Clinical studies with \textit{d}-fenfluramine\textsuperscript{1,2}

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\textbf{ABSTRACT} \textit{d}-Fenfluramine (\textit{dF}) (15 mg twice daily) has been studied in controlled trials in human obesity and has been shown to increase adherence to diet, to enhance its efficacy, and most importantly, to prevent weight regain when continued over 1 y. Few side effects, mostly transient, have been observed. A long-term use of \textit{dF} in the management of some obese patients could be foreseen. Additionally, evidence that \textit{dF} improves eating symptoms and dysphoric impairments in obese cravers, premenstrual syndrome, seasonal affective disorder, and smoking withdrawal syndrome has been presented. \textit{Am J Clin Nutr} 1992;55:173S–6S.

\textbf{KEY WORDS} Dextrofenfluramine, feeding behavior, pharmacotherapy of obesity

\textbf{Introduction}

Since \textit{d}-fenfluramine (\textit{dF}), the dextroisomer of \textit{dl}-fenfluramine, became available some years ago, several studies have been designed to test its therapeutic usefulness in human pathology. This short review will consider the most relevant data from the literature that is able to firmly document and/or to suggest that the use of \textit{dF} is of clinical importance in some human diseases.

\textbf{Body-weight control in obesity}

A number of pharmacological studies in animals and humans, reviewed in other sections of these proceedings (1–3) have shown that the main actions of \textit{dF} can be summarized as follows: 1) to reduce food intake by enhancing the serotonin-mediated satiating power of food; 2) to reduce motivation for eating in different paradigms, including stressful situations, and to modify the eating patterns; and 3) to increase diet-induced thermogenesis. Taken together the properties have been interpreted as indicating that \textit{dF} was able to act on both sides of the equation of energy balance, intake and expenditure, in a regulatory manner (4) and therefore that this drug could be an agent to be used in obesity.

However, as previously discussed elsewhere (5, 6), the pharmacotherapy of obesity is obviously limited by the well-known fact that the weight-lowering effects of all the available drugs, including fenfluramine, are most often rapidly abolished when they are withdrawn (7–10). Other types of treatments commonly used for outpatients, including severe restrictive diets (5, 11) and to a lesser extent behavior therapy (12), have been shown to end with the same weak lasting effects. Such an issue is not an unexpected one because obesity is a chronic condition that requires chronic treatments just as other chronic diseases, such as diabetes, hypertension or hyperlipoproteinemia, do. Except when some basic etiologic disturbance can be cured, a quite seldom (and often casual) event in the present state of knowledge, long-term maintenance of the initial weight loss, which is the true challenge, relies upon the possibility to maintain a permanent and bearable pressure to avoid relapse and weight regain. Among the limited numbers of procedures that could be reasonably proposed is long-term pharmacotherapy, a concept that deserves more attention than in the past and could be considered in the development of new drugs.

The main properties that an antiobesity drug must have to be used for a long term are the following: 1) a weight-lowering effect as demonstrated in short-term controlled trials; 2) good clinical tolerance, ie, not to be devoid of any side effect but to elicit bearable and/or transient side effects entailing few drop outs; 3) no addictive properties, particularly because a toxicomania predisposition seems quite frequent among the obese population; 4) sustained effects, ie, maintenance of the initial weight loss with no escape when treatment is continued; 5) no major hazards in humans after years of administration so that the benefit-risk ratio remains acceptable; and 6) known mechanisms of action to select the patients likely to be the best responders. The classical studies performed so far with \textit{dF} have shown that the drug fulfills a large number of the above-mentioned conditions.

\textbf{Short-term studies}

Three classical short-term controlled double-blind trials over periods of 3 mo were reported in 1987 (13). The administration of \textit{dF} 15 mg twice daily together with the prescription of a moderately restricted diet in subjects with mild to severe obesity induced a significant weight loss amounting to 6.6 ± 0.6 kg or 7.6 ± 0.7% of the initial body weight, whereas the weight loss was lower and nonsignificant (2.0 ± 0.7 kg and 2.6 ± 0.8%) with the placebo. In refractory obesity, weight loss on \textit{dF} was still significant whereas it was almost nil on placebo. These short-term studies failed to clearly identify the side effects due to the drug. All the conventional biological safety tests remained unchanged. A subsequent study in Italy (14) confirmed that \textit{dF}

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had to be considered as a weight-lowering agent with a satisfactory tolerance over a short term.

