Rivastigmine in the treatment of patients with Alzheimer's disease

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Abstract: Impairment of attention and memory in patients with Alzheimer's disease (AD) is associated with significantly lower levels of acetylcholine. Inhibition of the breakdown of acetylcholine by blocking the enzymes acetylcholinesterase and butyrylcholinesterase with rivastigmine improves this cholinergic depletion. Thus rivastigmine administration provides established, effective, long-term symptomatic treatment in AD and Parkinson's disease (PD) patients with dementia. A sustained treatment with cholinesterase inhibitors in general may also induce a certain deterioration of fine motor behavior, which may play a crucial role in the treatment of PD patients with dementia. Recent studies show that this altered balance between dopamine and acetylcholine due to cholinesterase inhibition, with its possible negative impact on motion behaviour, does not present a major problem in clinical practice in AD patients and may be compensated for by modification of dopaminergic substitution in PD patients with dementia. However, progression of neurodegeneration increases the vulnerability for psychosis in AD and PD patients with dementia in combination with dehydration and often requires additional application of neuroleptics. Since classical neuroleptics increase extrapyramidal symptoms, atypical neuroleptics are used. Out of these, quetiapine shows a distinct lower anticholinergic (muscarinergic) potency with beneficial effects on cognition. This favors its use in combination with rivastigmine.

Keywords: neurodegeneration, Alzheimer's disease, rivastigmine, movement

Introduction

Alzheimer's disease (AD) is the commonest cause of dementia affecting older people. Research advances have enabled a detailed understanding of the molecular pathogenesis of the hallmarks of the disease, ie, plaques, composed of amyloid beta, and tangles, composed of hyperphosphorylated tau. The neurodegenerative AD process is histopathologically characterized by nerve cell loss, extracellular deposits of beta amyloid protein, and intraneuronal formation of neurofibrillary tangles. These changes do not exclusively occur in the cerebral cortex but also in several subcortical nuclei. The nucleus basalis of Meynert is most severely affected. Its neurons are cholinergic and project into many cortical areas. Loss of these nerve cells results in a widespread reduction of the cholinergic activity in the cortex. Cholinergic depletion is associated with impairment of attention and memory; therefore the cholinergic deficit in AD presumably contributes to some of the core symptoms. However, as knowledge increases so does also the appreciation for the pathogenic complexity of the disorder. Familial AD is a very rare autosomal dominant disease with early onset, caused by mutations in the amyloid precursor protein and presenilin genes, both linked to amyloid beta metabolism. By contrast with familial disease, sporadic AD is very common with more than 15 million people affected worldwide (Blount et al 2002; Cummings 2005; Alva and Potkin 2003). The cause of the sporadic form of the disease is unknown,

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probably because the dementia and AD in particular is heterogeneous, caused by aging in concert with a complex interaction of both genetic and environmental risk factors (Blennow et al 2006).

The common mode of action of cholinesterase inhibitors (ChEI)

Pathological changes in AD involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. These are accomplished by decreased concentrations of acetylcholine, which are modulated by the enzyme cholinesterase. This enzyme is of neuronal origin and functions to metabolize acetylcholine at synapses throughout the nervous system. Cholinesterase breaks down acetylcholine, a neurotransmitter which assists in human memory and cognition processes. By inhibiting cholinesterase, more acetylcholine is available to the patient for memory and cognitive functioning. This is effective in treatment of AD, since acetylcholine is at significantly lower levels in AD patients than in normally functioning people. These drugs block the enzyme that inactivates the transmitter in the synaptic cleft. It should be noted that ChEI are a symptomatic, not causal, treatment of AD. ChEI increase the concentration of acetylcholine in the brain. As AD progresses and cortical neurons are lost, levels of acetylcholinesterase progressively decline, while levels of butyrylcholinesterase increase. Butyrylcholinesterase can and does take over the function of metabolizing acetylcholine at the synapse, when acetylcholinesterase is lost, a phenomenon that has been demonstrated in an acetylcholinesterase knockout mouse model and which probably occurs in AD (Polinsky 1998). Rivastigmine, but not its competitors, inhibits both acetylcholinesterase and butyrylcholinesterase by covalently binding to active sites on these enzymes, blocking their function. Breaking of these covalent bonds is the first and most important step in the degradation of rivastigmine, which is not metabolized in the liver (Greig et al 2002; Darvesh et al 2003; Eskander et al 2005).

