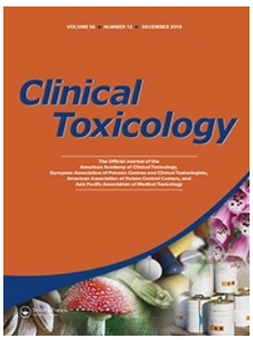

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CLINICAL RESEARCH

Long term use of donepezil and QTc prolongation

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ABSTRACT

Background: The neurocognitive benefits of donepezil are well recognised, but the potential side effects on cardiac conduction remain unclear.

Objective: To investigate whether long-term donepezil therapy is associated with electrocardiographic (ECG) changes and in particular to assess its effects on the QT interval.

Methods: We conducted a single centre retrospective analysis of patients admitted to our trust on donepezil therapy over a 12-month period. An admission resting 12-lead ECG was obtained and compared to their ECG prior to commencement of donepezil therapy to assess for any significant difference in ECG parameters.

Results: We identified 59 patients suitable for analysis. PR (177.0 ± 29.0 ms vs. 186.1 ± 34.2 ms, $p = 0.04$), QRS (101.7 ± 20.3 ms vs. 104.7 ± 22.3 ms, $p = 0.04$) and QT (393.3 ± 35.6 ms vs. 411.9 ± 44.6 ms, $p = 0.002$) interval prolongation were all associated with donepezil use. The increase in QT intervals remained significant on correction for heart rate; resulting in 8 (13.6%) patients developing high arrhythmogenic risk based on assessment using QT nomogram plots. Concomitant use of tricyclic antidepressants was associated with significant QT prolongation (QTcB: $r_{pb} = 0.344$, $p = 0.008$, QTcFred: $r_{pb} = 0.382$, $p = 0.003$, QTcFram: $r_{pb} = 0.379$, $p = 0.003$, QTcH: $r_{pb} = 0.352$, $p = 0.006$), while the use of rate-limiting calcium channel blockers was associated with significant PR prolongation ($r_{pb} = 0.314$, $p = 0.030$), and beta-blockers with a reduction in heart rate ($r_{pb} = 0.256$, $p = 0.050$).

Conclusion: Our results clearly demonstrate that long-term use of donepezil is associated with prolongation of the QT interval. We suggest ECG evaluation should take place before and after donepezil initiation, and clinicians should be even more vigilant in those prescribed tricyclic antidepressants.

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Donepezil; electrocardiography; cardiac arrhythmias; cholinesterase inhibitors

Introduction

Donepezil is an acetylcholinesterase inhibitor primarily used to treat mild to moderate Alzheimer's dementia (AD). While the neurocognitive benefits of donepezil are well documented, its adverse effects on cardiac conduction remain unclear. Several case studies have reported QT prolongation and subsequent Torsades de Pointes (TdP) associated with donepezil use in patients with AD [1–4], while others have reported bradycardia and PR prolongation, resulting in subsequent medication cessation [5,6]. Smaller-scale studies to date have shown that donepezil is relatively safe to use in the elderly population. Common parasympathetic side-effects have been associated with its use, but importantly these small-scale observational studies have not reported any sinister repolarisation abnormalities such as significant QT prolongation, subsequent arrhythmia, or syncopal episodes [7–9].

The British National Formulary (BNF) describes bradycardia as an uncommon side-effect and cardiac conduction disorders to be a rare or very rare side effect of donepezil [10]. First-degree atrioventricular (AV) block and supraventricular tachycardia were reported to be infrequent side-effects by the United States Food and Drug Administration (FDA) [11]. Physicians are advised to practise caution when prescribing donepezil in patients with cardiac conduction disorders, but despite these warnings there remains on-going debate as to whether a resting 12-lead electrocardiogram (ECG) is required prior to initiation of donepezil therapy [12].

The primary objective of our study is to investigate whether ECG changes are associated with donepezil therapy and in particular assess its effects on the QT interval. We also aim to evaluate whether gender, treatment duration, donepezil dose or concomitant use of medications are associated with conduction abnormalities and QT prolongation in patients prescribed donepezil therapy.

