Donepezil for Alzheimer’s Disease: Pharmacodynamic, Pharmacokinetic, and Clinical Profiles

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ABSTRACT

Donepezil was developed in order to overcome the disadvantages of physostigmine and tacrine. Its use is based on the cholinergic hypothesis. Donepezil is a piperidine-based, reversible acetylcholinesterase inhibitor, that is chemically unrelated to other cholinesterase inhibitors. It was developed for the symptomatic treatment of Alzheimer’s disease (AD). Donepezil is highly selective for acetylcholinesterase with a significantly lower affinity for butyrylcholinesterase, which is present predominantly in the periphery. Phase I and II clinical trials demonstrated donepezil’s favorable pharmacokinetic, pharmacodynamic and safety profile. There is no need to modify the dose of donepezil in the elderly or in patients with renal and hepatic failure. Pivotal phase-III trials in the US, European countries, and Japan showed that donepezil significantly improved cognition and global function in patients with mild to moderate AD. In long-term trials, donepezil maintained cognitive and global function for up to 1 year prior to the resumption of gradual deterioration. Donepezil is generally well tolerated; most of its adverse events are mild, transient and cholinergic in nature. Donepezil produces no clinically significant changes in laboratory parameters, including liver function.

The drug is approved for the treatment of mild to moderate Alzheimer’s disease, but donepezil therapy does not have to be discontinued if a patient continues to deteriorate. Possible new indications for donepezil in psychiatric and neurologic diseases, other than AD, include dementia with Lewy bodies, brain injury, attention deficit hyperactivity, multiple sclerosis, Down’s syndrome, delirium, mood disorders, Huntington’s disease and sleep disorders.