Sympathomimetic amine therapy may markedly improve treatment resistant headaches related to a vascular permeability defect common in women - presentation of two cases

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Summary

Purpose: To determine if sympathomimetic amine therapy, which has been effective in alleviating pain from various areas of the body in women previously refractory to conventional therapy, could help refractory migraine headaches. *Methods:* Two cases with severe migraines resistant to conventional therapy were evaluated to see the response to dextroamphetamine sulfate. *Results:* Both women dramatically responded. Case 1 showed that the treatment benefit is long lasting and not merely transient as long as the woman remained on the sympathomimetic amine therapy. Case 2 showed that even premenstrual migraines can respond to this therapy. *Conclusions:* It is not clear if therapy would only benefit women with an abnormal water load test or not. To determine if this therapy could be effective in refractory headache cases, even in women who pass the water load test, one would have to try the dextroamphetamine under similar circumstances and see the response. Similarly it is not known if it could help males with refractory headaches.

Key words: Sympathomimetic amines; Migraine headaches; Fluid retention; Cerebral edema.

Introduction

There is evidence that increased capillary permeability in the standing position is related to a deficit in the sympathetic nervous system [1]. The leakage of this fluid leads to various clinical conditions which frequently puzzle the consulting physician, because despite the frequency of this condition, intelligent physicians and patients are generally unaware of the condition known as idiopathic orthostatic cyclic edema [1].

One of the most common manifestations is the inability to lose weight despite proper dieting [2]. A randomized study comparing the efficacy of a diuretic, a converting enzyme inhibitor, spironolactone and a sympathomimetic amine on weight loss in diet refractory women found that only the latter in the form of dextroamphetamine sulfate demonstrated significant weight reduction over a six-month time span [2]. In fact, dextroamphetamine sulfate proved effective when given in the next six months to the three groups failing to respond for the first six months [2].

The diagnosis of a deficit in sympathomimetic amines is established by demonstrating an abnormal clearance of water load in the erect position and exclusion of other conditions that are associated with an abnormal free-water clearance, e.g., hypothyroidism, renal, or liver disease, or congestive heart failure [3, 4]. The original definition of an abnormal water load test was excretion of < 55% of a 1500 ml water load in six hours but we found that < 75% defines a greater population who suffer from this problem [2, 3]. There are several conditions that have proven refractory to conventional therapy that respond quickly and effectively to sympathomimetic amines.

There have been many anecdotal reports of relieving intractable pain syndromes quickly and efficiently with sympathomimetic amine therapy, despite failure with a multitude of other therapies. These include interstitial cystitis [5], pelvic pain that was attributed to endometriosis [6], gastrointestinal pain including esophagitis [7], gastroparesis [8], joint pain [9], fibromyalgia, and carpal tunnel syndrome [1]. It is not clear if the improvement in pain is related to a decrease in fluid retention or a direct effect of the sympathomimetic amines on the sympathetic nervous system. Sympathomimetic amine therapy has helped other conditions besides pain, e.g., chronic fatigue, vasomotor symptoms in young women not associated with decreased ovarian egg reserve [10], and chronic urticaria resistant to all other therapies [11, 12].

The present study demonstrates the efficacy of sympathomimetic amine therapy for treatment refractory headaches in two cases.

Case Reports

Case 1

The woman presented at age 33 for secondary infertility of two years duration. Her only previous pregnancy ended in a first trimester miscarriage. In taking her history she also mentioned severe intractable migraine headaches that had intensified to the point that they had been unbearable for the last two years and were on a daily basis. She had consulted several neurologists and pain management specialists but nothing abated the symp-

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toms including pharmacologic therapy of beta-blockers, ergotamines, gabapentin, and topiramate. She also failed to respond to biofeedback and acupuncture and had various other symptoms suggestive of idiopathic orthostatic cyclic edema.

