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Case Report Open Access

Apresoline Promoted Acrolein Reduction in Patient with Relapsing Remitting Multiple Sclerosis

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Abstract

Background: Acrolein has been implicated as an irritating/exacerbating factor in animal models of relapsing-remitting multiple sclerosis. In animal studies, Apresoline (Hydralazine) has acted as a successful acrolein scavenging agent and resulted in reduced behavioral deficits and decreased myelin damage. It has been hypothesized that Apresoline would be equally successful as a disease modifying treatment for relapsing-remitting multiple sclerosis.

Objective: To describe the case of acrolein reduction in a patient with relapsing-remitting multiple sclerosis taking Apresoline.

Methods: Case study.

Results: The patient was diagnosed with relapsing-remitting multiple sclerosis and found to have an elevated level of acrolein. After 60 days of Apresoline treatment, the patient's acrolein level was reduced to a normal level. Dosage was reduced to establish a minimum effective dosage with no assessed increase in relapsing-remitting multiple sclerosis activity.

Conclusion: Elevated levels of acrolein were documented in this relapsing-remitting multiple sclerosis patient. Apresoline was demonstrated to be an effective acrolein scavenger in this patient and a minimum effective dosage was established.

Keywords: Acrolein; Apresoline; Case study; Multiple sclerosis; 3-HPMA

Introduction

Acrolein is a toxic β-unsaturated aldehyde which initiates and perpetuates oxidative stress and is capable of damaging the membrane, myelin and mitochondria within the central nervous system (CNS). A recent study conducted in experimental autoimmune encephalomyelitis (EAE) mice, the animal model of Multiple Sclerosis [1], reported elevated levels of acrolein were present in CNS tissue as symptoms peaked [2]. Additionally, it has been reported that the FDA-approved compound, Apresoline, typically used to treat hypertension, has been successful in dampening the symptom severity and slowing the progression of the disease in EAE animal studies [1].

The case of a patient recently diagnosed with relapsing-remitting multiple sclerosis (RRMS), while already treated with the immunomodulant Gilenya (Fingolimod) for approximately 6 months, who subsequently began a regimen of Apresoline, is reported. With the addition of Apresoline to the patient's established treatment regimen, acrolein levels decreased to, and remained at, levels consistent with the general population. These results were achieved at a significantly lower dosage than hypothesized by previous research [1].

Case Report

A 45 year old man with no significant medical history was diagnosed in 2015 with optic neuritis and RRMS via neurological studies after experiencing impaired vision for two weeks. Cranial and cervical magnetic resonance imaging (MRI), performed on June 20, 2015 and July 2, 2015, respectively, showed multiple lesions in the deep white matter of the brain as well as a possible lesion of the spinal cord at C3-4. Additional ill-defined abnormalities were noted at the level of 10 and to a lesser degree at T7-8. The patient reported no history of functional loss or other symptomology consistent with RRMS and an initial diagnosis of clinically isolated syndrome (CIS), typically associated with the first relapse of RRMS, was assigned. At that time, Gilenya (0.5 mg once per day) was prescribed.

In collaboration with the patient's physician, the potential influence of acrolein as a metabolite of the lipid peroxidation process, which is associated with MS, was recognized as a potential consideration for the patient's treatment regimen. Since acrolein is a highly reactive aldehyde, it is difficult to quantify directly. However, recent studies have demonstrated that a stable metabolite of acrolein, N-acetyl-S-3-hydroxypropylcysteine (3-HPMA) can be measured in urine as a reliable biomarker of acrolein [3]. With the aid of the EAE animal studies and the known safety and effectiveness of Apresoline [1,4], the patient's acrolein level was established through evaluation of his 3-HPMA level, and an initial dosage of Apresoline was prescribed.

