CEOG Clinical and Experimental Obstetrics & Gynecology
Case Report

Use of sympathomimetic amines to correct premenstrual urticaria and anaphylaxis

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Summary

Purpose: To see if the use of sympathomimetic amines, which have been shown to treat cases of hives, can help prevent cyclical urticaria and anaphylaxis associated with the late luteal phase that was resistant to standard treatment. *Materials and Methods:* Treatment with low dose dextroamphetamine sulfate to gain relief of symptoms was given to one young woman whose urticaria only occurred premenstrually, but was also associated with life threatening anaphylaxis. Patient 2 had chronic daily urticaria which was exacerbated premenstrually. *Results:* Both patients showed prompt 100% improvement in the urticaria. Patient 2 after 20 years of therapy ran out of medication for one month. Her severe urticaria quickly returned only to dissipate when dextroamphetamine sulfate was restarted. *Conclusion:* Use of dextroamphetamine sulfate was successful in treating the anaphylaxis and extensive luteal phase hives in patient 1 as well as treating chronic hives with a premenstrual exacerbation in patient 2. These cases are both consistent with the proposed mechanism of the sympathetic neural hyperalgesia edema syndrome, i.e., increased cellular permeability related to sympathetic nervous system hypofunction of specific permeability defects of certain tissues. In these cases, the hypothesis is that the increased permeability manifests as leakage from the vesicles that contain the histamines.

Key words: Progesterone; Luteal phase; Sympathomimetic amine; Urticaria; Sympathetic neural hyperalgesia edema syndrome.

Introduction

Premenstrual symptoms (PMS) and premenstrual dysphoric disorder (PMDD) are defined by a combination of physical, psychological, and behavioral symptoms that occur during the late luteal phase of the menstrual cycle. Many of the most common associated symptoms include cramps, abdominal pain, fatigue, nausea, bloating, breast tenderness, irritability, changes in mood, depression, and anxiety. Nonetheless, these commonly associated symptoms can occur in conjunction with unique and atypical symptoms such as: seizures, asthma exacerbations, dermatitis, and anaphylaxis. For these cases, a brief discussion of the normal pathophysiology behind PMS and PMDD, as well as noting unique cases in the literature, is warranted.

Premenstrual symptoms are believed to affect as many as 75% of women of reproductive age [1, 2] and an approximated 20% of adolescents experience PMS with functional impairment [2]. It has been reported that up to 8% of women experience PMDD [1-3]. Thus, treatment and prevention is important for many female patients.

Despite years of efforts to determine a causal factor for PMS and PMDD, current research still had been unable to determine a definitive cause. Currently, theories are that changes that occur naturally in the menstrual cycle in conjunction with neuroendocrine dysfunction are believed to be responsible for this cluster of symptoms [4].

The sympathetic neural hyperalgesia edema syndrome is associated with a defect in cellular permeability which enables unwanted toxins to enter cells and either cause inflammation or adversely effects muscle function [5]. The basis of this disorder is related to hypofunction of the sympathetic nervous system. Sympathetic nerve fibers are responsible for decreasing cellular permeability. When toxins or unwanted chemicals enter various tissues this leads to a wide range of symptoms relative to the organ systems involved. The sympathetic neural hyperalgesia edema syndrome has been found to respond to dextroamphetamine sulfate [5]. Its role in symptom reversal is due to enhancing sympathetic function. It is thought to do so by either increasing dopamine secretion or by replacing the neurotransmitter that is deficient [5]. In fact, this disorder is now called the increased cellular permeability syndrome [6].

Numerous case reports have been mentioned in the literature of conditions that occur or exacerbate premenstrually including autoimmune progesterone dermatitis (APD), in-

Revised manuscript accepted for publication May 15, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 2, 2019
doi: 10.12891/ceog4727.2019

7847050 Canada Inc.
www.irog.net

Published: 10 April 2019

crease is seizure activity, and asthma exacerbation [4].

