

Improvement of Severe Chronic Pelvic Pain and Dysmenorrhea Following Treatment with Cabergoline

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ABSTRACT

There are various methods of treating pelvic pain. Laparoscopic laser vaporization or excision may be effective but frequently the relief is short lived. Furthermore, surgery may lead to decreased egg reserve which already may be diminished secondary to the pelvic inflammation associated with endometriosis. Standard medical treatments aimed to block or decrease estrogen are frequently ineffective, may produce significant side effects and, have not been found to improve subsequent fecundity. They preclude pregnancy while they are employed. One theory as to the etiology of pelvic pain is that this excessive cellular permeability of the pelvic tissues leading to an exaggeration of infiltration of irritants into pelvic tissue, which in a more moderate form, may be part of the mechanism used by the female body to induce post-ovulatory inflammation with an increase in natural killer cells in the fetal microenvironment to help create spiral arteries.

The theory contends that progesterone blocks dopamine, and dopamine acts to decrease cellular permeability. Whether the hypothesized mechanism is correct or not there has been considerable anecdotal experience demonstrating marked amelioration of active pain by purposely prescribing a drug known to release dopamine from sympathetic nerve fibers, i.e., dextroamphetamine sulfate. Unfortunately, for unknown reasons, amphetamines have been placed in the same category of drugs as potent opiates. This precludes their easy use by treating physicians. A pilot case with severe pelvic pain was chosen as a model case to determine if another drug that releases dopamine from sympathetic nerve fibers, cabergoline, could also prove effective in relieving pelvic pain. Indeed, in this one case there was marked reduction in pain. Thus, this case encourages the initiation of a larger study to determine if cabergoline can be a less controversial option for treating pelvic pain, while not precluding pregnancy.

Keywords

Dopamine, Endometriosis, Natural Killer Cells, Pelvic Inflammation, Sympathomimetic Amines.

Introduction

There is no known etiology for many pain syndromes. Sometimes the condition is thought to be of an “autoimmune” nature, e.g., arthritis, or abdominal pain related to Crohn’s disease, ulcerative colitis, or microscopic colitis. These conditions are frequently treated with drugs that suppress inflammation by non-steroidal anti-inflammatory drugs, or glucocorticoids, or drugs that suppress the inflammatory cytokine tumor necrosis factor alpha.

Sometimes these treatments are successful, but when used chronically, may lead to other pathological conditions, e.g., gastritis, bleeding peptic ulcers, increased risk of infection, increased risk of cancer, osteoporosis and diabetes mellitus. Unfortunately, despite the risks taken, often the patient does not experience a great deal of relief despite these aforementioned therapies.

Based on the hypothesized mechanism of how the pregnant female develops an inflammatory state for the purpose of remodeling thick-walled uterine arteries to form thin-walled spiral arteries, and thus allow nutrient exchange between mother and fetus, it was

considered that increased cellular permeability, leading to thymic helper 1 cytokine dominance, thus resulting in a shift toward an increase in cellular immunity (especially with increased natural killer (NK) cells), could be the etiology for various pain syndromes throughout the body. The localization to a specific organ system could be related to intrinsic or extrinsic weakness of a given tissue or organ, leading to the infusion of unwanted irritants [1-2].

Increased cellular permeability can cause pathologic states not just with infusion of unwanted substances into tissues, but also from leakage of irritants or fluids out of blood vessels or tissues. Kidney, liver, or heart disease may cause fluid retention leading to edema and weight gain. Over 60 years ago a condition of edema was described that was not related to a known etiology but was termed “idiopathic”. This edema was worse in the erect position, so Dr. Thorn called the condition idiopathic orthostatic edema [3]. He considered the edema related to a psychosomatic disorder, possibly related to depression. At that time one of the major drug treatments for depression was amphetamines.

