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CASE REPORT

Marked Relief of Pain from Burning Mouth Syndrome Following Treatment with the Dopamine Agonist Cabergoline-Case Report

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Abstract

Background: Many chronic conditions that frequently cause pain in certain areas of the body seem to be related to the infiltration of unwanted irritants across a mucosal barrier in certain tissues that have been weakened by genetic, traumatic, or infection factors. They all have in common that they are ameliorated following treatment with dopaminergic agonists. In the large majority of case reports, the patients were treated with the dopamine agonist Dextroamphetamine Sulfate (DS). However, the dopamine agonist cabergoline (Typically used to treat galactorrhea or prolactinomas) has also been successful in eradicating refractory pain syndromes. One pain syndrome that has been successfully eradicated by dopamine agonists is the Burning Mouth Syndrome (BMS). There is one case report showing great efficacy of treating BMS (Stomatodynia) with DS. The case reported here presents the second case of BMS completely eradicated by treatment with a dopamine agonist.

Methods: A 44-year-old woman had multiple pathological symptoms including a very painful tongue and palate with no visible lesions. She previously had a history of Premature Ventricular Contractions (PVCs). She was initially prescribed amphetamines, but it was stopped because she thought it increased the frequencies of PVCs. She was then treated with cabergoline. 0.5 mg two times per week

Results: Within one month her primary BMS was completely eradicated. She has been free of BMS for 4 years.

Conclusion: This is the second case of marked amelioration of BMS following the treatment with a dopamine agonist. It is the first case of eradication of BMS with the sole treatment with the dopamine agonist cabergoline.

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Introduction

Primary Burning Mouth Syndrome (BMS), otherwise known as stomatodynia, does not have a known etiology and is thus considered idiopathic [1]. In primary BMS there are no identifiable lesions causing the severe pain in the oral pharyngeal area which can include the lips, tongue, uvula, and palate. The International Headache Society described BMS as "An intra-aural burning or dysesthetic sensation recurring daily for more than 2 hours per day for more than 3 months without evident causative lesions++++++++ns on clinical examination and investigation" [2].

BMS is uncommon with a prevalence of only 0.11% in the general population. However, it increases with age so that it has a prevalence of 0.53% in women aged 70 - 79 [3-5], Though there are many drugs that have been used to treat primary BMS, in general, the clinical benefits have been disappointing [6]. These medications include drugs listed in the anti-convulsant family e.g., pregabalin, clonazepam, and gabapentin. Antidepressants have also been used e.g., trazodone and citalopram. According to a study by Grinspan D, et al. [7]. 500 women over 60 years of age experiencing burning mouth syndrome were commonly diagnosed with psychiatric disorders, such as anxiety and depression, which could significantly influence the severity of BMS. This may be due to the fact that anxiety and post-traumatic stress can disrupt adrenal steroid production, which could consequently alter neuroactive steroids levels. In menopausal women, who already have a preexisting decline in gonadal steroid production which may cause adrenal dysregulation of neuroactive steroids, this could ultimately lead to abnormal nerve signaling and a burning oral sensation [8]. There are many other medications that have been tried which are mentioned in the systematic review by Tan HL, et al. [6]. They state, however, "that no treatment has been found that provides at least a 50 % reduction in pain".

There has been a case of BMS where there was complete 100% long term eradication of pain from BMS with the dopamine agonist Dextroamphetamine Sulfate (DS) [9]. The chemical structure for dextroamphetamine sulfate is seen in figure 1. There have been many different types of refractory pain syndromes that have been successfully treated with the dopamine agonist DS [10-14]. The proposed mechanism as to why dopamine agonists e.g., DS, are so effective relates to the mechanism of this drug in reducing cellular permeability by releasing more dopamine from sympathetic nerve fibers. This supports the hypothesis that the main mechanism for various pain conditions and other chronic medical conditions is the infiltration of unwanted chemical irritants into various tissues related to these toxic elements traversing the mucosal barrier related to relative increased permeability of that tissue [12,14]. In stomatodynia, small sensory nerve fibers in the oral mucosa degenerate, leading to the burning sensation [15]. Drugs, e.g., DS, by increasing the release of dopamine from sympathetic nerve fibers lead to the correction of the increased cellular permeability defect of that tissue or tissues that are involved in a given clinical presentation [10-14].

