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Effect of Treatment with Dextroamphetamine Sulfate on Weight Loss Up To 5 Years in Women Unable to Lose Weight by Dieting and Its Efficacy on Some Other Unusual Manifestations of The Increased Cellular Permeability Syndrome

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ABSTRACT

Purpose: *To evaluate the efficacy of treatment with dextroamphetamine sulfate of refractory weight loss by dieting related to fluid retention secondary to the increased cellular permeability syndrome over a 5-year period.*

Methods: *Women were excluded for pathological causes of fluid retention, e.g., hypothyroidism, Cushing's syndrome, heart failure, or renal or hepatic disease. Dextroamphetamine sulfate was initiated at 15mg extended-release capsules with the option of increasing the dosage as necessary up to a maximum of 60mg a day.*

Results: *Forty-four percent of the women lost at least 10% of their initial body weight in 6 months and 42% still lost at least 10% by 5 years. For the first 4 years there were about 15% who lost about 15% of their initial body weight. At 5 years only 7% failed to have any weight reduction compared to their initial weight.*

Conclusion: *The amphetamines seemed to cause weight reduction by diminishing fluid retention rather than causing caloric reduction.*

Keywords

Refractory weight loss, Edema, Sympathomimetic amine, Increased cellular permeability syndrome.

Introduction

The three most common manifestations of the increased cellular permeability syndrome are pelvic pain, chronic fatigue syndrome, and inability to lose weight by dieting [1].

One cause of inability to lose weight despite dieting can be fluid retention. An extra quart of water weighs 2.2 pounds. Inability to adequately excrete a free water load may be found in heart failure, liver failure, and nephrosis. Hypothyroidism can cause weight gain related to fluid retention rather than hypometabolism. Thyroid hormone is a sympathomimetic amine.

When known causes of water retention, as mentioned above are excluded, the etiology is considered idiopathic. In fact, George Thorn, M.D., the head of endocrinology at Harvard Medical School in 1968, coined the term "idiopathic edema" [2]. Since many of these patients seemed to suffer from depression, Dr. Thorn considered this "idiopathic edema" condition as a possible psychosomatic condition. Credence to this theory was supported by improvement of the edema following anti-depressant therapy, which in those days, was amphetamines, especially dextroamphetamine sulfate [2,3].

However, an alternative hypothesis considered that the mechanism of action for dextroamphetamine sulfate helping edema was that the benefit was not on the psyche by lifting depression, but rather by correction of a capillary permeability defect. This

alternative hypothesis considered that dextroamphetamine sulfate predominantly acts to release dopamine from sympathetic nerve fibers and that dopamine acts to diminish cellular permeability thus correcting leakage of intravascular fluid into extravascular space [1].

We have a reproductive and medical endocrinology practice. Part of our basic science research involves looking at mechanisms of embryo implantation. A recent publication presents a model based on the accumulation of our research that not only leads to efficacious treatment correcting infertility and miscarriage issues, but also leads to unique therapies that are able to markedly ameliorate suffering from a large variety of medical conditions that had been refractory to standard therapy [4]. One of the reasons why patients (especially women, but not limited to them) consult with us is to see if they may have a medical condition to explain why despite dieting, or at least seemingly eating appropriately, they keep gaining weight.

We considered after evaluating their dietary habits (and assuming they were telling the truth) that fluid retention could explain the weight gain. Though sometimes edema was apparent, sometimes they only had premenstrual edema. Frequently they had no definite evidence of edema. The majority did not flunk the water load test as proposed by George Thorn [2].

The theory we proposed was that to allow uterine remodeling which would allow the conversion of some of the thick-walled uterine arteries to thin-walled spiral arteries which would allow nutrient exchange between mother and fetus, the body would block dopamine by progesterone and thus increase a cellular immunity to "attack" the cell walls of the uterine arteries [4]. The predominant cell involved in this autoimmune reaction would be the natural killer (NK) cell [4-6]. The model proposed that dopamine acts to diminish cellular permeability. To reiterate, progesterone was proposed to block dopamine and thus allow irritants to infuse into the pelvic tissues and endometrium leading to a brisk cellular immune response.

