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Donepezil for α-synuclein Constipation: An 18 Month Follow-Up

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Received Date: July 10, 2018 **Accepted Date:** July 20, 2018 **Published Date:** July 30, 2018

Citation: Charles M. Lepkowsky (2018). Donepezil for α-synuclein Constipation: An 18 Month Follow-Up. POJ Clin Case Rep. 1(1):1-4.

Abstract

In a series of case studies, four patients diagnosed with the α-synuclein or "Lewy body" disorders Parkinson's disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) at different stages of disease progression were treated for the symptoms of constipation, obstipation, and impaction with the acetylcholinesterase inhibitor (AChEI) Donepezil. Initial findings indicated that the use of Donepezil was associated with significant symptom reduction. The symptom status of each of the four patients was reviewed at six and twelve month intervals, with no apparent reduction in bowel motility, nor the emergence of any new symptoms. After eighteen months, the symptom status of each of the four patients was again assessed. Evaluation of the results suggests that the AChEI Donepezil may have long-term benefit for relieving the symptoms of constipation, obstipation and impaction in patients with α-synuclein disorders.

Keywords: Neurocognitive Disorder with Lewy Bodies, Parkinson's disease, constipation, Donepezil, acetylcholinesterase inhibitor

Introduction

In a series of case studies, four patients at different stages of disease progression diagnosed with α-synuclein protein pathology, or "Lewy body" disorders including Parkinson's disease (PD) and Neurocognitive Disorder with Lewy Bodies (NCDLB) were treated for the symptoms of constipation, obstipation, and impaction with the acetylcholinesterase inhibitor (AChEI) Donepezil [1]. The impetus for the studies was a body of research documenting α-synuclein protein impairment of the predominantly cholinergic neurotransmitter pathways in the myenteric plexus (MP) and the colonic submucosal plexus (CSMP) [2]. α-synuclein pathology in the MP and the CSMP impairs cholinergic function and thus bowel motility, leading to the observable symptoms of constipation, obstipation, and impaction [3-10].

Complicating the symptom picture, PD and NCDLB patients with significant Parkinsonian features are often prescribed L-dopa agents like Carbidopa-Levodopa (brand names include Sinemet and Stalevo) to preserve basic motor functions including gait and balance [11, 12]. Bowel immotility is included in the list of Carbidopa-Levodopa's potential side effects [13]. Often overlooked in the literature on PD and NCDLB, constipation, obstipation, and impaction have a significant negative impact on the quality of life for the patient, and complicate care provision [14, 15]. Perplexing to primary care providers and frustrating for patients, over-the-counter medications and other conventional forms of treatment have proven largely ineffective for treating the symptoms of constipation, obstipation and impaction in patients with α-synuclein pathology [16].

Cholinergic Agonist Use in NCDLB and PD: Donepezil and Constipation

Historically, patients diagnosed with α-synuclein disorders including PD and NCDLB have been prescribed acetylcholinesterase inhibitors (AChEIs) with the intention of mitigating α-synuclein pathology cholinergic impairment [17-22]. An AChEI with demonstrated effectiveness in reducing cholinergic impairment without increasing Parkinsonian symptoms or producing new symptoms is Donepezil [23-28]. Donepezil has also been used with nongeriatric affective patients specifically to address constipation, increasing bowel contractions 477% in a population diagnosed with severe bowel immotility [29,30].

Donepezil plays a dual role in reducing bowel immotility. As a specific, reversible acetylcholinesterase inhibitor, Donepezil

limits the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase, effectively increasing acetylcholine levels and mitigating the symptoms of cholinergic impairment [31-33]. Donepezil also independently facilitates neuronal nicotinic acetylcholine receptors [34]. Donepezil's "dual action" has made it an historical drug of choice for mitigating symptoms of cholinergic impairment [22, 23, 25, 31, 34].

Hypothesis

Based on Donepezil's documented mitigation of cholinergic impairment and demonstrated effectiveness for reducing symptoms of constipation in nongeriatric affective patients, as well as increasing bowel contractions in a patients with severe bowel immotility, it was hypothesized that the use of Donepezil for patients with α-synuclein pathology would mitigate symptoms of Lewy body cholinergic impairment in the MP and CSMP including constipation, obstipation, and impaction [23-30]. It was also hypothesized that Donepezil might mitigate bowel immotility associated with the use of Carbidopa-Levodopa, which is often prescribed to Lewy body patients exhibiting Parkinsonian features.

