DIETHYLPROPION IN THE TREATMENT OF OBESITY

A cross-over trial of a long-acting preparation

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DIETHYLPROPION ("Tenuate") has been shown to be useful in the treatment of refractory obesity (Seaton *et al.*, 1961). Appetite suppression with the standard preparation is reported to last about four hours (Spielman, 1959) and the drug must be taken at least three times daily. This paper reports the use of a long-acting preparation of the drug, which need be taken only once a day. It is marketed as "Tenuate Dospan" in which the active principle is incorporated with a hydrophilic colloid, which expands in the intestine and allows a continuous release of the drug. The advantage claimed, in addition to the virtual absence of undesirable central nervous stimulation (Wilson and Long, 1960; Nash, 1960), is that the sustained release tablet will provide hunger control for a full twelve hours.

Diethylpropion (α—diethylaminopropionophenone) is closely related structurally to amphetamine (B—aminopropylbenzene).

METHODS.

A double-blind cross-over technique was used. Patients with obesity who had been referred on this account to the general medical or metabolic departments of the Royal Victoria Hospital were considered for admission to the trial. Those with serious associated disease were excluded, and the remainder were asked if they wished to attend a special monthly clinic to help them lose weight. They were offered the attraction of a number of new drugs which might help in the treatment of their obesity.

They were fully examined at their first visit and a detailed family and dietary history elicited. They were weighed in normal indoor clothes, without shoes, by the same nurse on the same scales at each visit. (The scales are checked monthly for accuracy.) All patients were interviewed by the dietician attached to the Metabolic Clinic, and were given a standard 1100 calorie reduction diet containing 100 G. of carbohydrate, or told to continue their existing regime if they were already intended to consume less than 1100 calories on a recognised schedule. The discussion of methods of weight reduction was limited to encouragement to keep to the diet. The tablets were presented as an aid to weight loss, with no mention of their method of action, or possible side effects. The patients were not told that this was a double blind trial.

Those taking part in the trial were divided into two groups ("A" and "B") at their first visit, according to a sequence constructed from a table of random

numbers. Bottles, with detachable identification tags were available, containing four weeks' supply of either diethylpropion tablets (75 mg.), or an identically presented placebo. Each group commenced with one type of tablet, and after four weeks the distribution was reversed. Patients were instructed to take one tablet each morning before breakfast.

They were reviewed by one of us after four and eight weeks. No direct enquiries were made about the patients' subjective impressions of the drug or possible side effects. Only spontaneous complaints were noted. Neither the patients, the doctors, the dietitians nor the nursing staff knew which tablets contained the active preparation. A sealed envelope containing the manufacturer's key to the identification tags was opened when the trial was completed. It was then found that Group "A" had received the diethylpropion in the first month, and the placebo second; Group "B" had received the tablets in the opposite order.

TABLE 1.

STATISTICAL DATA CONCERNING THE TWO GROUPS.
Values are means, standard deviations and ranges.

	GROUP A 11 patients	GROUP B 11 patients	DIFFERENCE OF THE MEANS. Standard deviation	t	Level of significance
Age (years) - -	40 ±12.6 (17-59)	36 ±16.3 (13-56)	14.35	0.28	0.8>P>0.7
Height (inches) -	63 ± 3.4 (59-68)	63 ± 3.0 (59-70)	1.45	0.11	P>0.9
Initial weight (lb.) -	223 ±32.8 (167-272)	206 ±28.8 (160-239)	26.50	0.65	0.6>P>0.5
Standard weight (lb.)	144 ±14.2 (121-165)	144 ±19.5 (104-182)	7.30	0.05	P>0.9
Per cent. overweight	54.8±14.5 (23-72)	43.6±22.2 (22-84)	8.36	1.36	0.2>P>0.1

THE PATIENTS.

Twenty-two patients completed the trial out of thirty-eight who were initially accepted.

A comparison of the two groups of patients "A" and "B" who completed the two months' treatment is shown in Table 1. The groups, having been selected at random, are comparable as regards age and height, and hence also standard weight, which is derived from these (Tables of the Life Extension Institute of New York). The mean percentage by which the patients in Group "A" exceed their standard weight is not significantly greater than that of Group "B" and neither are the slight differences in mean initial weight and height.

Nine in each group had a history of obesity exceeding ten years' duration: six in Group "A" and five in Group "B" had made a previous attempt at dieting. There was one male in each group, and seven of the women in each group were married. The mothers in Group "A" had a total of thirty children, and those in Group "B" twenty-two children. Only two patients out of the whole series spontaneously complained of hunger as a possible cause of their obesity.

There were six cases of maturity onset diabetes mellitus, already controlled by restriction of carbohydrate. Six patients had angina of effort but in only three was ischæmia apparent on the electrocardiogram, and none showed evidence of fluid retention. One patient had been treated for several years with thyroid extract for mild hypothydroidism (confirmed by radio-iodine studies) but was euthyroid prior to and during the trial. One showed clinical and biochemical features of mild adrenal virilism.

TABLE 2.

RESULTS OF CROSS-OVER TRIAL OF DIETHYLPROPION.

NUMBER OF PATIENTS	MEAN WEIGHT LOSS IN LB.		
GROUP A 11	1st month diethylpropion 9.99	2nd month placebo 0.99	2 months combined 10.98
GROUP B 11	1st month placebo 2.54	2nd month diethylpropion 2.0	2 months combined 4.54

RESULTS.

