Neurological Disorders
ISSN: 2329-6895

Hiller et al., J Neurol Disord 2015, S:2
DOI: 10.4172/2329-6895.S2-002

Short Communication Open Access

Are Cholinesterase Inhibitors Effective in Improving Balance in Parkinson's Disease?

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Abstract

Background: Cholinesterase inhibitors have been reported to reduce falls in a double blind pilot study. The mechanism by which cholinesterase inhibitors reduce falls is unknown.

Methods: A pilot, double-blind, placebo-controlled, crossover study examined the effects of donepezil on posturography and frontal executive function. Participants received 6 weeks of treatment with placebo and donepezil in random order, separated by a month washout. Inclusion criteria were an MMSE $\geq$27 and balance impairment on clinical and sensory orientation posturography (SOT) assessments.

Results: Ten participants completed the study. Donepezil improved postural sway in SOT condition 4 (C4, eyes open, sway referenced surface) (p<0.03). The change seen in executive performance (measured by the Trail B-A time) when on donepezil correlated with improvement in SOT C4, r=0.80, p=0.001.

Conclusion: Cholinesterase inhibitors improved two functions related to fall risk, standing balance on an unstable surface and executive set-switching in subjects with PD. We hypothesized that the cholinesterase inhibitor, donepezil, affects fall risk by improving sensory orientation set-switching for balance related to improvements in executive set-switching.

Background

Most falls in Parkinson's disease (PD) appear to be due to a primary balance dysfunction rather than an environmental factor [1]. Accumulating evidence suggests that balance dysfunction cannot only be attributed to changes in the dopaminergic system that seems to be responsible for most of the other motor symptoms in PD [1]. The interventions often helpful in improving other PD symptoms, dopaminergic medications and deep brain stimulation, do not consistently improve balance and falls [2,3]. Degeneration in other brain areas, such as cholinergic cortex, the adrenergic locus coeruleus or the cholinergic/glutaminergic pedunculopontine nucleus may be the origin of the balance problems associated with PD [4].

Cholinesterase inhibitors have a positive impact on global assessments, cognitive function, behavioral disturbances, and activities of daily living in persons with PD with Dementia, Lewy Body Dementia, and PD with Cognitive impairment but without dementia (CIND) [5]. A pooled estimate of therapeutic benefit of cholinesterase inhibitors on cognitive function was found with a standard mean difference (SMD) of -0.34 (95% CI -0.46 to -0.23, p<0.00001) versus placebo. A study enrolling 23 subjects in a cross-over design, showed a reduction in falls in persons with PD without dementia when taking donepezil for six weeks. Fall frequency per day decreased from 0.25 ± 0.08 on placebo to 0.13 ± 0.03 on donepezil (p<0.05) [6].

It is not clear the exact role cholinergic function plays in gait, balance, and falls. It is clear that functional walking without falls requires executive function, such as the ability to switch attention quickly [7]. The relationship between cholinergic function and falls has been demonstrated with PET imaging [8]. The cholinergic system, specifically the pendunculopontine nucleus (PPN), may have direct effects on gait and balance. Loss of PPN cells is correlated with balance performance and may affect attention [9-11]. There are also extensive cholinergic projections to the cerebral cortex with the nucleus basalis of Meyert that suplies the marjority of input to the frontoparietal attention network [12]. The frontoparietal attention network has been implicated as a mediator of space-based attention that may be critical for switching attention among sensory systems for spatial orientation for postural control [13]. The cholinergic system, in this case, may play an indirect role on balance via executive function. In fact, patients with executive function deficits show more balance and gait deficits and falls [14]. It is possible that cholinesterase inhibitors could help reduce falls through direct effects on balance and/or via indirect effects on cognition.

The current work is a pilot study with a primary aim to determine the effects of donepezil (a centrally acting cholinesterase inhibitor) on cognition and balance in non-demented persons with PD compared to a placebo.

Design/Methods

Participants

Participants were recruited though Oregon Health and Sciences University (OHSU) movement disorders clinic. The Human Subjects Institutional Boards of OHSU approved the study. All individuals provided informed consent. The study was a randomized, double-blind, placebo controlled, crossover design. Participants received 6

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Received September 08, 2015; **Accepted** September 08, 2015; **Published** September 12, 2015

Citation: Hiller ALP, Nutt JG, Mancini M, Horak FB, Kareus S, et al. (2015) Are Cholinesterase Inhibitors Effective in Improving Balance in Parkinson's Disease? J Neurol Disord S2: 002. doi:10.4172/2329-6895.S2-002

weeks of treatment with either placebo or donepezil with assessments at the beginning and end of the 6-week period, followed by a month washout, then 6 weeks of the other treatment again with assessments at the beginning and end.

Inclusion criteria were 1) idiopathic PD (as determined by UK Brain Bank Criteria) with a Hoehn and Yahr score of 2 to 4, 2) treated with levodopa for at least a year and on a stable antiparkinsonian regiment for at least one month, 3) abnormal dynamic posturography on screening with a composite score of 70 or less. Exclusion criteria were 1) dementia, defined as an MMSE<27, 2) other medical conditions affecting gait 3) inability to stand unassisted, 4) already on cholinesterase inhibitors or anticholinergic medications, or 5) other medical or psychiatric co-morbidities that could interfere with compliance or safety.

