Cholinesterase Inhibitors used for the management of Alzheimer's disease: A review

Abstract

Alzheimer's disease (AD) is defined as a progressive neurodegenerative disorder which has lately become the top most reason of dementia in the elderly population (usually above 60-65 years). Most cases of the AD are sporadic in nature and have a late onset as mentioned before. This disease is characterized by impairment of higher cognitive functions like deficits in memory, language comprehension, coordination etc. The main pathophysiology behind Alzheimer's disease is loss of cholinergic innervation due to formation of neuritic (senile) amyloid beta plaques and tau protein containing neurofibrillary tangles (NFTs) in parts of the brain associated with memory functions. These neurofibrillary tangles (NFTs) and Amyloid β plaques, can together cause the induction of other aetiologies of Alzheimer's disease like neuroinflammation as well as central hyperexcitability. The main regions of the brain that are affected in Alzheimer's disease are the neocortex, basal nucleus of Meynert and the hippocampus, as these areas are associated with higher cognitive functions like memory, arousal, attention, sensory processing etc. Thus, cholinesterase inhibitors have been widely used as first line drug therapy for symptomatic relief in Alzheimer's disease. They function by inhibiting acetylcholinesterase or by catabolizing it and henceforth enhancing synaptic availability of Acetylcholine. The commonly prescribed drugs of this class include donepezil, galantamine, physostigmine, metrifonate and rivastigmine. This article will discuss the widely used cholinesterase inhibitors (old & new) for management of symptoms of AD in detail.

Keywords: Alzheimer's disease, neurodegenerative disorder, sporadic, senile neuritic plaque, dementia, amyloid beta plaques, tau protein, neurofibrillary tangles, neuroinflammation, central hyperexcitability, neocortex, basal nucleus of Meynert, hippocampus, acetylcholine, cholinesterase inhibitors.

Introduction:

Alzheimer's disease (AD) is defined as a progressive neurodegradative disorder which has recently become the global cause of dementia in elderly population (above 60 years usually), accounting for 70% of all sporadic, late onset dementia. (1) This disease is distinguished by progressive deterioration of higher cognitive functions together with a steep decline in the efficiency of daily activities and behavioural changes. AD is known to be the most common type of pre-senile and senile dementia. (2)

The brain regions most affected by the characteristic pathology of Alzheimer's disease include neocortex, hippocampus, basal forebrain, basal nucleus of Meynert and amygdala. To a lesser extent the dorsal tegmentum, medial nucleus of thalamus, locus coeruleus, paramedian reticular area and lateral hypothalamic nuclei may get affected. (3)

The majority of Alzheimer's disease cases are sporadic, with delayed onset (65 years) and an unknown cause. Age is the most accurate predictor of illness development. However, 5 to 15% of cases are familial; half of these cases have a young (presenile) onset (under 65 years) and are usually linked to specific genetic alterations.(1)

Objective:

The following narrative literature review article aims to explore and provide a quick and brief account of AD, its neuropathology and various medicines belonging to the class of cholinesterase inhibitors used for the symptomatic treatment of Alzheimer's disease in adults.

Neuropathology of Alzheimer's

The neuropathological manifestations of AD include the deposition of mainly two types of eccentric aggregates of protein- amyloid-β that form neuritic plaques and hyper phosphorylated tau protein that form neurofibrillary tangles causing massive disintegration of cholinergic neurons in the basal part of forebrain that leads to loss of neurotransmission of acetylcholine to other areas of the brain, mainly the neocortex via basal nucleus of Meynert

and the hippocampus, as these areas are associated with higher cognitive functions like memory, arousal, attention, sensory processing etc that are lost in AD.(1)

The neurofibrillary tangles of tau protein consist of eccentric aggregations of abnormally phosphorylated tau within the peripheral cytoplasm belonging to certain neurocytes The poorly structured neurites or neuronal processes in the neuritic senile plaque are surrounded by an inner core of beta amyloid and a 4-kD peptide. Other neuropathological lesions may also be seen in Alzheimer's disease, but these two significant lesions define and identify the condition. Other abnormalities include eosinophilic rod type looking structures and granular + vacuolar disintegration, which are poorly understood, known as Hirano bodies. . This morphological change i.e. the loss of the synaptic components has clear and marked impact on cognitive functioning.(2)

