The impact of risperidone on QTc interval in people with dementia

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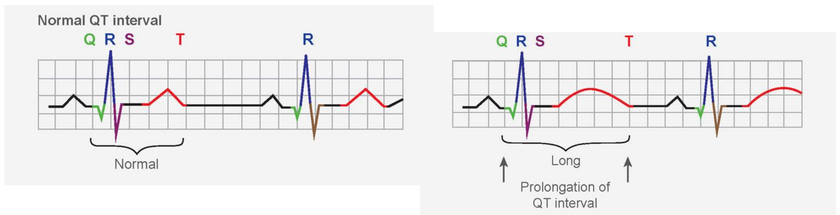
Background

- Antipsychotic drug treatment can cause prolongation of the corrected QT (QTc) interval, which is associated with potentially fatal arrhythmias



- People with dementia have heightened sensitivity to antipsychotic medication and associated side-effects
- People with dementia may have cardiac comorbidities and polypharmacy
- Little is known however about changes in the QTc associated with antipsychotic treatment in this population

Aims

- To describe the QTc interval in a sample of people with dementia and the changes associated with risperidone treatment

Hypothesis

- Risperidone doses above 1mg will be associated with emergent QTc prolongation (>500ms)

Methods

Source of data:

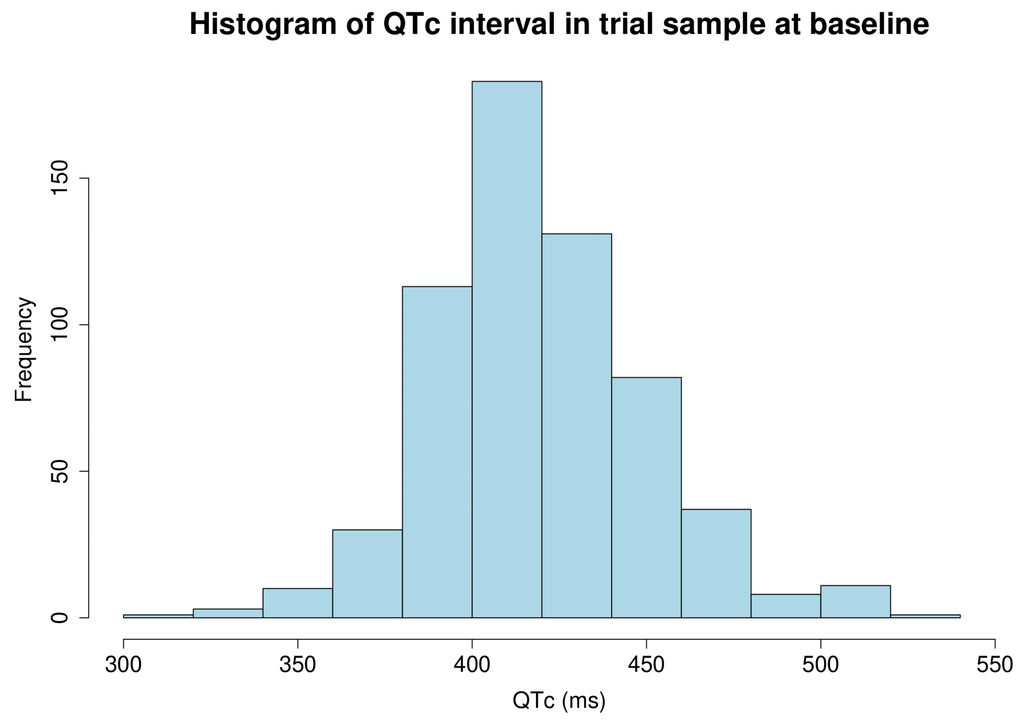
- Data from a randomized, double blind, placebo-controlled trial, 'A Study of the Effectiveness and Safety of Risperidone Versus Placebo in the Treatment of Behavioral Disturbances in Patients With Dementia' (NCT00253123) was accessed via the Yale University Open Data Access Project (YODA) platform
- Participants had diagnoses of Alzheimer's, Vascular or Mixed dementia and significant behavioural or psychotic symptoms
- In the trial 626 participants were allocated to either placebo group or risperidone treatment, which had three arms (0.5mg, 1mg or 2mg per day)
- Trial criteria excluded subjects with:
  - Unstable medical illness e.g. unstable angina, poorly controlled diabetes, labile hypertension
  - Medical conditions which contraindicated use of neuroleptics
  - Clinically significant laboratory or ECG findings
- Trial period was twelve weeks and ECGs were undertaken at baseline and weeks six and twelve

