VIII. 7. Quantitative Analysis of Donepezil Binding to Acetylcholinesterase Using PET and [5-\(^{11}\)C-methoxy]Donepezil

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The cholinergic system is one of the most crucial neurotransmitter systems in the brain, and it has very profound links with the manifestations of dementia. The activity of choline acetyltransferase, the enzyme catalyzing acetylcholine synthesis, and of acetylcholinesterase (AChE), the enzyme degrading brain acetylcholine, are both reported to be decreased in the neocortex and the hippocampus of patients with Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB), and this decreased activity correlates with the severity of cognitive impairment. Significant loss of cholinergic neurons in the nucleus basalis of Meynert has been reported in the brains of patients with both diseases. Based on these pathological findings, the rational use of reversible AChE inhibitors was proposed as means for potentiating cholinergic neurotransmission, with an aim to improve cognitive function. Currently, several AChE inhibitors are prescribed to improve the cognitive function of patients with dementia. Donepezil hydrochloride is an AChE inhibitor that has been proved to be effective in ameliorating the cognitive impairment of patients with AD and DLB, and it is widely prescribed for the treatment of the diseases.

[5-\(^{11}\)C-methoxy]Donepezil ([\(^{11}\)C]donepezil) was developed for the in-vivo visualization of donepezil binding to AChE using positron emission tomography (PET)\(^1\). We established the kinetic analysis of [\(^{11}\)C]donepezil by a dynamic study involving 60-min PET scans after intravenous injection of [\(^{11}\)C]donepezil to six healthy subjects\(^2\). The rank order of the mean total distribution volume (tDV) values of cerebral regions (cerebral cortices < hippocampus < thalamus < cerebellum < putamen) was consistent with that of...
AChE activity reported in a previous post-mortem study (Fig. 1).

Logan graphical analysis\(^3\) generated voxel-wise images of tDV, revealing the overall distribution pattern of AChE in individual brains (Fig. 2).

Subsequently, donepezil-PET imaging was applied to patients with AD\(^4\) and DLB. Compared with elderly normal subjects, patients with mild AD exhibited about 18–20% reduction of donepezil binding in the neocortex and hippocampus, while patients with moderate AD exhibited about 24–30% reduction of donepezil binding throughout the brain. Orally administered donepezil (5mg/day) induced 61.6–63.3% reduction of donepezil binding in AD brains. Patients with DLB exhibited about 19–26% reduction of donepezil binding throughout the brain compared with age- and sex-matched controls (Fig. 3).

In conclusion, \(^{[11]}\text{C}\)donepezil-PET enables pharmacokinetic study of donepezil and quantitative analysis of AChE in the human brain, which is useful in various situations for patients with dementia.

References


Figure 1. Mean total distribution volume (tDV) values of cerebral regions and post-mortem acetylcholinesterase (AChE) values in human brain obtained from the literature. Post-mortem AChE values are expressed as ratios to the mean AChE value of cerebral cortices.
Figure 2. Image of total distribution volumes (tDVs) derived with a Logan plot. tDV values were large in the thalamus, basal ganglia, and cerebellar hemispheres, and small in the cortices.

Figure 3. Regional distribution volume data in elderly normal controls (NC) and dementia with Lewy bodies (DLB) patients.