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Cholinesterase Inhibitor Induced Urinary Incontinence in Dementia: A Management Dilemma

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Abstract

Cholinesterase inhibitors are effective pharmacological modality of treatment in patients with Alzheimer's disease. Urinary incontinence is a relatively uncommon side effect of cholinesterase inhibitors. It is difficult to differentiate the incontinence as a result of progression of the neurodegenerative process of dementia or due to medications or due to underlying local pathology (age-related). It seems illogical to recommend anticholinergics, which are commonly recommended for treatment of urinary incontinence, in patients with dementia who have already acetylcholine-deprived brain. We here discuss the management dilemma of urinary incontinence in a patient with Alzheimer's disease with review of literature.

Keywords: Cholinesterase Inhibitors, Dementia, Urinary Incontinence

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1. Introduction

Cholinesterase inhibitors are effective pharmacological modality of treatment in patients with Alzheimer's disease, as found in several randomized controlled trials and meta-analyses.[1] In a meta-analysis (16 trials including 5159 patients), it was found that the safety of donepezil was better than rivastigmine and galantamine.[1]

Urinary incontinence is a relatively uncommon side effect of cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, which are commonly, used cholinergic agents in the management of dementia.[1-3] Dementia itself increases the risk of urinary incontinence. It is difficult to differentiate, whether the incontinence is a result of progression of the neuro-degenerative process of dementia or due to medications or due to underlying local pathology (age-related). In a study, on Dutch population with dementia, it was found that urinary incontinence is due to the progression of dementia, and the cholinesteraseinhibitors has little role in causing urinary incontinence.[3] Approximately, 7% patients report urinary incontinence with cholinesterase inhibitors, as found in the study by Hashimoto *et al.* (2000).[2]

Such incontinence presents a dilemma in management of these patients.

2. Case Report

A 70-year-old non-hypertensive, non-diabetic, retired executive male presented with complaints of progressive forgetfulness for 2 years along with disturbed sleep, increased irritability, and hyper-sexuality for last 8 months. Due to these complaints, there was significant impairment in performing the activities of daily living. Furthermore, due to the hypersexual behavior, there was a lot of social embarrassment. There was no past or family history of any psychiatric illness. He had undergone coronary artery bypass graft for a myocardial infarction, 12 years back. He was diagnosed with hypothyroidism 3 years back, and receiving supplementation of thyroxin 150 micrograms/day. An year back, benign prostatic hyperplasia was detected, for which he was receiving tamsulosin 0.4 mg/

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day, and his urinary symptoms were well-controlled with the medications. During this time, urodynamic studies were done, which revealed obstructive pattern.

Investigations revealed low folic acid levels. Routine haemogram, liver function tests, kidney function tests, thyroid function tests, and lipid profile were within normal limits. Abdominal ultrasound had revealed mild prostatic hypertrophy and a normal post-voidal residual volume. His computed tomography scan of head revealed diffuse cerebral atrophy. Mini Mental Status Examination (MMSE) score was 16/30. Differential diagnoses of Alzheimer's dementia with behavioral and psychological symptoms associated with dementia (BPSD) and dementia due to nutritional (folic acid) deficiency was considered. Over the next 6 months of follow-up, his folic acid level as well as thyroid function tests were within normal limits. His MMSE score was found to be 14/30. As there was no improvement in cognitive function despite normal folic acid levels and the thyroid profile, final diagnosis of Alzheimer's dementia was considered.

Before presenting to us, he had received combination of donepezil 5 mg and memantine 5 mg per day, from a private neuro physician. Urinary incontinence was reported after 2–3 days of initiation of these medications; however, the family members ignored this. In his follow-up, (2 weeks following the first consultation) when the dose of donepezil was increased to 10 mg, incontinence worsened; however, at this time urodynamic studies were not done. The family members stopped above medications, prior to presenting to our center. After stopping these medications, the urinary incontinence resolved completely.

Keeping in view of urinary incontinence with donepezil, we started memantine at a dose of 10 mg/day along with folic acid supplementation and quetiapine 25 mg/day for the management of BPSD. In follow-up, another psychiatrist added rivastigmine 3 mg/day, which again caused urinary incontinence. In subsequent follow-up, rivastigmine was stopped; memantine was increased to 20 mg/day, and urinary incontinence improved.

3. Discussion

Urinary incontinence in elderly individuals with dementia can be because of the dementia itself, due to age related changes in the urogenital system. or because of the medications.[4]Fragility of old age can also contribute to urinary incontinence in elderly population.[4]Our patient had mild prostatic hypertrophy, which was not significant enough to cause urinary incontinence but might have attributed to increased frequency. Underlying dementia and fragility might have contributed to urinary incontinence. However, the onset of urinary incontinence was temporally correlated with administration of cholinesterase inhibitors (donepezil and rivastigmine, on separate occasions) and improved completely on discontinuation of these drugs. This finding is suggestive of greater possibility of cholinesterase inhibitor induced incontinence over other possible reasons.

Behavioral intervention is an effective intervention to treat urinary incontinence in elderly individuals.[5,6] However, in patients with grossly compromised cognitive functions, it is difficult to do behavioral intervention, as seen in our case.

Anticholinergic agents are found to be effective in the treatment of urinary incontinence in patients receiving cholinesterase inhibitors in dementia.[7] Anticholinergic agents such as - oxybutynin, tolterodine, and trospium are effective in the treatment of overactive bladder,[8,9] but it seems illogical to recommend anticholinergics to dementia patients who have already acetylcholine-deprived brain. Prescribing anticholinergic agents for treatment of urinary incontinence in dementia patients may prove detrimental to the cognitive reserve.[6,7] Due to lack of awareness or over enthusiastic attitude, patients with dementia many times receive anticholinergic agents for their urinary incontinence, while it may be wiser choice to reduce the dose of the cholinesterase inhibitor or switch to a non-cholinergic anti-dementia agent such as memantine. [4]The management dilemma was whether to continue with donepezil or rivastigmine with addition of an anticholinergic drug to combat incontinence, or to choose a non-cholinergic anti-dementia medication. Grossly compromised cognitive function limited the utility of behavioral intervention. Evidences suggest that the risk of urinary incontinence is higher with donepezil (>5%) than rivastigmine (>2%) and galantamine;[10] hence, the latter two can be tried over the former one to minimize the risk of urinary incontinence, if at all there are no other alternatives.

Study by Sink *et al.* (2008) highlighted about long-term functional and cognitive decline with concomitant use of cholinesterase inhibitors and bladder anticholinergic. [11] However, in our patient, alpha-blocker tamsulosin

was used along with donepezil and rivastigmine, and the use of donepezil and rivastigmine was short-term due to side effects. Hence, the possibility of functional and cognitive decline is unlikely due to these medications. In our case, we found dose-dependent worsening of urinary symptoms, though we could not find any mention of this phenomenon in literature. If patients are tolerating cholinesterase inhibitors at lower doses, it may be safer to continue with the lower doses for the treatment of dementia.

We had chosen memantine as the preferred agent for the treatment of dementia over the other medications as continuing cholinesterase inhibitors and adding an anticholinergic agent to counter its side effects seemed irrational. Careful drug history and appropriate selection of medications are highly essential in management of urinary incontinence in dementia. If at all continuation of cholinesterase inhibitors is the only option, or highly essential and there is significant urinary incontinence (drug induced), then the clinician needs to choose judiciously between improvement of cognition or continence.

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