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Marked Improvement of Severe Treatment Resistant Migraine Headaches with the Dopaminergic Drug Cabergoline

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ABSTRACT

One of the hypothesized mechanisms for headaches is an increase in brain tissue permeability resulting in unwanted irritants permeating brain tissue leading to inflammation and pain. Support for this hypothesis was provided by the demonstration that treatment with the drug dextroamphetamine sulfate leads to very improved relief of pain even when standard treatments have failed. The reason for using dextroamphetamine sulfate was to release more dopamine from sympathetic nerve fibers to decrease cellular permeability, and thus inhibit infiltration of irritants. However, it is possible that this sympathomimetic amine functions in some different way to relieve headache pain other than diminishing cellular permeability by releasing dopamine. To test this hypothesis another drug, cabergoline, which is not in the amphetamine class of drugs, that releases more dopamine into the circulation, was given to a woman with severe headaches refractory to all standard therapy with the exception of dextroamphetamine sulfate. Similar to dextroamphetamine sulfate, cabergoline resulted in marked amelioration of the headaches thus supporting the hypothesized mechanism. From a practical standpoint, cabergoline can be tried in patients who have side effects from dextroamphetamine sulfate. Also, since cabergoline has no class II drug restrictions, patients and prescribing physicians may be more comfortable prescribing cabergoline over dextroamphetamine sulfate. Furthermore, it can substitute as an alternate treatment for patients in certain states, e.g., New Jersey, where off-label use of class II drugs is prohibited.

Keywords

Increased cellular permeability syndrome, Sympathomimetic amines, Tissue inflammation, Headaches, Dopamine.

Introduction

Treatment of severe treatment refractory headaches with the sympathomimetic amine dextroamphetamine sulfate was first published anecdotally in 2009. The first case was a 33-year-old woman with severe migraines that occurred daily and were considered unbearable for two years. No pathologic etiology was found, and thus the headaches were considered idiopathic migraines. She failed to respond to beta-blockers, ergotamine, gabapentin, topiramate, biofeedback and acupuncture. She quickly showed marked abrogation of the headaches following treatment with dextroamphetamine sulfate. She remained headache free for 3 ½ years. They immediately returned full force when she stopped the medication for a month until she restarted dextroamphetamine sulfate when they completely dissipated once again [1]. The second case with severe migraines that also showed dramatic improvement with dextroamphetamine sulfate, only had the headaches during the premenstrual time [1].

Another 33-year-old woman with severe daily migraine headaches of unknown etiology, not only demonstrated marked abrogation of the headaches shortly after starting dextroamphetamine sulfate (3 days), but similarly proved Koch's postulate in that though she had

100% relief for 4 years while taking dextroamphetamine sulfate, they returned within one week after stopping the sympathomimetic amine. The headaches completely disappeared within 3 days of resuming dextroamphetamine sulfate [2]. Dextroamphetamine sulfate was able to eradicate headaches presenting in a different manner, and even in cases where a known condition or circumstance was considered as a potential cause. One 44 year old woman developed severe headaches twice a month (but unrelated to her menstrual cycle) that lasted for a few days each time. They were treatment resistant. Interestingly, she would also get severe vasomotor symptoms only when she developed headaches. She would also get a very severe headache shortly after takeoff when riding in an airplane, which would last the entire trip on the plane and a few hours thereafter. Both the headaches and the vasomotor symptoms were completely eradicated following treatment with dextroamphetamine sulfate [3].

