Cardiovascular Complications of Acetylcholinesterase Inhibitors in Patients with Alzheimer's Disease: A Narrative Review

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While acetylcholinesterase inhibitors are used to treat a wide range of patients with Alzheimer's disease, acetylcholinesterase inhibitor use has also been associated with a variety of cardiovascular complications, including bradycardia and syncope. Herein, we review the pathophysiology and clinical evidence for cardiovascular complications caused by acetylcholinesterase inhibitors in patients being treated for dementia and discuss options for their management.

Key Words: Cholinesterase inhibitors, Alzheimer disease, Cardiovascular agents, Drug monitoring

INTRODUCTION

Epidemiology and Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia worldwide, affecting over 40 million people, primarily older adults.[1] The pathophysiology of AD is believed to result from the loss of cholinergic neurons, resulting in atrophy of cholinergic nuclei and reduced levels of the neurotransmitter acetylcholine in the brain.[2] Acetylcholine is involved in brain functions including attention, memory, motivation, and arousal, which are often affected in patients with the disease. The β-amyloid protein plaques found in the brains of patients with AD are also thought to negatively impact cholinergic synapses.[3] Acetylcholine is broken down into acetic acid and choline by acetylcholinesterase enzymes in the synaptic cleft, thereby ending signal transmission and postsynaptic receptor activation.

Management of Alzheimer's Disease

There are no well established disease-modifying treatments for AD; thus, prevention and behavioral interventions comprise the bedrocks of management. There has been a focus on improving cardiovascular (CV) and neural health using diet and exercise as preventative measures.[4] Implementing a Mediterranean diet and performing regular aerobic exercise have been shown to help reduce the risk of AD and preserve function in those with the disease.[5-7] Dietary elements that may modify AD progression and maintain brain health include polyunsaturated fatty acids, curcumin, magnesium, and vitamin supplementation.[8] Further lifestyle modifications include consistently engaging in neural-stimulating activities, maintaining social engagement, minimizing stress, and optimizing sleep patterns.[9]

The current pharmacologic treatment of AD consists of cholinesterase inhibitors with or without memantine, an NMDA receptor antagonist. Three acetylcholinesterase inhibitors are available for the treatment of AD: donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon). However, these treatments are hypothesized to slow disease progression and improve symptoms and do not directly modify the underlying disease process. Attention has also been paid to anti-amyloid therapy, such as monoclonal antibodies against amyloid-beta and tau-targeted therapies,[10] but none have yet been approved for use for clinical AD except for aducanumab (Aduhelm) that recently approved by the Food and

Drug Administration (FDA) for people with mild cognitive impairment or mild dementia stage of disease.

ACETYLCHOLINE AND ACETYLCHOLINESTERASE INHIBITORS

Mechanism of Action

Acetylcholine (ACh) is a neurotransmitter involved in the coordination of neuronal firing, modulation of rhythmic activity in the periphery, and induction of the transmission of excitatory signals from muscle cells to adjacent neurons, and vice versa. A specific class of enzymes, called acetylcholinesterases (AChEs), breaks down acetylcholine to prevent excessively high levels, thus halting coordinated synaptic firing and reciprocal neuronal signaling to various circuits, neurons, and cholinergic receptors. AChE inhibitors are drugs that competitively bind AChEs to prevent the degradation of ACh, which increases its levels in the synaptic cleft, thus enhancing the duration of cholinergic signaling and modifying the response of targeted neuronal networks. AChE inhibitors have clinical application in the treatment of myasthenia gravis and AD.[11]

AD is hypothesized to result from the degradation of cholinergic neurons, which play significant roles in mediating and reinforcing learning and memory pathways (the so-called "cholinergic hypothesis").[12] As such, results of experimental studies have demonstrated that increases in AChE inhibition are correlated with an overall improvement in cognitive function and in the capacity to perform activities of daily living in patients with AD.[13,14]

Clinical Profile

Although no disease-modifying treatments are available for clinical AD, AchE inhibitors have been shown to produce modest improvements in cognitive function and global function scores.[15-17] Additional analysis has also shown reduction in mortality in patients prescribed AChE inhibitors.[17,18] Three AChE inhibitors (donepezil, galantamine, and rivastigmine) have been approved by the Food and Drug Administration (FDA) to slow the progression of cognitive decline in patients with mild-to-severe AD.