Symptomatic drug treatment approaches

Since the introduction of the first ChEI in 1997, most clinicians and probably most patients would consider the cholinergic drugs donepezil, galantamine, and rivastigmine to be the first-line pharmacotherapy for mild to moderate AD. These drugs have slightly different pharmacological properties, but they all work by inhibiting the breakdown of acetylcholine, an important neurotransmitter associated with memory, by blocking the enzyme acetylcholinesterase. The most that these drugs could achieve is to modify the clinical manifestations, in particular the cognitive impairment, of AD. Moreover there is accumulating evidence that they also improve additional affected domains of global functioning, such as activities of daily living or behavior (Cummings 2000; Bonner and Peskind 2002; Clegg et al 2002).

Objective

Objective is to review the efficacy of rivastigmine in the treatment of AD and to provide an outlook of its effect in the treatment of dementia in Parkinson's disease (PD).

Essential clinical AD trials with rivastigmine

The safety and efficacy of rivastigmine were investigated in several placebo-controlled investigations (see Table 1). Participants, all AD patients, were evaluated in terms of their cognitive performance using the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-Plus). The ADAS-cog considers elements of memory, orientation, attention, reasoning, language, and praxis. Improvement in global functioning was measured by the CIBIC-Plus. This instrument of evaluation considers overall patient cognition, behaviour, and functioning. The patient population for these studies tried to reflect a real world population, since most of the patients used concomitant medications to treat other conditions during the studies. In a 26-week, US study, patients were divided into three groups, each receiving 1–4 mg/day of rivastigmine, 6–12 mg/day of rivastigmine, or placebo. At the end of the treatment period, both ADAS-cog scores and CIBIC-Plus ratings for those treated in either dose-group of rivastigmine were significantly superior to the scores of those who took placebo. Furthermore, the higher-dosage group had better ADAS-cog scores and CIBIC-Plus ratings than the lower-dosage group. Better scores in these assessments indicate greater improvement and less worsening in cognitive function (such as memory, recognition, ability to speak, and other symptoms of dementia) than the average placebo-treated patient. In another 26-week, global study, patients were divided into similar groups. Results of this study also indicated that the 6–12 mg/day group showed significantly

Table 1 Essential published rivastigmine trials in AD

	Study design	Study duration	Intervention and number of randomized patients	Relevant objectives
Corey-Bloom 1998	RCT, parallel, double-blind, multicenter	26 weeks	1. Rivastigmine 1–4 mg: n = 233 2. Rivastigmine 6–12: n = 231 3. Placebo: n = 235	ADAS-cog, CIBIC-plus, PDS Adverse events
Forette 1999	RCT, parallel, double-blind, multicenter Phase II study	18 weeks	1. Rivastigmine bid (6–12 mg/d): n = 45 2. Rivastigmine tid (6–12 mg/d): n = 45 3. Placebo: n = 24	ADAS-cog, CIBIC-plus, NOSGER Adverse events
Rösler 1999	RCT, parallel, double-blind, multicenter	26 weeks	1. Rivastigmine 1–4 mg: n = 243 2. Rivastigmine 6–12 mg: n = 243 3. Placebo: n = 239	ADAS-cog, CIBIC-plus, PDS Adverse events
Bullock 2005	RCT, parallel, double-blind, multicenter	24 months	1. Rivastigmine 3–12 mg: n = 498 2. Donepezil 5–10 mg: n = 500	SIB ADCS-ADL, GDS,NPI Adverse events

Abbreviations: ADAS-cog, Alzheimer's Disease Assessment Scale; CIBIC-Plus, Clinician's Interview Based Impression of Change; GDS, Global Deterioration Scale; NPI, neuropsychiatric inventory; NOSGER, Nurses Observations Scale for Geriatric Patients; PDS, Progressive Deterioration Scale; RCT, randomized controlled trial; b(t)id, 2 (3) times in one day; n, number of treated individuals; SIB, severe impairment battery.

