HYPOTHESIS, PROGRESS AND PROBLEMS - CURRENT TREATMENTS FOR ALZHEIMER’S DISEASE: A REVIEW

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ABSTRACT

Alzheimer disease is one of the most complex and challenging neurodegenerative disorders. It has recently received considerable attention, especially in areas related to new treatments. Alzheimer disease is clinically characterized by progressive cognitive decline associated with impairment in activities of daily living and progressive behavioural disturbances throughout the disease course. The cholinergic system plays a vital role for learning and memory, and the memory impairment severity in Alzheimer disease is mainly associated with cholinergic dysfunction. Hence, restoration of cholinergic neurotransmission may help in treating patients with Alzheimer disease. Studies have revealed encouraging results with cholinesterase inhibitors to increase acetylcholine concentrations in the brains of patients with Alzheimer disease.

INTRODUCTION

Alzheimer’s disease is a progressive dementia with loss of neurons and the presence of two main microscopic neuropathological hallmarks: extracellular amyloid plaques and intracellular neurofibrillary tangles. The distribution and degree of severity of neuropathological changes seen post mortem in brain tissue from AD patients is able to explain many of the symptoms seen in life. Generally there is atrophy, with a reduction in gross size, particularly in the temporal lobe and hippocampus: thinning of the cortical gyri and enlargement of the third and lateral cerebral ventricles. [1]

Alzheimer affects approximately 5% of the population older than 65 years. According to the US Centers for Disease Control and Prevention (2003), the number of people in the world who are over the age of 65 will increase to around 1 billion by 2030. It has also been projected that by 2050 the number of dementia cases will reach around 14 million in Europe and 13.2 million in the United States. Furthermore, it has been estimated that the annual incidence of AD in the United States will increase from the 337,000 cases recorded in 1995 to 959,000 cases in 2050. At the level of individuals, AD decreases the quality of life and shortens life expectancy. At the societal level, the long-term care of AD patients in nursing homes is an economic challenge in Western countries, as illustrated by a report in which Olesen and colleagues (2012) showed that in Europe the annual cost for patients with dementia was EUR 105.2 billion in 2010. The mentioned date certainly indicate the tremendous impact of AD in terms of the enormous number of patients with this disease, the pressure on their relatives, and the negative socioeconomic consequences. In short, it can be said that AD is one of the major public health problems in the world. [2]

Microscopic analysis reveals the characteristic extracellular amyloid plaques and intracellular neurofibrillary tangles. At least 80% of cases also show congophilic angiopathy, the deposition of cerebrovascular amyloid in the small vessels in the leptomeninges and cortices.

Neuronal loss and/or pathology may be seen particularly in the hippocampus, amygdale, entorhinal cortex and the cortical association areas of the frontal, temporal and parietal cortices, but also in subcortical nuclei such as the serotonergic dorsal raphe, noradrenergic locus coeruleus, and the
cholinergic basal nucleus. The motor area, primary visual areas, and sensory regions are largely spared. The deposition of tangles follows a defined pattern, beginning in the trans-entorhinal cortex; subsequently the entorhinal cortex, the CA1 region of the hippocampus and later the cortical association areas, where frontal, parietal and temporal lobes are particularly affected. There is evidence that neurofibrillary tangle formation occurs subsequent to α-beta accumulation and since plaques are found at the terminals of neurons with intracellular tangles it is likely that amyloid at the dendritic/axonal synapses has an effect retrogradely, such that tangles subsequently form within those neurons. The extent and placement of tangle formation correlates well with the severity of dementia, much more so than numbers of amyloid plaques. However the reason may be that it is easier to clear extracellular plaques as there are well defined clearing mechanisms such as the action of the enzymes insulin-degrading enzyme (IDE), angiotensin-converting enzyme (ACE), neutral endopeptidase (neprilysin), and tissue type plasminogen activator (tPA). In fact accumulation of amyloid in some cases of sporadic AD may be related to a deficit in this amyloid clearance system. [3]

