FENFLURAMINE IN THE TREATMENT OF HYPERTENSIVE PATIENTS WITH REFRACTORY OBESITY

by

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INTRODUCTION

OBESITY frequently co-exists with hypertension (Epstein et al, 1965) and the combination carries a higher mortality than either obesity or hypertension alone (Kannell et al, 1967). Weight reduction per se may lower the blood pressure (Fletcher, 1954; Salzano et al, 1958) and is therefore an essential part of any therapeutic regime for obese hypertensives (Chiang et al 1967).

The majority of obese patients can lose weight satisfactorily by dieting, provided regular visits to a dietitian or physician for advice and encouragement are arranged. However some patients require additional help in adhering to a reduction diet and to this end appetite suppressant drugs are widely prescribed (Duncan and Munro, 1968). Appetite suppressants of the amphetamine type have central nervous system stimulating properties, and antagonise sympatholytic antihypertensive agents (Day and Rand, 1962). Fenfluramine is an appetite suppressant which is claimed to be devoid of central nervous system stimulating properties (Oswald et al 1968), and to lower the blood pressure in hypertensive patients, including those on sympatholytic anti-hypertensive agents (Waal-Manning and Simpson, 1969; Stiglich, 1970; Bolodeoku et al, 1972). The present study was designed to evaluate the effect of fenfluramine on the appetite, weight and blood pressure of hypertensive patients with obesity which had proved refractory to serious attempts at dieting.

PATIENTS AND METHODS

During a six-month period 450 patients attended the hypertension clinic of the Royal Victoria Hospital, Belfast. One hundred and fifty-four (34 per cent) were 11 per cent or more above their standard weight (Metropolitan Life Insurance Co., 1960). These patients were placed on a 1000 calorie diet and reviewed at the clinic four weekly for 12 weeks by the doctor and dietitian. After this period most patients had lost at least 2 kg. The 26 patients who had lost less than 2 kg were invited to take part in a double blind cross-over trial of fenfluramine versus a placebo. The nature of the trial was explained to each patient and his general practitioner. Twenty-three patients agreed to enter the study. None was diabetic but six had

clinically stable ischaemic heart disease. All had been overweight for many years and had tried unsuccessfully to lose weight on at least two occasions.

Each patient received the active tablets (fenfluramine 20 mg) and the identical placebo tablets for consecutive 12 week periods, the order being determined randomly. The tablets were prepacked in labelled boxes which were coded in such a way that the patient, the doctor and the dietitian did not know which was being administered first. The key to each patient's code was kept in the hospital notes. The master code was held by the hospital pharmacist. Patients were instructed to take one tablet 1½ hours before the mid-day meal and two tablets 1½ hours before the evening meal. The patients were told to continue to diet and were seen every four weeks by the same doctor and dietitian. The weight was recorded and the erect and supine blood pressures were measured.

Of the 23 patients entering the trial, 3 attended poorly from the outset. Four patients withdrew during the first half of the trial because of symptoms which they attributed to the tablets; 3 of these had been taking the placebo. Fifteen of the remaining 16 patients completed the trial. One patient who died during the second half of the trial while on the placebo was included in the analysis.

An analysis of variance technique was employed to isolate independently the main sources of variation in the response to treatment, defined as weight change (kg) in each four week period. The sources of variation investigated were treatment, order of treatment, period of treatment (1-4, 5-8 and 9-12 weeks) and patients. Data relating to alterations in weight, blood pressure and serum biochemistry and details of the statistical techniques employed are available in the form of an appendix which can be obtained, on request, from M.E.S.

During the trial, alterations in the dosage of hypotensive drugs were avoided where possible. The occurrence and degree of anorexia (desired effect) were elicited at each visit and the patients were asked if they had developed any undesired effects. Estimations of serum electrolytes and liver function tests were performed at the start and end of each 12 week period. At the end of the trial each patient was exhorted to continue on the reduction diet and to return for review 12 weeks later.

Results

The average age of the nine females and seven males participating in the trial was 52 years. Their initial weights ranged from 77.4 kg to 123.2 kg. Their mean weight was 90.2 kg, which was 36 per cent above their standard weight. All received cyclopenthiazide plus potassium chloride throughout the trial. Six were receiving guanethidine, three methyldopa and three more received both these drugs. Two received debrisoquin and one, hydrallazine. The eight patients receiving fenfluramine first showed a mean fall in weight of 2.39 kg in the first 4 weeks and 3.41 kg in the full 12 weeks on the drug.