The adverse events associated with the use of these medications are generally related to the overstimulation of the central and peripheral cholinergic systems, which are found throughout the body. The most commonly associated symptoms are nausea, vomiting, diarrhea, weight loss, bradycardia, and syncope.[19,20]

Cardiovascular Effects of AChE Inhibitors

AChE inhibitors are chiefly used to target cholinergic receptors in the central nervous system but also affect other organs, including the heart. ACh mediates multiple crucial CV processes through cholinergic receptor stimulation. In the past decade, research has consistently shown that exposure to AChE inhibitors significantly increases ACh levels in the heart, leading to increased excitatory input.

Bradycardia and syncope

While available data on the CV effects of AChE inhibitors are mixed, some concerning results have been reported. For example, increased ACh levels can augment parasympathetic tone in the sinoatrial (SA) node, slowing the sinus rate and various complementary CV conduction systems.[21] Bradycardia, a noted adverse effect of AchE inhibitors that may cause or contribute to syncope, has also been reported, particularly when administered in excessive doses.[22,23] The results of an administrative database study showed that there was a 1.4-fold increased risk of bradycardia in patients with dementia treated with AChE inhibitor (compared to that in patients not taking these medications) and that there was a dose-dependent increase in risk for patients on donepezil.[24] A recent population-based study demonstrated a two-fold increased risk of bradycardia in older patients (aged 67 years or older) who had recently started AChE inhibitor regimens.[25]

In a population-based analysis in Ontario, Canada, after controlling for time to hospitalization, patients receiving AchE inhibitors had increased risks of hospitalization for syncope (hazard ratio [HR] = 1.76), bradycardia (HR = 1.69), pacemaker insertion (HR = 1.49), and falls (HR = 1.18).[19] Other studies also reported that the use of these medications was associated with increased risks of heart block, sinus bradycardia, and syncope.[26-28] Moreover, dizziness and syncope occurred in 1%–10% of patients, in addition to bradycardia, atrial arrhythmias, myocardial infarction, angina, seizures (0.01%–1%), and sinoatrial and atrioventricular block (0.001%–1%).[28]

Patients prescribed these medications are older and vulnerable to age-related changes that can predispose to them orthostasis and syncope, including impaired thirst mechanisms, abnormal baroreceptor and autonomic function, and myocardial diastolic dysfunction. They may also have pre-existing CV disease, which may exacerbate any tendency toward bradycardia (e.g., sinus node dysfunction, heart block), or the drug could interact with concurrent medications (i.e., beta-blockers, calcium channel blockers, and antiarrhythmic medications). Thus, there are valid concerns regarding the risks of adverse effects caused by the use of these agents.

Adverse effects of donepezil

Donepezil is a commonly prescribed AChE inhibitor with numerous reports of adverse CV effects. Moreover, the package insert for

donepezil warns that:

Because of their pharmacologic action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block in patients both with and without underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of Donepezil.

Donepezil overdose has been shown to result in profound sinus bradycardia, which is reversible with atropine.[23,29] In a randomized, open-label, real-world comparative trial, adverse effects accounted for 73.1% of discontinuations of donepezil, galantamine, and rivastigmine.[30] The adverse events listed as CV were "fast or slowed heart rate," and "irregular heartbeat," and the total CV adverse effects ranged from 6.5% for galantamine to 12.2% for rivastigmine. Other adverse events listed under other categories may have had, at least in part, an unrecognized CV contribution. Examples include fainting, dizziness, falls, and fatigue. The overall rates of discontinuation after the 18-week trial were 38.8% for donepezil, 53% for galantamine, and 58.7% for rivastigmine. These rates were much higher than those reported in pre-marketing clinical trials (5%–13% for mild-to-moderate AD).[30-33]