Another dopamine agonist that has been used to treat pain syndromes related to this increased cellular permeability syndrome is cabergoline [16-18]. The chemical structure for cabergoline is seen in figure 2. The aforementioned patient whose BMS was eradicated with DS for 10 years had noticed a very mild form of tardive dyskinesia as a side effect of the DS therapy. The

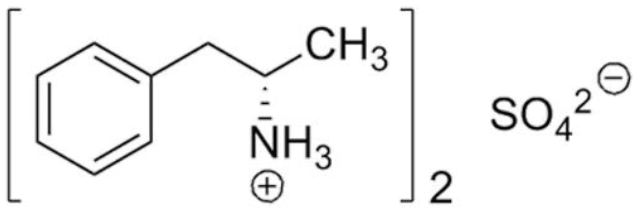

Figure 1 Chemical structure of dextroamphetamine sulfate.

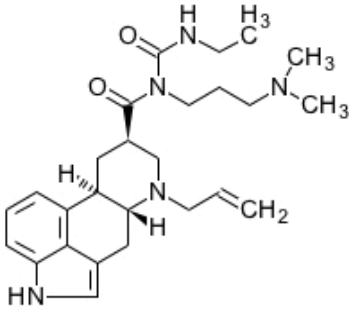

Figure 2 Chemical structure of cabergoline.

tardive dyskinesia was negated by decreasing the dosage of DS and adding cabergoline [19]. A case is presented here where complete eradication of BMS was achieved by the sole treatment with cabergoline.

Case Report

The patient first came to our medical practice at age 34 with primary infertility seeking help to become pregnant. We found that her only problem was a luteal phase defect and she conceived with vaginal progesterone supplementation in the luteal phase [20]. She was also found to have low thyroid function, and she was treated with thyroid hormone supplementation.

We continued to follow her for her hypothyroidism on a yearly basis. At age 44 she stated that she had been having a problem with weight gain and fatigue with normal thyroid, adrenal, renal, liver, and cardiac functions and the absence of anemia. We thus concluded that she was probably suffering from the increased cellular permeability syndrome [21-25]. She also stated that she had been under the care of a cardiologist for palpitations related to frequent Premature Ventricular Contractions (PVCs) of an unknown etiology. She also stated that she had developed a problem with severe burning of the tongue and palate, but her dentist did not notice any lesions to explain the pain. We believe that her history was consistent with the increased cellular permeability syndrome, and we prescribed amphetamine salts 15mg upon arising and at noon hoping it would correct her clinical symptoms without worsening the arrhythmia. Thirty mg of amphetamines salts provide 18.8mg of the active ingredient Dextroamphetamine Sulfate (DS). However, she thought that the palpitations may have increased with the amphetamine treatment, and thus it was stopped.

She was switched to cabergoline 0.5mg before bedtime with a non-protein food twice per week. Within one month her primary BMS was completely eradicated, and the fatigue was moderately improved. However, she did not lose any weight, but the steady increase did stop. She has been free of BMS for 4 years, and her weight has been stable, and her fatigue remains moderately improved.

Discussion

As mentioned, despite the multitude of different drugs and other therapies to treat BMS, even those with some efficacy do not seem to reduce the pain more than 50% [6]. Though there have only been 2 cases where BMS was treated with dopamine agonists, in the patient treated with DS, and the other treated with cabergoline, both showed 100% improvement with dopaminergic therapy [19]. Supporting these findings, a study by Hagelberg et al. examined the D1 and D2 dopamine receptors in the brains of patients with BMS compared to healthy individuals. They found that the D1/D2 ratio was 7.7% lower in the right putamen and 6.4 % lower in the left putamen. This reveals an imbalance of excitatory (D1) and inhibitory (D2) signals, and suggests a reduction of natural dopamine in that area of the brain [26].

Thus, this is the first case report demonstrating that primary BMS can be completely eradicated by the sole treatment with cabergoline. In general, however, we find that the efficacyof cabergoline treatment is inferior to DS when treating other manifestations of

the increased cellular permeability syndrome. At least in one case we found that whereas cabergoline did not provide as much relief as the patient had experienced with DS, carbidopa levodopa 10/100 mg twice daily was equally as effective as DS [27]. Both carbidopa levodopa and cabergoline are pure dopamine agonists. In contrast, DS releases not only dopamine from sympathetic nerve fibers, but also epinephrine and norepinephrine. Efficacy with the pure dopamine agonists supports the conclusion that the various manifestations of the increased cellular permeability syndrome are related to increased cellular permeability of certain tissues allowing unwanted irritants to traverse the mucosal barrier. Thus, the hypothesis that dopamine agonists work by decreasing cellular permeability seems to be a reasonable theory. However, this concept of the increased cellular permeability syndrome is hypothesis driven and as yet this concept is not widely accepted or even known by most clinicians or scientists. Hopefully these case reports will influence others to treat the various medical conditions that seemingly have resolved so well to dopamine agonists to either support or refute this concept that increased cellular permeability is "the root of all evil" but can be successfully treated by drugs e.g. dopamine agonists that negate the increased cellular permeability.

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