Cardiovascular effects of drugs used to treat Alzheimers'disease.

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Abstract.

Drugs that are used to treat Alzheimers'disease (AD) include the acetyl cholinesterase inhibitors (ACHIs) donepezil, rivastigmine and galantamine and the NMDA receptor antagonist memantine. Adverse cardiovascular events with these drugs are very uncommon. However, there is evidence that ACHI therapy is associated with a small but significant increase in the risk of syncope and bradycardia. There are also a few reports that these drugs may occasionally be associated with QT prolongation and torsades de pointes ventricular tachycardia. Adverse cardiovascular effects of ACHIs including syncope and bradycardia are less common than their adverse gastrointestinal effects, but they remain important considerations in susceptible individuals. In contrast, animal studies and some observational studies suggest that ACHIs may reduce myocardial infarction and cardiovascular mortality and have favourable effects on hemodynamics and survival in heart failure. Further research is required to confirm these potential beneficial effects. Little is known about the cardiovascular effects of memantine but there have been reports of bradycardia and reduced cardiovascular survival associated with its' use.

1. Introduction.

Alzheimers' disease (AD) is the most common form of dementia which is increasing in prevalence as the average age of the population rises. In 2013 it was estimated that 5% of the population over the age of 65 years had AD and that this proportion increased with age such that nearly 30% of the population older than 85 years was affected [1].

Drugs used to treat AD belong to two classes – acetyl cholinesterase inhibitors (ACHIs) (donepezil, galantamine and rivastigmine) and the NMDA receptor antagonist memantine. Approximately 80% of patients with AD receive therapy with these drugs, the majority receiving ACHIs of which donepezil is by far the most commonly used [2].

Acetylcholine containing neurones exist in the brain where they are found predominately in the cerebral cortex, and in the periphery where they are found in the autonomic nervous system and innervating skeletal muscle. Acetylcholine acts on two subclasses of receptors, nicotinic and muscarinic. Muscarinic receptors are further classified as Mn and Mm. Mm receptors are found in skeletal muscle while Mn receptor are found in the neurones of the central nervous system and parasympathetic nervous system. Nicotinic receptors are found in preganglionic neurons and the central nervous system. Donepezil, galantamine and rivastigmine are all selective centrally acting, reversible inhibitors of the enzyme acetyl cholinesterase which potentiate the effects of acetylcholine in the brain [3]. However, potentiation of the parasympathetic nervous system (principally the vagus nerve) also occurs which may produce bradycardia and gastrointestinal effects. Donepezil is the most widely used member of the class, and most of the published literature of adverse effects of ACHIs in the treatment of AD relate to this drug [4]. The common side effects of ACHIs are due to potentiation of acetylcholine within the gastrointestinal system (nausea, vomiting and diarrhoea) [4]. However, cardiovascular side effects have also been reported. ACHIs are indicated in mild to moderate severity AD.

Memantine is a non competitive NMDA receptor antagonist [5] that also has non competitive antagonist activity at 5 HT3 receptors [6] and nicotinic cholinergic receptors [7]. It also has agonist activity at D2 receptors [8]. It is indicated in moderately severe AD.

The current article reviews the cardiovascular effects that have been reported for the ACHIs and memantine when used as therapy for AD.

2. Search strategy.

A search of Medline and PubMed was performed using the search terms cholinesterase inhibitors, donepezil, galantamine, rivastigmine and memantine with cardiovascular, bradycardia or syncope. No quality criteria were set and no articles of relevance were rejected. Both preclinical and

clinical publications were included. Similar searches were also performed using the Google search engine.

3. ACHIs.

3.1 Syncope.

ACHIs may induce syncope by enhancing the activity of the vagus nerve or by enhancing vagally mediated reflexes. Increased vagal nerve activity may produce sinus bradycardia or heart block [9]. The proposition that ACHIs may induce syncope came from early case reports and studies of syncope in AD patients [10-12].

Gill et al [13] investigated the association between ACHI therapy and syncope in a cohort of patients with AD. The study included community dwelling subjects that had a diagnosis of dementia made within the preceding 5 years. 19,803 patients who were new users of an ACHI were compared with 61,499 patients who had not received an ACHI within the preceding year. The groups were well matched. The main outcome measured was the first hospital attendance for syncope and the study was continued for 2 years.

