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The Potential Role of Donepezil for the Treatment of Dementia with Lewy Bodies

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Abstract

Dementia with Lewy bodies (DLB) is a common form of dementia in the elderly and constitutes the second largest group of patients with degenerative dementia. To date, on the one hand, four cholinesterase inhibitors (ChEIs) have been approved for the treatment of Alzheimer's disease (AD). On the other hand, there are no drug for approved for the treatment of DLB. However clinical benefits and good tolerability have recently been reported in several clinical trials of cholinesterase inhibitors (ChEIs), particularly donepezil. This review describes various aspects of donepezil, including basic pharmacology and pharmacokinetics, with the primary focus on the clinical work.

Introduction

Dementia with Lewy bodies (DLB) is thought to be a common form of dementia in the elderly and constitutes the second largest group of patients with degenerative dementia, accounting for 10-15% of dementia [1]. The core clinical features of DLB include fluctuating cognitive impairment, recurrent visual hallucinations, and motor symptoms of parkinsonism. The involvement of central cholinergic systems in DLB is supported by several neurochemical studies [2]. Choline acetyltransferase (ChAT), an indicator of neocortical cholinergic activity is more depleted in DLB than in Alzheimer's disease (AD) [3] and the deficit of ChAT is correlated with the presence of visual hallucinations and global severity of cognitive impairment [4]. The relative preservation of postsynaptic muscarinic receptors in DLB in the absence of severe neo-cortical neurofibrillary tangle burden in most cases, led to speculation that cholinesterase inhibitors (ChEIs) are more effective in DLB than in AD.

Currently, there are two main types of drug approved for the treatment of AD - ChEIs and N-methyl-D-aspartate (NMDA) receptor antagonists. ChEIs include donepezil, rivastigmine and galantamine, and NMDA receptor antagonist is memantine. ChEIs are considered to be the first choice drug for the treatment for AD. In particular, donepezil is the drug most widely used for treatment of AD. Donepezil has been shown to be well tolerated and to improve cognition and global function in patients with mild to moderately severe AD. However, to date, donepezil is approved for the treatment of DLB only in Japan. Rivastigmine is the only ChEI that is licensed for the treatment of mild to moderate dementia in AD and Parkinson's disease in the UK (Medicines and Healthcare products Regulatory Agency) and the USA (Federal and Drug Authority).

Recently, Evidence supporting the use of ChEIs in DLB is also increasing and these studies have reported that ChEIs have positive effects on cognition, psychiatric symptoms and global function. This paper reviews data on the use of ChEI, particularly donepezil in the treatment of AD. Medline and PsychINFO search of the literature published between 1980 and 2014 that examined the clinical trial of ChEIs for the treatment of DLB or Parkinson's disease dementia (PDD) was conducted.

Mechanism of cholinesterase inhibitors

Although several therapeutic approaches have been attempted for enhancing cholinergic function and cognitive function in patients with AD, cholinesterase inhibition is the most successful strategy that has thus far proven to have significant effects in patients. Currently, three cholinesterase inhibitors (ChEIs), donepezil, galantamine, and rivastigmine, have been approved in Europe, North America, and Asia for the treatment of AD. Cholinesterase (ChE) degrades acetylcholine (ACh), decreasing its concentration in the synaptic cleft of cholinergic synapses. ChEIs bind to ChE resulting in increased ACh levels at the presynaptic receptors and maintain cholinergic activity in the brain of patients with AD. ACh is hydrolytically catabolized in the brain by two cholinesterase, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE slectively hydrolyzes ACh and BuChE hydrolyzes not only ACh but also other choline esters. The role of BuChE in humans is not completely understood. AChE predominates in the healthy brain and BuChE is considered to play a minor role in regulating brain ACh levels. On the other hand, BuChE activity rises while AChE activity remains unchanged or declines in the AD brain. The inhibition of BuChE may contribute to efficacy in treatment of AD.