She was advised that many of her symptoms, e.g., nocturia, swelling of the face and fingers in the morning and swelling of the feet in the evening, decrease in urination when standing or walking, and abdominal distention by the end of the day, were consistent with this condition [1, 13]. She was told that the possibility could exist that her migraines were related to this capillary permeability defect. She was further advised since this condition is associated with various other treatment resistant pain syndromes that respond to sympathomimetic amine therapy that her migraines could possibly also respond to therapy. However, she was told that since dextroamphetamine sulfate may possibly cause fetal harm that we should probably defer the investigation until after she delivered.

The patient decided to perform the water load test out of curiosity to see if she may have orthostatic water retention. She excreted supine in four hours 1650 ml of the 1500 ml water load that she ingested vs only 650 ml in four hours the second day in the standing position.

The headache pain was so intense she asked if she could begin therapy immediately since it could take several months before she achieved a pregnancy. She stated that she had not had one day of relief of pain from the headaches in six months and she could not bear the pain any longer.

She was started on dextroamphetamine sulfate 10 mg daily of sustained release capsules at 8:00 a.m. and noon. She called the next day to say that her headaches were completely gone. She continued to show marked improvement in the headaches but had occasional episodes of less duration and intensity. The dosage was increased to 15 mg morning and noon and the headaches completely disappeared.

Several months later she conceived so it was decided to stop the dextroamphetamine sulfate. Rather than abruptly stop she was decreased to 10 mg sustained release capsules once daily. The intense headaches returned and she could not bear the pain. She returned to 15 mg twice daily and the pain immediately disappeared and she was headache-free during the pregnancy.

Since she preferred not to stop the medication she was advised not to nurse. She remained headache-free for three and a half years. The laws changed in her state in that a physician could no longer use this drug off-label so prescriptions for dextroamphetamine sulfate could not be filled in her state unless for narcolepsy or attention deficit hyperactive disorder. She thought this might be a good time to test whether she could actually stop the drug. Unfortunately the headaches returned within three days and were not relieved despite the maximum dose of nonsteroidal anti-inflammatory drugs and narcotics. She then came to our office in another state, restarted the medication, and within two days the headaches completely disappeared. They have remained gone now for six months.

Case 2

Case 2 was a 45-year-old female referred by a pain specialist for migraine headaches. Since these headaches were associated with her menstrual cycle he referred her to a reproductive endocrinologist to see if a hormonal cause could be found with treatment directed to correct a potential hormonal imbalance.

The headaches lasted one day to one week and were so incapacitating that she was admitted to the hospital with an overdose of pain killers.

She did not have the classic symptoms of idiopathic orthostatic cyclic edema, i.e., no obvious swelling and no nocturia. However she did have an abnormal water load test (1700 lying 1070 ml standing with 1500 ml ingested).

The first treatment tried was progesterone supplementation during the luteal phase. She was then put on norithindrone acetate 5 mg twice daily. Neither treatment worked.

She next tried dextroamphetamine sulfate 10 mg morning and noon. For the first time in five years she did not get a premenstrual migraine headache. She has had six more menstrual cycles without any headaches.

It should be noted that previously over the course of five years this patient was treated with similar pharmacologic therapy (but no sympathomimetic amines) as Case 1 without any improvement.

Discussion

These two cases show that migraine headaches refractory to standard therapy may respond to sympathomimetic amine therapy. Both women had headaches that would fit with the diagnosis of migraines. For example in case 2, she stated that she would start with an indescribable feeling at the base of her skull. It would move up to her temple when she would develop intense pain, nausea and vomiting and flashing lights.

Though case 2 did not have the classic symptoms of idiopathic edema both women had abnormal water load tests. Interestingly case 2 lost 11 pounds after five weeks of treatment without lowering caloric intake. Whether this therapy could also be effective for refractory migraines in women passing the water load test remains to be tested.

Why headaches related to idiopathic edema may be premenstrual is not known for sure but it can be speculated that this may be the time that premenstrual edema peaks, thus adding additional premenstrual cerebral edema superimposed on a pre-existing generalized edema that previously did not attain a sufficient level to cause sufficient cerebral edema to cause the headache.

Thus migraine headaches can be added to the list of various pain syndromes previously resistant to standard therapy that dramatically responds to sympathomimetic amine therapy [5-9, 13].

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