Pharmacotherapeutic approaches in the treatment of Alzheimer's Disease

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Alzheimer's disease (AD) is the most common form of dementia and accounts for major cognitive impairment in the elderly. It is a progressive neurodegenerative disorder with distinct pathology. At present, the pharmacotherapy of AD involves the use of acetylcholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. The former imply neuroprotection hence slowing disease progression while the latter may block neuronal excitotoxicity.

Introduction

AD is the most common form of dementia accounting for about 50-60% of the cases. Its prevalence increases exponentially, from about 2-3% of the population at age 65 to nearly 47% after the age of 85. Given the trend towards an increase in the elderly population, the prevalence of AD is expected to double in the next forty to fifty years. Although no epidemiological studies have been carried out locally, it is estimated that the number of current cases in Malta almost reaches the 4,000 figure. In addition to the huge costs of treating AD, its psychological and social burden on caregivers and society are enormous. Caregivers usually become depressed, increasing their own use of medical resources, and are forced to reduce or terminate employment. Therefore, any interventions that slow down the rate of disease progression even modestly will have a major impact on public health.[1]

AD is an insidious neurodegenerative malady characterised by the presence of amyloid plaque deposits and neurofibrillary tangles in the brain in association with significant loss of cholinergic cell population in areas of the brain associated with learning and memory formation.[2] These pathological lesions and imbalance in cholinergic neurotransmission accelerate neuronal death.

The first stages of the disease is principally characterised by a decline in memory, especially loss of recent memory. Increasing signs of faulty judgment and personality changes also occur during this stage. At a later stage, memory decline worsens whereas language, attention, and executive functions become gradually impaired with patients losing the ability to perform activities of daily living such as dressing, washing and eating. Finally, the disease becomes so debilitating that the patients become mute, incontinent and unable to walk, with the consequence of becoming bedridden and prone to illness and infection.[3]

Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (AChEIs) were the first pharmacological treatments for AD approved by the US Food and Drug Administration (FDA). Currently four AChEIs are clinically available: tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®). Their major therapeutic effect is reported to be their ability to maintain cognitive function compared with placebo over a three year treatment period or even less.[4,5] Some studies also suggest that these drugs can stabilise and even reverse the neurotoxic effects of AD thus delaying the disease progression, especially if administered early in the course of the disease benefiting patients with mild to moderate AD.

Rivastigmine is also capable of blocking the action of another cholinesterase enzyme, butyrylcholinesterase (BuChE), which increases considerably in the brain of patients with AD changing from a ratio of 99:1 to 2:1.[6] This may have a favourable effect on sustained cholinesterase inhibition and subsequent disease stabilisation. On the other hand, galantamine's mechanism of action is sufficiently different from that of other AChEIs as it also acts on the nicotinic acetylcholine receptor (nAChR) sites increasing the receptor responsiveness to acetylcholine (ACh) facilitating its ionic channel opening.[7] Tacrine is rarely used nowadays because of its frequent dosing and the need to monitor liver enzymes for the development of hepatotoxicity.[2]

Nausea, vomiting, diarrhoea, dizziness, and anorexia are the most common adverse effects associated with acetylcholinesterase therapy (Table 1) and occur more frequently during dose escalation than during maintenance.[8] Gastrointestinal effects can be minimised by concurrent administration of food and the use of an anti-emetic. Insomnia, fatigue and muscle cramps occur less frequently whereas particular attention must be given in patients with bradycardia.[9] These drugs become inefficient in the treatment of severe forms of AD during which cholinergic cell population is significantly low in various areas of the brain.

The mode of action by which these drugs act is by blocking the breakdown of the neurotransmitter ACh. By inhibiting the enzyme acetylcholinesterase, the levels of the neurotransmitter at cholinergic synapses increase.

Acetylcholinesterase has also been found to promote the formation of amyloid plaques, thus inhibiting this enzyme by properly designed AChEIs might not only provide symptomatic relief but also inhibit the progression of the disease itself.[8]

Practice Points

- Alzheimer's disease should not be confounded with the mild cognitive decline that occurs in normal ageing. AD is a disease involving extensive impairment in various domains of cognition that are not characteristic of the normal ageing process.
- AD is usually accompanied by disturbance in behaviour manifesting itself in anxiety, depression, agitation, hallucinations, delusions, inappropriate behaviour and eating disorders. These neuropsychiatric disorders, which may occur in a considerable number of cases, are one of the main causes of care-giver stress.
- Health care professionals should be aware of the symptoms that characterise the disease, and if AD (or any other form of dementia) is suspected, the cases should be referred for consultation. Different forms of testing may be adopted including neuroimaging techniques as well as using assessment scales such as the Mini-Mental State Examination (MMSE).
- Community studies show that care-givers of AD patients are under significant amount of psychological stress with the majority of them ending up needing psychiatric care. Carers should be helped and provided with the necessary information of the best practices available in care-giving. In the local scene, organisations such as the Malta Dementia Society (www.maltadementiasociety.org.mt), aim to provide the best information about dementia care not only to carers and health professionals but also to the public in general.