Delivering medicine to the general circulation through the skin is seen as a desirable alternative to taking it by mouth or by oral route. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, bypassing the gastrointestinal (GI) tract would obviate the GI irritation that frequently occurs and avoid partial first-pass in activation by the liver. Further, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms. These advantages are offered by the currently marketed transdermal products[4]

**AMYLOID HYPOTHESIS**

The amyloid beta peptide is a normal metabolic by product of the amyloid precursor protein (APP). The gene encoding the amyloid precursor protein is located on chromosome 21, and it has been shown that trisomy 21 (Down’s syndrome) leads to the neuropathology of AD. APP is normally cleaved by proteases called α-, h-, and g-secretases, however, mutations along the gene encoding APP occur at these cleavage sites, eventually leading to the abnormal intramembranous processing of APP, and the consequential extracellular deposition of Ah. Likewise, these mutations influence the self-aggregation of Ah into amyloid fibrils. In addition, the presenilin proteins (PS1 and PS2, located on chromosomes 14 and 1, respectively) have been found to alter the APP metabolism by the direct effect of g-secretase. Fagan et al. have shown that the E4 isoform of the apolipoprotein E (chromosome 19) facilitates the formation of Aβ fibrils in genetically engineered mice. The collective effect of these processes is the increased production and accumulation of the (1–42) fragment of the amyloid beta peptide. The Ah (1–42) oligomerizes and deposits in the synaptic space as diffuse plaques. The result is synaptic injury, preceded by the microglial activation, followed by oxidative stress, neuronal death, and dementia.[5]

**THE METALLOCHEMISTRY OF AD/OXIDATIVE STRESS**

The Aβ peptide exists as three types in the brain: membrane-bound, aggregated (Aβ 1–42) and soluble (Aβ 1–40, found in biological fluids). Membrane bound Aβ is found in healthy individuals, while the aggregated and soluble peptide is located in the disease affected individuals. The normal brain shows increased metallation upon aging; in AD, some of these metals are found at extremely high levels in the neocortical regions. In particular, the transition metals such as copper, iron and zinc are implicated in the neurotoxicity of the Aβ. It is conjectured that a dyshomostasis, rather than toxological exposure to these ions, results in the pathogenesis of AD. The Aβ is physiologically associated with Cu2+, and copper is thought to aggregate Aβ in acidic conditions. The AhCu2+ catalyzes the generation of hydrogen peroxide (H2O2) through the reduction of Cu2+ and Fe3+, using oxygen and endogenous reducing agents. The H2O2 permeates the cell membranes, and if not broken down by catalyses, highly reactive hydroxyl radicals form (through the Fenton reaction), which disrupts the genetic material (DNA), and
modifies proteins and lipids. In addition, apoptosis is induced by the permeation of H2O2 through the cell membrane. Thus, the Aβ (1–42) has a higher binding affinity for copper than does the Aβ (1–40), which may account for the preferential aggregation of Aβ42. The neurochemistry of Aβ in the presence of iron is akin to that of copper. Namely, iron aggregates Aβ through redox chemistry-type reactions. The Fenton reaction generates H2O2 production, as is similarly seen in the Aβ interactions with copper. Likewise, analogous fates of the protein transpire. Zinc exerts effects in the AD brain in a manner different than those put forth by copper and iron. First, zinc precipitates Aβ at the physiological pH, whereas copper and iron require mild acidic conditions. Accordingly, the difference in pH accounts for a hastening of beta amyloid deposition by zinc. Yet another profound distinction classifying zinc from other metals is that it is redox-inert, and hence, inhibits the production of H2O2. Therefore, zinc’s role in Aβ physiology is as that of an antioxidant. Zinc’s inhibitory role in the production of H2O2 is attributed to the ion’s competitive nature against copper for the Aβ binding sites. However, zinc is not found concentrated enough in the brain to completely eliminate Aβ neurotoxicity.

