Sympathomimetic amine therapy found effective for treatment of refractory chronic complex regional pain syndrome (reflex sympathetic dystrophy)

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Summary

Purpose: To determine if treatment with sympathomimetic amines could improve the pain from complex regional pain disorder (CRPD) which was keeping a woman from trying to conceive her second child. *Materials and Methods:* Dextroamphetamine sulfate was prescribed. *Results:* Within a short length of time the woman's wrist pain considerably improved to the point that she is ready to try in vitro fertilization once again to have a second baby. *Conclusions:* Though sympathomimetic amines are used by some reproductive endocrinologists for unexplained infertility and unexplained recurrent miscarriages, the most common use by the gynecologist is for pelvic pain. Despite the thought by some clinicians and researchers that the etiology for CRPD may be related to sympathetic nervous system hyperactivity (and thus sympathomimetic amines could theoretically exacerbate the symptoms), in fact, the treatment with dextroamphetamine sulfate may turn out to be a new and possibly the most effective, least risky, and least expensive treatment to date for CRPD.

Key words: Complex regional pain syndrome; Reflex sympathetic dystrophy; Sympathomimetic amines; Dextroamphetamine sulfate.

Introduction

The gynecologist is most familiar with the use of dextroamphetamine sulfate, a sympathomimetic amine, for the treatment of various types of pelvic pain including chronic pelvic pain, dyspareunia, middleschmertz, vulvodynia, dysmenorrhea, and chronic pelvic pain of bladder origin [1-4].

Most of the data suggest that the mechanism by which the amphetamine relieves pelvic pain is by inhibiting the absorption into various pelvic tissues chemicals and toxins which then evoke an inflammatory reaction [4]. The sympathetic nervous system is responsible for controlling cellular permeability. When there is hypofunction a particular vulnerable tissue will be dependent on increased sympathetic tone to prevent absorption of noxious agents and thus becomes affected. Treating with a sympathomimetic amine empirically dextroamphetamine sulfate corrects the cellular permeability defect and thus markedly improves pain [4].

Thus, endometriosis may be the result of increased permeability but not the cause of the pain and is merely associated with the sympathetic neural hyperalgesia edema syndrome where there is a pelvic tissue permeability defect. This would explain why frequently, despite expert surgical treatments to remove endometriosis, the pain frequently quickly returns whereas it seems to not return following treatment with dextroamphetamine sulfate [4, 5].

The increased cellular permeability defect leads to pain in other areas of the body, e.g., migraine headaches and fibromyalgia [6]. The increased permeability defect leads to the inability to compensate for the increase in hydrostatic pressure when standing which would lead to extravasations of fluid from the intravascular to extravascular spaces thus causing edema because the sympathetic nervous system signal is insufficient to decrease capillary permeability [7,8]. Thus many, but not all, patients with this syndrome have edema or inability to lose weight despite dieting leading to the name sympathetic neural hyperalgesia edema syndrome. Sometimes absorption of noxious factors into muscles leads to abnormal motor function and thus can cause gastrointestinal motility defects, e.g., achalasia, gastroparesis, or pseudointestinal obstruction or chronic fatigue syndrome [9-12].

The gynecologist could get involved with these other pathologic entities in a few ways. For example, by taking a complete history the gynecologist may advise a woman who the gynecologist wants to treat with dextroamphetamine sulfate for pelvic pain, that her chronic migraine headaches that are not responding to her present medication may improve also and she can gradually discontinue the other medications.

Sometimes the gynecologist may be reluctant to treat a gynecologic condition with dextroamphetamine because theoretically another condition may become worse. The present case presents the dilemma of wanting to use dextroamphetamine sulfate for unexplained infertility but with

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the patient having complex regional pain syndrome (CRPS) (sometimes called reflex sympathetic dystrophy (RSD). There could be some concern because of fear the CRPS could get worse since some researchers believe this condition is related to sympathetic hyperactivity.