The above-mentioned hallmark protein aggregations of Alzheimer's dementia, Aβ plaques and neurofibrillary tangles (NFTs), can together induce other AD aetiologies like inflammation of neurons and central hyperexcitability. Inflammation of neurons results from the excessive activation of microglial cells and astrocytes that secrete inflammatory chemical mediators like cytokines due to the neural damages caused by Aβ plaques and NFTs, ultimately contributing into non-functioning of cholinergic synapses and death of neurons in basal forebrain. (3)

Beta-amyloid protein has been found to have neurotoxic effects. These effects take place through some secondary mechanisms, which include lipid peroxidation, oxidation, inflammation, formation of neurofibrillary tangles, stimulation of apoptotic cell death and glutamatergic excitotoxicity. (4)

Thus, the main pathophysiology behind Alzheimer's is the loss of cholinergic neurotransmission that manifests in following ways forming the 'Cholinergic Hypothesis' of Alzheimer':

- Loss of basocortical cholinergic projections.
- Decline in amount of cortical acetyl choline transferase required for ACh synthesis.
- Destruction of cholinergic neurons in the basalis nucleus or basal nucleus of Meynert.(5)

Hence, drugs that can improve the cholinergic function and overcome cholinergic insufficiency are important for management of AD. The widely used class of drugs for symptomatic relief in AD are Cholinesterase Inhibitors.

Cholinesterase Inhibitors

Most neurotransmitters and neuropeptides, particularly acetylcholine, the key memory neurotransmitter, fall in concentration inside the human brain as AD progresses. Several ways have been tried to improve cerebral acetylcholine levels in Alzheimer's disease. One most effective way is to inhibit cholinesterase enzyme that would make more Acetylcholine available for neurological transmission and hence lead to cognitive repair. (6)

Currently, the most effective treatment strategy in dementia associated with Alzheimer's disease is use of Cholinesterase inhibitors class of drugs. It is seen that the treatment effect is mainly symptomatic. In individuals suffering from memory loss (dementia), inhibitors of acetylcholinesterase target the decrease in concentration of acetylcholine caused by loss of neural cells from projections of nucleus basalis of Meynert. Hence it is justified that they are symptomatic treatments, with no evidence that they're neuroprotective or change the course of the disease.

They act by inhibiting the catabolic enzyme acetylcholinesterase responsible for hydrolysis and breakdown of acetylcholine in the synapses. This leads to higher availability of acetylcholine, thereby resolving the cholinergic deficiency of Alzheimer's.

There has been observed a marked improvement in the cognition, as to when patients are treated with cholinesterases such as galantamine and rivastigmine and donepezil which , in few regions of the brain dcrease acetylcholine, hence proving the correlation between acetylcholinesterase inhibition and observed cognitive improvement. (7)

Moreover, studies have shown that during the early stages of neuritic senile plaque formation, both butyrylcholinesterase (BuChE) and acetylcholinesterase have an important role in Aβ-aggregation. Therefore, by elevating the presence of Ach inside the brain and depleating the Aβ deposits, the inhibition of AChE and BuChE have shown to be critical targets for the successful management and treatment of AD. (8)

Following is a list of drugs which includes both ‘not in current use’ and ‘currently used’ cholinesterase inhibitors:

1. Tacrine

In 1993, tacrine became the first licenced medicine which was used in the management of Alzheimer's. Both AChE & BuChE can be potently inhibited by it. However, tacrine is no longer prescribed because it is poorly tolerated and causes a variety of adverse effects such as dizziness, seizures, diarrhoea, syncope, nausea and vomiting. The GIT side effects were attributable to peripheral cholinergic system overstimulation at or below 30% ChE inhibition, indicating dose-related tolerance. The administration and patient compliance was made difficult because of tacrine’s very short half-life and dosing four times a day (QID). In addition, due to hepatotoxic effects, individuals who took the medicine had to have their blood checked on a regular basis.(9)

Pharmacokinetics: Tacrine is rapidly and thoroughly absorbed following oral treatment. After a single doe of 20-50mg, the peak concentration of plasma is attainted in thirty minutes to three hours. Tacrine drug has a high distribution, as evidenced by its high volume of distribution. In animal models, organs like the liver, adrenals, kidney, and brain showed high concentrations of the drug. Tacrine has a low bioavailability after it is consumed orally, which is assumed to be due to substantial first-pass metabolism. The bioavailability of a drug can be enhanced by administering it rectally. In humans, the substance is rapidly and extensively metabolised. (10)