Data collection

Balance was measured using the sensory organization test (SOT) on the NeuroCom Balance Master Clinical Research System platform (Neurocom International, Inc), which tests sway in 6 sensory conditions: 1) eyes open, 2) eyes closed, 3) sway referenced visual surround with a stable platform, 4) sway referenced platform with eyes open and 5) sway referenced visual surround and platform. Center of Pressure (CoP) was calculated from the force plate recordings. Forces and moments were recorded at 100Hz sampling frequency, and data were exported and analyzed with a custom algorithm in Matlab (MathWorks, Inc). Unlike commercial posturography, we measured medio-lateral postural sway dispersion because it is most highly related to falls [15,16].

In addition, Parkinson's severity scales included United Parkinson's Disease Rating Scale Motor Section (UPDRS-III) and cognitive testing included the MMSE at baseline, Stroop, and Trail Making Tests. A general physical and neurological exam, heart rate, and blood pressure measures where completed at each visit. During the active treatment phase subjects were given donepezil 5mg for three weeks and if tolerated, increased to 10mg for weeks four through six.

A total of twenty one subjects were enrolled in the study; ten withdrew because of adverse events and one subject did not meet enrollment criteria (MMSE was too low). Five withdrawals were related to the study drug with 4 due to nausea, vomiting, or gastrointestinal discomfort and one who felt freezing and balance was worse after starting the study drug. One dropped out after a possible transient ischemic attack, one after a serious fall, two due to scheduling concerns, and one due to worsened radicular pain.

Ten subjects (5 male, 5 female, mean age: 70 ± 6 years, mean UPDRS motor score: 24 ± 7, mean PD disease duration: 10.5 ± 8 years, mean MMSE at baseline: 29.2 ± 0.4, Stroop conflict time: 105 ± 48 s, and mean Trails B-A difference: 59 ± 32 s) completed both phases of the study and their data were used in the analysis.

Data analysis

The Root Mean Square distance (RMS) was calculated for condition 1-6 of the SOT, in both the antero-posterior (AP) and medio-lateral (ML) direction from the COP measurements, as measure of sway dispersion. Due to the small sample size, the difference in RMS, UPDRS motor, and cognitive function between the end and the beginning of each treatment phase (placebo or active drug) were calculated and we used a Student's t-test to assess if the difference significantly differed from 0 (where 0 represents no change). A Pearson product-moment correlation was used to assess the relationship between balance and cognitive performances. Data analysis and statistics were performed by a blinded researcher (MM).

Results

Balance performance improved with donepezil. Specifically, the change in ML RMS in condition 4 of the SOT, during the donepezil phase (beginning-end), was significantly different from zero (p=0.03), reflecting a significant decrease in the ML RMS. In contrast ML RMS did not change during the placebo phase (beginning-end), as depicted in Figure 1, left panel. Individual subject results are showed in Figure 1, right panel. Specifically, out of 10 participants, 4 improved more than 40%, 4 between 15% and 30%, and 2 didn't show changes in postural sway during the active phase of the study. There were no significant differences seen in the AP RMS, nor in conditions 1-3, 5 or 6 of the SOT, in either the donepezil or placebo phase.

A significant correlation between improvement in the Trail B-A time and improvement in the ML RMS was found in the active phase, r=0.8, p=0.001 (Figure 2). In addition, the change in the Stroop conflict time and trails B-A were -13.3 ± 24s and 5.4 ± 44s after the placebo phase versus -14 ± 23s and -13.8 ± 20s after the donepezil phase. None of those changes reached statistical significance.

Conclusion

In this small, pilot study, we did find that the cholinesterase inhibitor, donepezil, improved a measure of balance in persons with PD without dementia, and that there was a relationship between changes in executive function and changes in balance. These findings are in keeping with previous intervention studies that have showed cholinesterase inhibitors improve cognitive function in persons with PD [17] and Alzheimer's disease [18,19]. The improvement in the Trail-making executive function might suggest that donepezil improved the ability to rapidly switch attention between letters and numbers.

The relationship between balance improvement and improvement in executive function may be causal or parallel effects. It is possible that attentional set-switching cognitive mechanisms are directly involved in switching attention among sensory systems for postural control, such as between somatosensory and vision in Condition 4 of the SOT. It is also possible that cholinergic innervation affects both executive function and balance in parallel and both factors influence fall risk. Perhaps the fall reduction seen in the study of Chung et al. could be attributable to improvements in both balance and executive function since an increase in mediolateral postural sway has been associated with falls [20,21] and cognitive impairments have been associated with falls [14].