**AVAILABLE DRUGS FOR USE IN ALZHEIMER DISEASE**

The drugs currently available for the treatment of dementia are acetylcholinesterase inhibitors (AChEIs) or NMDA glutamate receptor antagonists. The former include donepezil, rivastigmine, galantamine and few others that are still undergoing testing. They are used to increase synaptic levels of acetylcholine, which are reduced as a result of damage to cholinergic neurons in the amygdala, hippocampus and frontal cortex, the brain areas that are responsible for the maintenance of memory. NMDA receptor antagonists, like memantine, are used to prevent or reduce calcium-dependent excitotoxic neuronal cell death. AChEIs produced some degree of improvement in cognitive functions, but their effects were confined largely to patients with mild-to-moderate AD-like dementia, and the most marked effects observed during the first year or so of treatment. Thereafter, their efficacy declines progressively and disappears entirely after 2 or 3 years. Attempts were made to increase the efficacy of AChEIs by combining them with memantine, but it remains to be seen whether these associations are more effective than the single drugs alone.

**ACETYLCOLINESTERASE INHIBITORS DONEPEZIL**

Donepezil, (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-[phenylmethyl]-4-piperidinyl]methyl]-1H-inden-1-one hydrochloride, is extensively used to delay cognitive decline in subjects with mild-to-moderate AD. After oral administration, donepezil has an excellent bioavailability and plasma peak concentration is achieved in 3–4 h. The drug is tightly bound to plasma proteins and this could account for the prolonged half-life of ~70 h. This drug is metabolized by the liver, through the isoforms 3A4 and 2D6 of the cytochrome P-450 (CYP) and is mainly excreted by the kidney even if a small part of the drug is recovered in the feces. Important pharmacokinetic interactions occur if donepezil is administered together with inducers or inhibitors of CYP3A4 and CYP2D6, and this could be a common event considering that very often AD subjects are affected by concomitant diseases. From a pharmacodynamic point of view, donepezil is a selective, reversible inhibitor of AChE with only a minimum activity against butryrylcholinesterase (BChE). In addition, donepezil and galantamine act as allosteric potentiation ligands on a4- and a7-nicotinic ACh receptors. Through this mechanism, donepezil and galantamine activate pro-survival pathways such as the proto-oncogene Akt and protein Bcl-2 and down-regulate calcium-induced activation of nitric oxide synthase and the further increase of cytotoxic reactive nitrogen species, including peroxynitrite.

**ORAL DONEPEZIL THERAPY IMMEDIATE-RELEASE TABLETS**

Donepezil immediate-release (IR) tablets (5 or 10 mg) were approved for use in the US in November 1996 for the treatment of dementia of the Alzheimer’s. Donepezil interacts with AChE via hydrogen bonds and is demonstrated to be a reversible, non-
competitive, and selective ChEI that produces long-lasting inhibition of brain AChE without markedly affecting peripheral AChE activity. Due to properties such as low hepatotoxicity, high selectivity towards AChE inhibition ($IC_{50}$ AChE/$IC_{50}$ BuChE = 6.7/7400 nM), and a duration of action ($t_{1/2}$ = 90 h) that is sufficiently long enough to allow for convenient once-daily administration, donepezil has been widely used to treat AD patients worldwide. The long-term benefits and good safety profile of AChEIs shown by extended post-marketing studies allowed for the approval of donepezil for the treatment of the entire clinical spectra of the disease in 2007.