Table 1

Characteristics of pharmacological agents commonly used in the management of AD

Medication	Pharmacological class	Mode of action	Recommended use	Potential adverse effects
Donepezil hydrochloride (Aricept®)	AChEI	Block acetylcholinesterase enzyme	Mild-to-moderate AD	Anorexia, diarrhoea, dreams, fatigue, insomnia, muscle cramps, nausea, vomiting, weight loss
Rivastigmine tartrate (Exelon®)	AChEI	Block both acetyl- and butyryl-cholinesterase enzymes	Mild-to-moderate AD	Anorexia, diarrhoea, nausea, vomiting, weight loss
Galantamine hydrobromide (Reminyl®)	AChEI	Block acetylcholinesterase enzyme. Allosterically stimulates nAChRs	Mild-to-moderate AD	Anorexia, nausea, vomiting, weight loss
Memantine hydrochloride (Axura®, Ebixa®)	Glutamatergic-system modifier	Partial NMDA-receptor antagonist	Moderate-to-severe AD	Agitation, constipation, dizziness, hallucinations, headache, insomnia

AChEI: acetylcholinesterase inhibitor; AD: Alzheimer's disease; nAChRs: nicotinic acetylcholine receptors; NMDA: N-methyl-D-aspartate

Glutamatergic-transmission modifiers

Recent research indicates that the excitatory neurotransmitter glutamate may play an important role in the neurochemistry of AD. Glutamatergic neurotransmission has been shown to be important in learning and memory and is severely disrupted in AD. Overstimulation of the NMDA receptor by glutamate leads to an overload of intracellular calcium bringing about neuronal death which is characteristic of AD and other neurodegenerative disorders.[10] Memantine (Axura®, Ebixa®), a non-competitive antagonist with moderate affinity for the NMDA receptor, appears to block pathologic neural toxicity associated with prolonged glutamate release.[11] Therapeutic doses are well tolerated and do not appear to interfere with the acquisition or processing of cognitive information in which the NMDA receptor plays an important role.[12] Memantine has been shown to improve the symptoms and reduce the rate of clinical deterioration among patients with moderate to severe AD and was approved by the FDA for this indication in October 2003. In randomised clinical trials, the drug demonstrated the ability to delay cognitive and functional decline without a significance incidence of serious adverse events.[13,14] Some studies also suggest that the efficacy of memantine in combination with AChEIs therapy may be greater than AChEIs alone significantly improving activities of daily living. This combination was also found to be well tolerated by the majority of AD patients with no serious adverse drug reactions reported.[15]

Discussion

As recently as fifteen years ago, there was no effective therapeutic agent for symptomatic relief of AD, let alone one that might halt the progression of the disease. As modest as the benefits of current treatments are, they nevertheless represent a major step in the pharmacotherapy of AD. Modest improvements mean more than symptomatic relief – they offer hope to AD patients, their physicians, and their caregivers. Therefore the latest draft guidelines issued by the UK National Institute for Clinical Excellence (NICE) recommending that AChEIs should be made available with restrictions to patients via NHS and that memantine should only be considered for clinical trials were met with strong resistance. Various AD organisations across Europe voiced their concerns about this approach, highlighting the need for NICE to assess its views and the implications that result if such guidelines are not revised. Even Alzheimer's Europe, an umbrella organisation of 28 national Alzheimer's disease associations from 24 European countries, recently issued a press release that calls for NICE to revise its preliminary recommendations for the treatment of AD and allow patients at all stages of the illness to have access to the various drug treatments irrespective of the cost.

Indeed, there is strong evidence that these drugs enhance activities of daily living, reduce behavioural disturbances, stabilise cognitive impairment, decrease caregiver stress and may delay entry into nursing homes. Apart from reducing the symptoms of the disease, these drugs may offer neuroprotection, thus stabilising the degenerative process.

The future of pharmacotherapy in the treatment of AD looks very promising. Ongoing research has not only deepened our understanding of the disease but is also suggesting a number of different avenues that may be used to develop drugs to prevent and treat AD. These include agents that block the formation of plaques and tangles by inhibiting enzymes that help in their formation. Others include chemical compounds that dissolve amyloid and fibrils which are found in the brains of AD patients.[16] Development of such drugs could also help in treating cognitive decline associated with normal ageing.

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