Long-term studies

It was also shown that dF had no addictive risks (15) and that it was active at one-half the dose of the racemic compound (16). A previous study by Hudson (17) indicated that continuous administration of dF-fenfluramine led to weight loss that was maintained for 1 y with a low drop-out rate. More recently, Douglas et al (18) found that in a limited number of reduced obese patients, dF-fenfluramine prevented weight rebound over 1 y much more frequently than did a placebo (32% vs 9.5%). With this background a long-term trial attempting to test in more depth the feasibility of long-term treatments with dF could be considered.

The results of a 1-y trial, known as the International Dexfenfluramine Study (INDEX), were reported recently (19). It was a multicenter randomized placebo-controlled double-blind trial designed on an intention-to-treat basis. Eight hundred twenty-two obese patients of either sex were included. Four hundred four were prescribed dF, 15 mg twice daily; 418 were prescribed a placebo (P). All patients were also prescribed a diet because it was judged unethical to maintain patients under placebo alone > 1 y. The patients displayed a wide spectrum of overweight (from 120% to 306% ideal body weight). The only noninclusion criteria related to weight were represented by the patients who were 85% below their peak weight, who had lost > 3 kg in the previous 3 mo, or who had an unrealistic weight loss expectation. dF and placebo groups were similar in sex distribution and extent of overweight.

The first endpoint was an analysis of the withdrawals. At 12 mo it appeared that significantly more patients (P = 0.002) had withdrawn from P than from dF, representing 45% and 37% of the cohorts, respectively. Dissatisfaction with the weight loss was the only reason more frequently in the P than in the dF group (48 vs 49, P = 0.02), accounting for almost all the excess of withdrawals in the P group. It was thus concluded that dF had increased the adherence to the weight-lowering program.

The second endpoint was the analysis of weight loss. Because there is no agreed method of assessing weight loss, different analyses were used. The cohort analysis, which accounts the patients achieving a given weight loss, is probably the least-biased way to process the data and is more clinically relevant: it considers all the patients who enter the study and regard the dropouts as nonlosers. At each target weight loss the dF patients were far more numerous than the P patients (P < 0.001). For example, nearly twice as many patients on dF as on P achieved a weight loss of ≥ 10% of starting weight (34.9% vs 17%) or of > 10 kg (32.4% vs 15%). Complete failure (including withdrawals) was observed in 36.9% of dF patients.

Comparison of mean weight loss in the residual cohorts (completing patients) is a conventional method. It has the disadvantages of mixing weight losers and nonlosers and of being largely dependent on the drop-out rate. Consequently, it overestimated weight loss in the P cohort, which contained an excess of withdrawn patients. Even with these drawbacks, the dF completers had lost significantly (P < 0.001) more weight after 12 mo (9.82 ± 0.49 kg) than the P completers (7.15 ± 0.49 kg), i.e., 10.26% and 7.18% of starting weight. This difference could be estimated as a weak one but the extra weight loss of dF patients was 52% over that of P patients. It is important to note, however, that the significant weight loss achieved by the P cohort was likely to result from the combined effects of placebo, associated diet, and supportive management by the investigators and could be favorably compared with those of diet alone (7, 11). Overall results achieved with dF fell well within the range of that obtained with behavior therapy or combined conservative treatments (9, 12, 20).

Another important issue of INDEX was the time course of the weight loss (Fig 1). On the average a plateau was reached with dF after the sixth month, indicating that the action of the drug was then not to promote additional weight loss but to avoid weight regain. This type of evolution is typical of that observed with all the efficient weight-lowering procedures (except total fasting), including gastrointestinal surgery (21). The significant tendency for weight regain in the P group suggests that the patients had increasing difficulties in avoiding relapse despite a strict follow-up.