Adverse effects: diarrhoea, seizures, syncope, dizziness, nausea, and vomiting. (9)

As mentioned before, Tacrine was found to be hepatotoxic. It was, therefore, discontinued for treatment. Affinity to BuChE was thought to be the cause for the associated liver toxicity. (9,11)

2. Physostigmine

Physostigmine was the first AChEI which was used in studying the treatment of Alzheimer's disorder. It is a plant alkaloid which is isolated from the seeds of Calabar bean which is also known as ordeal bean. It's scientific name being 'Physostigma venenosum.' It's a parasympathomimetic which is capable of crossing the blood-brain barrier (BBB). Its use is made less effective due to its limited therapeutic index and short half-life. (9) To address this issue, various types of medication administration have been tested, most recently a controlled-release oral formulation and a transdermal skin patch. It was suggested as a possible treatment for the symptoms of Alzheimer's disease. (12)

Pharmacokinetics: To produce systemic effects, physostigmine is injected intravenously or intramuscularly. The half-life is brief due to rapid hydrolysis of the ester bonds by plasma cholinesterase. The active medication is only partially eliminated by the kidneys. At physiological pH, physostigmine is mostly in the ionised form, even though the non-ionized variant easily penetrates the BBB and has effects on the central nervous system. Unlike the quaternary amine cholinesterase inhibitors, which are unable to enter the Central nervous system post peripheral injection, quaternary amine cholinesterase inhibitors do.(13)

Adverse effects: Physostigmine also has several adverse effects due to which its use has been prohibited, some negative effects include nausea, vomiting, headaches, diarrhoea, and dizziness to name a few. Earlier, it was prescribed for the treatment of Myasthenia Gravis, glaucoma, and delayed gastric emptying.

However, due to the drawbacks described above, the Physostigmine was not licenced and was soon abandoned for its use in the management of Alzheimer's disorder and associated dementia. (9)

3. Donepezil

Donepezil is a medication that is used to manage symptoms of mild to moderate Alzheimer's disease. Donepezil is an acetylcholinesterase (AChE) blocker that elevates the amount of accessible ACh. This can help in AD as there's a destruction of functioning cholinergic brain cells which can be partially compensated by increasing the acetylcholine. Hydrolysis of

acetylcholine is prevented as Donepezil is a reversible and specific blocker of acetylcholinesterase (AChE). Donepezil can be of great use by maintaining steady and high levels of ACh, which helps to balance the destruction of functioning cholinergic neurons.

It has been shown to be effective for the three key components of Alzheimer's disease symptoms: functionality, behaviour and cognition. (4)

Pharmacokinetics: Donepezil has a practical once-daily administration dosage due to its 70-hour half-life. Within three months of treatment, the plasma concentration of donepezil achieves a steady state and remains stable. In the plasma, long-term donepezil concentrations are dose-proportional, which is consistent with its short-term concentration profile. (14)

Adverse effects: It is known that Donepezil has a relatively safe side-effect profile. The commonest adverse effects of donepezil include dizziness, malaise, nausea, insomnia and diarrhoea. Over excitement, agitation, aggression, irrational dreams and nightmares have also been found to be rarely associated with the use of Donepezil. Heart disturbances, arrhythmias and hepatic disorders were not reported with the use of this drug. (15)

For severe, moderate, and mild dementia, Donepezil has been approved and is used. It however, cannot be prescribed for other types of dementia. Even though this drug is not indicated for cognitive impairment, is has been observed that it improves these symptoms. (9)

4. Rivastigmine

Rivastigmine was first licenced in 2000 for its clinical application. Its was used in mild-to-moderate Alzheimer's disease, and was also approved for Parkinson's dementia. It is a carbamate pseudo irreversible inhibitor of Acetylcholinesterase and butyrylcholinesterase, which is known to inhibit ChE-I selectively in the central nervous system. Rivastigmine is highly capable of penetrating the BBB. (16) (9)

This drug is also available in the form of a skin patch or transdermal patch, hence, making the drug administration easier and increasing patient compliance to it.(17)

Both the esterasic and ionic sites of AChE and bound by Rivastigmine, inhibiting its ability to metabolise ACh, but it dissociates considerably more slowly than AChE ("pseudoir-reversible" action). At the synapse, AChE and BuChE metabolise rivastigmine.

