Original Article

A RANDOMIZED COMPARISON OF THE EFFECT OF TWO DIURETICS, A CONVERTING ENZYME INHIBITOR, AND A SYMPATHOMIMETIC AMINE ON WEIGHT LOSS IN DIET-REFRACTORY PATIENTS

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ABSTRACT

We hypothesized that women refractory to dietary weight loss may have a type of idiopathic edema. In a study of 200 women, we compared four drugs, used previously for treating idiopathic edema, to determine their efficacy in causing weight reduction. After 6 months of treatment, the percentage of treated groups losing at least 10% of baseline weight was 6% for hydrochlorothiazide, 8% for spironolactone, 68% for dextroamphetamine sulfate, and 4% for captopril. The percentage losing >20% and >30% of baseline weight in the same treatment groups was 28% and 10% for dextroamphetamine therapy but 0% for the other three groups. Of the women who failed to lose weight with one of the nonamphetamine therapies during the first 6 months, 132 were then treated with dextroamphetamine; 68% lost ≥10% of their baseline weight, and 30% and 7% of patients lost ≥20% and ≥30%, respectively. With use of the classic definition of idiopathic orthostatic edema (urinary output of <55% of ingested water load in 4 hours), only 58 of the 200 study patients had this diagnosis; however, 144 patients excreted <75% of the load. Comparison of the efficacy of amphetamine therapy in patients with <75% versus ≥75% urinary excretion showed 120 of 131 (92%) lost ≥10% in the former category versus only 4 of 51 (8%) in the latter. Of the 58 patients who excreted <55% of the water load, 52 (90%) lost ≥10% of baseline weight with amphetamine therapy. The patients noted no effects of therapy on dietary consumption. The responsiveness of the patients to amphetamine therapy during the second 6-month period despite failing to lose weight with the three other therapies suggests that no inadvertent bias was present in the randomization process. Thus, the results suggest that some women who are recalcitrant to dietary weight loss may have a mild type of water retention that is refractory to diuretics but responsive to amphetamines. **(Endocr Pract. 1995; 1:322-326)**

INTRODUCTION

Clinicians are frequently consulted by patients (primarily women) who complain that they are unable to lose weight despite dieting. Subsequently, assessment for hypothyroidism, Cushing's syndrome, or diabetes excludes these metabolic diagnoses in most cases. Of course, one explanation could be that such patients are not truthful about their consumption of calories. The fact that these patients seek help from an endocrinologist and not a diet center, however, helps minimize the number of patients who inaccurately describe their caloric consumption. Edema could also explain the weight gain, but except in rare cases, hepatic, renal, cardiac, or lymphatic causes cannot be found.

Idiopathic orthostatic edema is a condition associated with retention of fluid that could lead to weight gain (1-7). The diagnosis of this rare disorder is confirmed by demonstrating an abnormal retention of fluid in the erect position after a water loading challenge (8).

We designed a study to determine whether patients who failed to lose weight despite appropriate dieting might actually have a problem of fluid retention similar to idiopathic edema. Furthermore, the study would randomly compare the efficacy in causing weight loss with four therapies that have been claimed to be effective for idiopathic edema — hydrochlorothiazide (7,9), spironolactone (10), dextroamphetamine sulfate (11), and captopril (12,13).

MATERIAL AND METHODS

Inclusion Criteria

Only patients who complained of the inability to lose weight despite dieting were included in the study. Each patient registered was asked to continue with a usual pattern of eating for the next 2 weeks and to keep a careful log of foods ingested. The number of calories consumed was then evaluated. Patients were included in the study only if the total number of calories consumed in 2 weeks was at least 10% lower than the number obtained as follows: 14 x [1,000 + 100 a + 0.33 (1,000 + 100 a)], in which a = number of inches of height above 60. This number was thought to be a fair estimate of the amount of calories that should be consumed daily by each woman. The formula was based on the assumption that all patients were of medium build and had equivalent levels of exercise. This calculation assumes that a woman with a 60-inch (152.5-cm) medium frame needs 1,000 calories to maintain a basal state and that this basal requirement increases by100 calories per inch (2.5 cm). Another assumption was that an additional third of the basal calories would be consumed by daily activity. Obviously, thinner or heavier builds and more or less exercise would alter the results; thus, some patients included still might not have been dieting adequately. Nevertheless, any patients with inadequate dieting should have been equally randomized to the four treatment

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Table 1
Number of Patients Losing Weight During First 6 Months of Study, Stratified by Type of Treatment

% of baseline weight lost	HCT*		Spironolactone		Dextroamphetamine		Captopril	
	No.	%	No.	%	No.	%	No.	%
≤10†	47	94	46	92	16	32	48	96
>10	3	6	4	8	34	68	2	4
>15	1	2	1	2	26	52	0	...
>20	0	...	0	...	14	28	0	...
>25	0	...	0	...	10	20	0	...
>30	0	...	0	...	5	10	0	...

*HCT = hydrochlorothiazide.
† Proportion of patients losing at least 10% of weight on dextroamphetamine therapy versus other treatments was significantly different ($P<0.001$; χ^2).

groups. Better formulas may well exist for calculating calories consumed.

