QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients

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Summary

Background Sudden unexplained death in psychiatric patients may be due to drug-induced arrhythmia, of which lengthening of the rate-corrected QT interval (QTc) on the electrocardiogram is a predictive marker. We estimated the point prevalence of QTc lengthening in psychiatric patients and the effects of various psychotropic drugs.

Methods Electrocardiograms were obtained from 101 healthy reference individuals and 495 psychiatric patients in various inpatient and community settings and were analysed with a previously validated digitiser technique. Patients with and without QTc lengthening, QTc dispersion, and T-wave abnormality were compared by logistic regression to calculate odds ratios for predictive variables.

Findings Abnormal QTc was defined from the healthy reference group as more than 456 ms and was present in 8% (40 of 495) of patients. Age over 65 years (odds ratio 3·0 [95% CI 1·1–8·3]), use of tricyclic antidepressants (4·4 [1·6–12·1]), thioridazine (5·4 [2·0–13·7]), and droperidol (6·7 [1·8–24·8]) were robust predictors of QTc lengthening, as was antipsychotic dose (high dose 5·3 [1·2–24·4]; very high dose 8·2 [1·5–43·6]). Abnormal QT dispersion or T-wave abnormalities were not significantly associated with antipsychotic treatment, but were associated with lithium therapy.

Interpretation Antipsychotic drugs cause QTc lengthening in a dose-related manner. Risks are substantially higher for thioridazine and droperidol. These drugs may therefore confer an increased risk of drug-induced arrhythmia.

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Introduction

Cardiovascular mortality in psychiatric patients is high.[1] Reports of sudden unexplained death in those taking antipsychotic drugs[2,3] have raised the concern that part of this excess may be due to drug-induced arrhythmias, since many of these drugs have cardiac electrophysiological effects similar to those of quinidine.[2] The polymorphic ventricular arrhythmia known as torsade de pointes has been recorded in patients with psychotropic drug overdose[4] and provides a plausible mechanism for sudden unexplained death associated with drug therapy.[5]

Several psychotropic drugs are associated with lengthening of the rate-corrected QT interval (QTc) on the electrocardiogram,[2] which often precedes torsade.[6] There is no direct evidence linking the extent of drug-induced QTc lengthening with the risk of torsade or sudden death. However, QTc-interval lengthening is a predictor of sudden death in patients with cardiac disease[7] and the extent of drug-induced QTc-interval lengthening is thought to be an important marker of arrhythmia risk by drug regulatory authorities (see website: www.emeasearch.is.eudra.org/humandocs/PDFs/SWP/098696en.pdf). Risk of arrhythmia with drugs that lengthen ventricular repolarisation may also be indicated by the dispersion of repolarisation, which can be assessed by measuring QT dispersion.[8] Abnormal repolarisation may also cause non-specific abnormalities of the T wave, although there is no direct evidence to link such changes with arrhythmia.

Clinical guidelines advise caution in the use of high-dose antipsychotic therapy with special reference to the risk of sudden death, as well as regular monitoring of the QTc interval,[9] but evidence for this change in practice is small. Only one study has systematically examined QTc-interval abnormalities in psychiatric patients, and found an increased prevalence of abnormalities in a schizophrenic population compared with controls, and an association with high-dose antipsychotic therapy.[10] This sample was not large enough to detect differences between drugs, and no relation was found between drug dosage and QTc dispersion.

Therapeutics in mental illness is moving away from high-dose antipsychotic drugs to lower doses and newer drugs; both these strategies have proven benefits, but neither are free of cardiotoxic effects.[2,11] If lengthening of the QTc interval is to be adopted as a marker of arrhythmogenic risk in psychiatric patients, its relation with dose should be clarified and its association with all antipsychotic drugs, antidepressants, and other classes of psychotropics should also be examined.

We measured the frequency of QTc lengthening in a large heterogeneous population of psychiatric patients, and assessed whether QTc lengthening was associated with individual antipsychotic drugs, antipsychotic drug dose, and other risk factors.