Materials and methods

We carried out a retrospective analysis of all acute admissions of patients on donepezil treatment to our institution between March 2019 and March 2020. An admission resting 12-lead ECG was obtained and compared to their ECG prior to commencement of donepezil therapy. All data were

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collected from our local hospital electronic care record and memory clinic database. Patient characteristics and demographics were recorded, including indications for donepezil, comorbidities and left ventricular function (assessed using the Simpson's biplane method on images obtained from a recent transthoracic echocardiogram). Baseline serum electrolytes (magnesium, adjusted calcium, and potassium) and thyroid status were noted. Medications with potential side-effects on cardiac conduction or known to cause electrolyte disturbances, including beta-blockers, levothyroxine, rate-limiting calcium-channel blockers, diuretics, digoxin, tricyclic antidepressants, antipsychotics and selective serotonin reuptake inhibitor (SSRI)/selective serotonin noradrenaline reuptake inhibitor (SNRI) antidepressants were all recorded. In addition, the duration of donepezil therapy was established and rounded off to the nearest year.

A control group that was age, sex, ethnicity and comorbid matched was recruited to analyse for any changes in their QT intervals over 12 months of ageing. This was compared to our donepezil population in order to account for ageing as a confounding factor that may cause QT prolongation. Exclusion criteria for our study included recent initiation of donepezil therapy (<6 months), patients with electrolyte disturbances or deranged thyroid function on admission, patients with a paced rhythm on ECG and those patients in whom an ECG prior to commencement of therapy could not be obtained.

Measuring electrocardiographic parameters

All patients underwent a 12-lead resting ECG using a 25 mm/s paper speed and standardised at 0.1 mV/mm. The patient's heart rhythm was analysed by a cardiology registrar or consultant. Heart rate (HR), PR and QRS intervals were calculated automatically by the ECG apparatus. The QT interval was measured manually using the threshold method taken from multiple leads (chest leads V3–V6 and lead II) and the median QT was calculated.

Due to the discrepancies in formulae used for correcting QT intervals; all four commonly used formulae (Bazett, Fredericia, Framingham and Hodges) were included. The QT intervals were plotted on a QT nomogram (a plot of uncorrected QT interval against heart rate) to predict arrhythmogenic risk [13]. Since Bazett's formula remain the most widely used formula in clinical practice, we define a prolonged QTcB interval as ≥450 ms for men and ≥460 ms for women. In patients with bundle branch blocks or QRS intervals >130 ms, their QT intervals were measured from leads with a normal QRS interval. Where this was not possible, a correction factor was used [14].

Ethics

This survey was approved by the trust audit department with reference CB582. As a registry report using clinically collected, non-identifiable data, this work does not fall under the remit of National Health Service Research Ethics Committees.

Statistical analysis

Data were analysed with SPSS Version 26 software. Continuous variables were expressed as mean ± standard deviation and categorical variables were summarised as frequencies and percentages. The normality of all continuous variables was tested with the Kolmogorov–Smirnov test. Since the variables were not normally distributed, the Wilcoxon signed-rank test was used to compare the mean in all ECG parameters while the Mann–Whitney U test was used to compare the changes in ECG parameters between gender and donepezil doses. We performed point-biserial correlations to assess whether cardiac comorbidities and concurrent use of medications alongside donepezil were associated with changes in ECG parameters. The Kruskal–Wallis test was used to evaluate whether any changes in ECG parameters were associated with duration of donepezil treatment. Statistical significance was defined as p-value ≤0.05.

Results

We identified 59 patients on donepezil therapy and 53 controls that were suitable for inclusion in our study. Their baseline demographics and characteristics are summarised in Table 1. The duration of donepezil therapy for 13 patients was not discernible from their electronic records. Within our donepezil therapy group, 9 patients were in AF, hence, their PR intervals could not be assessed, while 1 patient with second-degree heart block was excluded from PR interval analysis. Five patients had a previously implanted permanent pacemaker (PPM); these patients' ECGs were suitable for inclusion as their rhythms were independent of pacing. Serum magnesium was not available in 22 patients, while serum calcium and thyroid functions were absent in 4 and 2 patients respectively.