**SUSTAINED-RELEASE TABLETS**

In 2010, the FDA approved sustained-release (SR) tablets containing 23 mg of donepezil to provide a higher once-daily dose while avoiding a sharp daily increase in peak concentration. Inactive ingredients in the 23 mg tablets are ethylcellulose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and methacrylic acid copolymer, type C. The film coating is composed of ferric oxide, hypromellose 2910, PEG 8000, talc, and titanium dioxide. These film-coated tablets were compared with the marketed formulation of 10 mg IR tablets in patients with moderate to severe AD who were on a stable dose of 10 mg/day Aricept for at least 3 months before screening. The 1500 enrolled patients received either 10 mg donepezil IR in combination with the placebo corresponding to the 23 mg donepezil SR formulation, or 23 mg donepezil SR in combination with the placebo corresponding to 10 mg of the donepezil IR formulation. The 23 mg donepezil SR ensured significant cognitive and global functioning benefits, but safety and efficacy of long-term administration are still under study.

**ORALLY DISINTEGRATING TABLETS**

Donepezil (Aricept) is also available as an orally disintegrating tablet (ODT), approved for use in the US in 2004. This formulation is particularly useful for patients who have difficulties swallowing tablets; moreover, they allow for administration once daily. These tablets contain 5 or 10 mg of donepezil hydrochloride, carrageenan, mannitol, colloidal silicon dioxide, and polyvinyl alcohol. The 10 mg tablets also contain ferric oxide (yellow) as a coloring agent.

**MARKETED DONEPEZIL TABLETS [7]**

- Aricept
- Donep
- Dopezil
- Donecept

**TRANSDERMAL DONEPEZIL THERAPY**

The large fluctuation of plasma levels after oral administration of donepezil were associated with frequent gastrointestinal symptoms including diarrhea, nausea, constipation, abdominal pain, vomiting, anorexia, and abdominal distention. A transdermal drug delivery system may offer considerable advantages over conventional delivery methods of ChEI for patients who have difficulties swallowing solids or liquids. Furthermore, certain adverse effects may be decreased by this route of administration; for example, first pass effects could be avoided, plasma level fluctuations could be greatly reduced, and the dosing schedule can be simplified. Moreover, when adverse side effects occur, prompt cessation of drug delivery can be obtained by simple patch removal. These improved tolerability and compliance profiles could potentially result in greater treatment adherence, and the patch might be favored over the oral route by the majority of caregivers in the near future.[3]

**RIVASTIGMINE**

Rivastigmine[(S)-N-ethyl-3-[(1-dimethylamino)ethyl]-Nmethylphenylcarbamate hydrogen], is well absorbed by oral route, the plasma protein binding is ~ 40%, the plasma peak concentration is achieved in 1 h and the half life is ~ 1.5-2 h. The metabolism of rivastigmine is rapid and extensive and occurs mainly through cholinesterasemediated hydrolysis to the NAP-226-90 metabolite which undergoes sulfate conjugation in the liver and is excreted by the kidney. Pharmacodynamically, rivastigmine is not a selective inhibitor of AChE because it also
inhibits BChE with equal potency.[9] In addition, rivastigmine forms a carbamoylated complex with both AChE and BChE, characterized by a covalent bond, which makes the complex more resistant to the hydrolysis and this likely affects the half-life of this drug. The main adverse effects include dizziness, anorexia, nausea, vomiting and dyspepsia. Significant differences in global function and measures of cognition favored rivastigmine in subjects with mild-to-severe AD. In a 26-week RCT, 725 subjects with mild-to-moderately severe AD received two dose regimens of rivastigmine: 1-4 mg/day or 6-12 mg/day. Only subjects treated with rivastigmine 6-12 mg/day maintained their baseline levels of cognitive performance and demonstrated favorable and significant differences in cognition, participation in activities of daily living and global evaluation. In the follow-up study, a larger difference was seen in ADAS-cog scores between the rivastigmine (6-12 mg/day) group versus the placebo group at 52 weeks but only subjects originally treated with rivastigmine 6-12 mg/day had better cognitive function. A retrospective analysis suggested efficacy of rivastigmine in subjects with moderate-to-severe AD. Data pooled from three 6-month RCT demonstrated that moderate-to-severe AD patients treated with rivastigmine 6-12 mg/day had better cognitive performance compared with the control group after 6 months from treatment. These results suggested that rivastigmine provides clinical benefit to patients with moderate-to-severe AD.