Methods

Participants

The study was carried out in six districts in north-east England with the approval of the North Tees Research Ethics Committee. All participants gave their informed written consent. All mental health facilities (including inpatient, day hospital, and outpatient departments) in each district were visited between March, 1994, and July, 1996. All patients aged 18–74 years present on study days were invited to participate. Exclusion criteria were failure to obtain informed written consent or change in drug therapy within the previous 2 weeks (3 months for depot preparations). The use of psychotropic drugs was not a requirement for inclusion in the study. Patients with atrial fibrillation or bundle-branch block were excluded from the analysis. Patients with pre-existing cardiac disease were not excluded because they may be a group at particular risk of drug-induced repolarisation abnormalities or arrhythmia.

101 healthy volunteers were recruited from hospital staff. We used this group to establish values for the upper limits of normal for measurements of QTc interval and dispersion. Inclusion criteria were age between 18 and 74 years and an absence of overt cardiovascular disease. These participants were studied by the same methods as for patients.

Data collection and analysis

A 12-lead electrocardiogram was taken at 50 mm/s with a high quality portable three-channel electrocardiography machine (Physiocontrol Mortara Lifenet STM, Physiocontrol, Basingstoke, UK). Age, sex, smoking and alcohol history, cardiovascular history (including arrhythmia, ischaemic or valvular heart disease, or hypertension), and other medical history were recorded. The clinical psychiatric diagnosis was noted as described in the patient's medical records. A note was made of all drug therapy taken within the previous 6 months. This included use of over-the-counter preparations and depot preparations. For analysis, drug use was defined as prescription or use for more than 1 week for oral medication and for more than 2 months for depot preparations. Antipsychotic doses were converted into chlorpromazine equivalents.[12–14] Doses were classified as standard (0–1000 mg chlorpromazine equivalents per day), high (1001–2000 mg chlorpromazine equivalents per day), and very high (>2000 mg chlorpromazine equivalents per day).

Automated QTc-interval measurements were generated by the machine by a computer algorithm. Electrocardiograms were coded and then analysed with a previously validated method[15] by one of the investigators (JGR), who was unaware of the origin of the electrocardiograms. A digitiser (CalComp 9000, CalComp, Phoenix AZ, USA) was used to analyse three representative complexes for each lead of the standard 12-lead electrocardiogram to obtain the RR, PR, QRS, and QT intervals (in ms). The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined as a return to the T-P baseline, or in the presence of U waves, the T-U nadir. When the end of the T wave could not be reliably identified the lead was excluded from analysis. Mean QT intervals for the 12 leads were corrected for heart rate by Bazett's formula ($QTc=QT/\sqrt{RR}$ interval) to obtain the QTc mean. Coefficients of variation within and between observers were measured as 0·7% and 0·8% for QT interval by use of electrocardiograms from healthy volunteers.[16] Unadjusted QTc dispersion was calculated as the difference between the maximum and minimum QTc value on the 12-lead electrocardiogram. No correction was made for the numbers of leads analysed. T-wave abnormalities were recorded by a single observer (SHLT), who was unaware of the patient's clinical or treatment status. Abnormalities were defined as present if the T wave was inverted, flattened, or bifid, unless the T-wave axis was in the same direction as that of the QRS complex.

A threshold figure for QTc lengthening was defined as 2 SD above the mean value seen in the healthy reference group. All electrocardiograms showing QTc lengthening on initial analysis and all electrocardiograms identified by the automated machine