Case Report

A young woman aged 15 in 1988 tore the triangular fibrocartilage complex (TFCC) in her right wrist while playing tennis. After having arthroscopic surgery to repair the TFCC, she recovered about 85% of her prior strength, endurance, and mobility in the right wrist. It bothered her off and on, and had to remain conscious of being careful with it, but she was able to play racquetball, garden (avidly), play the piano, and live a normal life. She was not able to play tennis or use a small roto-tiller, and if she severely overused the wrist, it would hurt for a few days, which she could just wait it out with the wrist in a brace. In late March of 2006, however, it did not recover after overuse. Instead, it seemed to improve over the course of four to six weeks of being very careful with it, but then normal use would aggravate it to the point where it felt like she had just injured it again.

On May 19, 2006, while trying to push a bulky grocery cart with her left hand, she sprained the left wrist, and now could hardly eat with either hand. A few days later it felt like she sprained the thenar area of her right thumb trying to crack it. In late May of 2006, she consulted the orthopedic surgeon who had performed her first surgery. The magnetic resonance imaging (MRI) of her right wrist showed a peripheral tear of the triangular fibrocartilage complex (TFCC) (on the ulnar side). This was consistent with his diagnosis on examining the wrist. She sprained her left wrist too close to the appointment date to get an MRI on that wrist before seeing the surgeon, but he felt a click on examination that suggested she had also torn something in that wrist. He wanted to wait 3.5 months to see if the wrists would heal on their own without surgery. He asked one of his occupational therapists to fit a molded brace to her hand, wrist, and lower arm.

In June, after a couple of weeks of wearing that brace, she started to get a peculiar shock pain in her right wrist. The symptoms changed from feeling like a sprain to feeling like nerve pain. It constantly felt like she had just hit a ball with a bat in freezing cold weather. She had to stop cooking, cleaning, and driving. She could not even strike a match without her hand going numb. She lost the ability to raise her right pinky or lift her ring finger. Her hands got very weak and slow as well as uncoordinated, and the pain became diffused throughout her hand and wrist and up her forearm. She became very sensitive to even light tough and she could not find a way to rest her right arm. Her right wrist could not take the weight of resting the arm on a chair armrest – the only comfortable position was straight up in the air with a brace on, resting on the elbow. To sleep she had to wrap the wrist and rest it on an extremely soft pillow while laying on her right side. She would lose circulation in the arm if she laid on her back or right side. She saw the surgeon again because of these new symptoms. He said he did not know what it was and instructed her to stop wearing all braces. He suggested a consult with a rheumatologist and a neurologist, and recommended a bone scan, electromyography (EMG), and a functional capacity test with a physical therapist. He told her to use the hand as much as possible. Over the next several months she lost 15 pounds due to difficulty with bringing a fork to her mouth with either hand.

By mid-August she had lost a good deal of strength in her right arm despite trying to use it. She would do well using it for a few days or maybe even weeks, and then she would tweak it doing some normal things, and it would be right back to square one.

On August 21, 2006 (after extensive blood work to rule out autoimmune disorders), she was diagnosed with CRPS by the rheumatologist she consulted. She started occupational therapy (OT) on August 30, 2006. On September 13, 2006, she saw the orthopedic surgeon again, and he agreed with the rheumatologist about CRPS. She did not have the common type of CRPS that causes severe edema and burning pain. She had the type referred to as "cold and stiff". Her right hand felt like ice and the range of motion in her right wrist and hand was very noticeably reduced. Trophic changes included stiffness, increase in dark hair over the affected region, decrease in sweating, atrophy of nails, osteopenia, muscle atrophy, and abnormal color changes.

In September, 2006 she injured her right elbow turning a shopping cart with her elbows since she could not use the wrists. It took about a year to completely resolve, and it made the CRPS symptoms worse. Now she could not even rest the wrist on her elbow because the elbow was extremely sensitive to pressure and touch. The orthopedic surgeon found nothing mechanically wrong with the elbow. The EMG was negative on both arms. She was started on low (but progressively increasing) doses of gabapentin as prescribed by the rheumatologist.