Analysis of a resting 12-lead ECG prior to commencing donepezil treatment was compared to the ECG obtained during their most recent acute hospital admission and demonstrated evidence of significant prolongation of the PR (177.0 ± 29.0 ms vs. 186.1 ± 34.2 ms, $p = 0.04$), QRS (101.7 ± 20.3 ms vs. 104.7 ± 22.3 ms, $p = 0.04$) and QT (393.3 ± 35.6 ms vs. 411.9 ± 44.6 ms, $p = 0.002$) intervals (Table 2). The QT corrected using Bazett, Fredericia, Framingham and Hodges formulae were also compared, and all confirmed significant QT prolongation during donepezil therapy. Analysis using the QT nomogram revealed that 8 (13.6%) patients (3 male and 5 female) went from low arrhythmogenic risk to high while on donepezil therapy (Figure 1). Of these 8 patients, 3 had evidence of prolonged QRS intervals (157.3 ± 3.9 ms); 2 of which were present prior to donepezil treatment and 1 developed right bundle branch block (RBBB) from a normal baseline QRS interval. The mean QRS interval on donepezil treatment for the remaining 5 patients was 94.4 ± 12.0 ms.

The longest QT interval observed in our cohort was 514 ms (570, 542, 529 and 527 ms if corrected by Bazett's, Fredericia, Framingham and Hodges formulae respectively). 11 female patients had a QTc ≥ 460ms and 16 male patients had a QTc ≥ 450ms on donepezil therapy; of which 5 female

Table 1. Patient demographics and characteristics.

Patient characteristics	Donepezil (*n*, %)	Control (*n*, %)
Total	59	53
Age (years)	86 ± 5 years	85 ± 5 years
Female	37 (63)	33 (62)
Ethnicity		
Caucasian	50 (85)	45 (85)
Others	9 (15)	8 (15)
Reason for admission		
Fall	30	24
Infection	16	16
Confusion/delirium	9	3
Exacerbation of heart failure	1	2
Others	3	8
Serum biochemistry		
Potassium (mmol/L)	4.43 ± 0.53	4.22 ± 0.46
Magnesium (mmol/L)	0.80 ± 0.17	0.83 ± 0.12
Adjusted calcium (mmol/L)	2.42 ± 0.12	2.43 ± 0.13
Thyroid-stimulating Hormone (mIU/L)	2.27 ± 2.60	1.98 ± 1.19
Comorbidities		
Hypertension	42	34
Ischaemic heart disease	16	14
Heart failure	13	13
Permanent pacemaker	5	3
Baseline rhythm		
Sinus rhythm	50	42
Atrial fibrillation/flutter	9	11
1st degree heart block	10	7
2nd degree heart block	1	0
Right bundle branch block	6	4
Left bundle branch block	2	1
Recent transthoracic echocardiogram	34	37
Left ventricular ejection fraction		
Normal >55%	20	26
Mild impairment 45–55%	6	8
Moderate impairment 35–44%	4	1
Severe <35%	4	2
Donepezil dose		
5 mg	25 (42)	
10 mg	34 (58)	
Indication		
Alzheimer's dementia	29 (49.2)	
Unspecified dementia	25 (42.4)	
Vascular dementia	3 (5.1)	
Mixed dementia	2 (3.4)	
Duration on donepezil (nearest year)		
1 year	20	
2 years	5	
3 years	10	
4 years	5	
5 years	6	

Table 2. Comparison of the ECG parameters before donepezil initiation and once patients were on donepezil treatment.

