Current Perspective

Aminorex to Fen/Phen
An Epidemic Foretold

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Over the years, a variety of diets and drugs for the treatment of obesity have come and gone. More recently, newspapers, radio, and television have featured the rise and fall of the latest appetite-suppressants, dexfenfluramine and the combination of fenfluramine and phentermine (fen/phen). The rise occurred after approval of dexfenfluramine by the Food and Drug Administration (FDA); the fall was prompted by an unexpected outbreak of valvular heart disease related to the use of anorectic agents.1

The outbreak of valvular heart disease was unexpected. Even though alarms had been sounded of an impending epidemic of pulmonary hypertension that would follow the turning loose of the appetite suppressants by the FDA,2,3 previous experience with these medications had not foretold an epidemic of valvular heart disease.

In this article, the pathogenetic mechanisms involved in the pulmonary vascular and cardiac valvular disease are explored within the larger framework of dietary pulmonary hypertension.4 Insights into these mechanisms appear to be relevant to avoiding similar epidemics caused by anorectic agents and in developing future weight-losing medications.

Obesity as a Target

One major weakness in the war against overweight and obesity is the blurred outlines of the targets. Although any degree of overweight is undesirable, not all degrees of obesity call for the same type of attack. For example, the goal of a 10% reduction in weight in an individual who is mildly obese and at risk for systemic hypertension and diabetes warrants more aggressive measures than does achieving the same weight loss by an individual determined to fit into last year’s bathing suit. In turn, both of these indications are much less compelling than weight loss in a morbidly obese individual in whom quick weight loss may be lifesaving. Moreover, no matter what the goal is in treating overweight and obesity, lasting success in losing weight calls for recognition that obesity is a chronic disorder that requires a long-term strategy for sustained success.5

The Aminorex Epidemic

The first epidemic of pulmonary hypertension caused by an appetite suppressant was precipitated by the anorectic agent aminorex fumarate (2-amino-5-phenyl-oxazoline).6a Aminorex (Menocil) resembles epinephrine and amphetamine in chemical structure, and its toxic effects have been attributed predominantly to the release of catecholamines and norepinephrine.7 Aminorex became available in 1965 in Switzerland, Austria, and Germany for over-the-counter sale. Between 1965 and 1972, the incidence of primary pulmonary hypertension in these 3 countries increased 10-fold. The frequency of pulmonary hypertension in individuals taking aminorex was on the order of 2000 cases per 1 million who took the medication, ie, an OR >1000. Of the thousands who used the drug, only 582 patients were involved in the epidemic; 61% of these had taken aminorex.6a Four times as many women as men were affected. Fifty percent of the patients weighed only 10% more than ideal. The latent period between the start of aminorex and clinical manifestations peaked at 6 months, and most who developed clinical manifestations came to the physician within 1 year. In Switzerland, 34 of 71 died by 1980. The epidemic ended when the drug was withdrawn from the market in 1972. Attempts to reproduce the human disease by feeding aminorex to experimental animals were unsuccessful.7

The epidemic of aminorex pulmonary hypertension taught several important lessons. First, substances taken by mouth can produce pulmonary vascular lesions that are confined to the small muscular arteries and arterioles. Second, only 2% of those who ingested aminorex developed primary pulmonary hypertension, suggesting genetic predisposition. Third, in keeping with this concept of genetic predisposition was the inability to elicit pulmonary hypertension by the feeding of aminorex to experimental animals selected at random. Fourth, although aminorex-induced pulmonary hypertension in humans often progressed after the drug was stopped, it did regress in 12 of 20 patients followed for >17 years; ie, the pulmonary vascular disease in these patients appeared to be reversible. Although aminorex was identified as the principal cause of the epidemic, noteworthy with respect to contemporary concerns about fen/phen-induced pulmonary hypertension was a significant association between the use of chlorphenetermine, which is closely related clinically to the phentermine of fen/phen (see below), and pulmonary hypertension.6b

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The Concept of Dietary Pulmonary Hypertension

The aminorex epidemic showed that substances taken by mouth could elicit pulmonary vascular disease that, in turn, resulted in pulmonary hypertension. This demonstration prompted the concept of “dietary pulmonary hypertension,” which postulated that food, beverages, or medications taken by mouth could directly or indirectly evoke pulmonary vascular disease and pulmonary hypertension.1