In October, 2006 she had a bone scan that was positive for possible RSD. In October she injured her right shoulder (likely the rotator cuff – but never saw a doctor about it) doing OT stretches to prevent frozen shoulder syndrome. That injury took about four years to resolve. It was over a year before she could raise her right arm over her head. That immobility further worsened the CRPS. On October 12, 2006 the orthopedic surgeon saw the bone scans and found them to be consistent with sympathetic over-activity. He also said the scans showed TFCC tears in both wrists, and reiterated that no mechanical correction to the wrists could be done until "the dystrophy component of her problem has subsided".

She started acupuncture and switched to a physical therapist (PT) that had been recommended by another neurologist. This therapist had great deal of experience treating atypical CRPS cases. He also felt that part of her problem was that she had thoracic outlet syndrome and gave her nerve glides to do that did help with the pain. In December, 2006 she injured her right knee in therapy doing squats and strained her patellar tendon and pulled her quadriceps. In December 2006 she aggravated the right knee further in therapy trying a new way to do a shoulder exercise. The PT wondered if the saphenous nerve was involved, and if this was part of "nerve irritation problem".

Related to the number of soft tissue injuries she had sustained in less than a year, her neurologist referred her to the genetics department at a University Hospital to rule out connective disuse disorders such as Ehlers-Danlos Syndrome (EDS), Marfan syndrome, and pseudoxanthoma elasticum (PXE). After the exam, interview, and family history the genetics experts decided blood tests were not indicated because they were sure she was negative for a connective tissue disorder.

She consulted another orthopedic surgeon to examine her right knee in January, 2007. He diagnosed her with patella-femoral syndrome and prescribed PT. In the middle of January she hurt her neck. The knee (car accident), neck (car accident, trauma), and shoulder (too many racquet sports) all had had previous problems, but now were in very bad shape. She was extremely weak at this time and was unable to function in simple daily chores. In February, 2007 she consulted another rheumatologist who also diagnosed her with CRPS. He suggested she try pregabalin as well as gabapentin.

Throughout the fall of 2006 and winter of 2007 she experienced gradual improvement in her hands. Acupuncture seemed to be the most helpful. A calcium channel blocker was added to the prega-

balin and gabapentin to help dilate vascular passage in the hope that it would increase nutritional flow to her right hand. Obviously she found PT to be dangerous, but it did improve the strength in her hands and wrists when she was not in too much pain to do the exercises. The addition of the knee injury really complicated things. She could not do stairs more than once a day, get on the floor with her daughter, use her legs to help lift her (back hurt because of that), and it was hard to sit and get out of chairs. She could not stand up out of a chair while holding her daughter. She was stuck upstairs until someone came over and brought her daughter downstairs since she could not navigate the stairs while carrying her. Also she could not do the most helpful shoulder exercise because it involved lying on her stomach on a bed, and she could not get up from that position because she could not roll over, and because of the leg injury, could not get off the bed while on her stomach.

Over the next several years she cycled through times of wrist improvement followed by an "injury" to the right wrist while doing something normal that could set her back to the starting point. Pregabalin and gabapentin seemed to dull the pain some, but little things like pushing tissues down in a trash can, trying to play the piano a little, stirring food, turning on a light, cutting meat, opening a doorknob, leaning a little bit on her right hand, etc., were all enough to erase months of painstakingly slow PT work.

By the winter of 2009, she was evaluated by the wrist surgeon again. He agreed that "time and testing" had shown that the tear in the right wrist was not going to improve on its own and thought that fixing the tear might lead to a resolution of the CRPS. He revealed after the surgery that it had been an agonizing decision, because the surgery could easily had led to "full-blown RSD". Up until the surgery, he thought she was about 60% of the way to "full-blown RSD".