Syncope occurred at a rate of 31.5 per 1000 patients years in the treated group compared to 18.6 per 1000 patient years in the control group (hazard ratio 1.76, 95% confidence intervals 1.57-1.98). Fractured hip, which may be a consequence of syncope, occurred at a rate of 22.4 per 1000 patient years in treated patients compared with 19.8 per 1000 patient years in controls (hazard ratio 1.18, 95% confidence intervals 1.04-1.34). The requirement for permanent pacemaker insertion occurred at a rate of 4.7 per 1000 patient years in treated patients compared with 3.3 per 1000 patients year in controls (hazard ratio 1.49, 95% confidence intervals 1.12-2.00).
Interestingly, a diagnosis of bradycardia was made at a rate of only 6.9 per 1000 patient years in treated patients compared with 4.4 per 1000 patient years in controls (hazard ratio 1.69, 95% confidence intervals 1.32-2.15), suggesting that either bradycardia was under reported or undetected or that other mechanisms such as augmentation of vagally mediated reflexes contribute significantly to the pathogenesis of syncope in these patients.

These results suggest that ACHI therapy in patients with dementia (presumably mostly due to AD) is associated with an almost 2 fold greater risk of syncope and that this is not necessarily accompanied by a diagnosis of bradycardia.

3.2 Bradycardia.

ACHIs may produce bradycardia by potentiating cardiac vagal activity. However, up until 2009 it was unclear to what extent this was a clinical concern. The major placebo controlled clinical trials in the phase II and phase III development program had shown that donepezil therapy was associated with a mean fall in heart rate of 1.6 beats per minute, but there was no evidence that bradycardia occurred at a rate that was significantly higher than placebo [4,14]. However, the relatively small number of patients in these studies may have made it difficult to detect a small but clinically significant difference in the incidence of bradycardia between active and placebo therapy. In addition, most of these trials specifically excluded patients with a history of syncope or bradycardia [15]. As a result we are restricted to data from post marketing studies to asses the cardiovascular safety of these drugs with respect to syncope and bradycardia.

In 2009 3 pivotal population studies evaluating the relationship between ACHI therapy and bradycardia were reported. The first of these, described above, was the study by Gill et. al. [13]. In addition to reporting that ACHI therapy was associated with an increased risk of syncope, they found a higher rate of bradycardia on ACHIs than the rate on placebo therapy (hazard ratio 1.69, 95% confidence intervals 1.32-2.15).

The second study was that of Hernandez et al. [16]. These investigators studied 11,328 patients with dementia from records of the Boston VA Healthcare system between January 1999 and June 2007. 3,198 patients were identified who had been receiving ACHI therapy and these were compared to 8,130 patients who did not receive ACHIs. The number of patients who had a diagnosis of bradycardia was compared between the 2 groups.

Bradycardia was significantly more common in treated patients than in controls (62.05 per 1000 patient years compared to 25.55 per 1000 patients years; adjusted hazard ratio 1.4, 95% confidence intervals 1.1-1.6). A significant dose response relationship was found for donepezil, but there were too few cases on other ACHIs to evaluate possible dose response relationships. A significantly higher incidence of bradycardia was found in patients receiving donepezil than in controls irrespective of whether they had a diagnosis of cardiovascular disease or were receiving negative inotropic drugs. The number of patients receiving ACHIs other than donepezil was too small to determine whether there were differences in the risk of developing bradycardia between different ACHI drugs.

The third study was that of Parke-Wyllie et.al [17] which used a case –time control design where patients act as their own control, comparing a period in which they were exposed to ACHIs with a period in which they were not exposed. Out of a total of 27,333 patients admitted to hospital with a diagnosis of bradycardia between January 1st 2003 and March 31st they identified 161 patients who had received ACHIs in either the risk period (3-0

months prior to hospitalisation) or the reference period (9-6 months prior to hospitalisation) but not both. The odds ratio for the association of ACHI therapy and bradycardia was calculated as the number of cases of ACHI use in the risk period divided by the number of cases that received ACHI therapy in the reference period.

Recent initiation of ACHI therapy was significantly associated with hospitalisation for bradycardia (odds ratio 2.13, 95% confidence intervals 1.29-3.51). The odds ratio was similar in patients previously diagnosed as having cardiovascular disease and in patients on negative chronotropic drugs. Fifty-seven percent of patients who developed bradycardia on ACHI therapy were recommenced on this therapy within 100 days of discharge from hospital.

In summary, although uncommon, ACHI therapy appears to be associated with about a 1.5-2 fold risk of developing bradycardia. The vast majority of patients receiving ACHIs will have normal ECGs and no significant hemodynamic changes [18-20]. There is insufficient data to determine whether there are differences between the individual class members of ACHIs and the risk of bradycardia as most of the data relate to donepezil therapy [19].