However, over the next 12 weeks, while receiving the placebo, the patients gained weight again so that at the end of the trial period the mean weight loss was 0.49 kg.

The eight patients receiving the placebo first showed a mean weight loss of 0.55 kg in the first 4 weeks and of 0.72 kg in the full 12 weeks on the placebo. Both these values are significantly less than the corresponding fall shown by the patients

receiving fenfluramine first ($P<0.01$). On switching to fenfluramine there was a further mean fall in weight of 1.43 kg in the first four weeks but thereafter there was an insignificant mean gain so that after the full 12 weeks on fenfluramine the mean weight loss was 1.19 kg. Both fenfluramine and placebo were significantly more effective when given first ($P<0.01$). In addition to this order effect there was a significant period effect for both fenfluramine and placebo, with progressive diminution in effectiveness in the second and third four week periods on each treatment. The rate at which the effectiveness of fenfluramine diminished in successive periods was significantly greater than that for the placebo ($P<0.05$).

The dosage of hypotensives was altered in 4 of the 16 patients. The dosage was reduced during fenfluramine therapy in 3 and increased slightly in one. Two of the patients whose dosage was reduced while on fenfluramine had it increased again when switched to the placebo. The degree of postural fall in blood pressure noted before the trial did not differ during treatment with either fenfluramine or the placebo.

In the 13 patients whose hypotensives were unchanged or reduced during fenfluramine therapy the mean fall in recumbent pressure was 15 (± 7) mmHg systolic and 9 (± 3) mmHg diastolic. For those receiving the placebo the mean fall was 1 (± 5) mmHg systolic and 2 (± 3) mmHg diastolic. In the former case the fall is significantly different from zero for systolic blood pressure ($P<0.05$) and also for diastolic blood pressure ($P<0.05$), while in the latter it is not. The magnitude of the fall in pressure tended to be greater when fenfluramine was given before the placebo (20/12 mmHg) than when given after it (+4/-6 mmHg).

The three patients who had to have their dosage of hypotensives reduced showed a mean fall in pressure of 38/22 mmHg. One patient whose hypertension had proved resistant to therapy, only came under reasonable control while taking fenfluramine and control was lost again on changing to the placebo. All 6 patients showing falls in systolic blood pressure of more than 20 mmHg while taking fenfluramine, were amongst the 8 patients being treated with guanethidine and methyldopa, or guanethidine alone. No striking changes in blood pressure were observed in the 2 patients on debrisoquin nor in the single patient on hydrallazine.

Anorexia was reported by seven of the eight patients receiving fenfluramine first and also by seven of the eight patients receiving it second. In 10 of the 16 anorexia was sustained throughout most of the 12 weeks on the drug. Five of the eight patients receiving the placebo first reported anorexia compared with one out of seven receiving it second: in only three cases out of fifteen was it sustained.

Side effects were given as the reason for withdrawal from the trial by four patients who are therefore included in the analysis of side effects. Among nine patients receiving fenfluramine first, one left the trial because of severe diarrhoea which returned with each re-exposure to the drug, and five others experienced: –weakness (3), drowsiness (1) and mild diarrhoea (1). Of the 11 patients receiving the placebo first, three withdrew early in the trial, partly because of alleged weakness (1), dizziness (1) and diarrhoea (1), and partly because of the discouragement occasioned by their failure to lose weight. Two patients felt mildly depressed for a few days after switching from the active tablets to the placebo.

The serum sodium, potassium, chloride, carbon dioxide, specific gravity, urea and six measures of hepatic function were estimated in participating patients before and after fenfluramine therapy. Hotelling's T^2 test of the null hypothesis of no alteration in each of these measurements simultaneously yielded a non-significant result ($P<0.05$). Furthermore, no individual patient, including two who had initially mild elevation of their SGOT and SGPT levels, showed any clinically important change in hepatic or renal function.

Discussion

In the management of obesity the role of anorectic drugs, including those possessing additional glycolyptic activity is unclear. The fact that 83 per cent of our hypertensive patients lost more than 2 kg with diet and encouragement alone indicates that most obese patients do not need drug therapy, at least initially.

To merit prescription for obesity a drug should be effective in patients who have proved incapable of losing weight without drugs, should not rapidly lose its effectiveness and should not aggravate or interfere with the treatment of common co-existing conditions such as hypertension. It should also be free from unpleasant subjective and dangerous metabolic side effects and from the risk of abuse. In this study fenfluramine met some but not all of these criteria.