ECG parameters	Baseline	On donepezil	Δ	*p*-Value
HR (beats/min)	76.2 ± 13.7	75.5 ± 17.1		0.513
PR interval (ms)	177.0 ± 29.0	186.1 ± 34.2	9.1	0.042*
QRS duration (ms)	101.7 ± 20.3	104.7 ± 22.3	3.0	0.040*
QT interval (ms)	393.3 ± 35.6	411.9 ± 44.6	18.6	0.002*
QTcBazett (ms)	438.9 ± 28.7	455.7 ± 43.4	16.8	0.009*
QTcFred (ms)	422.7 ± 26.2	439.6 ± 37.4	16.9	0.001*
QTcFram (ms)	422.2 ± 24.7	437.1 ± 35.4	14.9	0.003*
QTcHodges (ms)	421.7 ± 25.2	439.2 ± 34.7	17.5	0.001*

*Statistical significance.

patients and 11 male patients had normal QTc intervals prior to starting donepezil treatment (Figure 2). Of these 27 patients, 9 had evidence of prolonged QRS intervals (153.2 ± 8.1 ms); 6 had baseline prolonged QRS and 3 had evidence of RBBB morphology from normal baseline QRS intervals, none of which resulted in any adverse events. The

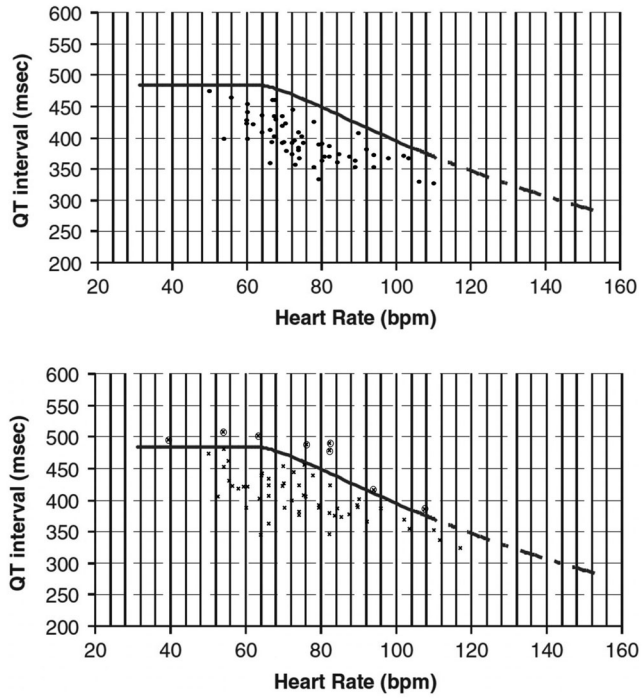

Figure 1. A comparison of QT nomogram plots before (top) and after (bottom) the initiation of donepezil therapy.

mean QRS interval on donepezil treatment for the remaining 18 patients was 104.1 ± 16.3 ms. In the control group, 12 months of ageing did not demonstrate any significant changes to the QT and QTc intervals (QT: 393.3 ± 36.1 ms vs 387.4 ± 37.0 ms [$p = 0.156$], QTcB: 439.9 ± 28.6 ms vs 438.8 ± 31.7 ms [$p = 0.720$], QTcFred: 423.4 ± 26.2 vs 420.5 ± 26.9 ms [$p = 0.597$], QTcFram 422.8 ± 24.1 ms vs 419.4 ± 24.2 ms [$p = 0.530$], QTcH: 422.5 ± 23.7 vs 420.8 ± 24.2 ms [$p = 0.626$]).

The most common reason for admission in our cohort was falling, and occurred in 30 patients on donepezil therapy; one of which had donepezil ceased on admission due to bradycardia and intermittent complete heart block. Cessation of donepezil resulted in normalisation of this patient's heart rate and resolution of their heart block. Another patient fell as a result of a syncopal episode and was found to be in AF with a slow ventricular response. A PPM was subsequently implanted. No other adverse cardiac events such as ventricular arrythmias or parasympathetic side-effects were reported. There was no significant change in mean HR, but 9 patients progressed to 1st-degree heart block from normal baseline PR intervals; these patients had not reported any adverse events.