3.3 Torsades de Pointes ventricular tachycardia.

There have been several case reports of Q-T prolongation and torsades de pointes ventricular tachycardia during ACHI therapy. Leitch et al. [21] described a 76 year old woman who developed QT prolongation and torsades de pointes ventricular tachycardia who was taking a combination of donepezil, escitalopram and propranolol. After ceasing these medications the ventricular tachycardia resolved and the QT interval returned to normal. Fisher et al. [22] described a case of QT prolongation associated with syncope in an 85 year old man treated with galantamine. He initially experienced an episode of hypotension and bradycardia after which the galantamine was ceased. However, when the galantamine was recommenced 2 weeks later he developed syncope and serious cardiac arrhythmias associated with QT prolongation. His symptoms resolved and the QT segments normalised when the galantamine was ceased. Tanaka et al. [23] reported 2 cases of QT prolongation in patients receiving donepezil. The QT segments in both cases returned to normal when the donepezil was ceased.

Takayata et al. [24] described a patient who had prior myocardial infarction that developed diarrhoea, vomiting and syncope on donepezil that was associated with QT prolongation and hypokalemia. Her ECG showed episodes of torsades de pointes. Her donepezil therapy was ceased and she was treated with potassium after which her symptoms resolved. However, it is unclear whether her QT segments normalised.

These cases suggest that QT prolongation and torsades de pointes may occur during ACHI therapy. However, in the absence of any epidemiological studies to address the association the incidence of these problems remains

unclear. A data mining of FDA adverse events reporting identified donepezil as one of 35 drugs with at least 10 reports of torsades de pointes [25].

3.4 Beneficial effects of ACHIs.

In contrast to the potentially adverse effects of ACHIs described above, beneficial effects have been reported on the cardiovascular system for these drugs.

At a preclinical level, donepezil (along with the cholinesterase inhibitor physostigmine) has been shown to inhibit atherogenesis in mice [26]. Donepezil therapy improved hemodynamics and prolonged survival in a mice model of cardiac failure [27], independent of effects on heart rate. In addition, donepezil has been reported to markedly prolong survival and improve hemodynamics in rats with heart failure following extensive myocardial infarction (in a similar manner to chronic vagal nerve stimulation) [28].

In humans, donepezil reduced elevated brain natriuretic peptide (BNP) levels (a marker of impaired cardiac function) in 49 patients with dementia over a 6 month period [29]. A study of a national database that was used to link ACHI use with myocardial infarction and death found that ACHI users had a statistically significant 34% lower risk of the combined endpoint of myocardial infarction or death than non-users [30].

A retrospective cohort study of the association between donepezil usage and cardiovascular mortality in patients with AD found that donepezil therapy was associated with a significant reduction in cardiovascular mortality [31]. Eighty-five patients prescribed donepezil were matched with 80 patients who did not receive ACHI therapy. Hazard ratios for total and cardiovascular mortality were 0.68 (95% confidence intervals 0.46-0.99) and 0.54 (95% confidence intervals 0.30-0.98) respectively. Although this study was small, it supports the evidence from other studies and animal models of a benefit in survival from cardiovascular disease for donepezil users. Randomised clinical trials are required to establish these potential benefits.

4. Memantine.

There is very little published information about the cardiovascular effects of memantine.

A review of reported adverse drug reactions from the French PharmacoVigilance Database found a small number of adverse cardiovascular events on memantine therapy, the most common being bradycardia. Most episodes of bradycardia where memantine was the sole suspected drug resolved when the drug was ceased [32]. It is unclear through what mechanisms memantine could produce bradycardia. In addition, memantime has been reported to increase the electrocardiograph PR interval associated with donepezil therapy in a patient with AD [32]. A comparison of

memantine users and non-users in two large population databases found an increase in fatal and non-fatal myocardial infarction in memantine users along with an increase in all-cause mortality. However, this may have been in part due to the selection of sicker individuals for memantine therapy [34].

Conclusions.

Adverse cardiovascular effects of drugs used to treat AD appear to be very uncommon. There is evidence of an increased risk of syncope and bradycardia with ACHIs, and the use of these drugs may occasionally be associated with QT prolongation and torsades de pointes. While adverse cardiovascular effects of these drugs are less common than gastrointestinal side effects, they remain an important consideration in susceptible individuals. However, ACHI therapy may be associated with improved cardiovascular outcomes although more data from well designed randomised trials are required to establish this possibility.

Little is known about the cardiovascular effects of memantine, although there are suggestions that it may be associated with bradycardia and impaired cardiovascular outcomes.

The clinical implications of the findings presented in this review are that prescribers should be aware of potential cardiovascular effects of drugs used to treat AD.

6. References.

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