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The metabolic effects, and the composition of the tissue lost, in weight reduction by obese patients on treatment with fenfluramine

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Summary

1. Three groups of obese patients were treated for periods of up to 6 months. One group of 52 individuals received 80–120 mg fenfluramine daily. The second group of 20 people had placebo tablets. The third group of 28 patients were on a dietary restricted régime.

2. Only the fenfluramine and dietary treated groups lost weight but there was no evidence of an increased metabolic rate after fenfluramine, either at rest or in standardized exercise. During the first month of treatment the mean weight loss in the group treated with fenfluramine was greater than that in the group treated by diet alone, but the difference was not significant ($P<0.05$). By the third month of treatment the mean weight loss was smaller in both groups, particularly in the women.

3. The composition of the tissue lost in the weight reduction had a mean fat content of 75% and did not differ significantly between the fenfluramine group and the diet-restricted group, except in women.

Introduction

The central effects of fenfluramine on the appetite control centres in the region of the hypothalamus have been excellently demonstrated by Anand (1971). He found that in unanaesthetized rhesus monkeys and in anaesthetized cats, intravenous injections of fenfluramine, 1·5–3·0 mg/kg body weight, increased activity of the medial hypothalamic area (the 'satiety' centre) whereas activity in the lateral hypothalamic area (the ' feeding ' centre) diminished. These effects might account for the appetite-depressant action of fenfluramine.

It has also been postulated that fenfluramine stimulates metabolic processes. Thus, oral administration of fenfluramine to 8 normal adults significantly increased free glycerol, free fatty acid and ketone levels in plasma (Pawan, 1969). In forearm perfusion experiments, the rate of glucose uptake in skeletal muscle was increased after fenfluramine (Butterfield & Whichelow, 1968). Subsequently, free fatty acids appear to be released from both adipose tissue and from muscle (Turtle, Burgess & Bauckham, 1971). In previous studies, we found a small but insignificant increase in total metabolic rate, both during rest and in standardized exercise, on 12 patients receiving fenfluramine for obesity (Durnin & Womersley, 1971). Moore & San-Yi (1971) found a thermogenic response in rats to fenfluramine, but this could be elicited only when these animals were at, or very near, their zone of thermoneutrality.

In previous experiments, fenfluramine was given to obese patients on a low-energy diet and it is possible that the restricted food intake may have at least partially inhibited any thermogenic stimulus of the fenfluramine. The present study was designed therefore to measure any change in oxygen consumption, either at rest or in standardized exercise, of a group of obese subjects undergoing fenfluramine therapy only. A second group of obese patients acted as controls and they received placebo tablets of identical size, shape and taste to the fenfluramine. A third group was treated with a restricted diet alone. The fat and fat-free mass in the tissue lost to the body was also measured on the three régimes as weight loss occurred.

Methods

Fenfluramine in doses of 80 mg daily was given to 52 patients. In the grossly obese subjects and in those who did not respond to this dose, the amount of fenfluramine was increased to 120 mg daily. The duration of the treatment varied from 4 up to 26 weeks. Placebo tablets in similar quantities were given to 20 patients. In neither of these two groups was any advice given on dietary restriction. A third group of 28 patients was treated with an 800, a 1,000 or a 1,200 kcal/day diet, the particular diet depending on the normal energy intake of the person—those with the highest normal energy intakes being given the 1,200 kcal/day diet and those with low normal intakes receiving the 800 kcal/day diet.

The number of men and women in each group, together with the mean body weights, ages, fat contents and their standard deviations, are given in Table 1. No overt disease was present in these patients, other than any disability due to obesity.

TABLE 1. *The mean body weights, ages and % fat contents (with standard deviations) of the subjects on the 3 different régimes*

	Fenfluramine		Placebo		Diet	
	M	F	M	F	M	F
No. of subjects	11	41	2	18	7	21
Mean age (years)	46±13	37±13	48±12	38±10	42±14	41±13
Mean body weight (kg)	87±13	75±13	83±12	72±13	83±6	74±9
Mean fat content (%)	34±6	40±7	36±5	38±5	34±5	40±5

In 5 cases (excluded from the analysis) the side effects of fenfluramine were so severe (3 cases of severe diarrhoea and 2 of acute sleeplessness) that the drug had to be discontinued forthwith. Of the 52 patients on fenfluramine therapy for periods of 1 month or over 19 reported no side effects. The others each reported at least one side effect, which varied considerably in severity and duration; despite the fact that full dosage was gradually worked up to over a period of 2–3 weeks symptoms usually began within 1 or 2 days of commencing treatment.