Increased tissue permeability could lead to irritants leaking into tissues but also allowing substances to leak out. Thus, we formulated a hypothetical model of edema and weight gain in the absence of heart, liver, or kidney failure, or hypothyroidism, or hypercortisolism (the latter two conditions were those entities for which patients sought our opinion on their weight issues or hyperinsulinism). The model proposed that sitting and standing is not the usual normal in the animal kingdom where walking parallel to the earth is most common. This abnormal posturing would thus cause an increase in hydrostatic pressure, which, in turn, would generate a state where intravascular fluid would leak out into the extravascular space. A decrease in intravascular volume could then lead to inadequate perfusion of blood to essential organs as the heart, brain and kidney leading to serious life-threatening consequences. Thus, the human species would have to develop an adaptation to allow for standing, and even sitting. The model proposes that the change in position triggers the sympathetic nervous system to release dopamine at the capillary level. The increased dopamine would then diminish capillary cellular permeability, thus maintaining an adequate intravascular volume.

The model proposes that when there is a mild inadequate release of dopamine, the intravascular volume can be replenished by triggering an increased response of the renin-angiotensin aldosterone system, thus preventing syncope or other more serious events, e.g., myocardial infarction, but with the milder consequence of edema (which may not always be obvious) and subsequent weight gain.

Many of these patients had been treated with standard diuretics, whose main target in the nephron was the ascending limb of Henle, and yet did not respond very well. This suggested that the main area of capillary leaks could be the proximal tubule. The possibility existed that the edema could be caused by an over exuberant response of the renin-angiotensin aldosterone system and thus drugs, e.g., spironolactone that block secondary hyperaldosteronism could prove effective in treating refractory weight gain possibly related to chronic edema. Similarly converting enzyme inhibitors, e.g., captopril, could prove effective in correcting the edema.

Evaluating weight loss in a 6-month period, dextroamphetamine was far more effective than 3 other potential therapies for chronic edema: hydrochlorothiazide, spironolactone, and captopril [7]. In fact, during the second six-month trial, a high percentage of the failures with the other 3 agents lost weight when given dextroamphetamine sulfate, thus showing no inadvertent bias of patient selection [7].

Many times, various diets or treatments result in initial weight loss only to be followed, subsequently, with not only return to the original weight, but to even exceed that level. The objective of this study was to evaluate the effect of dextroamphetamine sulfate on weight loss over a 5-year period of time.

Materials and Methods

A retrospective review over a five-year time period was performed on women looking for an endocrine cause of the inability to lose weight despite dieting. After history and physical examination, those women were excluded for cardiac, hepatic, renal, adrenal and thyroid etiologies for fluid retention. They were started on dextroamphetamine sulfate (either exclusively or as part of amphetamine salts). Women with morbid obesity, defined as greater than twice their ideal body weight, were excluded.

The percentage lost (or not) of their baseline body weight was then recorded up to 5 years. Thus, they had to begin therapy 5 years or more before the designated time to evaluate data.

The dosage of dextroamphetamine sulfate started at 15mg extended-release capsules. The dosage could be increased to 60mg based on response and side effects. When amphetamine salts were used 30mg was counted as 18.8mg of dextroamphetamine sulfate.

Results

There were 45 study patients. At 6 months, 42 patients lost at least 1% of their initial weight (Table 1). The three women who did not lose weight decided to remain on treatment because they had been steadily gaining weight, and at least they did not gain any weight during the first 6 months of therapy.

Table 1: Weight loss after various length of time of taking 15-60mg of dextroamphetamine sulfate.

Percentage of initial weight loss	½ year	1 year	2 years	3 years	4 years	5 years
30-39%	0%	0%	2%	0%	0%	2%
20-29%	0%	15.5%	15%	15%	13%	6%
10-19%	44.4%	51.0%	31%	46%	43%	34%
5-9%	31.1%	15.6%	28%	26%	18.9%	20%
1-4%	17.7%	13.3%	13.0%	8%	10%	13%
0%	6.6%	3%	2.2%	2.2%	8.1%	6.9%
stopped coming	1.5%	7.6%	8.8%	3%	7%	18%

Weight reduction compared to initial weight percentages of 45 treated patients. The percentages at end of year represent the percentages of patients losing various percentages of their initial weight.