better ratings for CIBIC-Plus than placebo, and significantly better scores on the ADAS-cog scale, compared with placebo and the 1–4 mg/day group. However, the 1–4 mg/day treatment group did not improve significantly over placebo with either assessment tool. These trials and other clinical trials not reported in detail in this review provided evidence for the clinical efficacy of rivastigmine in AD treatment (Spencer and Noble 1998; Rosler et al 1999; Tariot 2001; Wilkinson et al 2002; Ritchie et al 2004; van Dyck 2004; Wilkinson et al 2004; Takeda et al 2006).

Side-effects

The most common side-effects of rivastigmine, as experienced by patients in clinical studies, were nausea, vomiting, anorexia, dyspepsia, asthenia, and weight loss. These effects were experienced with greater frequency earlier in the treatment. Therefore it is recommended taking the drug with a meal. Side-effects often settle down with time.

Long-term administration of rivastigmine in the studies and in the real world

Limited data are available on the tolerability and effectiveness of ChEI therapy for periods up to 5 years. But all available data indicate that rivastigmine was well tolerated and efficacious. There is some evidence that early therapy with rivastigmine may confer some benefit in delaying long-term progression of symptoms, as has been suggested by analysis of the combined 26 weeks of double-blind and first 26 weeks of open-label data. Throughout the initial 26-week double-blind part, patients receiving placebo steadily deteriorated, while those treated with high-dose rivastigmine were able to maintain their baseline level of performance on the ADAS-Cog. This approximated a delayed-start design for the open-label portion, which demonstrated that patients who started rivastigmine late never "caught up" with patients who had been on high-dose rivastigmine from the beginning of the trial. This suggests a disease-progression-delaying effect of the drug, which may allow this population to maintain their autonomy for a longer period of time. However, it is important to emphasize the limitations of these data. They are retrospective, the sample was small, there were significant numbers of drop-outs, and the availability of free rivastigmine ceased with FDA approval that occurred near to the end of the study (Belle et al 2004; Farlow and Lilly 2005). More recent studies have demonstrated that efficacy and patterns of ChEI use are more complex than previously appreciated. Data now strongly support efficacy for ChEI across the progressive stages of AD. Using combined data from three randomized, placebo-controlled rivastigmine trials, Kurz et al found that rivastigmine maintained ADAS-Cog scores at or above placebo levels across mild, moderate, and severe stages, and the benefits of drug therapy were increasingly apparent at more advanced stages as the rate of decline accelerated in the placebo condition (Frankfort et al 2005; Kurz et al 2004). One study on rivastigmine involved 235 patients who were randomized to the study drug or placebo, 187 of whom subsequently crossed over to open-label treatment with rivastigmine (Farlow et al 2001). The study found that placebo patients who progressed faster during the