Eighteen patients reported dryness of the mouth and 12 tiredness or lethargy —one man commenting that on one occasion he became so tired that he had to stop driving his car. Eleven patients volunteered that their appetite had decreased and some of them said that their 'stomach appeared to have shrunk'. There were 6 reports of diarrhoea, 5 of dizziness or light-headedness and 4 of inability to get to sleep. There were 1 or 2 reports each of a bitter taste in the mouth, double

vision, a feeling of hotness, feeling cold, a loss of appetite for sweet things, and one man said that he felt better physically.

One patient on the placebo tablet complained of restlessness. There were no other reports of side-effects with the placebo.

On the first visit to the laboratory, the subjects were in the fasting state, not having eaten for a minimum period of 4 hours. Body weight was taken and body fat was measured by the densitometric technique of underwater weighing (Durnin & Rahaman, 1967). Residual volume at the time of weighing was measured using the nitrogen wash-out method. Oxygen consumption was determined using a polyvinyl chloride Douglas Bag while the patient reclined at rest, and again while walking on a treadmill at 3 m.p.h. (4·9 km/h) with a zero gradient. The oxygen content of the expired air was measured using a Servomex analyzer, calibrated at frequent intervals by use of known gas mixtures which, in their turn, were monitored by means of the Lloyd-Haldane apparatus. During treatment, return visits to the laboratory were made at 2–4 week intervals when the measurements of oxygen consumption at rest and in exercise were repeated. When an appreciable loss in body weight occurred—about 6–7 kg—the measurement of body fat by densitometry was repeated.

Results

The mean rate of weight loss achieved by the patients on the 3 different régimes, during the first and third month of treatment, is shown in Table 2.

TABLE 2. *Comparison of the mean weight loss (kg/week) achieved by subjects on 3 different régimes*

	Fenfluramine		Placebo		Diet	
	M	F	M	F	M	F
First month of treatment						
No. of subjects	11	41	2	18	7	21
Mean wt. loss (kg/week)	0·22	0·45	0·16	0·06	0·24	0·24
S.D.	±0·31	±0·32	±0·29	±0·49	±0·32	±0·32
Third month of treatment						
No. of subjects	8	22			4	10
Mean wt. loss (kg/week)	0·16	0·13	none		0·19	0·12
S.D.	±0·47	±0·29			±0·45	±0·36

Of the 52 patients on fenfluramine, 10 failed to lose any weight after treatment for between 4 and 10 weeks; none gained weight. The largest weight loss was 0·6 kg/week over periods of 10 to 13 weeks (3 patients); one individual lost 1 kg/week over 4 weeks.

Of the 20 patients on the placebo tablets, only one lost a significant amount of weight and 6 actually gained weight.

Twenty out of the 28 patients receiving just dietetic advice lost weight, and 4 gained weight.

The oxygen consumption *at rest* before, and after 4 weeks of treatment with fenfluramine, is shown in Table 3. Differences were not significant, as assessed by paired *t* tests, whether the results were expressed as ml O_2/min or as ml O_2/kg body weight/minute. Similar results were obtained while the patients performed a treadmill exercise (Table 4); again none of the differences were significant except in the case of the women whose metabolic rate during exercise was apparently lower after fenfluramine for 4 weeks than before treatment; this,

TABLE 3. *Mean changes in oxygen consumption at rest in* 8 *men and* 24 *women after* 4 *weeks treatment with* 80–120 *mg fenfluramine daily*

	Men		Women	
	ml/min	(ml/kg)/min	ml/min	(ml/kg)/min
Before treatment	257	2·95	232	3·09
During treatment	253	3·16	217	3·12
Significance of difference	NS	NS	NS	NS

TABLE 4. *Mean changes in oxygen consumption while walking at* 3 *m.p.h. on a treadmill in* 8 *men and* 24 *women after* 4 *weeks treatment with* 80–120 *mg fenfluramine*

	Men		Women	
	ml/min	(ml/kg)/min	ml/min	(ml/kg)/min
Before treatment	1004	11·54	815	10·87
During treatment	1016	12·70	664	9·55
Significance of difference	NS	NS	0·01	NS

however, was obtained only on the gross result for total oxygen consumption and was not significant when the values were compared as (ml 0_2/kg body weight)/minute.

The composition of the tissue lost, in those patients with reduced body weight, is shown in Table 5. Although the percentage of fat in the tissue lost varied considerably between the fenfluramine and dietetically treated patients, these values were within the limits found for the lipid content of adipose tissue.

