Plasma Cholinesterase Activity in Alzheimer’s Disease

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**Key Words**
Alzheimer’s disease · Butyrylcholinesterase · Plasma cholinesterase · Rivastigmine

**Abstract**
Cholinesterase inhibitors (ChEIs) are not allowed to be prescribed in combination, which means that we need to select 1 of 3 ChEIs for use in a patient with Alzheimer’s disease (AD). However, there is no quantitative analysis on the differences between these agents. In this article, we propose that plasma cholinesterase activity (pChE) could be used as the standard for differentiating between rivastigmine (Riv) and donepezil (Don) in the management of AD. To date, we have treated 6 patients with Riv 18 mg and 5 patients with Don 5 mg. The pChE is related to low-grade inflammation associated with AD, diabetes mellitus and lipid metabolic dysfunction. Moreover, low pChE is related to liver dysfunction. The pChE must be kept under control. We speculated that Riv is the most appropriate therapy for patients with relatively high pChE, whereas Don is best reserved for those AD patients with relatively low pChE.

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**Introduction**
In Japan, 3 cholinesterase inhibitors (ChEIs) are available: donepezil (Don), galantamine and rivastigmine (Riv). Because ChEIs are not allowed to be prescribed combined with each other, we should select 1 of these inhibitors in a patient with Alzheimer’s disease (AD).

Since Don has been available since 1999, it has long been prescribed and most used in Japan. One important issue is that we select Don or Riv without the ability to rationalize treatment based on objective parameters. Riv is unique in its pharmacological character to inhibit not only acetylcholinesterase (AChE), but also butyrylcholinesterase (BuChE) [1]. Although we previously reported that Riv should be prescribed for relatively young patients with mild AD [2], this was not based on quantitative analysis. In this article, we propose that plasma cholinesterase activity (pChE) can be used as the standard for differentiating between the use of Riv and Don in AD patients.

**A pChE as a Biomarker in AD**

The pChE is not AChE but BuChE [1]. Dyslipidemia or lipid metabolic disorder (LMD) and diabetes mellitus (DM) are also positively related to pChE activity [3, 4]. AD is also
thought to be related to LMD and DM [5]. Therefore, it is reasonable to assume that AD is positively related to pChE.

First, when amyloid increases, AChE activity decreases and BuChE activity increases [6, 7]. Amyloid-based BuChE in AD is also thought to be related to BuChE levels in the central nervous system (CNS) because BuChE mainly exists in the amyloid and glial cells [6]. Moreover, BuChE is located in regions that are known to be associated with AD [7]. AD is thought to be associated with inflammation, and the permeability of the blood-brain barrier increases as a consequence [8]. Therefore, BuChE in the CNS might be related to that in the peripheral system (i.e. pChE). Moreover, downregulation of acetylcholine (ACh) causes inflammatory hyperactivation of the CNS and peripheral nervous system [9, 10]. Therefore, we speculated that this inflammatory hyperactivation appeared simultaneously in both systems. Based on these two reasons, we further speculated that AD and pChE were correlated and that pChE should be kept under control in AD (i.e. at low levels).

Second, pChE is thought to induce ACh downregulation because it can catalyze the breaking of ACh into choline and acetic acids [3]. Because ACh can suppress inflammation in both CNS and peripheral tissues [9, 10], pChE hyperactivity also induces inflammatory hyperactivation via ACh downregulation. Therefore, pChE hyperactivation is not favorable in conditions such as AD, DM and LMD where inflammatory hyperactivation may be considered causative [11]. Although the underlying mechanism how inflammatory hyperactivation affects the pathologies of AD, DM and LMD remains unclear, we believe that inflammatory cytokines with anticholinergic activity appear and that in doing so they may accelerate the amyloid pathology [12–14].

Recently, Nakamura et al. [15] reported that a 40% reduction of pChE was needed to exhibit the effectiveness of Riv in AD. Das [11] reported that pChE may also be related to low-grade inflammation, LMD, DM and AD. These observations provide evidence of the relationship between low grade inflammation and AD [16, 17]. In AD, pChE hyperactivity is probably not favorable because pChE can reduce ACh, which can then cause inflammatory hyperactivation. If pChE is dependent on BuChE, Don could not sufficiently inhibit pChE on its own, whereas Riv could. Therefore, we believe that AD patients who have high pChE should be prescribed Riv, whereas those with lower pChE should be prescribed Don. Long-term observation is needed, using large samples, to assess the effects of pChE downregulation on cognitive function in AD. We are now studying the longitudinal changes in pChE and how this affects the cognitive function in AD patients.

Preliminary Results: pChE as a Biological Marker in AD

There are two main cholinesterases in humans. AChE exists mainly in nervous cells and erythrocytes, whereas BuChE exists mainly in the liver, plasma, glial cells and amyloid [1, 6]. Therefore, AChE is expected to decrease and BuChE to increase in AD. Perry et al. [6] reported that, in the AD brain, AChE gradually decreases and BuChE increases in a reverse-sigmoid fashion. Thus, we considered pChE to be an excellent biological marker for use when discriminating between the Riv and Don treatment.

In AD patients treated with Riv or Don, we are currently in the process of evaluating the association between changing pChE and cognitive function with these drugs. Mini-Mental State Examination (MMSE) scores [18] and pChE are compared in AD patients at their first visit to our memory clinic and 6 months later. pChE was measured using an automated evaluating system in the laboratory of our hospital.

To date, we have treated 6 patients with Riv 18 mg and 5 patients with Don 5 mg. Although there were no significant differences between the pChE and MMSE scores at the 1- and 6-month visits for any of the patients, plasma cholinesterase (pChE) decreased significantly after 6 months in all 6 patients who were prescribed Riv. Moreover, MMSE scores did improve in 3 patients prescribed Riv, and their pChE decreased more than 50%. Conversely, in the 3 patients whose MMSE scores worsened while being treated with Riv, their pChE decreased less than 50%. These preliminary results suggest that pChE is BuChE dependent because Don only inhibits AChE and is therefore unable to decrease pChE. However, Riv can inhibit both AChE and BuChE and was therefore able to decrease pChE. We speculate that the improved cognitive function was caused by the decrease in pChE. This is consistent with the work of Nakamura et al. [15], who reported that a decrease in pChE of more than 40% is associated with cognitive recovery in AD patients.

Conclusion

We propose that AD was related to pChE. This is based on observations that LMD and DM are associated with pChE [3, 4] and that AD is positively related to pChE [5] because pChE metabolizes ACh and causes inflammatory hyperactivation [17]. The preliminary results of our current study also suggest that the effectiveness of Riv was...
related to pChE downregulation. To date, it is unknown whether BuChE in the CNS is related to pChE. However, blood-brain barrier permeability may increase in AD because of inflammatory hyperactivity, suggesting that BuChE in the CNS correlates with peripheral pChE. Even if this is not true, high pChE is almost certainly associated with low-grade inflammation, and it should be avoided in AD patients. Conversely, low pChE should be avoided in AD patients because low-grade pChE is related with liver dysfunction [19]. Therefore, pChE should be maintained within an optimal therapeutic level that is neither too high nor too low, which could be achieved by rational therapy. We speculate that Riv should be prescribed to patients with relatively high pChE, whereas Don should be reserved for patients with relatively low pChE.

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Disclosure Statement


References


