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Is combining an anticholinergic with a cholinesterase inhibitor a good strategy for high-level CNS cholinesterase inhibition?

Donald E. Moss, Ph.D.

Department of Psychology, University of Texas at El Paso, El Paso, Texas 79968

Abstract

The currently approved cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) produce gastrointestinal toxicity which limits dosing to that which produces only about 25% to 35% CNS cholinesterase inhibition in Alzheimer's patients undergoing treatment, below the minimum therapeutic target of about 40% to 50% CNS inhibition considered necessary to treat cognitive impairment. A recent strategy for producing high-level CNS acetylcholinesterase (AChE) inhibition (50% or higher) is to co-administer a muscarinic anticholinergic with the AChE inhibitor to block the dose-limiting cholinergic overstimulation of the gastrointestinal system, allow more robust AChE inhibition in the CNS, and improve efficacy in the treatment of Alzheimer's disease. Unfortunately, most common muscarinic anticholinergics, including solifenacin, readily penetrate the CNS and are directly associated with long-term exacerbation of the underlying neuropathology of Alzheimer's disease and increased brain atrophy. The co-administration of an anticholinergic with an AChE inhibitor is a rational strategy for improving efficacy in the symptomatic treatment of dementia, but there are significant long-term risks that have not yet been considered. For long-term safety against accelerating the underlying disease processes in Alzheimer's, anticholinergics used to increase the tolerability of AChE inhibitors should not penetrate, or have very limited penetration, of the blood-brain-barrier. Neurotrophic-mediated mechanisms by which cholinergic drugs may affect neurodegeneration in Alzheimer's disease are explored and improved treatment options are suggested.

Keywords

Alzheimer's; dementia; cognition; cholinesterase inhibition; antimuscarinic; anticholinergic; solifenacin; trospium; nerve growth factor; brain atrophy

Cholinesterase inhibitors, especially acetylcholinesterase (AChE) inhibitors, are the mainline pharmaceuticals in the symptomatic treatment of Alzheimer's disease [1]. In addition to the expected benefits of cognitive enhancement, long-term AChE inhibitor therapy (a year or more) also produces an anti-neurodegenerative slowing of the disease. For example, *in vivo* high resolution magnetic resonance imaging shows that AChE inhibition therapy reduces atrophy of the whole brain, hippocampus, cortex, and other key structures as compared to mild to moderate Alzheimer's patients who were not receiving the therapy [2–5]. Earlier in the disease, in suspected prodromal patients, AChE inhibitor therapy slows the thinning of

the cortex [6], reduces atrophy of the hippocampus [7], and decreases tissue loss in the basal forebrain [8]. Although AChE inhibition may generally have significant disease-modifying benefits, butyrylcholinesterase (BChE) may also play a significant role, and cholinesterase inhibitors may have detrimental effects in some patients depending on age, gender, and genotype [9]. In contrast to repeated failures of other disease-modifying strategies [10], AChE inhibitors, in particular, appear to slow the underlying progression of the disease in a wide range of patients and there is significant clinical potential if improved CNS-selective AChE inhibition can be obtained.

The major obstacle to maximizing the clinical benefit of AChE inhibition in the CNS is that cholinergic overstimulation of the gastrointestinal tract causes dose-limiting nausea, vomiting and diarrhea [11,12]. *In vivo* PET imaging in Alzheimer's patients undergoing AChE inhibitor treatment shows that the doses tolerated by patients produce only about 25% to 35% CNS AChE inhibition [13–17], suboptimal as compared to the minimum of 40% to 50% CNS AChE inhibition that is considered necessary for good efficacy [11,12]. However, when freed from dose-limiting gastrointestinal toxicity, primates treated with a CNS-selective cholinesterase inhibitor tolerate up to 80% CNS AChE inhibition (biopsy confirmed), at the upper end of the therapeutic window [12], without the emergence of other troublesome effects [18]. These results suggest that there is a wide unexplored opportunity to improve AChE inhibitor efficacy in treating Alzheimer's disease, but only if gastrointestinal toxicity, the current barrier to high-level CNS AChE inhibitor therapy [11,18], can be overcome. There is a significant unmet need for high-level CNS AChE inhibition to maximize cognitive enhancement and to fully exploit the potential anti-neurodegenerative, or even prophylactic, uses of AChE inhibitor therapies.

