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Central acetylcholinesterase inhibitors in the treatment of chronic traumatic brain injury—clinical experience in 111 patients

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Abstract

Purpose: Theoretically, central acetylcholinesterase inhibitors (CAIs) could alleviate at least some of the main symptoms of chronic traumatic brain injury (TBI). The aim of this report is to describe clinical experience of the treatment of chronic TBI with these drugs.
General methods: From an outpatient clinic material, 111 patients were selected having chronic stable TBI with at least one of the following target symptoms: fatigue, poor memory, diminished attention or diminished initiation. Patients received in random donepezil, galantamine or rivastigmine. The evaluation of the treatment response was based on the subjective view of the patient.
Findings: As first treatment, 27 patients received donepezil, 30 galantamine and 54 rivastigmine. Altogether 41 patients tried more than one drug, but only three patients tried all three alternatives. In total, 61% of patients had a marked positive response and 39% a modest or no response. The clearest effect was in almost all responders a better vigilance and attention causing better general function. About half of the patients (55%) wanted to continue therapy with one of these drugs. The therapeutic response became very quickly and at low doses. There were no significant differences between the three drugs either in effect or tolerability. The age, sex, type of injury, severity of TBI or elapsed time after injury did not affect the response. The mean dose in maintenance therapy was 7.2 mg od for donepezil, 5.0 mg bid for galantamine and 2.3 mg bid for rivastigmine. Side effects or inadequate therapeutic response were the main causes for discontinuation with nearly equal frequency. Paradoxical responses were seen in some patients.
Conclusions: CAIs show a very promising therapeutic potential in the treatment of chronic TBI. There were no significant differences between the three drugs. Large-scale randomised double-blinded placebo-controlled studies are clearly needed.

Keywords: Donepezil; Galantamine; Rivastigmine; Traumatic brain injury

1. Introduction

Traumatic brain injury (TBI) is undisputedly the leading cause of long-term neurological disability in young and middle-aged adults. Based on epidemiological studies (McGuire et al., 1995; Thornhill et al., 2000) and estimates of direct and indirect costs (National Center for Injury Prevention and Control, 2003) of TBI, there are apparently at least 19 million people living in Europe and North America with a TBI-related permanent disability and with annual TBI-related costs of over 150 billion €. Given these figures, it is hard to find any other group of patients that is as badly neglected in modern medicine. For the well-known major consequences (Millis et al., 2001) of TBI—fatigue, poor memory, attention deficits and diminished initiative ability—there are practically no effective therapies available. With rehabilitative measures, the patients are helped to cope with these symptoms, but rehabilitation is not able to lessen or cure the symptoms themselves.

The defective brain functions in TBI (regulation of vigilance, attention and memory) are at least partly

Abbreviations: bid, twice daily; CAI, central acetylcholinesterase inhibitor; CNS, central nervous system; CT, computerized tomography; GCS, Glasgow Coma Score; GOS-E, Glasgow Outcome Scale—extended version; MRI, magnetic resonance imaging; od, once daily; PTA, posttraumatic amnesia; TBI, traumatic brain injury.

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cholinergically mediated (Semba, 2000; Bentley et al., 2003; Dekker et al., 1991). The major cholinergic centers lie in the basal forebrain, septum and upper brainstem, which are often affected by the primary pathology (Graham et al., 1995) of TBI. Moreover, studies in laboratory animals (Gorman et al., 1996; Schmidt and Grady, 1995) and in postmortem human brain (Murdoch et al., 1998) have shown disturbances in the cholinergic system in TBI. Earlier studies with cholinomimetic drugs (Cardenas et al., 1994; Levin et al., 1986) have suggested that manipulation of the cholinergic system might alleviate some symptoms of chronic TBI. Thus, there are all reasons to assume (Pike and Hamm, 1997; Griffin et al., 2003) that central acetylcholinesterase inhibitors (CAIs) developed for the treatment of Alzheimer's disease might be of value in the treatment of chronic TBI. Indeed, there are small studies with donepezil suggesting clinically significant improvement (Whelan et al., 2000; Whitlock, 1999; Masanic et al., 2001). In the largest of these open studies including 53 patients (Masanic et al., 2001), significant improvements were seen both in the general intelligence and especially in the clinical judgement.

The author takes care of hundreds of patients with TBI annually at the outpatient clinic of the Department of Neurology, University of Turku. From the beginning of year 2001, the author has prescribed CAIs for some of these patients in order to try to alleviate their disabling cognitive symptoms. The objective of this report is to analyse and describe the clinical experience with these medications.

2. Methods

2.1. Patient population

The material is selected from the patients with TBI attending at our outpatient department. In order to be a candidate for this kind of treatment, the patients had to fulfil the following criteria:

- Clinically definitive TBI (Kay et al., 1993) with chronic sequels;
- A fairly stable phase after the trauma, i.e. about 1 year or more from the trauma;
- At least one of the four target symptoms: fatigue, poor memory, diminished attention or problems with initiation, clinically caused by the TBI;
- Willing to test this kind of medication.

All patients had a clinically significant head injury (more than a slight concussion) that was proportionate with the symptoms caused. Further still, all patients had a neuropsychological examination and failed to show other obvious causes for their chronic symptoms. The exclusion criteria were uncertain diagnosis, other possible causes for the chronic symptoms, contraindications for the use of cholinesterase inhibitors, unstable or progressive symptoms, suspicion of degenerative dementia and refusal from the treatment trial. The target symptoms were identified with a thorough interview of both the patient and the relatives and neuropsychological examination. Patients with psychiatric illnesses were not excluded, because psychiatric symptoms and diagnoses are very common in this population, often caused by the trauma itself and the study material was intended to represent typical TBI patients in all respects.

As the drugs were prescribed in normal clinical practice, the patients did not receive or sign any informed consent. The author described the therapeutic rationale for the patient and the clinical experience so far, and asked if the patient was willing to try these drugs. With cumulating clinical evidence from the potential effectiveness of these drugs, it was decided afterwards to analyse the response systematically from the whole material.

The demographic features of the patients are shown in Table 1. Children were excluded and, typically for TBI, males predominated. All patients had passed the time of active healing being in a clinically stable phase. The severity of the injury varied in a large scale from mild to extremely severe as measured either with Glasgow Coma Scale (GCS) at arrival or duration of posttraumatic amnesia (PTA). Using GCS as a measure, the patients had on the average moderate injuries, and using PTA as a measure severe injuries, respectively. The causes of the injuries were ordinary, predominantly traffic accidents and falls. All patients had a closed head injury. A neuroradiological examination was done in all patients, either with computerized tomography (CT) or magnetic resonance imaging (MRI) or both. Based on their results, 63% of patients had solely a diffuse injury.

Nearly half of the patients had some other centrally acting drugs concomitantly, but their dosing remained stable throughout the trial. About every fourth patient had tried some other medications for the target symptoms earlier.

2.2. Drug administration

The patients received randomly one of the three CAIs, depending what happened to be available as sample packages. The dosing was always started with the lowest recommended dose, i.e. 5 mg od for donepezil, 4 mg bid for galantamine and 1.5 mg bid for rivastigmine. The dose was raised not sooner than after 1 week either if there was no therapeutic response in spite of good tolerability or if there was a partial response and good tolerability. The maximal recommended dose was not tried to reach except in some patients using donepezil. Donepezil was advised to take only in the morning, and both galantamine and rivastigmine in the morning and in the afternoon. All patients were informed to take the pills after meal.