Animal Trials of Dietary Pulmonary Hypertension

Animal experiments related to the concept of dietary pulmonary hypertension originally involved the feeding of Crotalaria spectabilis to rats and nonhuman primates (Macaca arctoides). Crotalaria is an annual shrub indigenous to the tropics and sub tropics. It was introduced into the United States about 70 years ago as an intermediate crop to protect the soil. After ingesting the shrub, both rats and monkeys developed pulmonary proliferative and inflammatory lesions of the small muscular pulmonary arteries and arterioles and hepatic veno-occlusive disease.8

The toxicity of the ingested Crotalaria is attributed to monocrotaline pyrrole, the reactive metabolite of the pyrrolizidine alkaloid monocrotaline. Intravenous administration of monocrotaline pyrrole to rats elicits delayed and progressive injury to the vasculature of the lungs that results in pulmonary hypertension and right ventricular hypertrophy.2 The earliest pulmonary vascular lesions are manifested by histological evidence of endothelial injury and leakage. These appear to trigger cascades of responses to injury in the vessel wall that culminate in inflammatory, proliferative, and obliterative pulmonary vascular disease.10 Although the pulmonary vascular lesions are not the same as those in human primary pulmonary hypertension, they do show that certain substances, taken by mouth, can damage the resistance vessels of the lungs after undergoing metabolic processing in the liver.

Liver Disease and Pulmonary Hypertension in Humans

Numerous reports have called attention to the higher prevalence of pulmonary hypertension in patients with portal hypertension than in the general autopsy population.11 In the National Registry on Primary Pulmonary Hypertension, 17 of 192 patients with unexplained pulmonary hypertension had portal hypertension.12 In a series of 17 901 autopsies at Johns Hopkins Hospital, the prevalence of unexplained pulmonary hypertension in the general population was 0.13% compared with a prevalence of 0.73% in patients with hepatic cirrhosis, a statistically significant difference.13 Such observations have led to the prevalent idea that inadequacies in liver function or products of abnormal liver function play a role in the pathogenesis of the pulmonary vascular lesions and that these lesions resemble those designated “plexogenic arteriopathy.”

Toxic Oil Syndrome

Between May and June 1981, an epidemic of scleroderma-like disease occurred in Spain caused by the ingestion of the toxic, denatured, and re-refined rapeseed oil that was fraudulently sold to the public as pure olive oil. In the process of attempting to remove the marker, the bootleggers created toxic products that defied identification. Between 1981 and 1990, >20 000 cases were reported.14,15 Of the 370 deaths attributed to the toxic oil syndrome, 23 were directly related to pulmonary hypertension; in 9 others, pulmonary hypertension was severe but not the immediate cause of death.16

The onset of the syndrome was characterized by radiological evidence of interstitial pneumonia, blood eosinophilia, and increased levels of circulating IgE. Within 3 months, neuromuscular disorders and Raynaud’s phenomenon predominated. Pulmonary hypertension occurred primarily in women, some of whom came from families with unrelated pulmonary hypertension, raising the possibility of genetic predisposition.17

Similar vascular lesions were found in most organs of the body and affected vessels of every type and size. The obstructive and proliferative lesions bore a close resemblance to the vascular lesions of primary pulmonary hypertension. In the small pulmonary arteries, arterioles, and capillaries, the endothelium seemed to be the initial site of injury, followed by lymphocytic infiltration of the vessel walls, cellular proliferation, and intimal fibrosis—all of which contributed to increased pulmonary vascular resistance.

Although several analine contaminants of the toxic oil were identified and tested, attempts to reproduce the disorder experimentally in animals were unsuccessful, in large part because of uncertainty about the particular substance(s) responsible for the vascular injury.

Biguanidines

In 1973, a report appeared of 2 patients who developed pulmonary hypertension during treatment with phenformin, a biguanide.18 Withdrawal of the drug was followed by gradual subsidence of the pulmonary hypertension. Phenformin has fallen into general disuse because it causes lactic acidosis.