MARKETED RIVASTIGMINE TABLETS [7]

- Exelon
- Rivastigmine
- Zeemine

TRANSDERMAL RIVASTIGMINE

Currently, an alternative route of administration was proposed for this drug, and the rivastigmine patch is the first transdermal treatment to be approved for mild-to-moderate AD in the USA and Europe. The main reason that the transdermal route was approved is based on the better pharmacokinetic profile of rivastigmine which, from the dermal patch, is continuously delivered into the bloodstream, thus avoiding the fluctuations in plasma concentration due to the oral route of administration. The first studies designed to test the efficacy of transdermal rivastigmine were 6-month RCT which demonstrated that a 10 cm² patch, which corresponds to 9.5 mg/day rivastigmine, provided similar efficacy to 12 mg/day rivastigmine capsule, and also guaranteed a threefold reduction in reports of nausea and vomiting. An updated paper compared the results from three RCT with rivastigmine patches versus capsules and reported that the former have better safety and tolerability profiles than the latter, and the risk of skin reaction can be decreased simply by rotating patch location. With regard to cognitive performance, a recent paper demonstrated that a 10 cm² rivastigmine patch improved cognitive and functional performance in AD patients. The rivastigmine patch is well tolerated and only mild adverse effects (erythema and pruritus) were recorded.

MARKETED RIVASTIGMINE PATCHES [7]

Exelon patch

GALANTAMINE

Galantamine (4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H benzofuro [3a,3,2-ef][2]benzazepin-6-ol), is a tertiary alkaloid that has been isolated from various plants, including narcissus species and the Caucasian snowdrop (Galanthus nivalis) and this drug is approved for clinical use in AD. Similarly to donepezil, galantamine has an excellent bioavailability after oral administration, but lower protein binding (15-30%) and both shorter time-to-peak concentration (1-2 h) and half-life (5-7 h). Galantamine is metabolized by the liver, through the isofoms 3A4 and 2D6 of the CYP and is mainly excreted by the kidney. Like donepezil, important pharmacokinetic interactions could occur if galantamine is administered together with inducers or inhibitors of CYP3A4 and CYP2D6. Galantamine shares with donepezil also the ability to stimulate Akt and Bcl-2 pathways and inhibit NO-induced cytotoxicity, and thus counteract neuronal death. Tariot et al. investigated the efficacy and tolerability of galantamine (8, 16 or 24 mg/day) in a 5-month RCT involving subjects with mild-to-moderate AD. Only
subjects treated with the two higher doses of galantamine had significant benefits in the cognitive, functional and behavioral symptoms of AD as compared with placebo.

MARKETED GALANTAMINE TABLETS [8]