Pharmacokinetics: Rivastigmine is rapidly absorbed after 0.8–1.7 hours and it's best to take it with food to avoid upset stomach. It has a 35 percent oral to intravenous bioavailability, attaining peak concentration in 1.4–3.8 hours but clearing quickly in 0.3–3 hours. Rivastigmine inhibits both Acetylcholinesterase and butyrylcholinesterase in a manner which depends on the dose of the drug administered, ranging from 20% to 24% at low concentrations (2 mg/d) to a maximum of 62 percent at high concentrations (12 mg/d). (18)

Adverse effects: Adverse effects are mainly cholinomimetic gastrointestinal symptoms. These effects include nausea, vomiting and diarrhoea. It did not prove to show any significant effect on cardiac function. It has been found that Rivastigmine is safe and effective in the management of most behavioural, functional and cognitive abnormalities of Alzheimer's disease. (13)

5. Galantamine

Galantamine, which is now artificially synthesized, was derived from many plants which included daffodil bulbs. Galantamine is an acetylcholinesterase inhibitor that is selective, competitive, and reversible. It has been found that this drug also enhances cholinergic nicotinic neurotransmission. This effect is due to its action on the nicotinic cholinergic receptors as an allosteric modulator. (19)

Galantamine's therapeutic effect is thought to be mostly related to its nicotinic acetylcholine receptor sensitising activity rather than overall cholinergic increase due to cholinesterase suppression. (9) Galantamine has a high bioavailability, a wide clearance volume, and low plasma protein binding. (20)

In February 2001, this drug was approved for the treatment of Alzheimer's disease (mild-to-moderate). (9)

Pharmacokinetics: The bioavailability of Galantamine is approximately 90%. It also shows a linear pharmacokinetic profile. It has a high distribution volume and a low protein binding rate. The isoenzymes which are principally responsible for its metabolism are CYP2D6 and CYP3A4 which are the members of cytochrome p450 family. Clearance of this drug is variable and the factors which govern it include age, bodyweight, and sex. (21)

Adverse effects: Adverse events seen in galantamine-treated patients usually depend on the dose of the drug administered. These side effects are usually associated with the GIT. As the side effects are dose-related, they can be minimized by decreasing the dose of administered drug. (20)

6. Metrifonate

Metrifonate is a drug which was used in the past to for the management of schistosomiasis. It is an irreversible, long-acting, cholinesterase inhibitor. Its ability to fortify the cholinergic transmission of acetylcholine in the central nervous system led to development of several clinical trials which were aimed at improving the treatment of individuals with Alzheimer's disease (AD). (22)

Metrifonate is metabolized and broken down non-enzymatically into a molecular form that forms a stable bond with the catalytic site of acetylcholinesterase (AChE). There is a long-lasting inhibition of both AChE and butyrylcholinesterase. This is the reason why Metrifonate is used one a day for the symptomatic relief in Alzheimer’s disease patients. (23)

Pharmacokinetics: Metrifonate is absorbed rapidly following oral treatment, and reaches a peak plasma concentration in about 1–2 hours. It goes through a chemical transition to become dichlorvos, the active compound. Dichlorvos is metabolised quickly and extensively, and it is primarily eliminated in the urine.(24)

Adverse effects: When Metrifonate was used for a short term, the side effects of metrifonate were limited and of low risk. However, when used for a longer duration, there were cases of respiratory paralysis and neuromuscular transmission malfunction, which was akin to a

myasthenic crisis.(9) A very rare side effect associated with metrifonate was severe bradycardia that could go as low as 5 beats per minute.(23)

It was seen that the beneficial consequences seen in patients treated with Metrifonate ranged from elevated cognition, enhanced behaviour, and improved daily function. These effects were found to be present several days and months after Metrifonate administration was originally started. (23-31)

Conclusion

It can be concluded that cholinesterase inhibitors are a class of drugs that prove to be quite effective against symptomatic relief in Alzheimer's disease. However, out of all the Acetyl cholinesterase inhibitors discussed above, Tacrine and Physostigmine are the ones that are not in use anymore because of their several undesirable adverse effects.

However, with new research there has been development of new drugs, latest being Aducanumab that directly acts at the root pathology of Alzheimer's disease and helps to actually treat the illness.

More extensive research for treatment of Alzheimer's associated dementia is necessary and certainly is the need of the hour.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

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