Assessment of the effect of donepezil on ECG parameters demonstrated that males experienced a significantly greater increase in their corrected QT intervals compared to females (Table 3). There were no significant differences in all ECG parameters when comparing donepezil doses (Table 4). Although there was a significant difference in QT interval between the different treatment duration groups, no significant difference was found once QT intervals were corrected. Duration of donepezil therapy did not affect the HR, PR interval or QRS interval (Table 5).

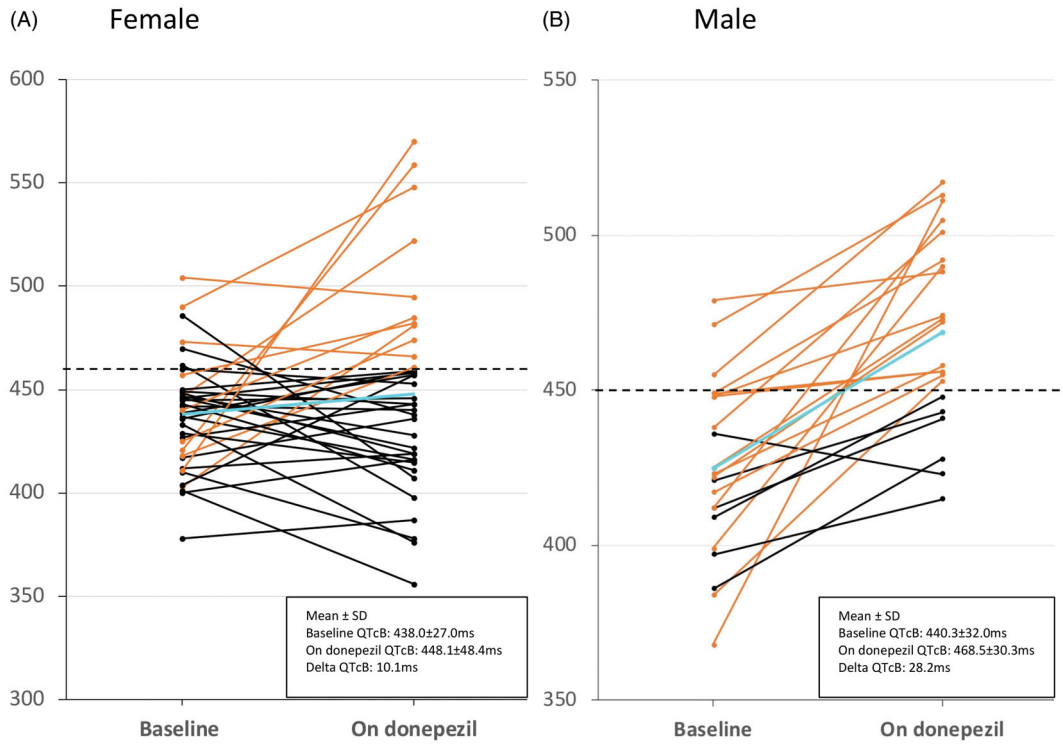

Figure 2. Difference in QTcB between genders – (A) female and (B) male – at baseline and after prolonged use of donepezil therapy. The dotted lines denote the threshold for prolonged QTcB, 460 ms for female and 450ms for male. 11 female patients had a QTc $\geq$ 460 ms and 16 male patients had a QTc $\geq$ 450 ms on donepezil therapy; of which 5 female patients and 11 male patients had normal QTc intervals prior to starting donepezil treatment.

Table 3. Comparison of how ECG parameters are affected by gender while on treatment with donepezil.