Other reports have noted QT prolongation and polymorphic ventricular tachycardia (torsades de pointes [TdP]) in patients taking donepezil for AD.[34-37] Furthermore, donepezil was recently added to the CredibleMeds database of medications with a known risk of causing TdP. This is their highest level of caution and is used to describe "drugs [that] prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended." Lower-level cautions in the database are characterized as "possible risk of TdP" and known to cause QT prolongation BUT currently lack evidence of TdP when taken as recommended," "conditional risk of TdP (these drugs are associated with TdP BUT only under certain conditions such as hypokalemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP)." The last category, "Drugs to avoid in congenital long QT syndrome," includes drugs from all of the other categories and "additional drugs that do not prolong the QT interval per se, but which have a special risk because of their other actions."

The mechanism by which donepezil increases the risk of TdP may, in part, be due to bradycardia, which increases the frequency of pause-dependent onset of polymorphic VT in patients with a prolonged QT. Edrophonium, an anticholinesterase, also showed a marked ability to induce syncope during head-up tilt-testing.[38] Notably, one study of syncope in AD patients treated with donepezil found that most patients who developed syncope had pre-exist-

ing CV conditions.[39] Thus, care providers (e.g., primary care providers and cardiologists) should carefully and critically evaluate patients on these medications before starting these agents as well as after a patient experiences a syncopal event.

Beyond bradycardia and syncope, these side effects can cause significant risks for patients on AChE inhibitors, leading to their discontinuation as therapy. Previous population-based cohort studies have demonstrated the associations between AChE inhibitors, hip fractures, and pacemaker placement.[19] More serious complications of syncope and falls, such as fractures or head injury, can lead to hospitalization, and even death, especially in frail older adults.

CV benefits of AchE inhibitors

It remains difficult to draw firm conclusions regarding the cardiac effects of AChE inhibitors. While some studies and reviews have shown adverse cardiac side effects associated with the use of AChE inhibitors, others appear to show beneficial cardiac effects. The possible mechanisms for these beneficial effects include anti-inflammatory actions and favorable effects on nitric oxide pathways and redox, mitochondrial, and calcium modulation.[40-43] A recent study from Taiwan reported a dose-response-dependent decrease in CV events in patients with AD administered AChE inhibitors (i.e., the higher the cumulative dose the patients received, the fewer the CV events they experienced).[44] The outcomes measured were a composite of CV events, including coronary heart disease, stroke, heart failure, and CV death. This was a retrospective cohort study from a health and welfare database that utilized propensity score-matching. However, the study excluded patients with pre-existing CV disease (stroke, coronary artery disease, heart failure, or sudden cardiac death), thus reducing the generalizability of the results as many older adults have these conditions. The additional limitations that the authors specifically mentioned included bias by indication as well as unmeasured confounders, an important limitation of non-randomized studies.

A meta-analysis and systematic review by Isik et al.[40] showed that AChE inhibitor use was associated with a greater risk of bradycardia but also resulted in a lower risk of other CV events such as stroke and acute coronary syndromes in patients with dementia. As noted by the authors, the limitations of the analysis included the absence of randomized controlled trials, leaving open the possibility that patients on AChE inhibitors were receiving different, and perhaps more aggressive or effective, preventative CV care. In addition, they acknowledged an inability to evaluate the impact of other medications that the patients had also been prescribed (i.e., that data were not available) in most of the included studies. As such, it is difficult to discern whether the use of antiarrhythmics,

anti-hypertensives, anti-platelets, anticoagulants, and other medications or procedures may have played a role in the measured outcomes.[40]