Pharmacology of donepezil

Pharmacodynamics: Donepezil is a specific and reversible AChE inhibitor that shows a relative selectivity for AChE as compared to butyrylcholinesterase (BuChE). The ratio of the 50% inhibition (IC50) of BuChE to AChE from rodents or humans was 1252:1 and 405:1, respectively [5,6]. There are also differences in inhibition of enzymes (IC50) isolated from various tissues like rat skeletal muscle, rat brain or human erythrocytes. Administration of single daily doses 5 mg or 10 mg donepezil produced steady state inhibition of acetylcholinesterase activity in erythrocyte of about 64% and 78%, respectively [7]. ChEIs for the treatment of AD differ in their pharmacological profiles and affinities for AChE and BuChE. Donepezil and galantamine are 1000- and 50-fold, respectively, more selective for AChE than for BuChE, whereas rivastigmine inhibits both enzymes with similar affinity [8].

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Pharmacokinetics: Donepezil is metabolized by the hepatic enzymes, CYP 450 isoenzymes 2D6 and 3A4, and undergoes hepatic glucuronidation. Donepezil may interact with drugs that inhibit these enzymes, such as cimetidine, ketoconazol, paroxetine, fluoxetine, and fluvoxamine. Cimetidine and ketoconazol increase donepezil plasma concentrations. These interactions were not considered clinically significant according to the United States Food and Drug Administration (FDA) guidelines. Formal pharmacokinetic studies have shown that donepezil does not inhibit the metabolism of theophylline, warfarin, cimetidine, or digoxin in healthy subjects [9-14]. The metabolites of donepezil are excreted in urine (5-O-desmethyl donepezil, 6-O-desmethyl donepezil, donepezil-cis-N-oxide, etc), about 11-17% of which are unchanged [15]. Pharmacokinetic properties have been assessed mainly in patients with AD. Tmax and elimination half-life (t1/2) are longer in elderly than in younger volunteers, the volume of distribution (Vd), larger than in younger volunteers [15]. The longer t1/2 in the elderly may be attributed to the increase in the steady state volume of distribution throughout the whole body since drug clearance is similar in the elderly and the young [15].

Tolerability: Cholinergic nerves are found throughout the human body, suggesting that a number of tissues and organs could be affected with inhibition of ChE. The most common donepezil-related adverse events are gastrointestinal symptoms, including diarrhea, nausea, vomiting, abdominal pain or abdominal distention, and can be attributed to the cholinergic action of the drug.

The occurrence of the predominant cholinergic adverse events is most pronounced in the first few weeks after initiating treatment. The incidence of side effects is higher during initiating to treatment or when doses are increased before steady-state is achieved. Rapid dose titration schedules had typically been used in most pivotal clinical trials of donepezil, in that patients randomized to donepezil 10 mg per day received donepezil 5 mg per day for the first 7 days and then 10 mg per day thereafter. However, in those trials, donepezil has been generally well tolerated and most of the adverse events are transient and generally mild in severity [16-19]. Subsequent trials have suggested that the rate of adverse events can be reduced by lengthening the period of time patients receive the lower dose before the higher dose initiated, with nausea reported by 11% and diarrhea by 7% of patients treated with donepezil 10 mg per day titrated up after 28 days on 5 mg, vs. 9% and 7%, respectively, for placebo [19,20]. Clinical physicians would be expected to exercise caution when prescribing ChEIs particularly to patients with known sick sinus syndrome, or who receiving other medications that may reduce heart rate, such as digoxin and beta-blocker. Any patient receiving ChEIs can be at some risk of bradycardia or cardiac block. However, in the pivotal clinical trials of donepezil, no consistent patterns of clinically significant treatment effects in cardiovascular indices have been reported to date, with no increase in serious arrhythmias found [16, 18,20-23].

Dosage and administration: In the treatment of mild to moderate AD, donepezil is given once daily in a dose of 5-10 mg, beginning with a dosage of 5 mg per day. An initial dose should be maintained for 4-6 weeks before increasing to 10 mg. A dose of 23 mg once daily can be administered once patients with severe AD have taken a dose of 10 mg once daily for at least 3 months. In Japan, the recommended dose are lower than in other countries (3 mg daily increasing to 5 mg after 2-3 weeks), because of retrospective pharmacokinetic analysis and population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with AD. However, according to an extension of the donepezil label to severe AD in 2007, a dose of 5-10 mg have been approved in Japan.