	Male			Female			
ECG parameters	Baseline	On donepezil	Δ	Baseline	On donepezil	Δ	*p*-Value
HR (beats/min)	75.1 ± 15.6	76.4 ± 20.4	1.3	76.8 ± 12.7	75.0 ± 15.0	1.8	0.638
PR interval (ms)	178.1 ± 21.1	188.1 ± 30.9	10.0	176.5 ± 32.7	185.1 ± 36.2	8.6	0.294
QRS duration (ms)	107.5 ± 22.6	107.0 ± 23.3	0.5	98.3 ± 18.3	103.3 ± 21.9	5.0	0.106
QT interval (ms)	398.4 ± 40.2	424.2 ± 51.0	25.8	390.3 ± 32.9	404.6 ± 39.2	14.3	0.060
QTcBazett (ms)	440.3 ± 32.0	468.5 ± 30.3	28.2	438.0 ± 27.0	448.1 ± 48.4	10.1	0.023*
QTcFred (ms)	425.4 ± 28.5	451.5 ± 30.6	26.1	421.1 ± 25.0	432.6 ± 39.5	11.5	0.049*
QTcFram (ms)	424.4 ± 27.0	449.5 ± 30.4	25.1	421.0 ± 23.5	429.8 ± 36.5	8.8	0.021*
QTcHodges (ms)	425.0 ± 28.3	452.9 ± 26.6	27.9	419.7 ± 23.4	431.0 ± 36.7	11.3	0.015*

Table 4. Comparison of how ECG parameters are affected by the dose of donepezil.

	5 mg			10 mg			
ECG parameters	Baseline	On donepezil	Δ	Baseline	On donepezil	Δ	*p*-Value
HR (beats/min)	79.2 ± 14.2	75.0 ± 19.7	4.2	73.9 ± 13.1	75.9 ± 15.1	2.0	0.074
PR interval (ms)	178.6 ± 31.9	186.9 ± 34.8	8.3	175.9 ± 27.1	185.6 ± 34.4	9.7	0.819
QRS duration (ms)	98.9 ± 20.6	100.6 ± 21.0	1.7	103.7 ± 20.1	107.6 ± 23.0	3.9	0.452
QT interval (ms)	382.2 ± 36.0	411.7 ± 45.3	29.5	401.5 ± 33.6	412.0 ± 44.8	10.5	0.158
QTcBazett (ms)	435.0 ± 26.5	451.8 ± 43.0	16.8	441.7 ± 30.3	458.6 ± 44.1	16.9	0.565
QTcFred (ms)	416.1 ± 25.0	437.3 ± 34.4	21.2	427.6 ± 26.4	441.3 ± 39.8	13.7	0.824
QTcFram (ms)	416.1 ± 23.0	433.8 ± 32.2	17.7	426.7 ± 25.3	439.5 ± 37.9	12.8	0.988
QTcHodges (ms)	415.9 ± 23.8	438.0 ± 32.4	22.1	425.9 ± 25.7	440.0 ± 36.8	14.1	0.736

Table 5. Effects of the duration of donepezil therapy on changes in ECG parameters.

	Duration (years)					
ECG parameters	1	2	3	4	5	*p*-Value
Δ Heart Rate (bpm)	−4.3 ± 16.4	15.6 ± 23.4	−1.3 ± 15.1	24.0 ± 34.7	−10.2 ± 21.3	0.159
Δ PR Interval (ms)	6.53 ± 31.0	49.0 ± 59.4	13.1 ± 27.2	−3.0 ± 24.9	17.3 ± 30.8	0.595
Δ QRS Interval (ms)	−1.6 ± 12.4	6.5 ± 15.9	10.5 ± 14.9	0.4 ± 5.7	5.0 ± 5.0	0.302
Δ QT Interval (ms)	27.6 ± 46.1	5.0 ± 61.8	12.3 ± 31.4	−50.6 ± 68.8	64.3 ± 24.2	0.012*
Δ QTcB Interval (ms)	14.5 ± 58.9	51.4 ± 34.6	8.1 ± 35.6	9.2 ± 21.8	40.0 ± 61.0	0.201
Δ QTcFred Interval (ms)	18.8 ± 50.2	34.6 ± 35.9	9.3 ± 23.4	−12.6 ± 15.9	45.3 ± 39.3	0.051
Δ QTcFram Interval (ms)	16.4 ± 45.9	28.6 ± 35.4	6.7 ± 24.6	−13.6 ± 17.9	46.8 ± 33.8	0.052
Δ QTcH Interval (ms)	20.2 ± 47.6	32.6 ± 32.4	10.0 ± 19.1	−8.4 ± 16.3	46.7 ± 36.9	0.080