Other long-term studies in more selected obese patients have confirmed the action of dF to prevent weight regain and to increase weight loss. Recently, Finer et al (22) induced a 14-kg weight loss in severely obese patients by an 8 wk very-low-calorie diet program. Then the patients were randomized blindly into dF or P treatments associated with a less restrictive diet for a 26-wk period. dF patients continued to lose weight (5.8 kg) whereas P patients regained 2.6 kg. Also Noble (23) administered blindly dF or P during a 24-wk period to obese patients who had lost weight and were stabilized while still more or less dieting. Again dF patients lost 6.2 kg on an average (P < 0.001) and P patients only experienced a nonsignificant 2.6 kg additional weight loss.

Tolerance and safety

No major hazards imputable to dF were reported in the INDEX study. Major biological parameters were either unchanged or improved (unpublished data). The only symptoms that were significantly more frequent in dF than in P patients were tiredness, diarrhea, dry mouth, polyuria, and drowsiness, occurring most often during the first or second month of treatment.
Therefore, they must be considered as the true side effects of the drug. They could be expected with a serotoninergic drug.

All of these findings have shown that continuous administration of dF helps many obese patients to adhere to a diet, to enhance its effects, and to maintain the weight loss without harmful side effects. Obviously, a 1-y period, albeit a rather long one for a trial, would appear quite a short period with respect to the life-long treatment that is needed. Much remains to be known, including the identification of the responders, when to include dF in the treatment, maintenance of compliance and/or action over very long periods, safety after years of administration, etc. As for other drugs only an extensive use with a careful follow-up will provide evidence concerning the two last points. However, dF can be considered for long-term therapy of some obese patients in addition to diet.

Obesity-related metabolic abnormalities

Blood pressure and blood glucose are likely to be decreased with weight loss making it difficult to specify a specific role of drugs inducing weight loss. Recently, Andersson et al (24) showed dF to decrease both supine and standing systolic and diastolic blood pressure in normotensive obese women independently of any weight loss or modification of food intake. Plasma noradrenaline and renin were reduced whereas cortisol, β-endorphin, and thyroid hormones did not change. In obese women with non-insulin-dependent diabetes, but not in nonobese diabetic obese women, Scheen et al (25), reported a 1-wk dF administration to reduce fasting blood glucose and plasma free fatty acids, whereas insulin metabolic clearance rate remained unchanged and glucose metabolic clearance rate was significantly enhanced. This improvement in insulin sensitivity was achieved without weight change. These data could be interpreted in keeping with the actions of dF on the hormonal and metabolic reactions to stress (26) and would suggest the drug to be well suited in hypertensive or diabetic obese patients.

Behavioral disturbances

Recent studies have reported dF to influence favorably some abnormal eating patterns, mainly intermeal craving, leading to hyperphagia. These symptoms are quite frequently observed among obese populations (27) and could be a factor of weight gain or could prevent adherence to diet. They have been associated with some affective disorders such as Seasonal Affective Disorder (SAD) (28), premenstrual syndrome (PMS) (29), and smoking withdrawal syndrome (30). The possible involvement of impaired serotonin transmission has been considered as a major pathophysiological component of these disorders (31), a discussion that is still open and that is clearly not under the scope of this review. However, it is noteworthy that the ability of drugs to enhance serotonin transmission to improve or to relieve these symptoms has been contributory.

In a series of short-term clinical investigations conducted by the Wurtman’s group in Boston, it has been shown that dF was able to reduce the frequency of snacking and the daily calorie intake in obese carbohydrate and noncarbohydrate cravers (32); to revert increased calorie, carbohydrate, and fat intakes during meals and snacks in the luteal phase of the menstrual cycle to the levels of follicular phase in women with PMS, whereas mood scores were improved by some 60% (29); to improve depression scores by some 70% during autumn in patients with SAD (33); and to reduce subjective distress, to prevent increase in calorie and carbohydrate intakes both at meals and between meals, and to induce a weight loss in female chronic smokers who stop smoking (30).

Conclusion

The clinical data obtained with dF in obesity and related disorders clearly indicated that this drug should be seriously considered in the therapeutic strategies to be developed for the management of many obese patients, particularly for reinforcing the effects of and the adherence to diet and possibly for preventive weight gain in some typical situations. It must be emphasized however that the prescription of drugs must not dodge a thorough evaluation of the underlying problems nor prevent other types of useful interventions.

References