Severe headaches may be associated with other medical conditions all of which improve following dextroamphetamine sulfate. One woman had severe ocular migraines that failed to improve with standard therapy, but markedly improved with dextroamphetamine sulfate. Interestingly, this drug besides eradicating the ocular migraines, completely eradicated treatment resistant interstitial cystitis of 12-year origin as well as dyspareunia [4]. Dextroamphetamine sulfate also eradicated long standing severe retroorbital headaches that were attributed to keratoconus, but yet failed to respond to two corneal transplant surgeries that were performed to relieve the pain [5]. The fact that sometimes these "idiopathic" headaches are associated with other pathological conditions that similarly respond to dextroamphetamine sulfate might suggest a common etiology. Indeed, vasomotor symptoms and interstitial cystitis have demonstrated marked improvement with dextroamphetamine sulfate therapy even when not associated with headaches [6-9]. Patients with pelvic pain, e.g., dyspareunia, dysmenorrhea or chronic pelvic pain or vulvodynia without headaches have also demonstrated marked amelioration of pain when treated with dextroamphetamine sulfate [10-12]. The concept of a common etiology for these conditions was supported by not only eradicating dysmenorrhea, chronic pelvic pain and mittelschmerz, but also Crohn's disease following treatment with dextroamphetamine sulfate [13]. There have been other cases of treatment refractory Crohn's disease, ulcerative colitis, and microscopic lymphocytic colitis that similarly respond to dextroamphetamine sulfate that was not associated with headaches [14-16]. Thus, it seems possible that certain conditions, possibly genetic, including, but not limited to brain tissue, may be more susceptible to absorption of irritating elements related to increased tissue permeability that may be corrected by treating with a drug, e.g., dextroamphetamine sulfate, which by releasing more dopamine by sympathetic nerve fibers, diminishes cellular permeability of these tissues, and thus prevents inflammation and pain or organ dysfunction. Perhaps a genetic defect or tendency exists, but needs a subsequent adverse event, e.g., a virus infection, that increases the permeability defect to a level that allows infiltration of noxious substances. Alternatively, there could be a genetic basis for relative insufficient release of dopamine from sympathetic fibers leading to increase permeability of several organ systems. However, trauma in itself seems to create increased tissue permeability resulting in severe headaches. One teenager who never complained of headaches before, had constant unrelenting severe headaches every minute of the day while he was awake which was a result of 17 brain surgical procedures for a choroid plexus papilloma type of brain tumor. Through the surgical procedure finally eradicated the tumor, the pain persisted for 3.5 years, and did not respond to standard therapy. The pain disappeared 1 hour after taking dextroamphetamine sulfate and did not return except when he occasionally ran out of medication [17].

A very similar scenario was found in a 22-year-old male with two years of severe daily headaches that occurred following his seventh concussion playing college ice hockey [17]. Severe post-concussion headaches ensued in two teenage girls who had concussions from a school bus accident that persisted for weeks and precluded them from returning to school. Interestingly, they both had severe stuttering following the accident with no prior history. Both showed not only marked improvement in their headaches, which were resistant to standard therapy, but their stuttering immediately completely ceased [18]. For some strange reason dextroamphetamine sulfate has been assigned to the same class of drugs as serious opiates, e.g., oxycodone, oxycontin, and fentanyl. Thus, there has been a general reluctance by many physicians to prescribe this drug especially with the crack-down of doctors prescribing class II drugs. Thus, it would be a great benefit to the treatment of severe headaches to find an alternate drug that releases dopamine, but has no prescribing restrictions. One such potential drug is cabergoline.

A pilot case using cabergoline to treat a woman with very severe frequent migraine headaches that were very resistant to standard therapy but had responded extremely well to dextroamphetamine sulfate for many years is being presented. She had stopped this treatment because of a new interpretation by the Attorney General of her geographic state. The state of New Jersey has a law that does not allow a physician to write a prescription for an off-label use of a class II drug. The new interpretation was that this law would apply to patients seeking treatment in another state where no such law exists if that patient wants to still be a resident of New Jersey. This circumstance did provide her neurologist the opportunity to try new drugs approved for migraine headaches, but since they were ineffective for the return of her severe headaches, she was willing to be the first test case to see if cabergoline could provide her with some relief.

Case Report

The patient began noticing migraines in age 22. They were never associated with her menstrual cycle. In the beginning, she would get a migraine about four times a month, and they would be considered a rating of 8 out of 10 in severity and quite debilitating. She had been treated with carbamazepine, propranolol, gabapentin, and pregabalin, but none of these medications provided significant improvement to be worth the side effects.

She started amphetamine salts containing dextroamphetamine sulfate (Ds) 11 years ago at the age of 44. Thus, she had at least 20 years of migraine headaches that were not well relieved by any of those other medications. She started amphetamine salts containing 9.4mg DS, which reduced her headaches moderately. The dosage was gradually increased to 30mg three times daily amphetamine salts (about 56mg dextroamphetamine sulfate) which completely eradicated her headaches. However, since she was a resident of the state of New Jersey she had to abruptly stop the dextroamphetamine sulfate with the Attorney General's new interpretation of an old law. Though there were no withdrawal symptoms, her severe migraine headaches returned within a week. She was prescribed newer anti-migraine medications by a consulting neurologist but did not show any significant improvement with antogepant, savegepant, or rimegepant. We decided to treat her with a different dopaminergic drug – cabergoline 0.25mg twice weekly. She had improvement of her headaches but noticed that she would get her migraines back right before her next pill was due. Thus, she was prescribed 0.25mg three times per week which was gradually increased to 0.5mg 3x/week and the headaches were much improved but still not as good as DS.