The woman had a previous infertility history of unexplained etiology. She had failed to conceive for 18 years despite trying since age 21. She was treated in our reproductive center and had 18 months of intrauterine insemination with luteal phase progesterone supplementation. Her infertility was unexplained but at her present age it was assumed that she at least now had a luteal phase defect. She had not proceeded to in vitro fertilization-embryo transfer (IVF-ET) for financial reasons.

Finally she attempted an IVF cycle using mild ovarian stimulation. She failed to achieve a pregnancy. She repeated a mild stimulation IVF cycle preceeded by lymphocyte immunotherapy [13, 14]. This was successful and she had a full-term delivery of a healthy baby girl.

This problem with CRPS and RSD was not mentioned when she initially sought our infertility help. The reason it was discussed when she returned six years later for help in conceiving a second child was that we discussed an alternative to lymphocyte immunotherapy (which would have forced her to travel to Mexico for therapy since this requires a cost-prohibitive new drug application in the United States). The alternative therapy suggested was the use of dextroamphetamine sulfate which would theoretically inhibit absorption of chemicals and toxins into the endometrium [15].

The woman was concerned that the treatment with sympathomimetic amines could worsen her complex regional pain syndrome Type I (reflex sympathetic dystrophy) since the condition is believed by many clinicians to be related to hyperactive sympathetic outflow to the peripheral regions and that the sympathetic outflow is somehow causally related to the pain [16]. However we explained to her that the role of the sympathetic nervous system as an etiologic factor in RSP is not well understood [17]. Our argument was that since present therapy had not been so effective and since there exists the syndrome known as the sympathetic hyperalgesia edema syndrome which is notorious for causing pain in various parts of the body, yet despite generally being refractory to "standard" therapy, almost always the pain either completely disappears or is markedly impaired shortly after initiating treatment with dextroamphetamine sulfate [18].

We further explained to the woman that we have demonstrated remarkable improvement of frequent bowel movements and pain with Crohn's disease that had been quite resistant to conventional therapy with demonstration of Stage 4 to Stage 0 within a very short time following treatment with dextroamphetamine sulfate [19]. This could be understood based on the suggestion that Crohn's disease is associated with para-sympathetic hyperactivity with associated hyposympathetic neuropathy [20, 21]. In contrast, the data supported the hypothesis that ulcerative is the opposite, i.e., related to sympathetic hyperactivity with parasympathetic dysfunction [20, 21]. Thus theoretically treatment with a sympathomimetic amine, e.g., dextroamphetamine sulfate could worsen ulcerative colitis. However we have found dextroamphetamine sulfate therapy to be highly effective for ulcerative colitis also [22]. Thus we suggested that she try sympathomimetic amine treatment and if the pain worsens, we simply stop the medication.

Despite the concept that sympatholytic drugs which enhance sympathetic tone are the appropriate choice for RSD, the woman decided to try dextroamphetamine sulfate because of its vast benefits in other pain disorders (the syndrome is called the sympathetic neural hyperalgesia edema syndrome). The woman showed considerable improvement on a dosage of just ten mg extended release capsule which is a starting dosage and usually insufficient to help the majority of the various disorders that constitute the sympathetic neural hyperalgesia edema syndrome [18]. She was able to stop expensive physical therapy. She stopped visiting a chiropractor for expensive weekly visits. She even became stronger with the cold weather which usually was her worst time of the year. She withstood cold for 90 minutes with bare hands when typically she would require very insulated mittens in cold weather or her wrist pain would become intense. Her ability to rebound after muscle soreness and strain was nearly normal and she stated she was feeling almost as good as before the CRPS began. She was even able to play the piano again and do activities that she would not perform while involved with the RSD.

She is now in her second trimester following frozen ET and is taking the dextroamphetamine sulfate throughout the pregnancy.

Discussion

Complex regional pain syndrome has had other earlier names but the one still commonly used is RSD. The CRPS syndrome usually occurs following an injury to a limb although in some instances a traumatic event cannot be recalled.