The point-biserial correlation found that concomitant use of rate-limiting calcium channel blockers was associated with significant PR prolongation (r_{pb} = 0.314, p = 0.030), while beta-blockers in combination with donepezil were found to significantly reduce the HR (r_{pb} = 0.256, p = 0.050). All corrected QT intervals whilst on donepezil were significantly prolonged by the use of tricyclic antidepressants (QTcB: r_{pb} = 0.344, p = 0.008, QTcFred: r_{pb} = 0.382, p = 0.003, QTcFram: r_{pb} = 0.379, p = 0.003, QTcH: r_{pb} = 0.352, p = 0.006). There was no significant correlation between cardiac comorbidities and changes in ECG parameters.

Discussion

Our study clearly demonstrated that the use of donepezil for more than a year is associated with significantly prolonged PR, QRS and QT intervals. Male patients had a significantly greater prolongation of their QTc interval compared to females, and concomitant use of tricyclic antidepressants significantly increased the risk of QT interval prolongation, while no dose or treatment duration related differences were found.

The QT interval is an electrocardiographic representation of the time taken for depolarisation and repolarisation of the ventricles. Measuring the QT interval and understanding its significance can be difficult since it is influenced by multiple factors including heart rate and disease-associated ECG changes. The use of corrected QT intervals is more useful in the clinical setting, but the applicability of each formula remains debatable because of over or under correction at extremes of heart rate [15].

A prolonged QT interval has been used as a surrogate marker for predicting the subsequent risk of ventricular arrhythmias. However, its significance varies between individuals and is affected by multiple factors including medications, underlying heart rhythm, asystolic pauses and genetics. Furthermore, the relationship between the QT interval and the risk of TdP is non-linear. It should, therefore, be interpreted with caution and not in isolation, with consideration of the aforementioned confounding patient characteristics [15]. Despite the above caveats, the risk of ventricular arrhythmias and increased cardiac morbidity and mortality in the presence of a prolonged QT interval are well established. Although its consequences may be unpredictable, QT prolongation does frequently lead to adverse outcomes [1,2,15,16].

Our study confirmed that the use of donepezil for a duration of at least 1 year was associated with a significant increase in the QT intervals. Donepezil enhances the cholinergic function of the brain while also causing undesired systemic cholinergic side-effects, with gastrointestinal disturbances such as nausea, vomiting and diarrhoea being the most common. The adverse effects on the heart are unpredictable. The heart is an organ rich in cholinesterase enzymes (ChE). Inhibition of these enzymes leads to increased acetylcholine, which deactivates the membrane-bound voltage-gated calcium channels. Phase two of the cardiac action potential is also known as the plateau phase, which is defined by the membrane potential remaining constant due to the concurrent influx of calcium ions and efflux of potassium ions. Donepezil may delay this phase by increasing cardiomyocyte acetylcholine concentrations, hence deactivating the voltage-gated calcium channels, while simultaneously causing direct inhibition of delayed rectifier potassium channels. This results in QT interval prolongation and subsequent increased risk of ventricular arrhythmias [4,16–18].

Most studies to date have evaluated ECG changes in patients taking donepezil for up to four months. Significant prolongation of the PR interval is a common finding, with no associated change in the QT interval [8,9,19]. We postulate that a longer duration of donepezil therapy may be necessary to demonstrate a significant QT interval prolongation, as found in our study. This finding raises concerns since the adverse effects of QT prolongation and subsequent TdP have only been previously identified in case studies, resulting in the risk being underestimated by clinicians [1,2]. Furthermore, it is known that the QT interval increases with age and this may exacerbate the risk of ventricular arrhythmias in an elderly population [19]. This risk may be further amplified by polypharmacy, electrolyte derangements and concurrent cardiac comorbidities or conduction disorders.