double-blind phase responded more robustly to subsequent rivastigmine treatment (according to the ADAS-Cog and Progressive Deterioration Scale [PDS] scores). Other studies have found that factors besides drug safety and efficacy influence patterns of ChEI use. Gill et al, in comparing 6400 new users of donepezil versus 3400 subjects enrolled in 10 randomized, controlled trials, found that 51%–78% would not have been eligible to participate in randomized trials because of advanced age, medical additional morbidities, or residence in long-term care. In addition, 28% of new users had stopped taking donepezil by 8 months of treatment, with discontinuation more likely in patients with greater additional morbidities (Gill et al 2004). This suggests that physicians may not be confident in prescribing ChEI for patients who differ from typical participants of randomized, controlled trials, and that more data are needed on clinical outcomes in these "real world" patient populations. With rivastigmine it is obvious that in comparison with the fixed-dose regimen with donepezil, a more flexible-dose rivastigmine titration regime enables improved drug tolerability through slower escalation of dosing with individualized titration. Caregivers and social demographic factors also play an important role in decisions about ChEI use. Belle and colleagues examined predictors of use by patients with dementia whose caregivers were enrolled in the multi-site caregiver intervention Resources for Enhancing Alzheimer's Caregiver Health (REACH) trial (Belle et al 2004). Only 31% of care recipients used a cognitive enhancer at baseline; use was predicted by race (white), higher levels of education, less severe dementia, care giving time, and being a spouse rather than a parent of the caregiver. Over the course of the study, a higher proportion of patients stopped taking ChEI than started the treatment. This study suggests that educating caregivers about the benefits of long-term treatment could improve rates of sustained use required for optimal outcomes. The long-term effects of rivastigmine have been examined in an open-label extension of the placebo-controlled trials. Regardless of the treatment arm to which patients had been allocated until week 26, they were restarted on rivastigmine and titrated upward to the maximum tolerated dose, but not exceeding 12 mg/day. Patients already on a high dose in the double-blind study phase remained above their cognitive baseline level until week 40 and slowly declined thereafter. Patients who had received a low dose of rivastigmine or placebo in the double-blind study phase showed a rapid improvement when restarted on rivastigmine but did not catch up with the high-dose group. This implies that for maximum benefit, treatment should be started as early as possible. After week 40 cognitive ability slowly declined also in the two latter groups. Importantly, all three groups performed better on the ADAS-cog at 1 year than the placebo group had performed at 6 months. Apparently patients benefit from treatment even after the 40-week period of cognitive stabilization (Farlow et al 2000; Darreh-Shori et al 2002; Erkinjuntti et al 2002; Farlow 2002; Farlow et al 2003; Darreh-Shori et al 2004; Farlow and Lilly 2005). To date, there is only one relevant head-to-head trial on the efficacy of ChEI, rivastigmine, and donepezil. This study describes similar efficacy of rivastigmine and donepezil on cognition and behaviour, and greater benefit in activities of daily living and global functioning in the rivastigmine arm is concluded (Bullock et al 2005; Winblad et al 2006).

Essentials points to sustained ChEI treatment

Sustained treatment requires consideration of individual differences between patients, the magnitude of therapeutic response, the likelihood of response to a specific drug, and tolerance for dose escalation. Active anticipation, management, and monitoring are required for additional morbidities such as heart or lung disease, urinary incontinence, and complications of dementia (eg, dehydration, hypotension, obstipation, undernutrition, falls). In addition, an attitude of realistic optimism about management and a perspective rooted in principles of chronic disease management are key attributes of physicians and families caring for patients with dementia. A comprehensive, long-range, collaborative dementia care partnership, with a focus on the goals of slowing decline and prolonging quality of life, is the means by which overall outcomes can be optimized (Giacobini 2000; Frankfort et al 2005, 2006).

Novel delivery approaches of rivastigmine – the IDEAL study

Transdermal drug delivery systems (usually by drug "patches") are designed to provide controlled, continuous delivery of drugs through the skin, thereby maintaining more consistent blood levels of the drug. Patches also minimize processing of the drug in the liver, stomach, and intestines. These advantages may make it easier to achieve therapeutic levels of the drug in the bloodstream with lower dosages than pills, thereby possibly reducing side-effects. Since AD initially affects memory, reasoning, and decision-making abilities, it can be a problem for people with the disease to