Spontaneous recovery is possible but about 15% will not experience any improvement and 30% remain severe enough that even though they were able to gain employment before CRPS started they can no longer work [23].

Initial presentation can vary with limbs reported to be hot or cold, shiny, swollen or thin, red or blue, scaly skin or clammy skin [24]. Some patients cannot tolerate slight air movement on their skin whereas other complaint of numbness. Joints are reported to be stiff and weak [24].

Goebel describes eight major concepts about the etiology of CRPS [24]. One of them is that CRPS is a sympathetically mediated disorder. There is evidence that the

aspect of CRPS that produce red color and warmth may be related to low rather than high centrally mediated sympathetic outflow to cutaneous vasoconcentration [25].

In 1974 Harrington-Kiff suggested that agents that deplete the limb autonomic nerve endings of noradrenaline, such as regional guanethidine, should, therefore, be effective in treating CRPS [26]. Thus, theoretically based on this assumption the use of sympathomimetic amines should worsen not ameliorate the symptoms of CRPS. Indeed four randomized controlled studies with guanethidine failed to show improvement with CPRS [27]. Thus presently experts in the field have de-emphasized the importance of the concept of sympathetic hyperactivity as the main etiologic factor with de-emphasis on sympatholytic therapies.

One therapy involves the concept of central sensitization. It has been observed that after a period of intense or repeated noxious stimulation, innocuous stimuli now become painful and remain painful even if the initial noxious stimulus has been removed [28]. N-methyl D-aspartate (NMDA) is important in central sensitization [28]. This has led to the treatment of CRPS with the NMDA antagonist ketamine. Indeed two randomized controlled trials (RCTs) found IV ketamine to improve pain from CRPS [29, 30]. However, there is no evidence for high dosage ketamine comas as treatment for CRPS [31].

It should be noted that there is evidence that repeated ketamine treatments may be neurotoxic [32]. Furthermore, ketamine therapy is expensive and either requires a five-day hospital stay or a ten-day out-patient program taking the patient out of normal activities including work.

It is beyond the scope of this manuscript to review the other therapies mentioned in the review by Goebel but those readers interested should refer to Goebel' review [24]. Another elaborate hypothesis was presented by Coderri and Bennett [16].

There are a multitude of treatment regimes which are all time consuming and expensive and unfortunately have had only limited success. The treatment with oral sympathomimetic amines provides an inexpensive therapy with little or no side effects that does not inconvenience the patient at all. The main concept as to how does treatment with dextroamphetamine sulfate help so many ubiquitous pain syndromes varying from headaches, to fibromyalgia, arthritis, gastrointestinal, pelvic, and bladder is related to the function of the sympathetic nervous system in controlling cellular permeability (the theory contends that hypofunction of the sympathetic nervous system leads to the absorption into tissue of chemicals and toxins that would normally be precluded and this leads to inflammation and pain) [18]. Support for this concept was provided by the initiation of pain with potassium infusion into the urinary bladder in patients with interstitial cystitis which is no longer present when treatment with sympathomimetic amines were given (personal observation).

It is the hope that this case report will stimulate some therapists to attempt RCTs using dextroamphetamine sulfate for CRPS. It is further hoped that the physiologists explaining the etiologic mechanism for CRPS will consider the reported benefit from sympathomimetic amines which could alter their hypothesis to etiology and possibly lead to new novel therapies for a variety of chronic pain syndrome.

For the practicing gynecologist, it is known that the most effective therapy for chronic pelvic pain is dextroamphetamine sulfate treatment [4]. The dramatic ameliorative response to CRPS to dextroamphetamine sulfate in this case report should provide the courage for the practicing gynecologist to prescribe dextroamphetamine sulfate to a woman for pelvic pain even she also has CRPS, i.e., fearing that increasing sympathetic tone could make CRPS worse. The patient should be advised that there is at least a precedent that CRPS would not be hurt by treatment but the pain could even reverse with treatment with sympathomimetic amine therapy.

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