Autoimmune progesterone dermatitis is fairly common among the more unique symptomatologies [7]. However, cases of angioedema and anaphylaxis associated with APD are much less common [7]. Premenstrual asthma has also been reported [8].

Multiple forms of treatment have been used to attempt to abate various premenstrual dermatologic symptoms. However, these treatments involve immunosuppression (e.g. cyclophosphamide, cyclosporine, rituximab), hormonal alteration (e.g. danazole, growth hormone releasing agents, tamoxifen) surgical treatment (e.g. total hysterectomy and/or bilateral oophorectomy), all of which carry with them significant side effects [7]. If dextroamphetamine sulfate can be used to treat this condition, then it would be a superior treatment option since the most common sequale associated with dextroamphetamine sulfate (transient insomnia, transient anorexia, and dry mouth being the most common) are significantly more favorable than those of the treatments mentioned.

Seizure exacerbation secondary to premenstrual cerebral edema has also been found to occur [1]. This has been treated with the anti-androgen drospirenone mainly for its antimineralocorticoid effect due to its competitive inhibition of aldosterone [9].

Dextroamphetamine sulfate has previously been found to treat cases of cerebral edema associated with pseudo tumor cerebri [10]. In this case reported, the headaches and papilledema had no premenstrual component. This further enhances the argument of treating various symptoms associated with edema or other symptoms that do not occur just premenstrually, but all the time as well. It would be interesting to see if the patient who had premenstrual edema and seizures only would have responded to the dextroamphetamine sulfate as well [9]

Despite the seemingly unrelated nature of these symptoms, it is possible that they all fall under or are associated with the increased cellular permeability syndrome, and that treatment with dextroamphetamine sulfate may be beneficial in treating these various ailments through the previously explained mechanism [6, 11]. Thus there may be a generalized defect of decreased sympathetic tone during the follicular phase that is not a severe enough defect to cause a problem. However, possibly the premenstrual state is associated with further diminished sympathetic neural activity, which when combined with the generalized defect, there is increased permeability leading to the influx of chemicals and toxins into a particular effected tissue or organelle because a critical level of increased cellular permeability has been reached. Sympathetic tone is then restored by treatment with the sympathomimetic amine dextroamphetamine sulfate. A vivid example of the manifestation occurring only with a further impairment of the sympathetic nervous system was a woman who had diplopia with paresis of the extraocular muscles for 30 minutes only when she had an orgasm [12]. Her sixth cranial nerve palsy was abrogated by treatment with dextroamphetamine sulfate. This suggests that a generalized defect in the extra-ocular muscles exacerbated by a decrease in sympathetic tone co-exist at the time of orgasm caused an influx of chemicals into the extra-ocular muscles. The extra-ocular muscles were impermeable under normal circumstances, but with further insult to the sympathetic nervous system, brought about through orgasm, toxins entered the tissue causing the aforementioned symptoms related to paresis of the extra-ocular muscles.

Case Report

Case 1

In 2011 a 12-year-old female presented to the emergency department for her first of five instances of anaphylaxis. Prior to this, she had several instances of severe hives that were unexplained. As she started to develop more regular menses, it became obvious that her outbreaks of hives and periodic anaphylaxis preceded her menses.

Due to the potential life threatening nature of this condition, her mother began to seek help. She was evaluated and treated by immunologists, rheumatologists, and endocrinologists prior to presenting to Cooper Institute for Reproductive and Hormonal Disorders. She was diagnosed with the increased cellular permeability hyperalgesia edema syndrome, and started on 15 mg of dextroamphetamine sulfate in the morning. Her symptoms dramatically improved. For the first three months, she had no symptoms. She then started to develop hives again, though not nearly to the degree she had prior to the medication. As such, her dosage was raised from 15 to 45 mg of dextroamphetamine sulfate. Her subsequent premenstrual times were hive free.

