Case Report

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Donepezil in traumatic brain injury: Report of two cases

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Abstract: Adults with traumatic brain injury (TBI) are often severely impaired and inadequately rehabilitated due to deficits in memory and behavioral problems like apathy, irritability and depression, and it has been suggested that an acetylcholine deficit could be contributory to these deficits. Central Acetyl cholinesterase Inhibitors (CAI) are being reported to have a beneficial impact in treatment of memory deficits in adults with TBI, with Donepezil studied most extensively. The authors present two patients with TBI with long term static dysfunction of memory and behavior who responded to Donepezil in terms of attention, memory and apathy. Donepezil appears to be a valuable pharmacological option for treatment of memory and behavioral deficits in TBI.

Keywords: central acetyl cholinesterase inhibitors, Donepezil, head injury, traumatic brain injury

INTRODUCTION

Significant memory deficits, especially of recent memory, along with behavioral problems such as apathy, irritability and depression, greatly impairs daily functioning of many adults with severe traumatic brain injury (TBI), even when they are otherwise not significantly impaired in other domains[1,2]. These problems generate considerable pharmacological therapeutic nihilism and hugely impacts on their rehabilitation.

After having established their usefulness in improving memory and some aspects of behavior in certain types of dementias, central acetyl cholinesterase inhibitors (CAI) are increasingly being reported to have beneficial impact in treatment of memory deficits and chronic cognitive and behavioral sequelae during rehabilitation of adult survivors of TBI[2, 3]. Evidence is accumulating to suggest that TBI frequently results in injury to acetylcholine rich hippocampal regions, which are responsible for short-term memory. Similarly, acetylcholine dysfunction has also been linked to impairment of focused and sustained attention, memory and executive functions[1,2]. Such deficits of cognition often lead to behavioral problems like apathy and irritability leading to consultation with psychiatrist. We present 2 cases of severe TBI referred to us for behavioral problems successfully treated with a CAI, Donepezil, alone.

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CASE REPORTS

Case 1

Mr. A, a 35-year-old man fractured his left frontal bone in inebriated state in September 2000 and was comatose for 10 days. He was managed conservatively by Neurosurgeons. The posttraumatic amnesia lasted several days. Subsequently, he spoke sparingly, exhibited dysnomia and had persistently impaired recent memory. He was apathetic most of the time, with occasional outbursts of irritable and violent behavior. He was significantly impaired in activities of daily living, like eating, dressing and bathing and was doubly incontinent. For these reasons he was unable to work. Prior to his psychiatric referral he had received Ginkgo Biloba for a year but with no appreciable improvement in memory. After his first assessment in Psychiatry in September 2002, he was empirically commenced on an antidepressant, Mianserin, by one of the authors (S.A.) without improvement. MRI brain revealed frontal lobe atrophy. In October 2002, donepezil was also started at a dose of 5mg/day, which was increased after 6 weeks to 10 mg/day. Within 2 months of being on this dose, both patient and his family members reported some improvement in his memory, daily living activities and apathy, which was maintained for 5 months, although not to the point where patient could be occupationally rehabilitated. Due to the dire financial condition of the family, his compliance with Donepezil became poor and he discontinued it. Around the same time he had a change of psychiatrist as S.A. left the institution and so Mr. A was treated only with Sertraline at adequate

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dosages from May 2003 to August 2004 (15 months). However, during this period Mr. A deteriorated in all activities of daily living, again becoming apathetic and forgetful.

After Mr. A's reassessment (by A.L.A. and D.B.) in August 2004, he agreed to recommence donepezil. Baseline scoring was established on the Mini Mental State Examination (MMSE), a scale designed for assessing cognitive status (with maximum score of 30 indicating no cognitive impairment), which revealed score of 20. He was also rated on the Disability Rating Scale (DRS) for traumatic brain injury, (a scale intended to measure functional changes over the course of recovery, with maximum score of 29 indicating extreme vegetative state and zero indicating no disability), on which he scored 12. Sertraline was replaced by Donepezil monotherapy (10 mg/day). Within 2 months, his wife reported that he was able to perform activities of daily living adequately. He had become less apathetic and irritable and there was improvement in his memory. Occupational rehabilitation was possible and he started working regularly. His wife reported more than 50% improvement in his functioning in 3 months. Objective measurement showed improvement in scores- MMSE score improved to 24 and DRS score improved to 6. He continues to show consistent improvement on follow up.