A recent strategy for obtaining high-level CNS AChE inhibition is to co-administer a muscarinic anticholinergic with the AChE inhibitor [19,20]. The hypothesis is that the peripheral action of the muscarinic anticholinergic will reduce the otherwise unavoidable AChE inhibitor-induced cholinomimetic overstimulation of the gastrointestinal tract to permit higher and more effective CNS AChE inhibition. Indeed, the co-administration of solifenacin (an antimuscarinic anticholinergic approved for overactive bladder) increased the tolerability of donepezil (an AChE inhibitor approved for Alzheimer's) from the standard dose of 10 mg/day up to 40 mg/day in Alzheimer's patients, and improved cognitive performance [19]. These results support the expectation that greater CNS AChE inhibition may produce improved cognitive performance [19,21].

Muscarinic anticholinergics, however, pose significant risks to the elderly and Alzheimer patients. Most, if not all, currently approved muscarinic anticholinergics, including solifenacin, readily penetrate the CNS and show strong *in vivo* binding on muscarinic cholinergic receptors in the brains of rats, monkeys, and humans [22–25], and produce CNS adverse events in patients being treated for overactive bladder [26,27].

Whereas the cholinomimetic effect of AChE inhibition has an anti-neurodegenerative effect in Alzheimer's disease, it can be expected that anticholinergics, with the opposing mechanism of action, would have disease accelerating effects. In fact, CNS-penetrating anticholinergics appear to accelerate cognitive decline and neurodegeneration in

Alzheimer's disease. Long term (> 2 years) blockade of CNS muscarinic cholinergic receptors is associated with a 2.5 fold higher amyloid plaque density and increased neurofibrillary tangles in human post-mortem CNS tissues [28]. Long-term use of muscarinic cholinergic blockers, including solifenacin, is also associated with significantly increased incidence of dementia, accelerated progression from normal function to mild cognitive impairment (MCI), increased progression from MCI to Alzheimer's-type dementia, and increased Alzheimer's-associated brain atrophy in most [29–33], but not all [34], studies. Antimuscarinic anticholinergic use in the elderly results in a 50% increase in both Alzheimer's as well as vascular dementias [35]. Cognitively normal older adults who show elevated β -amyloid in the CNS, presumably preclinical Alzheimer's, are especially sensitive to cognitive impairment from muscarinic cholinergic antagonism [36]. CNS penetrating muscarinic anticholinergics, therefore, may accelerate cognitive decline and neurodegenerative changes that may outweigh the advantage of increasing the tolerability of AChE inhibitors in the symptomatic treatment of cognitive impairment. At the very least, the risk of accelerating the underlying neurodegenerative disease associated with long-term use of CNS-penetrating muscarinic anticholinergics should be recognized and considered in clinical evaluations wherein they are co-administered with AChE inhibitors.

The mechanism(s) by which antagonism at muscarinic cholinergic receptors accelerate the progression of Alzheimer's disease are not well understood. Neurotransmitter-dependent control of the synthesis, release, and internalization of neurotrophic factors from neurons and astrocytes [37–39], including muscarinic and nicotinic acetylcholine receptor participation in nerve growth factor (NGF) release, may be a key issue [40,41]. NGF is essential to the maintenance and survival of cholinergic cell bodies in the basal forebrain and cholinergic receptor antagonism would result in lessened NGF synthesis and release and reduced survival of the basal forebrain [37,40–43]. Any further reduction of NGF in Alzheimer's, a condition in which there is an NGF deficit [44–46], would exacerbate the loss of the cholinergic cell bodies of the basal forebrain. The potential role of NGF in Alzheimer's is being tested by NGF replacement therapy as a strategy for slowing or delaying the progression of Alzheimer's [47,48]. Conversely, the complementary anti-neurodegenerative effects of cholinesterase inhibition and the beneficial effect of the resulting increased cholinergic tone is increased synthesis and release of NGF and increased survival of cholinergic cell bodies in the basal forebrain [49,50]. Overall, anticholinergics could act to decrease, and cholinesterase inhibitors could act in the opposing direction to increase, acetylcholine-dependent NGF synthesis and release. Thereby, anticholinergics are expected to accelerate, and cholinesterase inhibitors to slow, NGF-mediated changes in the rate at which basal forebrain neurons are lost. The relationship between basal forebrain cholinergic control over the neurotransmitter-dependent NGF release and the progression of Alzheimer's disease deserves further study.

In summary, combining an anticholinergic with an AChE inhibitor such as donepezil, rivastigmine, or galantamine might be a rational strategy for achieving high-level brain AChE inhibition that is commensurate with maximizing potential efficacy [19,21]. However, the anticholinergics used should be limited to those which have limited CNS penetration such as quaternary ammonium compounds (e.g., trospium [51,52]). Another strategy is to use a CNS-selective AChE inhibitor [18]. Achieving high-level CNS AChE inhibition is the

next step in meeting the critical unmet need for more effective symptomatic treatment of dementia as well as maximizing potential anti-neurodegenerative effects in the treatment of Alzheimer's disease.

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