Clinical evidence supporting the use of donepezil against dementia with Lewy bodies

The first trial of a ChEI for the treatment of DLB or Parkinson's disease dementia (PDD) was a small, open-label study of patients treated with tacrine, who showed improvement in cognition and visual hallucinations [24]. The similar case report and case series literature suggested that donepezil was also an effective treatment for DLB, particularly with respect to neuropsychiatric symptoms, and several reports highlighting improvements in fluctuating confusion [25-30]. Shea et al. reported in 1998, that treatment of nine DLB patients with donepezil for 12 weeks most commonly improved hallucinations, and sometimes improved cognition and overall function [30] (Table 1).

Other preliminary study showed that patients with DLB exhibited greater cognitive improvement on the Mini-Mental State Examination (MMSE) scale than patients with AD [29]. Both DLB and AD patients were prescribed donepezil 5 mg per day and, at baseline and at 6 months, underwent cognitive testing with the MMSE and assessment of psychological assessment using the Behavioral Symptoms in Alzheimer's Disease (BEHAVE-AD) scale. AD patients had only a slight increase in cognitive scores, while DLB patients' mean MMSE scores increased to a significantly greater degree. An increase in MMSE scores across 6 months of treatment correlated with an improvement in BEHAVE-AD scores [29].

In 2004, Aarsland et al. reviewed 14 small studies that focused on ChEI treatment in patients with DLB or PDD [31]. These studies had an open-label or randomized crossover design and included 144 patients treated with tacrine, donepezil, rivastigmine or galantamine between 1996 and 2003. Overall mean MMSE scores improved by approximately two points, and more than 90% of patients reported an improvement in their visual hallucinations. A large, 2-year RCT comparing donepezil and rivastigmine for the treatment of AD suggested a modest advantage for rivastigmine in the subgroup of patients who met criteria for possible DLB, but the diagnostic status of these patients is very unclear [32]. Dubois et al. suggested a limited efficacy and safety study of donepezil in PDD a more recent large, multi-centre, double-blind,

Trial (year)	Design	Outcome
Shea et al. (1998)	Case series (n=9), 12weeks	Commonly improved hallucinations, and sometimes improved cognition and overall function
Samuel et al. (2000)	Open label study (n=4/12 AD), 30 weeks	Significant improvement on MMSE and BEHAVE-AD
Touchon et al. (2006)	Retrospective analysis of RCT (n=49/945 AD), 2 years	Significant improvement on SIB, MMSE, GDS and NPI
Dubois et al. (2009)	RCT (n=550), 24 weeks	Significant improvement on MMSE and CIBIC-plus, but not on ADAS-cog
Mori et al. (2012)	RCT (n=140), 12 weeks	Significant improvement on MMSE and NPI
Ikeda et al. (2013)	RCT (n=108), 52 weeks, extension study of Mori et al.	Significant improvement on MMSE and NPI

AD = Alzheimer's disease; MMSE = Mini Mental State Examination; BEHAVE-AD = Behavioral Symptoms in Alzheimer's Disease; SIB = Severe Impairment Battery; GDS = Global Deterioratio Scale; NPI = Neuropsychiatric Inventory; CIBIC-plus = Clinician's Interview-Based Impression of Change plus; ADAS-cog = Alzheimer's Disease Assessment Scale–cognitive subscale; RCT = Randomized controlled trial

Table 1: Summary of clinical trials of Donepezil in patients with dementia with Lewy bodies.

placebo-controlled study [33]. In this study, PDD patients (n=550) were randomized to donepezil (5 or 10 mg) or placebo for 24 weeks. Two scales, the Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog) and Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC1; global function), were originally defined as coprimary end points. CIBIC1 mean changes from baseline to week 24 showed significant benefit for the 10-mg group, but not 5-mg group. ADAS-cog did not revealed significant benefits for both donepezil doses compared with placebo. A few years later, the authors reanalyzed the results removing the treatment-by-country interaction term from the model and suggested that the alternative ADAS-cog analysis revealed dose dependent benefit with donepezil [34].

