweight users at 55 per million/year. This implies that obesity might be a co-factor for the development of PPH, but there is much controversy as to whether obesity is independently related to PPH. The IPPHS data indicate that about 36% of the 95 patients with PPH had a body mass index of ≥ 30 compared with only 18.3% in the control group (the controls having been matched with the cases for age and sex only). The difference is probably explained by obese women being more likely to use anorexigens and the authors concluded that the effect of anorexigen intake on PPH “was the same whatever patients had a high body mass index or not.”

However, obese patients are not infrequently depressed and they may also be hypoxic. It is not known whether hypoxemia or the concomitant use of anti-depressants in anorexigen users poses an increased risk for PPH. Experiments in dogs have shown an increase in pulmonary vascular resistance with a combination of hypoxiaemia and fenfluramine administration.

In 1996 about 10 million prescriptions for fenfluramine (total sales $190 million in 1996), and approximately 2.5 million prescriptions for dexfenfluramine were written in the USA. Whereas the profit margins for the diet pill clinics are apparently greater than those in the restaurant business, little concern is being expressed about the prospects of successful long term weight loss. Little is known from clinical studies about the efficacy of any of the currently prescribed anorexigens, but Weight Watchers International has advised that “people will take the drug for as long as they need to achieve their weight loss goal and they should continue to take the drug to maintain their weight loss” (May 1996).

All this is worrisome when one considers that the pharmaceutical industry does not generally screen new compounds for their potential to cause pulmonary hypertension. By contrast, drugs do not usually reach the market if they raise the systemic blood pressure. Given the uncertainty of currently available “diet pills” to cause successful long term weight loss, and the risk of developing a lethal disease, the risk-benefit ratio could be considered unacceptably high. The introductory article has lessoned previous uncertainty and, as the number of anorexigen users in the USA approaches 20 million, we may soon witness a much greater incidence of PPH in that country as in Europe, anywhere from 400 to 1000 additional new cases of PPH per year.

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