Years before preceding her treatment with dextroamphetamine sulfate she had Bell's Palsy, which spontaneously remitted, but left her with continuous twitching of her left eye. This completely disappeared when she was treated with dextroamphetamine sulfate. Though the cabergoline helped the migraine headaches, it did not relieve the eye twitching at all. At times when attending certain social events she would borrow some dextroamphetamine from friends and the eye twitching would disappear immediately. She is now age 55 and she is doing well with no untoward side effect from the cabergoline. When she consulted the neurologist she also complained that subsequent to stopping the dextroamphetamine sulfate she had swelling in both legs, ankles, and feet. Besides improving her migraine headaches and eye twitching, DS markedly improved marked edema of her legs [19,20]. She stopped DS, the edema quickly returned. The neurologist who prescribed the new drugs targeting the calcitonin gene related peptide (CGRP) was the opinion that the edema was related to chronic regional pain syndrome. The edema resolved once again when she reached the dosage of cabergoline 0.5mg 3 times per week.

She has now been on cabergoline for one year and she is doing well with the headaches and there has been some improvement in the left eye twitching. The twitching gets worse with stress so at that time she borrows some dextroamphetamine sulfate which works better for the eye twitch.

Discussion

Since the early 1990's serotonin receptor activation of chemicals known as triptans have been the standard of care for treating acute migraine headaches and to prevent them. Based on studies of the pathophysiology of migraine headache, pharmaceutical companies have developed and attained United States Food and Drug Administration (FDA) approval for anti-migraine drugs that have more specific targets that can reduce the intensity of the number of days per month that a patient has migraine headaches and also reduces the intensity. Many of these new drugs target the CGRP. These drugs may target CGRP by monoclonal antibodies or monoclonal antibodies directed against CGRP receptor abbreviated anti-CGRP-R mabs), e.g., erenumab, galcanexumab, fremanezumab and eptinezumab, or small molecule CGRP receptor antagonists, e.g., gepants [21]. A good review on new oral anti-migraine drugs that had been developed over the last 5 years has been published by Karsan and Goodsby [22]. They also discuss new target molecules and mention drugs that are presently being evaluated in clinical trials [22].

It generally costs over one billion dollars for a pharmaceutical company to get a drug to market. Thus, the costs of new drugs without third party reimbursement is generally prohibitive. Even when covered by insurance, the copays may be extremely high and thus many patients who are resistant to standard therapy will not have access to these new drugs. The same applies for botulinum toxin A which has been used for refractory cases, but most often is not affordable [23]. In contrast, generic dextroamphetamine sulfate and generic cabergoline are relatively very inexpensive even if not covered by prescription plans because of off-label use. However, it has been our experience that despite off-label use, most insurances will pay for these drugs even if the indication is headaches, not attention deficit hyperactivity syndrome. There are many proposed mechanisms for the cause of migraines, and inflammation of brain tissue or surrounding tissue because of increased cellular permeability is just one of them. Thus, it may be that dopaminergic drugs, by diminishing cellular permeability and preventing infiltration of inflammatory agents into brain tissue, will prevent and/or lessen the intensity of migraine headaches or headaches with other etiologies only when the mechanism is inflammation. Hopefully, this case report will encourage the pharmaceutic industry to manufacture "better" dopaminergic drugs for migraine headaches that are less controversial or even more effective. The decision to try DS to treat headaches was not a fortuitous finding but was based on research into the mechanism of successful implantation [24]. Evidence supported the need to create an autoimmune reaction during the luteal phase directed against thick-walled uterine arteries to develop some thin-walled blood vessels known as spiral arteries which are needed to allow nutrient exchange between mother and fetus. Progesterone (P) was hypothesized to diminish cellular permeability. The model developed from the research suggested that P blocked dopamine, thus increasing cellular permeability allowing irritants to infuse into pelvic tissues leading to the inflammatory response to allow uterine artery remodeling. Thus, a drug was sought that would release more dopamine from sympathetic nerve fibers.

At that time more than 45 years ago, the only dopaminergic drugs known to the lead author was levodopa and DS. The latter was thought to be better tolerated so DS was tried to improve pelvic pain but also other medical conditions. In fact, the first publication of the efficacy of DS for treating medical problems was published in 1984 where it completely eradicated very severe treatment refractory chronic urticaria [25].

Bromocriptine and later cabergoline were drugs developed to increase the prolactin inhibiting factor (which actually is dopamine) to treat galactorrhea and prolactinomas, were not available as yet on the pharmaceutical market when we considered treating various pathological conditions (especially those associated with inflammation and pain). Related to such great responses to DS, there had not been a great need to try other dopaminergic drugs. Nevertheless, similar to DS, cabergoline has been found to provide marked amelioration of pelvic pain [26]. Sometimes pelvic pain may be present the entire menstrual cycle but sometimes only occurs pre-menstrually. This has been attributed to the further increase in infusion of irritants into pelvic tissue related to P blocking dopamine. Similarly, some women only get migraine headaches premenstrually [4].

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