Other studies (included in the analysis by Isik et al.) showed improved CV and all-cause mortality in patients administered donepezil.[21,45] The Donepezil Cardiac TEst Registry (DOCTER) study examined the CV effects of donepezil in a 6-month prospective cohort study of 49 patients with dementia with New York Heart Association Functional Class I or II (asymptomatic or mildly symptomatic) congestive heart failure (CHF). The researchers observed no adverse CV effects during the treatment course or the 6-month follow-up period. However, they noted a reduction in brain natriuretic peptide (BNP, a marker for heart failure) levels in patients with subclinical (based on mildly elevated BNP) CHF.[46] Other studies examining donepezil in older adult patients with AD showed no significant changes in electrocardiogram (ECG) parameters (heart rate, PR, QT, QTc, QRS duration) or arterial blood pressure relative to the controls.[47] These results suggested that further research is needed to more fully evaluate the various CV effects of AChE inhibitors and identify factors that may enhance the risk of adverse CV events, particularly in patients with and without pre-existing CV disease or with multiple risk factors for CV disease.

MANAGEMENT OF (POTENTIAL) SIDE EFFECTS

Because the understanding of the development of bradycardia, syncope, and other adverse effects of AChE inhibitor use is incomplete, there are few guidelines regarding the management of patients on or being considered for placement on these agents.[19] The suggestions for managing possible AChE inhibitor CV side effects include monthly pulse checks and symptom monitoring. If bradycardia is noted (< 50 bpm) or if syncope or seizures are reported, the investigation of all possible causes is recommended before attributing these signs to AChE inhibitors.[28]

While it may be tempting to simply stop the medication if a patient on one of these agents presents with syncope and/or symptomatic (or asymptomatic) bradycardia to see if the symptoms resolve or improve, this approach should not be undertaken lightly. Clinicians should consider the drug dose, as a dose reduction may lessen side effects. Clinicians must also consider other possible etiologies of the adverse effect, the impact of other concurrent medications that may contribute to the effect, and whether the patient appears to be responding cognitively to the AChE inhibitors.

Many patients are on other medications as well as AChE inhibitors; thus, there is the potential for harmful drug interactions between AChE inhibitors and, in particular, other CV agents that can

reduce the heart rate. Many studies have suggested caution in prescribing AChE inhibitors to patients taking such medications,[28,48] including beta-blockers, calcium channel blockers, and digoxin, which are commonly used in older adult patients who have high rates of coronary artery disease (including those with post-myocardial infarction or angina), heart failure, atrial fibrillation, or other tachyarrhythmias (supraventricular or ventricular). Antiarrhythmics such as amiodarone may also affect heart rate and predispose patients to other arrhythmias. Thus, episodes of bradycardia and syncope must be carefully evaluated to determine the underlying cause. It is important to note that virtually all the adverse CV events mentioned in this article can be multifactorial and may not necessitate cessation of AChE inhibitor use.

Although AChEIs are not considered disease-modifying agents, they provide some clinical improvements.[49] At some point, the disease is expected to progress, and providers may elect to stop the medication due to concerns regarding polypharmacy and diminishing benefits. Some data suggest that patient cognitive and neuropsychiatric conditions may deteriorate if these medications are stopped abruptly, and withdrawal-like symptoms have been reported.[50-52] Thus, simply stopping the agent may not be a wise option for all patients.

If a patient may benefit from an AChE inhibitor, it may be advisable to consider ways to mitigate the effects of possible adverse effects instead of completely stopping them. This can be accomplished through interdisciplinary efforts by working with the patient's care team (e.g., geriatricians and/or primary care physicians, geriatric psychiatrists, neurologists, cardiologists). When symptomatic bradycardia or syncope is a concern, evaluations including EKGs, Holter or longer-term rhythm monitors, or other cardiac testing, such as exercise treadmill tests to evaluate chronotropic competence, may be indicated. If there is a concern for seizures, this should be evaluated as well.