Weight loss, as percentage of initial weight, from 6 months to 5 years is seen in Table 1. Some patients stopped coming because either their insurance did not cover the drug, or there were mild side effects, or a different physician took over their management.

For those not losing weight who continued taking the medication, none gained more than 4% of their initial weight in the 5 years. Thus 44% lost at least 10% of their initial body weight in 6 months.

There were still 42% losing at least 10% of their body weight at 5 years. This percentage could be lower if the reason for dropping out was failure to lose weight. However, we ascertained that the main reason for the higher drop out rate from year 4-5 was the patient stopping medication because their insurance no longer covered the extended-release capsules. Most were switched to immediate release tablets, but they were eliminated from the study. Nevertheless, the tablets also proved effective (unrecorded data). The second most common reason for drop out is that some patients come from large distances, and a geographically closer physician became willing to treat their condition. The median dosage of dextroamphetamine sulfate was 30mg extended-release capsules.

Discussion

The permeability defect proposed in the mechanism of idiopathic chronic edema and weight gain considers fluid leaking out of capillaries into extravascular tissue is the cause of the weight gain. Actually, the first published case report from our group using dextroamphetamine sulfate for a permeability disorder with substances "leaking out" was a woman with extremely severe urticaria of many years failing to respond to antihistamines and glucocorticoids, but who showed complete quick remission after starting dextroamphetamine sulfate [8]. Her main reason for the consult was for the urticaria, hoping to find an endocrine cause of this life altering serious malady. Since she also had unexplained weight gain, we reasoned that her permeability defect could extend to the vesicles containing histamines. Interestingly, this patient never missed one day of dextroamphetamine sulfate and for 25 years never had one urticarial lesion. She lost a month's worth of her medication, and since it is a class II drug, her prescription could not be filled for a month. Within three days she was covered in hives and they disappeared quickly when the amphetamine was restarted. She has not had a hive for 10 years since restarting.

Every case we have treated for chronic urticaria has responded to dextroamphetamine therapy [9,10]. We have similarly treated many cases of angioedema with great success. One of the most interesting cases was presented at the 2016 meeting of the American Association for Clinical Endocrinologists, but it was never published.

A 47-year-old woman presented with not only a history of dysmenorrhea, but also a strange condition following a tooth extraction. She developed severe angioedema of the tongue, where she would have to open her mouth wide to allow the tongue to protrude (which appeared as a giant red globular mass). The uniqueness of her condition would be the frequency of her episodes. Sixty to 100 times a day her tongue would rapidly swell and protrude from her mouth, causing breathing difficulty, and then spontaneously remit to normal after about 5 minutes.

She had failed to gain relief from corticosteroids or a variety of antihistamines. She had extensive workups at 3 major well-known university-based medical centers. Based on our experience with urticaria, we had also successfully treated several cases of angioedema with dextroamphetamine sulfate but had never reported the cases. We hoped that this strange case might also respond to this therapy, especially since she also had dysmenorrhea, which is well known to respond to dextroamphetamine sulfate [11-13]. She was thus started on amphetamine salts extended-release capsules in which the main ingredient was dextroamphetamine sulfate.

After one month of 15mg dextroamphetamine sulfate daily she reported no improvement. With 30mg once daily she noted mild improvement. Every month the dosage was increased. She noted less frequent episodes with shorter duration. When she exceeded 60mg, she was switched to lisdexamfetamine dimesylate, which comes in 70mg dosages (amphetamine salts extended-release capsule has a maximum of 30mg).

With a total of 130mg of lisdexamfetamine dimesylate her angioedema episodes of her tongue were diminished to 1-3 episodes per month lasting only a few seconds. Her dysmenorrhea also completely abated.

This marked degree of amelioration remained for 1½ years of therapy. Related to uterine leiomyomata, she was still having menorrhagia. She wanted a hysterectomy. The treating physician wanted to reduce her dosage of lisdexamfetamine to the lowest dosage possible that would control her symptoms prior to the surgery. Though the 130mg dosage did not raise her blood pressure, and her heart rate averaged 84 beats/minute, the anesthesiologist also wanted her to be on as low a dosage as possible prior to surgery.