take drugs on a regular schedule. As the disease advances, people may not know what drugs are for or even what they are. With further advance of the disease, sometimes the ability to swallow is affected. Transdermal drug delivery has the potential to eliminate issues such as forgetting to take the drug or to take it at the right time, and also ease challenges associated with getting the person with Alzheimer's to take or swallow a pill. It also provides visual reassurance for the caregiver that the medication has been taken. At the same time, possible skin irritation and the presence of a new or unknown object on their body may be confusing or annoying to the person with Alzheimer's, so a skin patch may not work for everyone (Muhlack et al 2006; Priano et al 2006). The IDEAL (Investigation of TransDermal Exelon in ALzheimer's disease) was a 24-week, multi-center, randomized, double-blind, placebo- and active-controlled evaluation of once-daily rivastigmine patches versus twice-daily capsules in 1195 patients with moderate stage Alzheimer's. Patients were 50–85 years of age. Tested patch sizes were 10 cm^2 (9.5 mg/24 hours) or 20 cm^2 (17.4 mg/24 hours), and capsules were 6 mg twice-daily. Primary outcome measures were the ADAS-cog and Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). The rivastigmine patch showed statistically significant benefits versus placebo on both of these measures and the ability to perform activities of daily living. The recommended target dose 10 cm^2 patch showed similar efficacy to the highest doses of rivastigmine capsules with three times fewer reports of nausea (7.2% vs 23.1%) and vomiting (6.2% vs 17.0%), which are well-known side-effects of ChEI. The 20 cm^2 patch showed improved cognitive scores versus capsules and similar tolerability to capsules. Local skin tolerability was good. Abnormal redness of the skin was present at moderate or severe levels in only 7.6% and 6.2% of patients receiving 10 and 20 cm^2 patches, respectively. A questionnaire was given to more than 1000 caregivers whose loved ones were AD patients. The caregivers significantly preferred the patch to capsules for ease of following the treatment schedule, overall ease of use, and less interference with daily life (Winblad et al 2006).

Rivastigmine and its impact on motor behavior in AD, and PD, patients

There are reports on deterioration of fine motor behavior during treatment with ChEI, but concomitant application of typical and atypical neuroleptics confounded study outcomes or case reports in AD, or PD, patients with dementia (Heinze et al 2002; Richard et al 2002; Werber and Rabey 2001; Bohnen et al 2004). A further drawback of these reports was a missing compliance control of AD individuals due to oral ChEI administration with their sometimes nausea-inducing effects. One placebo-controlled trial showed a discrete, non-significant improvement of smoothness of hand movements following oral intake of donepezil during a 12-week interval with the use of a standardized handwriting paradigm (Hegerl et al 2003). This positive effect was independent of changes in cognitive function, and confirmed outcomes of a study suggesting normalization of disturbances in the motor cortex of patients with AD treated with donepezil (Liepert et al 2001). However, writing with the non-dominant hand in particular is rather complex and demands a certain cognitive load, and moreover hand dominance may influence outcomes of assessment of motor activity (Van Hilten et al 1993). Therefore more simple instrumental motor tests are also suitable, to address this issue on impact of cholinesterase inhibition on motion. A standardized peg insertion procedure is such a tool. It requires conduction of a complex motion series. This instrumental tool did not show a significant change of outcomes during an open label treatment with donepezil during an interval of 12 weeks, whereas there was a non-significant trend for improvement of simple motions apparent within a finger tapping paradigm (Bohnen et al 2004). A further trial that investigated the impact of transdermal rivastigmine administration on motor performance with an altered standardized peg insertion paradigm showed that patients with predominant cholinergic neurodegeneration need longer for performance of the peg insertion paradigm in comparison with controls. Thus this study confirms a deterioration in carrying out of complex motion series in neurodegenerative processes, because this was also shown in disorders with preponderant functional basal ganglia disturbances, ie, Huntington's disease or PD (Müller et al 2000; Saft et al 2003, 2004). This trial also confirmed that assessment of co-ordinated movements with the non-dominant hand better reflects disturbances of fine motor behavior during neurodegeneration probably due to regular training and use (Müller et al 2000, 2003b; Pal et al 2001; van Vugt et al 2001; Saft et al 2003, 2004). An improved brain plasticity of the dominant brain hemisphere with secondary better compensation of motor deficits may additionally be responsible for the inferior sensitivity of the applied instrumental paradigm to reflect motor disturbances of the upper limb during a neurodegenerative process (Van Hilten