- Razadyne

NMDA GLUTAMATE RECEPTOR ANTAGONIST MEMANTINE

Memantine (3,5-dimethyladamantan-1-amine) binds NMDA receptor channels, thereby inducing a non-competitive block. After administration of an oral dose, memantines is almost completely absorbed, reaches the peak plasma values in 6-8 h and its half-life is 60-80 hours. About 50% of the drug is excreted unchanged by the kidney, whereas the remainder is converted into glucuronide derivatives and excreted in the urine. The main side effects of memantine are dizziness, constipation, cataracts, nausea, dyspnea, confusion, headache and urinary incontinence. Caution should be used in the case of concomitant administration of memantine and inducers or inhibitors of UGT-glucuronosyltransferase(s). Three large multicenter 6-month RCT confirmed the efficacy of oral memantine (20 mg/day) alone or in combination with donepezil, in moderate-to-severe AD. The results from these RCT demonstrated that Memantine improved only the activities of daily living without any significant effect on cognitive function. When administered in moderate-to-severe AD patients already treated with donepezil, memantine improved cognitive function and the activities of daily living. In a recent study, subjects with mild-to-moderate AD randomized to receive either donepezil or memantine for 6 months, did not show any change in cognitive function as well as in neuronal density (evaluated by measuring N-acetyl aspartate and choline) in temporal, prefrontal, posterior cingulated and occipital areas of the brain. Recently, Schneider et al. analyzed the results of three RCT and demonstrated the lack of efficacy of memantine to improve cognitive function and activities of daily living in mild AD patients. Memantine was also associated with both oral and transdermal rivastigmine in mild-to-moderate AD subjects. In a 25-week open label study, subjects with mild-to-moderate AD were treated with memantine alone or in the presence of rivastigmine patches (4.6 mg/day rivastigmine patches for 4 weeks and then with 9.5 mg/day patches for further 20 weeks). The results showed that changes in cognitive and global function were similar between the two arms of treatment, whereas the activities of daily living scores worsened in both the groups, even more than in those patients treated with memantine alone. The incidence of adverse effects did not significantly increased when memantine was given concomitantly with oral or transdermal rivastigmine and the most common adverse effects were nausea, vomiting and dizziness.[9]

MARKETED MEMANTINE TABLETS [8]

- Namenda

DRUGS STILL UNDER DEVELOPMENT

ACETYLCHOLINESTERASE INHIBITORS LATREPIRDINE

Latrepiridine [2,3,4,5-tetrahydro-2,8-dimethyl-5-(2-[6-methyl-3-pyridyl]ethyl)-1H-pyrido[4,3-b]indole] also known as dimebon or dimebolin. Dimebon was initially developed as a orally active non-selective antihistamine drug, but due to the development of newer and safer antihistamine drug, it was withdrawn from the market. The interest on latrepiridine was renewed at the beginning of the 2000s when this agent exhibited neuroprotective effects in preclinical models of AD and Parkinson disease. This evidence prompted neurologists to design ad hoc clinical trials to evaluate the effect of dimebon in subjects with mild to moderate AD. In a RCT, Doody et al. demonstrated that dimebon 20 mg three times a day significantly improved cognitive function (measured as ADAS-cog score) over 26 weeks of treatment. In the extension phase of the trial, patients taking dimebon were followed-up for further 26 weeks and they still exhibited a significant improvement in cognitive function (ADAS-cog, MMSE and CIBIC-plus scores) with respect to those treated with placebo. More recently, a larger RCT (CONNECTION) involved 598 subjects with mild-to-moderate
AD treated with dimebon 5 or 20 mg three times a day. This study demonstrated that 6-month treatment with both the doses of dimebon did not improve cognitive and global functions in AD subjects, and the development of dimebon was partially discontinued. However, the Phase III CONCERT study which evaluated the effect of dimebon in AD patients treated concomitantly with donepezil is still ongoing.[10]

NICOTINIC RECEPTOR AGONISTS
ISPRONICLINE

Ispronicline, is an oral active α4β2 nicotinic acetylcholine receptor-selective agonist with neuroprotective effects in humans. After oral administration, ispronicline reaches the peak plasma concentration after 1-2 h and the terminal half-life is ~ 3.5 h (single doses) and ~ 3.9 h (repeated doses). The development of a novel α4β2 receptor agonist, named AZD 1446, has been prioritized over further development of ispronicline in AD.[11]

CONCLUSION

Success in future therapeutic avenues will benefit from an understanding of how the many risk factors are able to affect the molecular pathology to produce this progressive dementia. Although the enormous in vitro and in vivo lines of evidence produced over the last few years, several issues in the pathogenesis of AD remain still poorly understood. There are two groups of medications currently approved for the treatment of Alzheimer’s disease. Neither will cure Alzheimer’s disease. Many studies have described the possibilities of using nanoparticles for the targeting drugs in CNS. Further innovative studies are required for the treatment of Alzheimer’s disease.

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