As her dosage of lisdexamfetamine sulfate was gradually reduced, her tongue swelling episodes gradually increased in frequency. With 70mg/day she was experiencing one episode per day lasting 1-3 minutes. Successful hysterectomy was performed on this dosage. She has resumed the 130mg dosage and now only experiences again 1-3 short episodes per month.

Though in the above case the pelvic pain only occurred premenstrually, the angioedema of the tongue was the same throughout the menstrual cycle with no premenstrual exacerbation. As mentioned, based on the embryo implantation model the suppression of dopamine effect could lead theoretically to some of these medical conditions only occurring premenstrually or increased during this time period. In fact, we published a case report of a woman who had a great response to dextroamphetamine sulfate whose urticaria and anaphylaxis was restricted to the premenstrual time period [14].

In the aforementioned case of angioedema of the tongue she had a permeability defect leading to fluid leaking out, but with her dysmenorrhea, she was also an example of increased cellular permeability resulting in irritants leaking into tissues causing increased inflammation and pain. Pelvic pain may not always be associated with fluid retention, but other manifestations of increased cellular permeability. One case was reported of dextroamphetamine eradicating ocular migraines, interstitial cystitis and dyspareunia [15]. Another woman had all of the following symptoms relieved with dextroamphetamine sulfate – dysmenorrhea, chronic pelvic pain, mittelschmerz, and Crohn's disease [13]. These latter two cases did not have fluid retention.

Related to the frequency of having edema for a period of time this syndrome was referred to as the sympathetic hyperalgesia edema syndrome [16,17]. One of the common manifestations of this condition is chronic fatigue [18,19]. Yet one woman whose chronic fatigue markedly improved following dextroamphetamine sulfate, neither had pain nor edema [20]. Thus, it seemed prudent to change the name from the sympathetic hyperalgesia edema syndrome to the increased cellular permeability syndrome, which would encompass descriptions of the various presentations [21].

There are a few summary articles that illustrate the extremely large number of pathological entities that were frequently not responding very well to standard therapy yet showed great response to sympathomimetic amines [4,21-23]. One woman exemplifies this syndrome in the extreme. She was referred to our group for her polycystic ovarian syndrome, but in addition she had been diagnosed by many different specialists with 19 other clinical disorders as seen in Table 2.

Table 2: Twenty-two various clinical disorders of a 22-year-old woman.

1. polycystic ovarian syndrome
2. pelvic pain allegedly from endometriosis (1-3)
3. interstitial cystitis (4,5)
4. orthostatic light-headedness (6)
5. severe muscle spasticity (varying between chronic and sporadic throughout different muscle groups) (7)
6. pelvic floor dysfunction (8)
7. bladder sphincter dysssynergia (4,5)
8. history of transient ischemia attacks (9)
9. chronic migraine headaches (8,10-14)
10. low frequency hearing loss (15)
11. chronic fatigue syndrome (16)
12. postural orthostatic tachycardia syndrome (POTS) leading to frequent syncopal episodes
13. vasovagal syndrome (17)
14. labile blood pressure (18)
15. pulmonary valvular stenosis
16. asthma
17. chronic hyperventilation syndrome related to a functional abnormality of the diaphragm
18. severe constipation (19)
19. gastroesophageal reflux disorder (GERD)
20. non-functional pituitary adenoma
21. fibromyalgia (20)
22. Edema and weight gain

A muscle biopsy diagnosed this 22-year-old woman with the syndrome of mitochondrial encephalopathy, lactic acidosis and stroke like symptoms (MELAS) which could explain several but not all of her symptoms. Interestingly, dextroamphetamine sulfate had been reported to markedly help another woman with the MELAS syndrome. Unfortunately, the most important improvement was inadvertently not mentioned, i.e., she was able to walk within three months of taking the amphetamine despite being confined to a wheelchair for 25 years [24]. In the case of the woman with 22 different conditions most of them improved very much following treatment with dextroamphetamine sulfate.

This condition of the increased cellular permeability syndrome can also be found in males though they are less likely to have the edema and weight gain which are more frequently seen in women [25].

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