More recently, Mori et al. reported a randomized, placebo-controlled trial of 140 DLB patients who received placebo or 3, 5 or 10 mg of donepezil daily for 12 weeks [35]. This exploratory study had no prespecified primary endpoint but rather examined a variety of cognitive, behavioral, global function, and caregiver outcomes. Efficacy was assessed at baseline and at weeks 4, 8, and 12. At the final evaluation, 5 or 10 mg donepezil treated patients benefited from a 2.0 to 3.8 points on the MMSE, which is a larger difference than that reported in other studies of ChEIs in DLB, AD and PDD. The Neuropsychiatric Inventory (NPI) scores were significantly more improved over the course of the study in the 5 mg and 10 mg donepezil groups compared with placebo. Significant improvements were also seen in several neuropsychiatric domains affected by DLB, especially delusions, hallucinations and cognitive fluctuations, for patients receiving donepezil. Global function scores also were significantly higher in all active treatment groups compared with placebo. Caregiver scores were improved in the 10-mg group only compared with placebo, and that difference was not significant after baseline adjustments.

Furthermore, the same research group reported the safety and efficacy of long-term administration of donepezil in patients with DLB [36]. 108 patients enrolled in the 52-week, multicenter, open-label extension study, showed improvements in cognitive function and dementia-related behavioral symptoms, including cognitive fluctuations, after the start of donepezil treatment, and improvement was maintained for 52 weeks. Reduction in caregiver burden observed in the preceding RCT returned to the baseline level at 52 weeks.

There is some evidence that different types of anti-dementia drugs also may be effective in the treatment of DLB. A multicenter trial of rivastigmine in 120 DLB patients for 20 weeks, published in 2000, reported that rivastigmine (mean 7 mg/day) provided significantly greater benefit than placebo [37]. In this study, 30% improvements were shown in a four-item NPI subscore(delusions, hallucinations, apathy, anxiety) as the primary outcome measure. Although not statistically significant, attentional performance in the rivastigmine treated patients also improved with a mean one-point advantage on the MMSE. The preliminary literature relating to use of rivastigmine in DLB emphasized the need for an RCT, which culminated in a large, parallel-group RCT of rivastigmine in 541 patients with DLB for 24 weeks [38]. Over the treatment period, rivastigmine-treated patients benefited from a mean one-point advantage on the MMSE, an almost three-point mean advantage on the ADAS-cog. The mean total NPI score also improved significantly, albeit modestly, by two points, although no specific breakdown of benefits in specific subscores was reported. There was no overall significant worsening of parkinsonism, but, compared with placebo, there was a significant increase in tremor as a reported adverse event in the rivastigmine-treated patients and an increased likelihood of nausea and vomiting. Mortality rates were significantly lower in the rivastigmine-treated patients (1.1% vs 3.9% in the placebo group).

Conclusions

Overall, global clinical benefits and good tolerability were reported in several clinical trials of ChEIs, particularly donepezil and rivastigmine although evidence is not strong and needs more clinical trials, particularly long-term trials, to assess the efficacy of ChEIs in treatments of DLB. Lewy bodies, constituted by alpha-synuclein aggregation, occur in many brain areas in patients with DLB. The nucleus basalis of Mynert, which synthesise actylcholine and project to cortical areas, is also affected. The severe decrease of cortical levels of acetylcholine and its enzyme for synthesis, and the relative preservation or up-regulation of muscarinergic and nicotinic receptors in patients with DLB [39]. These findings suggest that ChEIs may indicate a greater potential effectiveness in DLB compared to AD. As shown in this review, some preliminary studies or RCT suggest that patients with DLB may have a greater response to ChEIs than AD patients. Actually, in Japan, donepezil was approved for the treatment of DLB in September, 2014.

Clinical criteria and assessment scales developed in the past decade may allow the identification or differentiation of patients with DLB from other dementia subtypes. However diagnostic accuracy still need to be improved at this stage. The pathological heterogeneity that occurs in the aging brain makes distinctions between DLB and other dementia subtypes more difficult. Actually coexisting Lewy bodies and Alzheimer-type pathology in DLB is often observed in the postmortem brains of DLB patients [40]. More than half of patients with DLB have some of the hallmark changes of AD pathology in the brain without having the usual clinical features of the disorder and approximately 50% of those with AD also have some Lewy body changes in the brain as well [41,42].

Progress may be difficult given the inevitable pathological heterogeneity that occurs in the aging brain. As mentioned above, many patients with DLB have substantial additional pathology that modifies the core clinical features and makes those cases difficult to diagnose by existing clinical methods [43]. Therefore, in future, the assessment of patients with DLB for co-existing Alzheimer's-related pathology may be critical for treatment decisions as well as planning for clinical trials in DLB.

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