These are recorded in Table 2. The best results were achieved in those who were treated first with diethylpropion, and these patients lost almost 10 lb. on average in this month. The mean loss in one month on diethylpropion for the whole series of twenty-two patients was almost 6 lb., which is significantly greater than the mean loss on the placebo, which was 1.75 lb. ($0.02>P>0.01$). As the drug was given under a "double blind" technique, this proves the effectiveness of the long-acting preparation of diethylpropion in the treatment of obesity. The "crossover" design allows assessment of the effect of the order of treatment. When diethylpropion was given first, the weight loss in the first month was significantly greater than the subsequent loss on the placebo ($P<0.001$). When placebo was given first, the weight loss in the two periods was not significantly different ($0.7>P>0.6$). Thus, the drug was no more effective than the placebo when given in the second month.

The total weight loss in Group "A" after two months' treatment was not significantly different from that in Group "B" ($0.2>P>0.1$). The greatest individual weight loss during the two months was 40 lb., and one patient gained 9 lb. in spite of the treatment. There was no correlation between loss of weight and age, sex, height, initial weight or the amount by which the standard weight was exceeded. The patients placed little emphasis on the effects of the tablets on their appetite but eight volunteered that they felt less hungry while taking the diethylpropion. Two stated that appetite was reduced equally by the two agents; two others claimed that the placebo was more effective.

Side Effects.

These were not enquired after directly, and only spontaneous statements by the patients of their own observations were noted. Only three of the total series made any reference to alteration in their sleeping habits. One stated that there was a very slight interference with sleep; the other two claimed increased somnolence, all during the period on diethylpropion. Four patients mentioned dryness of the mouth, accompanied by a salty taste but this was in no way troublesome. There were no complaints of restlessness or headache. There was no evidence of the development of schizophrenic symptoms or addiction to the tablets. None of the group, including those known to have mild coronary artery disease, experienced angina pectoris while on the trial. Treatment did not have to be stopped in any case.

Discussion.

It is generally accepted that physiological weight loss can only be achieved following a negative calorie balance. Most patients who are already obese are unable to keep to a strict calorie limitation unaided. To encourage them to lose weight high fat or high protein diets, bulking agents and tranquillizers with or without psychotherapy have all been advocated, and shown to have some benefit. Appetite suppression, which was discovered as a side-effect of the amphetamine group of drugs, is a logical adjunct provided that the primary stimulant effect of these substances on the central nervous system is not troublesome. Previous reports and experience in the present trial have shown no evidence of such stimulation with diethylpropion.

During the course of treatment there was no evidence of the development of psychotic behaviour. The amphetamine-group of drugs are probably all equally liable to cause this if abused. Addiction and schizophrenia are well recognised following amphetamine (Connell, 1958; McConnell and McIlwaine, 1961) and a similar picture has been reported with phenmetrazine. There are, as yet, no reports of addiction or psychosis due to diethylpropion or any of the newer derivatives.

The mean weight loss in this series (5.99 lb.) is considerably greater than that reported by Seaton *et al.*, 1961 (2.58 lb.) after one month on diethylpropion. We consider our group more representative of obesity in general, as only about half would fall within their definition of "refractory" obesity (failure to respond to dietary instructions during the previous year). The results in the first month (9.99 lb.) are also superior to those reported by Briggs *et al.* (1961) in a more comparable group, taking phenmetrazine hydrochloride (6.5 lb.). Stevens (1961) reports a trial of a long-acting preparation of diethylpropion 60 mg. daily, which gave an average weight loss on the active tablet of 1.9 lb. in one month. He suggests that the dose should be slightly higher and the considerably better results in our own series confirm the effectiveness of 75 mg. daily. We would not advise further increase in dosage, as this may increase the liability to side effects.

Diethylpropion in long acting form was considerably less effective when given following a month on placebo. Jaffe (1961), in a trial in general practice, found

that weight loss during the first two months of a six-months period was greater than subsequently and this aspect is also well illustrated by the results of Seaton *et al.* (1961), where very little weight was lost after the first month. It would seem wisest to recommend the use of anoretic drugs of this type in intermittent courses of a few weeks' duration.

One aspect of the treatment of simple obesity is the extremely high incidence of defaulters (sixteen out of thirty-eight in the present series). This makes a large series difficult to accumulate, and is probably a further example of the general mental attitude of many who allow themselves to become overweight.

The price of one month's treatment with "Tenuate Dospan" is 11s. 2d.

Summary.

A double-blind cross-over trial of diethylpropion (in a long-acting preparation) in the treatment of simple obesity in conjunction with a low calorie diet, is described.

The drug in this form is effective and without side effects.

Diethylpropion caused the greatest weight loss when it was given at the commencement of the trial. It was considerably less effective when administered after a month's treatment with a placebo. For this reason it is recommended that its clinical use should be restricted to short intermittent courses.

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References.

Briggs, J. H., Newland, P. M., and Bishop, P. M. F. (1960). *Brit. med. J.*, **2**, 911.
Connell, P. H. (1958). *Maudsley Monograph* No. 5, London.
Jaffe, G. V. (1961). *Med. Press*, **245**, 41.
McConnell, W. B., and McIlwaine, R. J. (1961). *Ulster med. J.*, **30**, 31.
Nash, J. (1961). *J. Irish med. Ass.*, **48**, 15.
Seaton, D. A., Duncan, L. J. P., Rose, K., and Scott, A. M. (1961). *Brit. med. J.*, **1**, 1009.
Spielman, A. D. (1959). *Michigan Acad. of General Practice Symposium.*
Stevens, A. E. (1961). *Brit. med. J.*, **2**, 312.
Wilson, R., and Long, C. (1960). *J. Irish med. Ass.*, **46**, 86.