Methods

To assess Donepezil's effectiveness in reducing α-synuclein pathology-mediated bowel immotility, a case study was conducted. Four patients at varying levels of disease progression diagnosed with PD and NCDLB exhibiting symptoms of constipation, obstipation and/or impaction were orally administered Donepezil in daily doses varying from 5 to 10 mg. Two of the patients had been diagnosed with PD based on a series of MRI's, neurological assessments, and CT scans. The other two patients had been diagnosed with NCDLB, based on scores on a series of MRI's, CT scans, neurological evaluations, and scores on the Mini-Mental State Examination (MMSE), the Quick Dementia Rating System (QDRS), and the Lewy Body Composite Risk Score [35-37]. The patients were assessed before treatment, and then at intervals of two, four, and six weeks after treatment had begun. The same four patients were later assessed at intervals of six, twelve, and eighteen months.

Results

For all four patients, assessment at two weeks, four weeks, and six weeks after the introduction of orally administered Donepezil (at 5 or 10 mg HS doses) indicated significant reductions in the symptoms of constipation, obstipation and impaction. At each interval there was no increase in existing symptoms, nor the emergence of new symptoms [1].

Using the methods described above to establish initial diagnosis, six months later, the same four patients were again assessed in a follow-up study. Although there had been progression of some α-synuclein cognitive and movement pathology in two of the patients diagnosed with NCDLB, there was no increase in the symptoms of constipation, obstipation, or impaction, nor was there emergence of any new symptoms [38]. One patient with NCDLB whose cognitive interference (short-term memory loss and difficulty with word-finding) had increased at the six month assessment had their daily dosage of Donepezil increased from 5 to 10 mg.

Another follow-up study using the same assessment procedures was conducted with the same four patients twelve months after the introduction of Donepezil. The NCDLB patient whose dosage of Donepezil had been doubled at six months demonstrated recovery of cognitive function (reductions in short-term memory loss and difficulty with word-finding). More pertinent to the original case study, assessment of the four patients showed no increase in the symptoms of constipation, obstipation, or impaction, no apparent progression of any other α-synuclein symptoms, and no emergence of new symptoms [39].

The same four patients were again assessed eighteen months after the initial introduction of Donepezil, using the same system of evaluation as in the previous assessments. In each of the four patients, assessment indicated no increase in constipation, obstipation, or impaction; no progression of cognitive interference, movement disorders, or other α-synuclein pathology; and no emergence of new symptoms.

Discussion and Conclusions

In four patients at varying levels of disease progression with PD and NCDLB, oral administration of Donepezil in daily doses varying from 5 to 10 mg was associated with significant reduction in the symptoms of constipation, obstipation and/or impaction. In none of the four patients was there progression of cognitive interference, movement disorders, or other α-synuclein pathology, nor the emergence of new symptoms. Symptom reduction for constipation, obstipation and/or impaction was consistent over time, assessed at intervals of two, four and six weeks, and later, at intervals of six, twelve, and eighteen months [1, 38, 39].

The findings support the hypothesis that Donepezil might reduce cholinergic impairment in the ENS, specifically the MP and CSMP, with consequent reductions in the symptoms of constipation, obstipation and/or impaction. The findings also support the hypothesis that Donepezil might mitigate or counteract bowel immotility in patients using Carbidopa-Levodopa.

It appears that Donepezil achieves such symptom reduction through it "dual action:" in part, specifically and reversibly limiting the action of the acetylcholine-hydrolyzing enzyme acetylcholinesterase; and in part, by independently facilitating neuronal nicotinic acetylcholine receptors [31, 32, 34]. The combined effect of these two mechanisms is to effectively increase acetylcholine levels and mitigate the symptoms of cholinergic impairment [33].

The consistency of findings over an eighteen month period in patients diagnosed with degenerative α-synuclein neurocognitive and movement disorders is also consistent with previous research demonstrating that Donepezil is effective for slowing or reversing cognitive symptom progression in α-synuclein disorders, including short-term memory loss, difficulty with word-finding, hallucinations, and cognitive interference [17, 18, 19, 20, 21].

Further research is recommended following patients over an extended time frame to establish longitudinal outcomes, and using larger numbers of subjects matched for diagnosis, age, gender, and other variables.

Informed Consent

Written consent was provided by each of the four patients described in the case studies to release the clinical information contained therein. Patient identifiers have been kept to a minimum.

Declaration

The authors declare no conflict of interest.

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