Another condition that leads to edema is hypothyroidism. Thyroid hormone is similar to amphetamines in that they are both sympathomimetic amines. Consideration was given to the possibility that the mechanism of action of amphetamines was more related to its effect on the sympathetic nervous system rather than depression. The sympathetic nervous system releases dopamine, and dopamine diminishes cellular permeability. Indeed, treatment with dextroamphetamine sulfate was found to relieve idiopathic edema and its associated weight gain [4-6].

Another condition where amphetamines demonstrated marked improvement in a condition related to substances leaking out related to increased cellular permeability is the leakage of histamines causing urticaria, with dramatic improvement following treatment with dextroamphetamine sulfate, despite a history of treatment resistance [7-11].

The first case of treating severe urticaria by dextroamphetamine sulfate was a patient who was covered from head to toe with severe urticaria for seven continuous years, without any significant abatement with antihistamines or glucocorticoids. She showed immediate resolution of the urticaria following treatment with dextroamphetamine sulfate, and the benefits persisted. Before publishing this case, to be sure it was not merely fortuitous, the same treatment was tried on a second case with intractable urticaria with the same positive outcome [7].

Interestingly, the first patient who never missed one dose of dextroamphetamine sulfate for 25 years, one month failed to receive her medication by mail. Though there were no withdrawal symptoms after abrupt cessation after 25 years, her severe urticaria returned in 3 days and persisted for that entire month. However, it quickly resolved once again when the amphetamine was restarted. Subsequently, other interesting anecdotal cases of urticaria and anaphylaxis have been reported emphasizing the marked

beneficial effect of treatment with the sympathomimetic amine, dextroamphetamine sulfate [7-10]. This includes an extremely unusual case of multiple daily episodes of rapidly exacerbating and remitting angioedema of the tongue [11].

Though the majority of patients in the early days sought therapy for unexplained weight gain and edema, it was clear that this condition of orthostatic cyclic edema was associated with other clinical manifestations, besides urticaria. Thus, patients consulted our group for various pain syndromes. One interesting case was a woman with severe intractable chest pain, believed to be esophageal in origin, that was refractory to various treatments. She responded quickly and very well to dextroamphetamine sulfate, and we deemed this case worthy of publication to help promulgate the information to other treating physicians [12].

It soon became clear that sympathomimetic amine therapy could effectively treat various pain syndromes despite failure to respond to standard therapy [13]. Interestingly, cases of pain relief were found for bladder pain related to interstitial cystitis [14,15]. The drug was found to be very effective for headaches without a known cause or where a cause, e.g., trauma, was known [16-22]. Frequently, a patient could present with pain in more than one tissue or organ system and show response in all areas of pain following amphetamine treatment. Patients with the combination of interstitial cystitis and headaches have shown improvement in both areas following treatment [23]. There are other non-pain conditions that can be improved with dextroamphetamine, that may, or may not, be associated with pain syndromes also. For example, dextroamphetamine sulfate was found effective for both headaches and vasomotor symptoms in a case report. She also had edema and weight gain that improved [24]. Because the edema was frequently associated with pain syndromes which responded to sympathomimetic amines, a more suitable name for this condition was sought, and for a while, it was referred to as the sympathetic hyperalgesia edema syndrome [24]. However, some patients may have neither edema nor pain, yet their chronic disorder is improved by dextroamphetamine treatment. For example, the drug can correct vasomotor symptoms and heat intolerance [22,25,26]. Other conditions not associated with pain were subsequently found where the only effective treatment was dextroamphetamine sulfate. This included chronic fatigue syndrome [27-29], skin conditions besides urticaria, e.g., eczema [30], autoimmune hearing loss [31], severe urinary incontinence related to a neurogenic bladder [32], and yet they were not associated with pain or edema. Since these conditions were all thought to be linked by increased cellular permeability, a more appropriate name for the syndrome was considered the increased cellular permeability syndrome [33].

Abdominal pain is frequently one of the manifestations of this syndrome, and it can be associated with diarrhea or constipation, weight loss, vomiting, or just pain [22,34-42].

