VIII. 4. Quantitative Analysis of Donepezil Binding to
Acetylcholinesterase Using Positron Emission
Tomography and [5-\(^{11}\)C-methoxy]Donepezil

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Backgrounds

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\(^{1,2}\). 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 and Parkinson’s disease with dementia\(^{3,4}\), and this decreased activity correlates with the severity of cognitive impairment\(^5\). Significant loss of cholinergic neurons in the nucleus basalis of Meynert has been reported in the brains of patients with both diseases\(^{6,7}\). 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 Alzheimer’s disease\(^8\), and it is widely prescribed for the treatment of the disease.

Objective

The objective of this study was to establish kinetic analysis of [5-\(^{11}\)C-methoxy]donepezil ([\(^{11}\)C]donepezil), which was developed for the in-vivo visualization of donepezil binding to AChE using positron emission tomography (PET) (Fig.
1)\(^9\).

**Methods**

Six healthy subjects took part in a dynamic study involving a 60-min PET scan after intravenous injection of \(^{11}\text{C}\)!donepezil. The total distribution volume (tDV) of \(^{11}\text{C}\)!donepezil was quantified by compartmental kinetic analysis and Logan graphical analysis\(^10\). A one-tissue compartment model (1TCM) and a two-tissue compartment model (2TCM) were applied in the kinetic analysis. Goodness of fit was assessed with \(\chi^2\) criterion and Akaike’s Information Criterion\(^11\).

**Results**

Compared with a 1TCM, goodness of fit was significantly improved by a 2TCM. The tDVs provided by Logan graphical analysis were slightly lower than those provided by a 2TCM (Fig. 2). The rank order of the mean tDV in 10 regions agreed with the AChE activity reported in a previous post-mortem study\(^12,13\) (Fig. 3). Logan graphical analysis generated voxel-wise images of tDV, revealing the overall distribution pattern of AChE in individual brains (Fig. 4). Significant correlation was observed between tDVs calculated with and without metabolite correction for plasma time–activity curves, indicating that metabolite correction could be omitted.

**Conclusions**

This method enables quantitative analysis of AChE in the human brain, which is useful in various situations for patients with dementia. \(^{11}\text{C}\)!donepezil-PET study can be exploited not only for the assessment of cholinergic dysfunction in patients, but also for the prediction of efficacy of treatment with AChE inhibitors. Moreover, by performing PET scans before and after treatment with AChE inhibitor, the AChE binding occupancy of orally administered AChE inhibitor can be measured, which facilitates the determination of clinical doses of AChE inhibitor.

**References**


Figure 1. Chemical structures of [5-¹¹C-methoxy]donepezil and donepezil metabolites. [5-¹¹C-methoxy]donepezil is synthesized from 5'-O-demethylprecursor (M2).

Figure 2. Total distribution volumes estimated by the two-tissue compartment model (2TCM) were compared with those estimated by Logan graphical analysis. All regions of interest (ROIs) obtained from all subjects are plotted.
Figure 3. Mean estimated total distribution volume (tDV) values of cerebral regions and post-mortem acetylcholinesterase (AChE) values in human brain obtained from the literature\(^{12,13}\). Post-mortem AChE values are expressed as ratios to the mean AChE value of cerebral cortices.

Figure 4. 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.