The objective was to recruit 200 patients for the study; to accomplish this goal, we interviewed 277 patients. Most of the 77 women excluded from the investigation had underestimated the number of calories ingested. A small number were excluded because of endocrine and medical abnormalities (four patients with hypothyroidism and one patient with proteinuria). Otherwise, no patients had abnormalities of their serum thyroxine, triiodothyronine uptake, or thyroid-stimulating hormone (thyrotropin); 24-hour urine specimen for free cortisol; serum fasting glucose, electrolytes, or liver function tests; or urinalysis. Twelve patients declined to participate in the study, and 11 were excluded because of side effects to the drugs during the first 2 weeks.

Water Load Test

Water load tests were performed in all patients. The patient drank 1,500 mL of water during a 30-minute period, urinated and recorded the volume, and then measured the urinary output for 4 hours (on the first day, supine for 4 hours; on the next day, erect for 4 hours after the same instructions had been followed). Although the treating physicians were aware of the water load test results, the data should not have been biased because assignment to treatment groups was randomized, with no relationship to water load tests.

Treatment Groups

The patients were randomized, on the basis of their social security number, to one of four treatment groups: (1) if the last two digits were even — hydrochlorothiazide, 50 mg/day; (2) if the last two digits were odd — spironolactone, 200 mg/day in divided doses; (3) if the last two digits were odd — dextroamphetamine sulfate, 10-mg Spansule twice daily; and (4) if the last two digits were even — captopril, 25 mg two times daily. After 50 patients had been enlisted in a group, that group was closed. State law allowed dispensing of only 50 capsules of dextroamphetamine per prescription. Therefore, prescriptions were rewritten at 7-week intervals; accordingly, some control was exercised over patients taking too few or too many capsules. At 7-week intervals, all patients were also weighed and examined.

Each therapy was evaluated after 6 months by comparing each patient's baseline morning weight immediately before treatment with the morning weight after treatment. If a patient dropped out of the study because of side effects or other reasons, the very next patient appropriate for the study would be substituted, regardless of social security number.

Patients were advised to eat 10% less than the mean number of previously calculated daily calories consumed. For 1 day each week, with the day progressing by one each sequential week (for example, Sunday during the first week, Monday during the next week, and so forth), patients were to calculate their total calories consumed.

After 6 months, those patients who had not lost a reasonable amount of weight were to be offered the treatment with the best results (of the four options) during the first 6 months. These patients also were required to log their total calories ingested for 1 day each week.

RESULTS

The patients had a dramatic response to dextroamphetamine but not to any other therapy (Table 1). Of the patients who were given dextroamphetamine, 68% lost at least 10% of baseline weight, in comparison with only 6% of those who received other therapies ($P<0.001$; χ^2 test). The mean age, weight, and height of patients in the four treatment groups are shown in Table 2.

The 150 women from the groups treated with nonamphetamine drugs were then offered dextroamphetamine therapy for the next 6 months. A total of 132 patients agreed to participate. The results showed that 90 patients (68%) lost at least 10% of their initial baseline weight, 59 (45%) lost more than 15%, 40 (30%) lost at least 20%, 19 (14%) lost at least 25%, and 9 (7%) lost at least 30%.

Table 3 shows the response of the 182 patients treated with amphetamine, based on whether their orthostatic water retention during their water load testing was less than 55%, 55 to 74%, or 75% or greater. The best results (number of patients who lost weight and the amount of weight lost) occurred in the patients who retained the most fluid in the erect position.

In the classic definition of idiopathic edema, the patient must retain at least 55% of the ingested water load

Table 2
Comparison of Age, Weight, and Height of Study Patients in Four Treatment Groups*

Factor	HCT†	Spironolactone	Dextroamphetamine	Captopril
Age (yr)	37.1 ± 8.3	35.6 ± 8.9	35.8 ± 9.6	36.5 ± 8.1
Weight (lb)	160.1 ± 19.8	157.0 ± 21.2	163.1 ± 21.6	159.4 ± 20.6
Height (in)	63.4 ± 1.9	62.8 ± 1.7	63.9 ± 2.1	63.5 ± 2.3

*Data are presented as mean values ± SD. No significant differences were noted between groups (analysis of variance).
†HCT = hydrochlorothiazide.

in 4 hours. With use of this definition, 58 of the 200 women (29%) in the study fulfilled this criterion for idiopathic orthostatic edema. Of these patients, 52 lost at least 10% of their baseline weight, 2 failed to lose sufficient weight, and 4 were in the group of 18 who refused dextroamphetamine therapy.

Normal persons excrete 75% or more of an ingested water load in 4 hours in both the supine and the erect position. Therefore, the response to amphetamine was correlated with excretion of less than 75% of the water load in the erect position. On this basis, 144 patients (72%) had abnormal orthostatic water retention, including 120 amphetamine responders, 11 nonresponders, and 13 from the group of 18 who refused amphetamine therapy. Thus, only 58 of the 182 women (32%) treated with dextroamphetamine failed to lose weight, and 47 of these failures (81%) were in the group with 75% or greater excretion of the water load (Table 3). In contrast, only 11 of 131 women (8%) failed to lose at least 10% of their initial weight when the water load excretion was less than 75%.