Sympathomimetic amine therapy has been used mostly in women for the increased cellular permeability syndrome, but

this condition also occurs in men, e.g., severe constant headaches from concussions, or from multiple brain surgery, or very severe abdominal pain and vomiting from mesenteric sclerosis, or gastrocolic reflex with sudden diarrhea [22]. Dextroamphetamine sulfate quickly abrogated severe intractable pain from post-herpetic neuralgia of 5-year duration despite no relief from anti-neuropathy drugs, analgesics and even high dosage of opioids in an 89-year-old man [43].

Sympathomimetic amine therapy has been effective for treatment refractory joint, ligament and muscle pain, e.g., rheumatoid arthritis [44], fibromyalgia [45], chronic complex regional pain syndrome [46], frozen shoulder syndrome [47], the aromatase-induced arthralgia syndrome [48], and severe long-term pain from multiple fractures following exposure to an improvised explosive device (IED) allowing the patient to quickly cease high dosage opioids, including fentanyl, that did not adequately relieve his pain [22].

Dextroamphetamine sulfate has been beneficial for various neurological and muscle disorders, e.g., improving fatigue and sometimes allowing improved muscle function such as Parkinson's Disease, multiple sclerosis, hereditary spastic paraplegia and the mitochondrial encephalopathy lactic acid stroke-like syndrome (MELAS) [22,27-29,49]. Sometimes the symptoms are only associated with certain periods in the menstrual cycle. Amphetamines have been successful in treating chronic pelvic pain, mittelschmerz, dysmenorrhea, dyspareunia and vulvovaginitis [23,41,50-53].

Not only have premenstrual backaches responded to dextroamphetamine sulfate but so have chronic backaches even when the backaches seemed to be related to herniated discs [54,55].

Despite extensive use of dextroamphetamine sulfate for over 40 years without any single person developing an addiction or serious complications, the drug is considered a class II drug, in the same category as potent opiates!! Because of its class II status, most physicians have shied away from its use. Recently, the prejudice about using this class of drugs has magnified with the push to preventing patients from developing addiction to narcotics. In the state of New Jersey, where our medical school and hospital are located, and where our main practice exists, there is a law that states that one cannot use any class II drugs off-label. The majority of the patients treated did not also have an on-label use, e.g., attention deficit syndrome, but we were able to overcome this problem by consulting these patients in our Pennsylvania office (where there is no such law).

However, in January 2021, the Attorney General of New Jersey, before he resigned from office, made a decision, that in his opinion, treating patients in another state, where the New Jersey law did not exist, was breaking the law, both by the patient being treated and by a doctor especially with a medical license in both states. Though this opinion was considered unconstitutional after consulting a

former Attorney General of New Jersey and an Attorney General of another state, there was no way for the treating physician to defy the new mandate.

It had been hypothesized that the mechanism of action of the sympathomimetic treatment was by its release of dopamine from sympathetic nerve fibers, which was the biogenic amine responsible for decreasing cellular permeability [33]. Thus, we sought to explore the possibility that a different dopaminergic drug, that has no prescribing restrictions for its use (even if off-label), could also improve the various manifestations of the increased cellular permeability syndrome. Thus, we sought a convincing test case for pelvic pain to see if using the dopaminergic agent cabergoline could also prove to be effective, in relieving the pelvic pain, and thus provide an alternate treatment to at least one clinical manifestation of this increased cellular permeability syndrome.

Case Report

A test case was sought to evaluate whether taking cabergoline 0.5mg 2x/week would ameliorate severe dysmenorrhea and mittelschmerz. The study would be terminated if the first case showed marked improvement or no women in five attempts showed improvement. The case selected for evaluation was a 22-year-old woman seeking to become pregnant who had severe mittelschmerz and dysmenorrhea beginning one week before menses that was described as incapacitating. Furthermore, she could not remember any menstrual cycle in the last 10 years without the severe pelvic pain. Cabergoline was started on day one of her menstrual cycle. The patient reported little or no pelvic pain, either mittelschmerz or dysmenorrhea, even in the first treatment cycle and she has had no pelvic pain for the past 11 months.