Case 2

In 1985, a 29-year-old female who was physically active on a daily basis, and participated in triathlons, developed a sudden onset of hives during a workout. The hives were present all over her body wherever there was trauma due to a bump, a scratch, or a rubbing waist band, shoe, or other article of clothing. She noted that these unusual symptoms became even more exaggerated during her late luteal phase. The hives continued to form from this point despite over the counter medication, so she sought help from medical professionals. From 1985 to the mid 1990's she saw 19 specialists in rheumatology, immunology, allergy, and dermatology. She was placed on a cocktail of medications from glucocorticoids, to high dose immunosuppressant's, to anti-histamines, and various other medications all of which showed no sign of improvement. She noted that though the hives were always present, they were definitely worse premenstrually.

The patient was traumatized by her chronic condition and it greatly impacted her quality of life. Over this time, she continued to gain weight due to swelling and life style modifications. Her condition reached a point that wearing long sleeve dress shirts would cause her wrists and forearms to grow larger than her upper arm simply from the rubbing cuff. The patient was nearing the end of her mental rope and contemplating suicide when one of her allergists referred her to Cooper institute for reproductive endocrinology. Here she underwent a water load test which was found to be abnormal [11].

She was started on 10 mg of dextroamphetamine sulfate. Within days her hives completely disappeared. She continued on this dose for almost an additional 19 years without a single recurrence of

hives, and she experienced a significant decrease in weight (41 kg) due to improvements in swelling and edema. She had no recurrence in her symptoms until her mail-order medications did not come one month. Due to the fact that this is a class 2 drug, she could not get another prescription filled. Within three days she developed severe diffuse hives again. This lasted one month. When she was able to get her prescription filled again and she experienced remission of her symptoms again within days.

Since starting treatment with dextroamphetamine sulfate she has had no side effects, even those which were mentioned as more common to occur, and she continues to experience no exacerbation of her symptoms as long as she continues to take her 10 mg dose daily. Despite taking the drug for 19 years with abrupt stoppage, there were no withdrawal symptoms.

Discussion

The successful treatment of severe urticaria with dextroamphetamine sulfate dates back to 1984 [13]. Subsequently other cases similarly showing dramatic response to sympathomimetic amines have been reported [14, 15]. However, the majority of clinicians are not aware of its efficacy and thus resort to much less efficacious treatment that have far greater side effects and risks.

Generally the hives are not related to the menstrual cycle, e.g., the premenstrual time. Case 1 was the first time that we encountered a woman whose urticaria worsened during the pre-menstrual time.

In over 30 years of treating increased cellular permeability including many cases of urticaria, case 1 represents the first time that the urticaria was restricted to the pre-menstrual time. This suggests that the secretion of progesterone may decrease sympathetic tone to some degree. Some conditions may have mild hypofunction of the sympathetic nervous system with the potential for increased cellular permeability. Thus the clinical conditions that result from the defect are not severe enough until compromised by further decrease in sympathetic tone that may occur in the mid to late luteal phase. The increased cellular permeability syndrome is known to cause edema and weight gain by not allowing sufficient sympathetic signals to the capillaries to diminish capillary permeability in response to the increase in hydrostatic pressure that occurs in the erect position [16]. This mechanism could explain the well known phenomenon of premenstrual edema. In the case of premenstrual hives, the vesicles containing histamine would leak under condition of further compromise of diminished sympathetic tone associated with the premenstrual time.

The response of these cases of premenstrual urticaria and other previous published cases of more female predominant autoimmune disorders to dextroamphetamine sulfate, a drug not known to be an immunosuppressive agent, suggests that the main role of progesterone in these disorders may be to further diminish sympathetic tone thus allowing toxic elements to permeate tissues which, in turn, leads to inflammation [17-20].

Indeed there is evidence that by progesterone suppressing dopamine, endometrial permeability is increased leading to irritating elements permeating the uterus leading to an inflammatory state that allow remodeling of the thick-walled uterine arteries to become thin-walled spiral arterioles allowing nutrient exchange between mother and fetus [21, 22].

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