et al 1993; Müller et al 2000, 2003b; van Vugt et al 2001; Ioffe 2004; Saft et al 2004). The impaired motor function found supports the concept of subclinical motor cortex disinhibition during chronic cholinergic neurodegeneration. This results in functional motor disturbances in AD and may be aggravated by the cholinergic dysfunction and the resulting frontal dysbalance of dopaminergic and cholinergic neurotransmission (Liepert et al 2001; Jefferson et al 2002; Di Lazarro et al 2004). However, further future trials with enrolment of more participants, serial evaluation, and better clinical characterization of the cognitive deficit are needed to address this issue in dementia-related processes. However, no deterioration of complex motion performance was found during this transdermal rivastigmine application in AD (Muhlack et al 2006). This finding is of interest, since there is a controversial debate on onset of extrapyramidal symptoms during cholinesterase inhibition in AD patients or patients with parkinsonism in dementia with lewy bodies (Heinze et al 2002; Richard et al 2002; Hegerl et al 2003; Di Lazarro et al 2004). One may conclude that rivastigmine does not cause an impairment of complex movement performance with its demand for additional various forms of complex information processing with visual, cognitive, and sensory inputs (Pal et al 2001; Müller et al 2003a, 2003b). This may be due to the pharmacological profile of rivastigmine with its selective inhibition of the G 1 cholinesterase isoform, which is predominantly located in cortical and hippocampal regions and may therefore favor the use of rivastigmine in PD patients with dementia (Weinstock 1999).

Symptomatic treatment of cognitive deficits in PD patients with dementia

ChEI improve dementia in PD patients, which results from a distinct cholinergic deficit (Tiraboschi et al 2000). The multi-center EXPRESS study compared the efficacy of rivastigmine, an inhibitor of both acetylcholinesterase and butyrylcholinesterase, with placebo. In this trial, rivastigmine produced a moderate but significant improvement in PD patients with dementia. The mean rivastigmine dosage was 8.6 mg at the end of the dose-escalation phase and remained stable throughout the maintenance phase. Predominant cholinergic adverse effects, ie, nausea or vomiting, occurred. The rivastigmine-treated participants mostly characterized these side-effects as mild to moderate and accordingly the rate of premature withdrawal was relatively low. These trials supported the accumulating evidence that ChEI also improve symptoms of dementia in PD patients and allied conditions (Emre 2004), which remained stable in the open extension phase of this trial (Poewe et al 2006). Predominant open-label, earlier, smaller trials with donepezil and rivastigmine also demonstrated an improvement of cognitive function in various kinds of patients with impairment of motor and cognitive function (Werber and Rabey 2001; Giladi et al 2003; Leroi et al 2004). The controversial debate on onset or aggravation of extrapyramidal symptoms during cholinesterase inhibition in PD patients is not finally answered by the EXPRESS study, since this trial allowed a modification of the dopaminergic substitution as a minor adverse event.

Symptomatic treatment of psychosis in AD, and PD, patients with dementia

There is a relationship between progression of neurodegeneration, cognitive deficits, and psychosis in AD, and PD, patients with dementia (Merims et al 2004). Vivid dreams, fear, predominant optic illusions, anxiety, paranoia, hallucinations, and sleep loss are initial clinical signs. Each antiparkinsonian drug may support onset of psychosis in particular in combination with dehydration. Since classical neuroleptics increase extrapyramidal symptoms, atypical neuroleptics are used for treatment of psychotic symptoms in PD. The atypical antipsychotic agent clozapine is well tested in clinical trials. It shows additional sedative and tremor-reducing components and prevents recurrence of psychosis (Parkinson Study Group 1999; Factor et al 2001). However, rare induction of leucopenia and transient low fever limit its use. The metabolism of clozapine via CYP1A2, CYP3A4, CYP2C19, and CYP2D6 may increase levels of compounds, which share these metabolic pathways. Quetiapine has structural similarities to clozapine and the same antipsychotic efficacy. This drug has a distinct lower anticholinergic (muscarinergic) potency in comparison with clozapine (Matheson and Lamb 2000). Therefore open trials with quetiapine reported improved cognition in PD patients. This suggests that quetiapine is more suitable for long-term use than clozapine in neurodegenerative disorders, ie, AD or PD, or both (Juncos et al 2004; Morgante et al 2004).

Conclusion

Rivastigmine provides a distinct benefit for AD, and PD, patients with dementia. There is some evidence that a

clinically relevant deterioration of motion behavior does not occur during sustained rivastigmine application in AD patients. From this point of view rivastigmine is also suitable for the treatment of PD patients with dementia.

Disclosures

The author has no conflicts of interest to disclose.

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