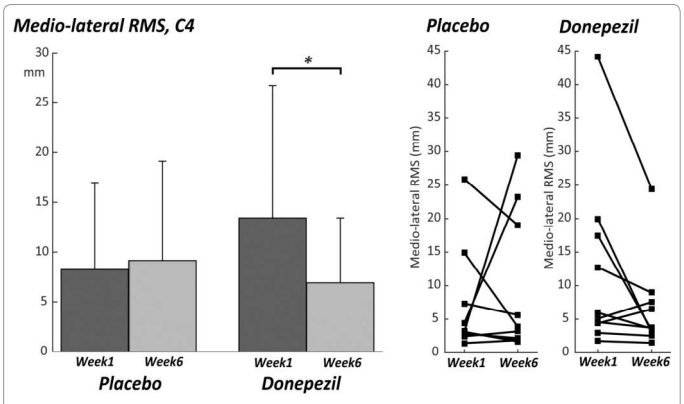

Figure 1: Left panel: Mean ± STD of the medio-lateral RMS during condition 4 of the Sensory Organization Test at the beginning and after 6-weeks of treatment with a placebo and Donepezil. Right panel: Medio-lateral RMS in single subjects at the beginning and after 6-weeks of treatment with a placebo and Donepezil.

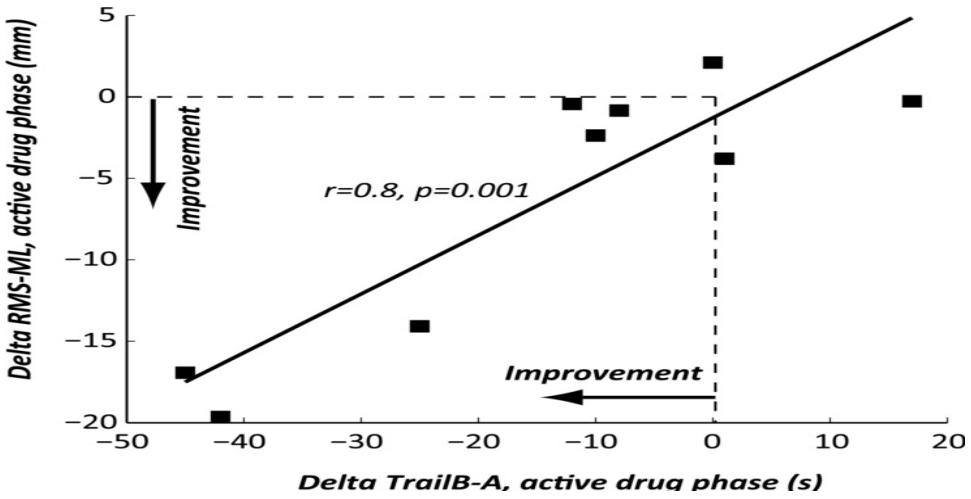

Figure 2: Association between the change in executive function (measured by the TrialB-A time) and the change in medio-lateral sway (measured by the ML-RMS in condition 4 of the SOT) during the 6-weeks of active drug treatment.

Increased postural sway has been associated with thalamic cholinergic denervation in subjects with PD [22]. The effects specifically on SOT condition 4 support a role for the PPN-thalamic cholinergic projections in sensory integration [22]. The decreased ML RMS in the active phase of the study during one of the most problematic balance conditions for PD is when the sensory integration is between somatosensory altered information and visual-vestibular information. Control of standing balance depends on the ability to switch attentional focus among visual, proprioceptive, and vestibular systems, as needed when the environmental conditions change [23]. Previous studies indicated that integration of somatosensory with visual information is affected in PD [24], and that patients with PD show excessive postural sway in conditions with limited or inappropriate sensory feedback [25,26]. Therefore, we hypothesized that cholinergic treatment in PD may ameliorate postural instability, particularly in condition 4, in which somatosensory information is altered. In addition, the conditions including standing on a moving support surface have been associated with increased falls [20]. This is promising for future studies and suggests that cholinergic treatment in PD subjects may ameliorate postural instability and reduce falls through improved postural sensory integration function.

There are multiple limitations of this study. Our dropout rate was very high, which is concerning but seems atypical relative to other studies with donepezil in PD. Dubois completed a large study with 195 randomized to donepezil 5mg and another 182 to donepezil 10mg. Dropout rates in the active arms were 24.1% and 23.6% versus 17.9% in the placebo group with adverse events reported in 13.8%, 17%, and 11% respectively [17].

Also we only saw changes in one of the SOT conditions. This may represent a bias due to our small population or it could support previous results finding that poorer postural control has been reported in PD in situations where somatosensory information was impaired, perhaps reflecting difficulties to use or integrate visual or vestibular feedback, as reflected in condition 4 of the SOT [24,27]. This small pilot study is meant to inform future study direction and design. The improvements seen in certain measures of balance are promising and suggest further investigation is certainly warranted and should include in-depth measures of balance, specifically SOT4, and cognitive function as well as perhaps some dual task testing. With a lack of pharmacological or surgical treatments to improve balance and falls in PD these results are certainly exciting and deserve further investigation.

Acknowledgments

This study had support from VA Career Development Award, PADRECC fellowships, and the National Institute of Aging. We thank Michael Fleming for data collection.

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This article was originally published in a special issue, **Microglia and Synaptic Reorganization** handled by Editor(s). Dr. Hiroshi Nakanishi, Kyushu University, Japan