Eosinophilia-Myalgia Syndrome

In late 1989, an outbreak of a syndrome similar in many respects to the toxic oil syndrome occurred in New Mexico. By the beginning of 1990, 1269 cases had been reported to the Centers for Disease Control.19 Predominantly non-Hispanic, white women were affected. The syndrome included scleroderma-like skin manifestations, myalgias, arthralgias, peripheral eosinophilia, pulmonary hypertension, and pulmonary infiltrates. The estimated frequency of pulmonary hypertension in individuals with the syndrome was 5% to 7%.20 The cause is believed to have been an impurity in L-tryptophan taken as a nutritional supplement or therapeutic agent; the source of the L-tryptophan was traced to a single manufacturer.21,22 The origin of the syndrome was attributed to activation of eosinophils and release of major basic protein and eosinophil-derived products into the extracellular space.23 As in the case of the toxic oil syndrome, genetic susceptibility was suggested as a possibility.24

The Fenfluramines

The fenfluramines, like aminorex, are congeners of the amphetamines and are, in turn, related to the phenylethyl-
amines. Both \( \text{N}-\)fenfluramine and dexfenfluramine have been used as anorectic agents. Because fenfluramine (sold as Pondimin) lacked specificity and caused depression, the racemic form of the drug, dexfenfluramine (sold as Redux), rapidly took its place in the market. Dexfenfluramine increases serotoninergic activity by stimulating serotonin release from cellular stores, notably nerve endings and platelets; inhibiting serotonin uptake into presynaptic neurons; and directly stimulating presynaptic serotonin receptors. Serotonin is an intense pulmonary vasoconstrictor that stimulates proliferation of vascular smooth muscle by interacting synergistically with platelet-derived growth factor. Dexfenfluramine is metabolized to dextofenfluramine, which also releases serotonin into synapses and activates serotonin \( \text{5H}_2 \) receptors.

Isolated reports of pulmonary hypertension caused by fenfluramine began to appear in the European literature in the 1980s and 1990s. In 1993, Brenot et al., as the result of an epidemiological survey, linked the use of anorexigenics, fenfluramine in particular, to an increased frequency of pulmonary hypertension. At that time, fenfluramine had been approved by the FDA for short-term use. In 1996, the report of the International Primary Pulmonary Hypertension Study (IPPHS) indicted anorexigenics, particularly fenfluramine or its congener, dexfenfluramine, as etiological agents. The report, based on case-control epidemiological studies conducted in 5 European countries over a 2-year period, dealt with 95 patients with primary pulmonary hypertension. When anorectic drugs were used for >3 months, the adjusted OR increased from 1.8 to 23.1, ie., >10 times. However, not all were equally concerned about the harmfulness of the anorectic drugs. An editorial in the same issue of the journal concluded that “the possible risk of pulmonary hypertension associated with the use of dexfenfluramine is small and appears to be outweighed by the benefit (from treating obesity) when the drug is used appropriately.”

About 2 months before the appearance of the IPPHS on April 29, 1996, the FDA had approved dexfenfluramine for use in the United States. Approval did not have easy passage: the vote for approval was close, 6:5. After approval, a unanimous vote insisted on postmarking studies and careful labeling concerning patient selection.

Dexfenfluramine appeared in drug stores under the trade name Redux in June 1996 in a blitz of advertising. In the 5 months after its release, 1.2 million prescriptions were filled. Little heed was paid to the manufacturer’s cautions about duration of use or to drug interactions with other serotonin releasers. No information was provided—because none was available—about the effectiveness and consequences of taking the drug for >1 year. Lost in the hyperbole of advertising was the limited efficacy of the drug, ie., that continued usage leads only to small sustained weight loss averaging 10% compared with the 6% weight loss of control subjects.

Enthusiasm for the use of all anorectic agents was dampened dramatically after an alarm set off by the report of Connolly et al. They reported a high incidence of both left- and right-sided lesions on the valves of the heart in 24 women who had taken the fen/phen combination for 5 to 19 months. Reports from other institutions followed closely on the Mayo Clinic news. Within a few months, the Centers for Disease Control had collected 33 reports of women with echocardiographic evidence of left-sided valvular disease who had taken fen/phen for 1 to 28 months.

**Fen/Phen**

In 1984, it was reported that the anorexigenic effects of fenfluramine could be duplicated and its side effects minimized by the use of smaller doses of the drug in combination with phentermine, an amphetaminelike agent. Subsequent reports by the same group reinforced the impression of the safety and effectiveness of the combination. In 1996, >18 million prescriptions were filled for fen/phen, predominantly for women overweight by 20 to 30 lb. Little heed was paid to occasional reports of pulmonary hypertension in association with the use of fenfluramine or phentermine alone.