On August 15, 2015, it was established that the patient had an elevated level of acrolein in his system. The normal range for acrolein is 0-0.5 μg/mg creatinine. The range for chronic smokers is 0-7.5 μg/mg creatinine. Acrolein toxicity is >2.0 μg/mg creatinine. The patient's acrolein level was established as 48.36 μg/mg creatinine. On August 28, 2015, the patient began an oral regimen of Apresoline (10 mg per day). After 48 days of the prescribed regimen, the patient's level of 3-HPMA was found to be greatly reduced (29.76 μg/mg creatinine), yet still in the above normal range. Apresoline dosage amount was then increased to 50 mg per day. After 35 days of the revised regimen, the patient's level of 3-HPMA was found to be 0.43 ug/mg creatinine, which is within established normal range. Assessment of 3-HPMA continued at varying intervals over the next 120 days to monitor the continued

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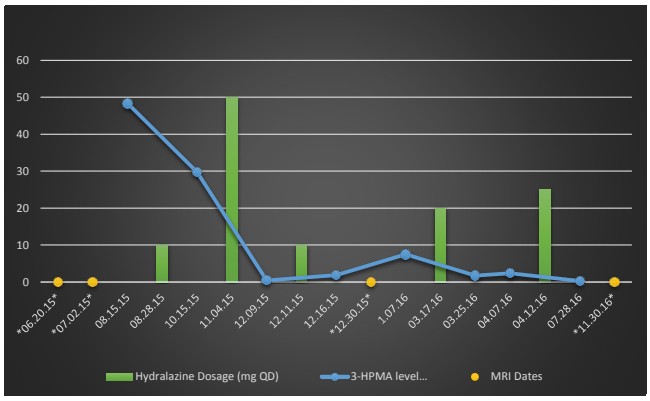

Figure 1: Apresoline promoted acrolein reduction.

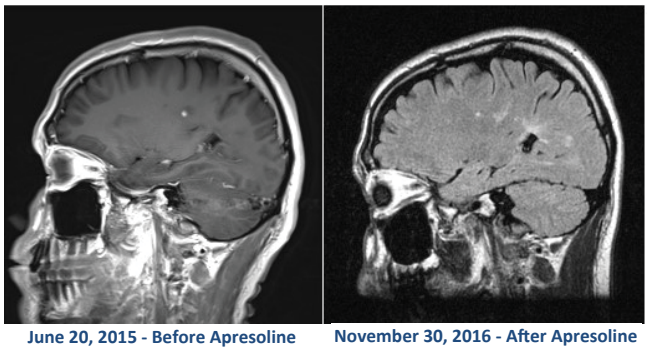

Figure 2: MRI comparisons.

reduction of acrolein as well as to establish a minimum effective dose. On April 12, 2016, the dosage amount of Apresonline 25 mg once per day was deemed effective at maintaining the reduced level of 3-HPMA for this patient (Figure 1). During the course of treatment for RRMS, the patient received multiple MRIs to monitor the progression of the disease as well as to assess any correlation between the reduction of acrolein and gadolinium enhanced lesions (GEL) activity or motor deficits. The first two MRIs were performed on June 20, 2015 and July 2, 2015, during the initial diagnosis of RRMS, when no treatments had been administered. The third MRI was performed on December 30, 2015. It was determined that GEL activity had been reduced by 50% along the spine, but no change had been observed in GEL activity in the brain. More specific comparison to prior MRI results indicated decreased size of the lesion at C3-4 with no indication of additional spinal cord lesion. On November 30, 2016, a third MRI was performed. Findings indicated no change in GEL activity along the spine or in the brain. More specifically, the lesion at C3-4 was noted to be stable and no significant change in the appearance of the brain could be appreciated (Figure 2).

Discussion

To our knowledge, this is the first report of human outcomes that confirm the benefit of Apresoline as a possible treatment to decrease the severity of symptoms associated with multiple sclerosis by countering the effects of acrolein. Since the inception of the above described treatment regimen, the patient has retained his normal level of function and has experienced only mild symptoms related to RRMS. At the time of this publication, there have been no noted side effects from the prescribed regimen and no indication of need to modify the doses prescribed.

While research efforts continue to expand the body of knowledge related to acrolein and its debilitating effects on the central nervous system, this study should be considered as the impetus and catalyst for additional research intended to develop innovative and affordable treatment regimens for patients diagnosed with RRMS. Due to the simplicity of the regimen and the existing research efforts of Hamann and Shi [5], it is hoped that Apresoline will soon become an ntegral part of the standard of care for patients with RRMS [1-3].

Conflict of Interest

None declared.

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