Emergent Complications Following Donepezil Switchover to Galantamine in Three Cases of Dementia With Lewy Bodies

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Delayed disease progression and symptomatic improvement occur with cholinesterase inhibitors (ChEIs) in dementia with Lewy bodies (DLB). In this study, complications (insomnia, dyskinesias, agitation, and delirium) occurred in three patients switched from donepezil to galantamine. The authors describe evidence-based recommendations for ChEI switchover in DLB.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2005; 17:552–555)

Dementia with Lewy bodies (DLB) is a relatively recent dementia entity, perhaps accounting for 11% to 20% of all dementias.[1] Clinically, a triad of features characterizes DLB: fluctuating cognition; recurrent visual hallucinations; and spontaneous parkinsonism.[2] Since the advent of cholinesterase inhibitors (ChEIs), a new therapeutic option has emerged with the demonstration of beneficial role for ChEIs in DLB.[3] However, as is the case with Alzheimer disease (AD), not all patients benefit from the initial ChEI.[4] Nonresponse occurs from the outset or emerges during treatment.[5] In the following report, we describe findings from three consecutive DLB patients, initially treated with donepezil who were switched to galantamine following treatment-refractoriness, and the ensuing difficulties. Due to scant literature on ChEI complications in DLB, we review the literature and present suggestions for pharmacotherapy management.

CASE REPORTS

Case 1

EK, a 74-year-old right-handed man with possible DLB, who presented with a 1-year history of parkinsonism (bradykinesia, rigidity, and cogwheeling); fluctuating memory (ranging from several hours to a day); and sleep disturbances (nighttime agitation without hallucinations). Baseline cognitive testing noted: Folstein Mini-Mental State Examination (MMSE) score 21/30; Boston word-naming test score 11/15; and poor visuospatial skills on clock-drawing. Diffuse moderate cortical atrophy was noted on computed tomography (CT)-scan. The patient was treated with donepezil 10-mg daily for approximately 1 year before loss of efficacy and emergence of behavioral symptoms.

His family reported increasing and longer episodes of confusion, along with suspiciousness and paranoia of spousal infidelity. They also noted visual hallucinations involving strangers at nighttime. Due to increasing behavioral and sleep disturbances in excess of cognitive changes (MMSE 18/30), a Neuropsychiatric Inventory (NPI)[6] was done, noting a score of 50/144. Due to deterioration, alternative ChEI was considered, with donepezil being discontinued and galantamine started immediately at 4-mg twice-daily (BID). Two weeks later, the dose was raised to 8-mg BID.

Within 2 weeks of donepezil discontinuation, the patient developed complete insomnia, increased nighttime agitation, delusions, and well-formed visual hallucinations (NPI 62/144). Adjunct nightly trazodone 50-mg and quetiapine 50-mg were added, and at 3-month follow up, NPI score had diminished to 37/144, while MMSE remained at 18/30.

Received May 3, 2004; revised June 28, 2004; accepted June 29, 2004.
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Case 2

RB, a 70-year-old left-handed male with probable DLB, presented with 3-year history of parkinsonism (rigidity and cogwheeling); visual hallucinations; fluctuating cognition and mild aphasia. Baseline MMSE score was 28/30, Boston word-naming 14/15, and grossly impaired clock-drawing. He was treated with donepezil 10-mg daily for 1 year, with gains in attention and initiative.

Emergence of delusions of spousal infidelity and food hoarding led to reevaluation. Cognitive testing noted: MMSE 26/30 and NPI 14/144. Due to behavioral deterioration, donepezil was stopped and galantamine 4-mg BID introduced, with further increment to 8-mg BID 2 weeks later. Two weeks following donepezil discontinuation, the patient was found to have restlessness, concentration difficulties, and new-onset lower limb dyskinesias.

Despite persistence with galantamine for 1-month, the adverse effects persisted. Therefore, galantamine was stopped and donepezil 10-mg restarted. The complications stabilized, although they did not remit completely. Clinically, the patient has continued to fare poorly, with 3-month follow-up scores of NPI 21/144 and MMSE 25/30. Adjunct *L*-dopa/carbidopa was added for the dyskinesias.

Case 3

OG, a 76-year-old right-handed married male, with probable DLB who presented with a year-long history of cognitive complaints (fluctuating concentration and memory difficulties), recurrent visual hallucinations, and hand tremor. His baseline MMSE score was 18/30, Boston word-naming test 12/15 and gross visuospatial difficulties. He was treated with donepezil 10-mg daily with satisfactory stabilization for a 2-year period.

Behavioral deterioration was reported by his family, with longer periods of disorientation, aggressivity and repetitive behaviors as well as increasingly distressing vivid visual hallucinations. Although MMSE score was 16/30, the NPI better reflected the deterioration, which was 72/144. Alternative treatment with galantamine was considered.

Donepezil was maintained (due to oversight) while galantamine started at 4-mg once-daily. At second week, donepezil was discontinued and galantamine increased to 4-mg BID. At week 3, the dose was further adjusted to 8-mg BID. Two weeks after donepezil cessation, the patient abruptly developed delirium and required hospitalization for agitation, confusion and combativeness. No etiology was found, and the patient was discharged a week later on galantamine 8-mg BID with clonazepam PRN for insomnia. At 3-month follow up, due to minimal gains on galantamine (NPI 58/144 and MMSE 16/30), the patient was switched back to donepezil 10-mg daily with no sequelae.