Risk factor	Total number exposed	Exposed cases (QTc >456 ms)	Missing data	Unadjusted odds ratio (95% CI)	p
Demography					
Age >65 years	52	10	8	3·2 (1·5–7·0)	0·005
Sex (male)	298	17	. .	0·46 (0·24–0·88)	0·03
Heart rate >99 beats/min	62	6	. .	1·3 (0·51–3·1)	0·81
Smoking (ever)	360	28	15	0·84 (0·40–1·7)	0·77
Cardiovascular disease	71	8	1	1·5 (0·68–3·5)	0·41
Psychiatric disorder					
Schizophrenia	217	15	3	0·78 (0·40–1·5)	0·57
Mood disorder	219	23	3	1·9 (0·97–3·7)	0·08
Neurotic disorder	30	2	3	0·82 (0·19–3·6)	1·00
Personality disorder	31	1	3	0·37 (0·05–2·8)	0·51
Organic disorder	18	1	3	0·67 (0·09–5·2)	1·00
Eating disorder	6	1	3	2·3 (0·26–20·7)	0·97
Substance misuse	36	1	3	0·31 (0·04–2·3)	0·38
Alcohol excess (current)	21	1	1	0·56 (0·07–4·3)	0·87
Drug therapy					
Droperidol	37	6	4	2·5 (0·96–6·3)	0·10
Thioridazine	64	15	3	4·9 (2·4–10·0)	<0·001
Chlorpromazine	61	4	3	0·77 (0·26–2·2)	0·82
Haloperidol	36	5	4	2·0 (0·73–5·5)	0·15
Flupenthixol	58	2	8	0·38 (0·09–1·6)	0·27
Risperidone	35	4	5	1·5 (0·52–4·6)	0·51
Trifluoperazone	20	1	11	0·62 (0·08–4·7)	0·95
Fluphenazine	34	4	11	1·6 (0·54–4·9)	0·58
Sulpiride	26	2	10	0·95 (0·22–4·2)	1·00
Clozapine	27	2	4	0·92 (0·21–4·0)	1·00
Procyclidine	121	11	3	1·2 (0·57–2·4)	0·80
Tricyclics	97	13	6	2·3 (1·1–4·6)	0·04
Serotonin-specific reuptake inhibitors	92	8	8	1·1 (0·50–2·5)	0·95
Monoamine oxidase inhibitors	8	2	9	4·0 (0·77–20·4)	0·26
Benzodiazepines	94	9	5	1·3 (0·59–2·8)	0·67
β-blockers	21	1	3	0·55 (0·07–4·2)	0·87
Lithium	87	7	4	1·0 (0·43–2·4)	1·00
Zopiclone	38	2	13	0·63 (0·15–2·7)	0·76
Diuretics	15	3	3	3·0 (0·80–11·0)	0·22
Carbamazepine	56	1	1	0·19 (0·03–1·4)	0·12

Table 1: **Risk factors for QTc lengthening**

analysis alone as showing lengthened QTc (greater than a standard value of 440 ms) were reanalysed twice and only included in the QTc-lengthening group if the mean of the three readings was above or equal to the threshold value. The overall point prevalence of QTc-interval lengthening was calculated in psychiatric patients and in subgroups including those with schizophrenia and affective disorder. A similar analysis was used to calculate a cut-off value for abnormal QTc dispersion and its point prevalence, and the prevalence of T-wave abnormalities in patients was also calculated.

Statistical analysis

Lengthened QTc interval was defined as the outcome variable for a logistic regression analysis. The statistical software package SPSS (version 8) was used. Cross-tabulations with QTc lengthening were done for a range of possible predictive variables including specific drug therapy, age, sex, cardiovascular disease, alcohol consumption, and smoking. Adjusted odds ratios were then obtained by logistic regression. We used backward elimination and forward selection stepwise regression to establish the important explanatory variables, for which adjusted odds ratios were calculated. Variables were retained in the model if their significance level was less than 10%.

Results

495 psychiatric patients were enrolled in the study (297 [60%] men, 198 [40%] women; mean age 45 years, range 18–74). 271 participants were from inpatient wards (55%), 86 from outpatient clinics (17%), 111 from day units (22%), and 27 from nursing homes (5%). 71 (14%) patients had a history of cardiovascular disease. Table 1 shows details of patients' diagnoses. 339 patients were taking antipsychotic drugs (dose range 25–4788 mg chlorpromazine equivalents/day). Of these, 41 (12%) were taking high doses and 18 (5%) were taking very high doses. 34 (7%) patients were on no medication.

Electrocardiograms were also studied from 101 healthy volunteers (41 men, 60 women; mean age 35 years, range 20–53). From this sample, abnormally lengthened QTc intervals were defined as greater than 456 ms. Abnormal values were present in 40 (8%) of 495 patients overall, 23 (8%) of 286 who were taking antipsychotic drugs alone, five (11%) of 44 on tricyclic antidepressants alone, and eight (15%) of 53 who were taking combinations of antipsychotics and tricyclic antidepressants.

