Too late, again?

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Recently, I returned from a long vacation in Europe; news of Canada is hard to come by there, even with the help of the Internet, and I was anxious to catch up with the events of the previous few weeks. On turning on the radio to the Canadian Broadcasting Corporation's *Metro Morning Show* (May 9, 2001), I heard a report by reporter Timothy Sawa on the plight of Ann Gilmore, a patient with primary pulmonary hypertension (PPH) who had taken a 'diet pill' in 1995. She is one of a number of people who have launched a class action suit against the French manufacturer of the fenfluramine-containing drugs Ponderal and Redux, and the Canadian distributor of the drugs (Servier Canada). Sawa interviewed Dr Yola Moride of the Jewish General Hospital, Montreal, Quebec, who was one of the principal investigators in a 1995 study that linked 50 cases of PPH to the use of diet pills containing fenfluramine and dexfenfluramine (1), and led to restrictions being placed on the use of the drugs in France. Health Canada requested that Servier pull the drugs off the market in 1997. However, Sawa pointed out that the association between PPH and the use of such drugs had been known since at least 1993, when a study published in the *British Medical Journal* (2) of 15 PPH cases in patients taking diet pills led Servier Canada to inform Health Canada of the heart and lung damage related to their use. Also, Dr David Langleben, a member of the Montreal research team, had written to Health Canada about the risks of PPH before publication of his study with the International PPH Study Group (3). Although Health Canada issued a warning regarding the danger six months later, it also approved another dexfenfluramine drug, Redux.

Even in my jet-lagged state, the broadcast set bells ringing; the association between PPH and anorectic drugs seemed to have been recognized so long ago that I found it hard to believe that the problem was still more or less current. In the days following the broadcast, I was not able to find anything about it in the papers (which was a surprise), and I set about refreshing my memory of the topic.

The story began with the report of the Swiss physician Gurtner, who drew attention to a 20-fold increase in the incidence of PPH in Berne, Switzerland (4). Gurtner and his colleagues reported that the patients were often obese

and suffered from a rapidly progressive disease; most of the patients were taking an amphetamine-related drug, aminorex fumarate, to help them lose weight. Similar increases in the incidence of PPH were found in Austria and Germany, leading to the application of the term 'epidemic' to PPH at that time. A World Health Organization conference on the disease was held in 1973 (5). Although the administration of aminorex to experimental animals did not produce chronic elevations of pulmonary arterial pressure, the temporal relationship between the use of aminorex and the incidence of PPH led to the withdrawal of the drug in 1968, which was followed by a fall in PPH incidence in the subsequent three years (6).

The fenfluramines reduce hunger by increasing brain serotonin levels. Fenfluramine was introduced as an anorectic drug in 1964, and approved in the United States for prescription use in 1995; for dexfenfluramine, the dates were 1987 and 1996, respectively (6). However, both drugs were used widely in Europe well before their approval in the United States. PPH in patients taking fenfluramine was reported by Douglas et al (2) in 1981, and PPH in patients taking dexfenfluramine was reported by Roche et al (7) in 1992. These reports were followed by the publication in 1996 (1) of the results of the International PPH Study Group, which recruited patients between 1992 and 1994. It was shown that PPH was 23 times more likely to occur in patients taking these drugs for three months or longer than in control subjects. Following its publication, there was a vigorous debate in the correspondence section of *The New England Journal of Medicine*, partly because the United States Food and Drug Administration had yet to approve the drugs. Noteworthy in the correspondence was a letter by Alfred P Fishman (8) – surely the doyen of researchers into the pulmonary circulation – pointing out the parallels between

PPH in aminorex and fenfluramine users, and that history was at risk of being repeated. A few years later, Dr Langleben was able to point out that history had indeed been repeated (6), and he noted what should be learned from this tragic course of events.

I have been at pains to identify dates in this history, and, having done so, find that they appear quite confusing. This is because, in retrospect, it seems hard to understand how approval was given in the first place and how long it took for approval to be removed, especially in view of the fact that the distributor of the drug in Canada was aware of its effects for several years. This confusion and sense of tragedy is heightened by the finding that these drugs have not been proven to be as effective in promoting weight loss in morbidly obese individuals. The lessons are obvious, which is why I felt some jogging of our memory might be in order.

I will not review the research into the mechanisms of PPH in patients taking anorexigens; Drs ED Michelakis and EK Weir of the University of Alberta, Edmonton, have recently published an informative review of the basic science background (9) in which they propose that this unfortunate drug reaction may shed light on the mechanisms underlying PPH of previously unknown cause.

This is a cautionary tale that must not be forgotten, first,

because patients whose PPH is due to anorectic drugs need to be identified and informed, and second, because we need to constantly be on guard for drug reactions and persistent in our efforts to control them.

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