TABLE 5. *The fat content of the tissue lost* (1) *while on treatment with* 80–120 *mg fenfluramine daily and* (2) *while on a restricted diet*

		Mean body weight (kg)		Mean body fat content (%)		% fat in tissue
	n	Initial	Final	Initial	Final	lost
(1) Men	5	85·5	78·2	34·0	31·2	70
Women	14	75·3	69·7	40·0	37·6	66
(2) Men	3	99·6	85·1	31·0	22·0	86
Women	8	89·1	83·7	43·6	40·8	82

Discussion

The results of this study confirm the efficacy of fenfluramine in achieving weight reduction, even when the patients were not instructed to reduce their food intake. During the first month of treatment on 80–120 mg fenfluramine daily, the weight loss of about 0·4 kg/week is similar to the 0·3 kg/week lost by the patients of Silverstone, Cooper & Begg (1970) on 60 mg daily and the 0·55 kg/week lost by those of Bolodeoku, Adadevoh & Palmer (1972) on the same dosage as we have used; in none of these investigations were the patients asked to eat less. Other authors have found greater rates of weight loss when dietary restriction has been also prescribed (e.g. Traherne, 1965; Brodbin & O'Connor, 1967; Lawson & Roscoe, 1971).

On the other hand, the marked decline in weight loss by the fourth month of treatment contrasts with our previous study, where 12 obese subjects on 60 mg fenfluramine daily and a 600–1,000 kcal/day diet continued to lose weight at a fairly uniform rate for 4–5 months, and with the similar findings of Lawson & Roscoe (1971). It might be, therefore, that fenfluramine is most effective as a long-term agent when taken in conjunction with a restricted energy diet.

It is impossible to be sure that our subjects treated with fenfluramine did not voluntarily reduce their food intake although, if that were the case, we would not expect any difference between the fenfluramine treated and placebo treated groups. The fact that the placebo group achieved only a very small weight loss suggests that the greater weight loss of the fenfluramine group was the result primarily of the drug.

No evidence was obtained from these experiments that fenfluramine was affecting metabolic rate significantly, either at rest or during standardized exercise. The unexpected result on the women while exercising (Table 4) is explained by the lower body weight after treatment with the drug and when the results are calculated per kg of body weight, no significant effect is seen. This suggests that the weight loss in the subjects treated with fenfluramine may have been achieved by unconscious reduction in food intake, that is by appetite suppression. It should, however, be pointed out that the metabolic stimulus required to account for these weight losses is of the order of only 3–5% and that detection of this would be very difficult because of the inherent variability in the metabolic rate of any individual (Durnin & Namyslowski, 1958). If such a stimulus is one of the properties of fenfluramine, even though it appears to be small, it might yet be of practical importance in the long-term treatment of obesity.

The mean initial weights of the subjects referred to in Table 5, who were treated by diet alone are considerably greater than those of the fenfluramine-treated group. There was no way in which these 2 groups could be matched since it was necessary for a loss of at least 7 kg to occur in any individual before a second estimate of total body fat was worth making. The subjects who lost this amount of weight were not representative of the initial group, at least as far as body weight is concerned. However, the proportion of fat was similar in both the men and the women in the 2 groups.

The lipid content of the tissue lost, estimated by the densitometric measurements (Table 5) was within the range of values derived for the lipid content of adipose tissue by the early work of Keys & Brozek (1953) and since verified by several investigators (e.g. Passmore, Strong & Ritchie, 1958 ; Johnson & Bernstein, 1955 ; Entenman, Goldwater, Ayres & Behnke, 1958). It seems likely, therefore, that the tissue lost was mostly adipose tissue.

There seem to be differences between the fenfluramine-treated and diet-treated groups in the proportion of fat in the tissue lost, although this only reached significance in women ($P<0{\cdot}05$). This suggests that fenfluramine may not act simply by causing a reduction in food intake.

TABLE 6. *The fat content of the tissue lost by 5 obese patients undergoing therapeutic starvation in hospital*

Body weight (kg)		Body fat content (%)		% fat in tissue lost
Initial	Final	Initial	Final	
94·1	87·7	49	50	30
94·8	88·1	37	37	42
94·1	88·3	48	48	45
81·3	70·6	49	48	45
99·3	84·4	59	58	55
			Mean	43%

These findings differ from our observations in patients undergoing severe dietary restriction or complete starvation. Table 6 shows measurements on 5 obese patients on complete starvation in hospital, where the lipid content of the tissue lost varied from 30 to 55% (mean 43%). This clearly signifies loss of considerable quantities of fat free tissue as well as of adipose tissue. This finding is comparable to that of Barnard (1969) whose 7 totally starved patients lost from their initial body weight an average quantity of 43·7 kg but of this amount, almost half was fat-free tissue. The relatively small amount of fat-free tissue lost by either dietary restriction or by treatment with fenfluramine might suggest that complete starvation should be used only in special circumstances.

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