If, after an appropriate workup, it is ultimately determined that a patient is experiencing a significant (even dangerous) side effect that is likely to be from the AChE inhibitor or the patient has comorbidities that place him or her at an increased risk of adverse outcomes that outweigh the possible cognitive benefits, then AChE inhibitors should be tapered off (or not started).[53] Drug doses should be tapered before cessation due to reports of adverse cognitive effects following abrupt cessation.[54]

Given the aforementioned side effects, these subtle and overt CV complications should be strongly considered when prescribing AChE inhibitors, especially in at-risk patients. Most patients using AChE inhibitors are older adults. The ability to increase heart rate decreases with increasing age, as does the incidence of conduction system disease, including sinus node dysfunction, which may often

be subclinical. Given the possibility of adverse, and sometimes unknown, underlying interactions, particular caution should be taken when devising treatment plans for older adult patients on AChE inhibitors, taking into consideration the possibility of bradycardia and syncope, which may be induced by medication alone or in combination with other medications, comorbidities, or age-related changes.

One suggested approach for cardiac evaluation and monitoring of patients on AChE inhibitors is shown in Fig. 1. Some considerations should be given to a baseline ECG, heart rate monitoring, medication review, and rhythm monitoring if symptoms are observed. This approach should be evaluated prospectively to evaluate its possible benefits.

Baseline & Periodic Evaluation

1. Review heart rate on routine vital signs (each visit). Monthly HR checks during titration, and then q6mo.

2. Obtain 12-lead ECG (baseline, and q 1 year or with symptoms)
    a. Heart rate (presumes asymptomatic)
        i. HR < 50 bpm, consider not starting AChEi immediately, search for causes
        ii. HR 50-60 bpm, carefully weigh risks and benefits of starting or continuing or dose reducing AChEi or other contributing medications, consider rhythm monitor or more frequent assessments for symptoms
        iii. HR >60, standard follow-up
    b. Heart block
    c. Sinus pauses or other rhythm disturbances
    d. Prolonged QTc

3. Review past medical history for diagnosed cardiovascular diseases or risk factors for them (each visit)

4. Review medications (each visit)
    a. Agents that may induce or exacerbate bradycardia (e.g. beta-blockers, calcium channel blockers, digoxin)
    b. Agents that may prolong the QT interval (e.g. certain antibiotics, antipsychotics, (CredibleMeds.org))
        i. Offending agents should typically be stopped or dose reduced with re-measurement of the QTc

5. Screen for symptoms of bradycardia or other arrhythmias (each visit)
    a. Exercise intolerance
    b. Dyspnea on exertion
    c. Syncope or pre-syncope*
    d. Palpitations

6. If symptoms are present, the evaluation may include**
    a. Long-term rhythm monitoring
        i. 24/48h Holter
        ii. 1-2 week Patch monitor
        iii. 4-week Event monitor or mobile telemetry
        iv. Implanted Loop Recorder
    b. Formal or informal exercise test for chronotropic competence

*Syncopal episodes especially in the setting of a prolonged QTc should prompt urgent consultation with a cardiologist or electrophysiologist

**At any point in the evaluation, referral to Cardiology can be considered

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Fig. 1. Suggested approach to the cardiac evaluation and monitoring of patients being considered for or taking an acetylcholinesterase inhibitor. Unless otherwise indicated, each item should be reviewed at each visit.

CONCLUSION

Currently, there remains a lack of a complete understanding of the interplay between AChE and patient factors that can predispose patients to adverse effects and potentially life-threatening clinical outcomes. Therefore, more studies are needed to clarify these pathways to maximize the positive effects and minimize the negative impacts of the use of these agents. The most prominent CV side effects of AChE inhibitors are bradycardia and syncope, which can result in devastating outcomes such as falls, fractures, and other trauma as well as necessitate pacemaker placement. Given the aging of the world's population and the attendant increase in the global population of patients with AD, this is an important area for further research. When a patient has experienced a possible side effect, in consultation with the provider who prescribes the AChE inhibitor, the patient or their surrogate should undergo a thorough history and evaluation, including a medication review, rhythm monitoring, consideration of neurologic symptoms, lowering the doses of other medications that might contribute to bradycardia, stopping or reducing the AChE inhibitor dose, or even pacemaker placement. Many of these factors should be considered before the initiation of these medications and periodically thereafter to optimize patient care and mitigate possible adverse events.

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