Fenfluramine did help our patients to lose weight. As in earlier studies (Traherne, 1965; Munro et al, 1966; Brodbin and O'Connor, 1967; Gaind, 1969; Stunkard et al 1973), fenfluramine performed significantly better than a placebo. This superiority was especially marked during the first four weeks of treatment. The progressive diminution in the rate of weight loss indicates that tolerance occurred (Stunkard et al 1973). The magnitude of the weight loss over the 12 weeks was disappointing, though other anorectic drugs studied under carefully controlled conditions have given similarly disappointing results (Stunkard et al 1973; Silverstone et al 1970; Follows, 1971). The fact that the patients' mean weight was as great 12 weeks after the end of the trial as at its commencement indicates that fenfluramine did not have the lasting beneficial effects found by Lambusier (1965) and Hähnel (1973).

Fenfluramine had a significant overall hypotensive effect on our patients. The mean fall was not marked and no patient became hypotensive. However, patients on hypotensive drugs, particularly guanethidine and methyldopa, should have their blood pressure checked regularly on being given fenfluramine and again on its withdrawal. Waal-Manning and Simpson (1969) found a similar hypotensive effect in patients on guanethidine and methyldopa and also those on reserpine. They suggested that these three hypotensive agents may partly counteract the anorectic effects of fenfluramine. In spite of the possibility of such an effect, our patients reported sustained anorexia more frequently with fenfluramine than with the placebo.

Side effects were commoner during consumption of fenfluramine than with the placebo, but as in most other studies they were relatively mild. In the only patient to withdraw because of a side effect (diarrhoea) while on fenfluramine, the reappearance of the same side effect on subsequent exposures indicated a true cause and effect relationship. In contrast the three patients who withdrew because of side effects which they attributed to the placebo and who would not sample it again,

may have been influenced as much by disappointment at not losing weight as by the severity of the side effects. The incidence of side effects in patients on fenfluramine was comparable to that found by Gaind (1969), Silverstone et al (1970) and Lawson et al (1970) but less than that found by other authors (Stunkard et al 1973; Hollingsworth and Amatruda 1969). The absence of any alteration in renal or hepatic function in our patients is reassuring, though more exhaustive evidence would be required before the safety of fenfluramine in patients with substantial impairment of renal or hepatic function could be established.

The mild depression noted by two patients at the time of switching from fenfluramine to placebo agrees with experimental observations made in the sleep laboratory (Oswald et al 1971). No episodes of serious depression were observed on withdrawal of fenfluramine but it would seem prudent to use fenfluramine cautiously in patients who have been depressed and to withdraw it gradually (Anderson 1972; Harding 1972).

We conclude that the administration of fenfluramine to hypertensives with intractable obesity is helpful in initiating weight loss. A course of treatment lasting not more than four weeks may help to convince such patients that weight loss is possible. However since tolerance develops rapidly prolonged treatment with fenfluramine does not appear to be indicated in their longterm management. In view of its relative freedom from side effects its hypotensive action merits further study in patients with mild hypertension.

Summary

A double blind cross-over trial of fenfluramine and placebo tablets, each given for 12 weeks, was performed on 23 hypertensive patients with refractory obesity. Weight loss with fenfluramine was significantly greater than with a placebo, especially in the first four week period, but the absolute weight loss was disappointing. A statistically significant order effect was noted in that both fenfluramine and placebo resulted in greater weight loss when given first. Twelve weeks after the trial the patients had returned to their original weight.

There was a significant fall in blood pressure with fenfluramine therapy but not the placebo. Fenfluramine therapy was associated with more anorexia and a slightly higher incidence of side effects than the placebo. It produced no alteration in renal or hepatic function.

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BOOK REVIEWS

THE EPILEPSIES. MODERN DIAGNOSIS AND TREATMENT. By J. M. Sutherland, H. Tait and M. J. Eadies. Second Edition. (Pp. 149, figures 30. £2.50 (soft back)). Edinburgh and London. Churchill Livingstone .1974.

EPILEPSY is a common symptom and about 6–8 persons per 1000 of the population suffer from some form of this distressing disorder. Few doctors are likely to escape the responsibility of management of patients suffering from epilepsy. This is an up-to-date sensible and practical guide to the subject for senior medical students, postgraduates and practitioners. The tables and summaries at the end of each chapter should be particularly useful for examination candidates. The illustrations are clear and numerous and the text easy to read.

The chapter on anticonvulsant drug therapy is outstanding and the authors emphasise the value of estimating the plasma levels of hydantoins and barbiturates in the management of patients.

Strongly recommended and good value for money!

J.H.D.M.