Female gender has been reported in the literature to be an independent risk factor for QT prolongation, due to their greater baseline QT interval and oestrogen mediated gender differences in the expression of cardiac delayed rectifier potassium channels [20]. Interestingly our study demonstrated that male patients experienced a significantly greater prolongation of their corrected QT interval compared to females. While females tend to show a longer QT interval at younger ages, gender differences decrease with age due to males having a more pronounced age-related increase in their QT interval [20]. This is observed within our cohort with both elderly males and females having a similar QT interval prior to commencing donepezil therapy (Table 3).

A possible explanation is that male patients have a greater sensitivity to the increase in cardiac acetylcholine concentrations caused by donepezil, which results in a greater prolongation of the QT interval [4]. Naturally, there is an increase in vagal tone and acetylcholine release when patients undergo a carotid sinus massage. Male patients exhibit increased sensitivity to carotid sinus massage and have an increased prevalence of carotid sinus disease, which could theoretically be due to an underlying oversensitivity to acetylcholine [21–23]. Further evidence of this is that male patients are less responsive to muscarinic receptor antagonists such as atropine [24]. This mechanism may explain why male patients exhibit a greater prolongation of the corrected QT interval compared to females, but our results would require confirmation in a larger study.

Another manifestation of the increase in vagal tone caused by donepezil is prolonged PR and QRS intervals, as seen in our study population [25]. Underlying cardiac conduction disease and the concomitant use of commonly prescribed negatively chronotropic medications could exacerbate this further. We demonstrated that concurrent

use of rate-limiting calcium channel blockers and beta-blockers in those on donepezil therapy was associated with significant PR prolongation and a reduction in heart rate respectively. One patient in our study population developed symptomatic bradycardia requiring admission. Cessation of donepezil therapy reversed the bradycardia and resulted in normalisation of heart rate. Previous studies have similarly reported hospitalisation for donepezil associated bradycardia, with a proportion of patients developing syncope and irreversible heart block requiring PPM implantation. Careful consideration must be taken when initiating donepezil in patients already prescribed negatively chronotropic medications [5,6,26].

Our study did not demonstrate a correlation between the duration of donepezil therapy and further QT prolongation (Table 5), but its prolonged use theoretically carries an increased risk of ventricular arrhythmias. The neurocognitive benefits of donepezil are most pronounced in the initial months of treatment and continue for up to two years. Following two years of treatment, the overall benefit of donepezil remains unclear [27]. We noted that several of our patients had extended donepezil therapy for longer than the beneficial 2-year treatment period. We, therefore, suggest that such patients should be reassessed at this point and termination of treatment with donepezil should be considered if the risks of adverse events are deemed to outweigh any clear neurocognitive benefit.

Limitation

Our study was conducted in a single centre acute hospital setting with a predominantly Caucasian population, which may limit the generalizability of our results to other hospitals or community settings. We also recognise that ECG recordings took place during acute hospital admissions and the parameters measured may have been affected by confounding factors such as a concurrent acute illness e.g. infection. As all ECGs were compared in yearly intervals, we cannot completely conclude that the changes in ECG intervals observed are secondary to donepezil alone. We also acknowledge there may be a degree of human error in the manual analysis of rhythm and QT interval measurement.

Our results were based on resting 12-lead ECGs before and during donepezil treatment, and despite providing valuable information they are only a snapshot of the patient's cardiac conduction, and may not be representative of their predominant rhythm. A Holter monitor would provide a more reliable assessment of cardiac conduction abnormalities and would also capture intermittent arrhythmias. Therefore a larger prospective study with prolonged cardiac monitoring and longer follow-up period would be of interest.

Conclusion

The results demonstrate that donepezil therapy is associated with a significant prolongation in the PR and QT intervals. Therefore, we urge clinicians to exercise caution and pharmacovigilance when prescribing donepezil, particularly in patients with pre-existing cardiac comorbidities or among those already prescribed medications known to cause QT prolongation such as tricyclic antidepressants. We suggest a resting 12-lead ECG should take place before and after donepezil initiation and where there is suspicion of QT prolongation, utilisation of a QT nomogram can reliably assess arrhythmogenic risk.

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Author contributions

All authors contributed to the design and implementation of the research, to the analysis of the results and the writing of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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