The numbers of patients (by treatment group) in the first 6-month study who were calculated to have consumed less than 90% of the mean calories needed for weight maintenance were as follows: hydrochlorothiazide, 6; spironolactone, 12; dextroamphetamine, 9; and captopril, 7. Of the 132 women treated with dextroamphetamine only during the second 6-month study, 26 ingested less than 90% of their mean calculated needed calories, but 19 also ingested an insufficient number of calories during nonamphetamine therapy in the first 6 months of the study.

Table 3
Response to Amphetamine Therapy Correlated With Water Load Test Results in 182 Women*

	Water load results in erect position†		
Wt loss (%)	<55%	55-74%	≥75%
10	52	68	4
15	39	45	1
20	29	25	0
25	19	10	0
30	9	5	0
<10‡	2	9	47

*Wt = weight.
†Data are presented as number of patients.
‡$P<0.05$ when weight loss of <75% was compared with ≥75%.

DISCUSSION

The cause of the inability to lose weight in a group of women who seemed to be dieting appropriately was hypothesized to be fluid retention. We conducted a comparison study with a standard diuretic (hydrochlorothiazide) and three other therapies that have demonstrated efficacy in the treatment of idiopathic orthostatic edema (spironolactone, dextroamphetamine, and captopril). A placebo control was not possible because these highly motivated patients were seeking help and would not have agreed to use of a placebo; however, a genuine attempt was made to be equally encouraging about all four therapeutic options.

The best response occurred in the patients taking amphetamine; although this drug is known to be an appetite suppressor, the mechanism of action in these cases did not seem to be caloric restriction. A possible explanation for failure to respond to diuretic therapies may be that fluid is lost proximally; thus, the water load may be inadequate at the site of action of diuretics. In contrast, amphetamines may minimize proximal water loss by decreasing capillary permeability through the sympathetic nervous system (4).

Only 29% of these patients seemed to have classic idiopathic orthostatic edema. By relaxing the degree of water retention to at least 26% instead of 46%, however, the majority of these patients (72%) demonstrated orthostatic fluid retention. Whether the patients in the group who excrete more than 55%, but less than 75%, of the ingested water load have a milder variant of idiopathic orthostatic edema remains to be proved. Nevertheless, this modified water load test can predict those patients likely to lose weight with amphetamine therapy. Close questioning of the patients revealed many signs and symptoms similar to those attributable to idiopathic edema—for example, pedal edema and abdominal distention by the end of the day, nocturia, and decreased urination when standing.

In contrast to its effect on appetite suppression (wherein development of tolerance to the drug necessitates constant increments in dosage), tolerance to amphetamine does not seem to occur when it is used to treat fluid retention. At the dosage used in the current study, side effects were minor—paranoia in five patients, depression in three, palpitations in two, and insomnia in one—and only a few patients were unable to continue therapy because of adverse effects.

Unfortunately, amphetamines at higher doses may be addictive and have the potential for abuse. Therefore, many governmental agencies have limited the use of amphetamines. We hope that studies such as ours will encourage research efforts to identify a drug possibly

having its action on capillary permeability but without the potential problems of amphetamines. Until such a drug is found, if amphetamines are to be used for recalcitrant overweight problems, we support governmental regulation of these drugs, and we emphasize that our data support that the patients most likely to respond are those who are already dieting appropriately and apparently have some degree of orthostatic fluid retention. In such patients, all other medical reasons for decreased ability to excrete a free water load must be excluded by appropriate clinical and laboratory studies.

The response to amphetamines without restriction of calories does not prove that the mechanism of action was inhibition of fluid retention. Another metabolic effect may have been responsible. For example, even if the use of dextroamphetamine did not reduce the caloric intake apparent to the patient, it may have done so more subtly or perhaps at least decreased the carbohydrate intake. The failure to respond to hydrochlorothiazide is more supportive than nonsupportive of the fluid retention hypothesis because the classic idiopathic orthostatic edema responds to amphetamines but not to standard diuretics. As further support for orthostatic fluid retention as the cause of the overweight problem in the current study group, 29% of the patients had severe orthostatic water retention and 72% had a mild variant—in comparison with a group of 50 women (unpublished data) who had infertility and no problem with weight control, among whom none had more than 45% fluid retention and only 12% had more than 25% orthostatic water retention.

Further insight and documentation of the mechanism of weight loss by dextroamphetamine therapy might be determined in future studies by measuring total body water by impedance or lean body mass by underwater weighing. Perhaps an improved control group may be obese women who lose weight easily—that is, determine their water load test results and their relative weight loss to the various therapies. Nevertheless, other causes of recalcitrance to dietary weight loss exist besides idiopathic edema, and amphetamines may cause weight loss by some other mechanism. The current study needs to be corroborated by other researchers, and it could also be improved by measuring lean body mass and ensuring patient compliance with taking the medications.

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