Discussion

This case report demonstrates that cabergoline can provide effective relief of pelvic pain, in at least one case. Thus, this test case could stimulate interest in evaluating the efficacy of cabergoline in relieving pelvic pain in a larger series, either completely observational, or randomized to compare to another treatment modality. Without financial backing from a pharmaceutical company, with no extra compensation for participating, it does not seem ethical to evaluate the efficacy of the drug in a placebo-controlled study.

There are many anecdotal cases demonstrating benefits of dextroamphetamine sulfate for pelvic pain. Nevertheless, the reader may be left without a clear understanding whether the beneficial effect is the exception or the rule. A larger case series presented did show the efficacy of dextroamphetamine in relieving pelvic pain in the majority of a case-controlled study [56].

Most of the medical treatments of pelvic pain inhibit the women from conceiving while on the medication [51]. Furthermore, there is little evidence that these drugs, that suppress or compete with estrogen, improves the woman's subsequent chance for conception [51]. Though laparoscopic surgery for endometriosis can provide

predominately-transient pelvic pain relief, it may be at the expense of causing diminished ovarian reserve (DOR) by either damaging ovarian blood supply or the ovaries directly [57]. Because of chronic pelvic inflammation, many people with pelvic pain have DOR, even without surgical compromise [58,59].

There is evidence that progesterone blocks dopamine during the luteal phase to purposely allow irritants to infuse into pelvic tissues. This establishes a purposeful inflammatory response so that there are 70% NK cells and 20% macrophages in the fetal-placental microenvironment [1,2]. One of the main purposes of this increased cellular immune response is to remodel some thick-walled uterine arteries to develop thin-walled spiral arteries to allow sufficient nutrient exchange between mother and fetus [1,2].

The BCL6 endometrial marker is associated with pelvic inflammation and endometriosis [60]. One study of women with pelvic pain found 52 of 69 women to be positive for this BCL6 marker. In the 17 women negative for BCL6 there was a 58% live delivered pregnancy rate following fresh embryo transfer. However, for the 52 women positive for the marker there was only an 11% live delivered pregnancy rate [60]. Thus, excessive endometrial inflammation may be a cause of implantation failure by immune rejection of the fetal semi-allograft. There was a study in women ≤ 39 who had pelvic pain and were undergoing in vitro fertilization-embryo transfer (IVF-ET) where, not only did the pelvic pain markedly improve in those taking dextroamphetamine sulfate, but the live delivered pregnancy rates were even slightly higher in those with pelvic pain compared to women without pelvic pain not taking amphetamines [61]. For women age 40-42, the live delivered pregnancy rates per fresh ET were twice as high in the group with pelvic pain taking dextroamphetamine sulfate vs. the controls [62]. Thus, if larger studies demonstrate equal efficacy in relief of pelvic pain with cabergoline compared to dextroamphetamine sulfate, one should also determine if it is equally efficacious in correcting infertility issues. Our group is considering performing a comparison study evaluating the efficacy of cabergoline for New Jersey patients in relieving pelvic pain and subsequent correction of infertility vs. dextroamphetamine sulfate for patients living in most other states where off-label use is not precluded.

In the pipeline are studies to evaluate efficacy of cabergoline for other manifestations of the increased cellular permeability syndrome. Already anecdotally, we are observing efficacy for headaches even when traditional treatments have failed. Sometimes the dosage of dextroamphetamine sulfate may be needed to be increased to maximally correct one of the manifestations of the increased cellular permeability syndrome. However, side effects from the drug may preclude the dosage increase. Possibly, adding cabergoline in addition to the amphetamine could improve symptoms without increasing side effects of the amphetamines, if higher dosages are required.

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