DISCUSSION

DLB is a common dementia with overlapping features with AD and Parkinson's Disease (PD). Despite the overlap, the pathophysiology appears distinct from AD.[7,8] Lack of neurofibrillary tangles as well as absence of significant tau pathology, both hallmarks of AD, characterize DLB. Neocortical cholinergic activity (assessed by choline acetyltranferase activity) also appears more severely depleted, which correlates with visual hallucinations and global cognitive impairment.[8] In DLB, postsynaptic muscarinic receptors appear better preserved and functionally more intact than AD, in part due to absence of neocortical neurofibrillary tangles. All these findings suggest that ChEIs might offer better outcomes in DLB despite its more aggressive course.[7] A randomized, double-blind, placebo-controlled trial demonstrated rivastigmine to have greater improvements in attention and apathy, while reducing anxiety and psychotic symptoms.[3] Open-label follow up over 96-weeks also showed ongoing stabilization.[5] It remains to be seen whether long-term treatment can affect the rate of decline when compared to the natural course of the disease. In our series, patients had a 2–3 point decline in MMSE over the 1- to 2-year follow up; in addition, significant neurobehavioral symptoms emerged despite ongoing maintenance treatment. To patients and caregivers, these symptoms are more disconcerting than MMSE performance. The behavioral changes increase caregiver burden and lead to dissatisfaction with the previously effective pharmacotherapy.

The progressive and sometimes spiraling downward course often leads clinicians to consider alternative ChEIs; yet the evidence is scant in support of alternate ChEI in DLB. Switching is presently unknown for DLB, although there appears to be some merit for this in AD.[9,10] Similar to the case for use of alternate selective serotonin reuptake inhibitors (SSRIs) in depression nonresponders, Ballard argues that each ChEI exhibits different pharmacologic activity, so as to make switching a

valid option.[9] In one open-label trial involving 382 AD subjects, over half of donepezil nonresponders (56.2%) had successful response to rivastigmine.[10] While it is tempting to generalize these findings to DLB, clinicians should be wary since the DLB population is particularly medication-sensitive.

There are several mechanisms that could account for the deterioration. It is possible that overlap of two ChEIs may have led to additive toxicity, so-called "cholinergic toxicity." Centrally, this is manifest as confusion, sedation, coma, and possibly seizures and peripherally as miosis, lacrimation, salivation, bradycardia, bronchospasm, emesis, and diarrhea. Only one case of aspiration pneumonia, coma and death has emerged following donepezil and rivastigmine titration.[11] None of our patients experienced symptoms suggestive of cholinergic excess.

Alternatively, donepezil discontinuation could lead to a discontinuation syndrome similar to SSRIs.[12–14] In an open trial involving PD and DLB, abrupt donepezil discontinuation led to delusions, irritability and hallucinations.[14] Although formal follow up in this study was reported only one-and-half months following discontinuation, 11 of 19 subjects were unable to tolerate the discontinuation and resumed donepezil within 2 weeks of discontinuation.[14] Our patients were closely followed in the first 2-week period following the switch, which enabled thorough ongoing assessments. The 2-week period appears critical since it reflects donepezil's half-life of 70 hours, and where five half-lives (or approximately 2 weeks) are required for complete donepezil elimination.[15]

The cases pose the clinical dilemma of pharmacotherapy adjustment in DLB. Theoretically, there is a risk of "cholinergic toxicity" if two ChEIs are combined or overlapped.[11,15] In our series, introduction of the second ChEI did not lead to immediate sequelae. Delayed deterioration has also been noted by others[14] and thus suggests a need for gradual dosage reduction and ongoing vigilance when discontinuing donepezil.

Finally, there is concern whether abrupt ChEI discontinuation and ensuing complications can lead to irreversible deterioration. This issue remains unresolved. Our patients did not appear to return fully to baseline at 3-month follow up. In the open-label series, return to baseline was reported,[14] although the large dropout rates make this interpretation difficult. Therefore, given the limited data and follow up, in patients who appear to be deteriorating or developing adverse effects, dosage tapering remains the preferred method to avoid accelerated decline. Dosage reduction is also recommended for patients whose clinical improvement is unclear.[14]

CONCLUSION

The advent of ChEIs has helped DLB management, with patients and families obtaining much relief from the disturbing aspects of the illness. While ChEIs have shown symptomatic gains, ongoing disease progression and loss of efficacy remain ongoing concerns. Discontinuing or switching donepezil to alternate ChEI requires vigilance, particularly for the first 2 weeks, since discontinuation symptoms may emerge after a delay. Although our findings are preliminary and require placebo-controlled trials for confirmation, emerging literature supports this recommendation.

Presented in part at the International Psychogeriatrics Association Eleventh Annual Meeting, Chicago, August 17–22, 2003.

The authors thank Dr. Keith Edwards for reviewing and providing thoughtful comments and critiques of the manuscript.

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