Case 2

Mr. B, a 34-year-old male sustained head injury in the frontal region, which left him in coma for 4 days whilst working with heavy machinery in January 2004. Hematoma was drained by craniotomy. As he had also sustained multiple fractures of the nasal bones and mandible, corrective surgery was also performed in the following month. Subsequently, he had persistent neurological sequelae including diplopia on downward gaze, anosmia, hearing impairment and root pain due to malocclusion arising from mandible fracture. He had persistent impairment of recent memory and could not remember even the meal he had recently. Behaviorally, he was predominantly irritable and at times apathetic. He had impairment in performing activities of daily living, such as eating dressing and bathing. Head CT scan after 8 months of injury revealed parenchymal gliosis in left frontal lobe.

He was referred for psychiatric opinion regarding his behavioral and memory problems and was independently and jointly assessed by the authors A.L.A. and D.B. in December 2004. He scored 20 on Mini Mental State Examination (MMSE) at initial evaluation. He scored 10 on the Disability Rating Scale (DRS). He was prescribed donepezil 5mg/day, which was increased to 10mg/d after 2 months. Within 3 months of starting donepezil improvement in memory was observed both by patient and his wife. He reported a better ability to attend to and remember conversations as well as daily events like eating and bathing than before treatment. His MMSE score improved to 23 and rating on the DRS also improved to 5.5. In addition, his wife also reported a marked reduction in his behavioral problems of irritability and apathy. His wife reported 50% improvement in his daily functioning and he continues to show consistent improvement on follow up.

DISCUSSION

Of various CAI, donepezil has been most widely used in TBI although most recent evidence indicates that other CAI such as rivastigmine and galantamine are also equally effective[3].

Taverni et al were the first to report beneficial effect of donepezil 5 mg in 2 TBI patients in an open label 3-week trial[1]. Donepezil not only improved memory but also caused increase in alertness and awareness of their memory problems. Objective measures (Rivermead and Ross Immediate Processing assessment) were used for one case only. The authors reported 60% improvement in the first case, whereas their next patient improved in alertness and attention[1]. In contrast, both patients reported by us responded at higher dosage (10 mg) and required more time (2 – 3 months) to show a response.

Morey et al also reported improved memory of 7 patients of severe TBI on donepezil 10 mg in a 6-month trial[4]. Many participants elected to stay on donepezil, saying 'it cleared the cobwebs', although no participant was able to elaborate specifically on this[4]. Self-report of our patients closely approximates Morey's, wherein phrases used include 'I can see light at the end of the tunnel', 'I now know my mistakes'. More robust evidence for memory enhancing property of donepezil in TBI is provided by Zhang[5], who conducted a 24 weeks randomized placebo-controlled double blind crossover trial on 18 TBI patients using measures only for memory and attention and concluded that cholinergic augmentation by donepezil facilitates cognitive recovery in post-acute TBI, particularly short-term memory and

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sustained attention[5]. Recently, a Finnish study randomly assigned 111 patients of TBI to CAI and reported better vigilance and attention in 61% patients[3].

Wheelan published their experience on cognition of 53 TBI patients treated with donepezil 5 to 10 mg for up to 2 years, assessing them at baseline and after 12 months[6]. Although no memory measures were used, but statistically significant improvement from baseline was observed in mood, affect, grooming and social interest in patients. However concurrent treatment effects were not controlled for[6]. Similarly Masanic et al reported statistically significant improvement to 0.4,1.04 and 0.83 standard deviation above baseline value on RAVLT total recall, short term recall and long term recall in 4 TBI patients with Donepezil, up to 10 mg, in 16-week open label trial. They also found improvement in emotional and behavioral functioning, especially anxiety, apathy and depression[7]. Bourgeois et al also reported improvement in cognition and behavior in a case of TBI treated with donepezil, risperidone and venlafaxine[8], although use of multiple psychotropic medications makes it difficult to attribute the observed improvement solely to donepezil. In contrast Kaye et al found improvement only in behavior with donepezil (up to 10 mg/d) in 10 TBI patients prompting their conclusion that donepezil might be of greater benefit in the overall functioning of the individual rather than the specific domain of memory[9].

These were the only cases of severe TBI referred and both patients showed appreciable improvement with donepezil. The strength of our first case lies in the robust improvement in memory and apathetic behavior with donepezil being evident in the naturalistic A-B-A design, where the treatment gains were evident only when patient was on Donepezil and the improvements diminished when not on donepezil for a long period. The other strength of both cases is that patients were not receiving any other psychotropic medication and therefore confounding variables are further minimized.

CONCLUSION

Several studies, including a double blind placebo controlled trial, have consistently documented improvement in memory with donepezil in TBI patients. Few authors have also documented improvement in behavioral and functional measures, most notably in apathy and activities of daily living. Donepezil thus appears to be a viable option for TBI patients suffering with significant memory impairment and behavioral problems. Future studies focusing on a broad range and long term of outcome measures are required to delineate the clinical characteristics of responders to CAI.

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