Although the report by Connolly et al implicated the fen/phen combination in the pathogenesis of the left-sided valvular lesions, it only addressed in passing the mechanisms by which the combination enables high levels of circulating serotonin to reach the left side of the heart. One likely mechanism seems to be failure of clearance of serotonin by the lungs (Figure 1).

Involvement of the lungs in clearing serotonin (5-HT) from the blood was first appreciated about three quarters of a century ago. In 1924, Eicholtz and Verney found that lungs had to be included in the perfusion circuit of their isolated, perfused kidney preparation to maintain its viability. In 1953, Gaddam et al. showed that without lungs in the circuit, 5-HT in the blood damaged the kidneys by eliciting intense renal vasoconstriction. In 1967, Thomas and Vane showed that the lungs could remove up to 98%
of 5-HT in a single circulation (Figure 1). Between 1973 and 1981, the mechanisms involved in the pulmonary clearance of 5-HT were elucidated. 5-HT is removed from the blood by pulmonary vascular endothelium by a process that is carrier mediated and Na⁺ dependent; a similar process is involved in the accumulation of 5-HT by nerve endings, synaptosomes, and platelets. Within the pulmonary endothelium, 5-HT undergoes oxidative deamination by monamine oxidase.

In the 1970s, the handling by the lungs of various amines, including serotonin, began to be systematically explored. In the 1980s, experiments by Agevine and Mehendale and Morita and Mehendale indicated that the uptake and metabolism of serotonin by the isolated rabbit lung could be severely compromised by the appetite suppressant chlorphenetermine, chemically related and qualitatively similar in its actions to phentermine.

The cardiac valvular lesions in patients who have taken fen/phen are identical grossly and histologically with those of primary pulmonary hypertension. Three mechanisms can account for this association (Figure 2). First, high concentrations of free serotonin act directly on the heart valves and pulmonary vessels. Serotonin is a powerful pulmonary vasoconstrictor, and vasoconstriction has been proposed as an initiating mechanism for primary pulmonary hypertension. Second, there are hemodynamic consequences of the left-sided valvular regurgitant lesions; mitral and aortic valvar regurgitation are well-established causes of pulmonary vascular oblitative and proliferative lesions. Third, combined mechanisms, such as intense pulmonary vasoconstriction, left-sided valvular regurgitation, and phospholipidosis, are caused by phentermine in some species.

It is noteworthy that in contrast to the genetic predisposition that has been postulated as a sine qua non for the pulmonary vascular lesions caused by aminorex or fenfluramine, the pulmonary hypertension that accompanies the left-sided valvular lesions produced by anorexic agents can be attributed to direct toxic effects of serotonin on the small muscular arteries and arterioles and the secondary hemodynamic effects of the valvular insufficiencies, without need for invoking genetic predisposition.

**Conclusions**

The use of appetite suppressant agents that act by way of releasing neurotransmitters such as serotonin (or norepinephrine or dopamine) is handicapped by potential side effects of these agents on other parts of the body, especially if mechanisms for clearing these agents from the body are compromised. In the case of the fenfluramines, the risk of inordinate levels of circulating serotonin is greatly increased by combination of the anorectic agent with another drug, such as phentermine, which interferes with its elimination by the lungs. Anatomical lesions consequent to intense vasoconstriction and valvular insufficiencies can add to the functional impairments caused by the anorectic amines.

Two different mechanisms seem to be involved in pulmonary vascular toxicity caused by anorexigen: (1) Inherited susceptibility, as in the aminorex and fenfluramine epidemics, predisposes individuals to vasoconstriction and oblitative lesions confined predominantly to the precapillary muscular arteries and arterioles of the lungs, and (2) impaired clearance by the lungs of biologically-active substances, such as serotonin, enables toxic concentrations of the agent to reach and damage the valves of the left side of the heart. Although novel appetite suppressants seem to be in the
offing, it seems clear that all run the risk of eliciting toxic side effects unless their mode of action can be circumscribed to the brain so as to depress appetite without causing undesirable systemic side effects. Alternatively, a variety of agents that are directed at other mechanisms for weight loss, such as lipase inhibitors that interfere with intestinal absorption of fat, are currently being explored. However, until safe and effective agents that are directed at central nervous mechanisms that control weight materialize, behavior modification relating to diet and physical activity seem to afford the more salutary approach for the great majority of individuals who are overweight, while anorectic agents are held in reserve for the morbidly obese.

References


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