Analysis

- Data extracted included age, gender, race, heart rate, QTc interval, pharmacokinetic data and adverse events
- Participants without ECG data or with extreme QTc measurements were excluded (i.e. QTc <300ms or >600ms due to suspected measurement or data entry error)
- Different authors / groups have suggested different means to calculate QTc and different thresholds for QTc prolongation in males and females. The proportion of males with a QTc >440ms and >460ms and females with QTc >470 were described
- QTc interval at baseline (pre-treatment) and week six of risperidone treatment were compared in the treatment and placebo groups
- Treatment emergent QTc prolongation (QTc >500ms) was compared between groups (those with QTc prolongation at baseline were excluded)
- Frequency of cardiac adverse events between groups was described as was mean plasma concentration of the risperidone and active metabolite 9-OH risperidone and the active moiety (risperidone and 9-OH risperidone combined)
- All analyses were undertaken in R

Results

- At baseline 610 trial participants provided ECG data. Mean age was 82 years, 68% were female and 88% Caucasian
- At baseline 24.9% of males had a QTc >440, 11.7% of males had a QTc >460, 4.4% of females had a QTc >470 and 2.0% of sample had a QTc >500



- At week six 360 risperidone-treated participants remained and emergent QTc prolongation was observed in 2 participants (0.56%) compared to none in the placebo group.
- Plasma concentration of risperidone and 9-OH risperidone in the participants with emergent QTc prolongation in the 0.5MG group was and 0.48ng/ml and 4.7ng/ml and in the 1MG group 4.0ng/ml and 14.0ng/ml, respectively
- At week six, there were 10.1 cardiac adverse events per 100 participants in the placebo group and 12.2 cardiac adverse events per 100 participants in the risperidone treated group.
- In the risperidone group there were 11.5 cardiac adverse events per 100 participants in those with a normal QTc at baseline and 21.2 adverse cardiac events per 100 participants in those with a prolonged QTc at baseline (QTC >460 for males and >470 for females)
- The most frequent cardiac adverse event codes in the risperidone treated groups were: hypotension (17), ECG abnormal (5), hypertension (5), cardiac failure (4), AV block (3), bradycardia (3), cardiac arrest (3), tachycardia (3)

Table 1			Placebo	Risperidone 0.5mg	Risperidone 1mg	Risperidone 2mg
Baseline	Mean heart rate (bpm)		75	75	74	74
	Mean QTc (SD)		421 (29.0)	423.6 (31.3)	422.6 (32.2)	417.3 (30.0)
	(range)		(350 to 523)	(332 to 520)	(320 to 520)	(340 to 516)
Week 6	Mean heart rate (bpm)		77	75	76	77
	Mean QTc (SD)		420.0 (29.8)	425.0 (33.7)	425.1 (34.1)	413.6 (27.8)
	(range)		(320 to 495)	(340 to 541)	(340 to 533)	(330 to 498)
	Treatment emergent QTc prolongation (QTc >500ms)		0 (0%)	1 (0.8%)	1 (0.9%)	0 (0%)
	Frequency of adverse cardiac events (per 100 participants) in participants with: a) Normal baseline QTc b) Prolonged baseline QTc		a) 9.9 b) 12.5	a) 9.3 b) 0.0	a) 11.2 b) 54.5	a) 13.5 b) 12.5
	Mean concentration (ng/ml)	Risperidone	0	1.5	4.1	5.7
		9-OH Risperidone	0	4.9	11.3	20.5
		Active Moiety	0	6.3	15.4	26.2

Limitations

- Trial documentation does not state how QTc calculated (e.g. manually or automatic) or what formula used
- Lower than expected incidence of treatment emergent QTc prolongation, and it was not possible to determine the relationship with dose or plasma concentrations of risperidone and 9-OH-risperidone
- ECGs were only performed at baseline, Week 6 and 12 and QTc may fluctuate between readings

Conclusion

- At baseline QTc prolongation was not uncommon
- Treatment emergent QTc prolongation was infrequent after starting Risperidone
- Overall risperidone-treated participants who had a prolonged QTc at baseline experienced greater cardiac adverse events than those with a normal QTc but this relationship is unclear

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