Table 2 shows the results of the assessment of potential risk factors for QTc lengthening in psychiatric patients. Four variables remained significant predictors after adjustment for potential confounding influences: age over 65 years, and use of tricyclic antidepressants, droperidol, or thioridazine. These risk factors were confirmed by forward (data not shown) and backward stepwise regression (table 2). Lengthened QTc was not significantly associated with any specific psychiatric disorder, alcohol misuse, cardiovascular disease, or any other drug therapy. Because non-significant variables were removed in stepwise regression, these four predictive variables showed stable and significant adjusted odds ratios.

We assessed the effect of total antipsychotic dose by a second logistic regression analysis compared with non-users. Increasing antipsychotic dose was associated with increased odds ratios for QTc lengthening (table 3). Backwards stepwise regression analysis indicated that age over 65 years, tricyclic antidepressants, and female sex were also significantly associated with QTc lengthening.

No other antipsychotic drug showed a significant association with lengthened QTc, so we assessed whether the association with antipsychotic dose was the result of the robust associations with thioridazine and droperidol by use of a further logistic regression analysis on the subgroup of patients not taking these two drugs. The dose relation was preserved (high dose 4·0 [0·43–36·9], p=0·22; very high dose 19·8 [2·0–196·6], p=0·01).

Risk factor	AOR (95% CI) from full model	p	AOR (95% CI) via backwards stepwise regression*	p
Demography				
Age >65 years	3·0 (1·1–8·3)	0·04	2·7 (1·1–6·5)	0·03
Sex (male)	0·69 (0·29–1·6)	0·39		
Heart rate >99 beats/min	1·2 (0·37–4·0)	0·75		
Smoking (ever)	0·88 (0·35–2·2)	0·78		
Cardiovascular disease	0·62 (0·17–2·3)	0·48		
Psychiatric disorder				
Schizophrenia	0·62 (0·12–3·2)	0·57		
Mood disorder	0·93 (0·21–4·2)	0·93		
Neurotic disorder	0·52 (0·08–3·5)	0·50		
Personality disorder	0·38 (0·03–4·7)	0·45		
Organic disorder	0·73 (0·05–11·5)	0·82		
Eating disorder	2·1 (0·11–40·9)	0·61		
Substance misuse	0·51 (0·05–4·9)	0·57		
Alcohol excess (current)	0·99 (0·09–10·1)	0·99		
Drug therapy				
Droperidol 0·004	6·7 (1·8–24·8)	0·004	4·5 (1·6–12·6)	
Thioridazine <0·001	5·3 (2·0–13·7)	<0·001	4·9 (2·3–10·6)	
Chlorpromazine	1·4 (0·37–5·3)	0·62		
Haloperidol	3·6 (0·96–13·6)	0·06		
Flupenthixol	0·61 (0·11–3·2)	0·56		
Risperidone	1·8 (0·45–6·9)	0·42		
Trifluoperazone	1·18 (0·12–11·7)	0·89		
Fluphenazine	3·4 (0·76–15·3)	0·11		
Sulpiride	3·65 (0·61–21·7)	0·16		
Clozapine	2·5 (0·38–16·6)	0·34		
Procyclidine	1·5 (0·58–4·1)	0·38		
Tricyclics	4·4 (1·6–12·1)	0·004	2·8 (1·3–6·2)	0·01
Serotonin-specific reuptake inhibitors	1·7 (0·56–5·4)	0·33		
Monoamine oxidase inhibitors	5·1 (0·49–53·5)	0·17		
Benzodiazepines	1·0 (0·36–2·7)	0·99		
β-blockers	0·46 (0·04–5·2)	0·53		
Lithium	0·73 (0·25–2·1)	0·57		
Zopiclone	0·37 (0·07–2·1)	0·26		
Diuretics	3·0 (0·39–22·9)	0·29		
Carbamazepine	0·18 (0·02–1·6)	0·13		

AOR=adjusted odds ratio. *For significant values.

Table 2: **Risk factors for QTc lengthening by logistic regression and backwards stepwise regression**

With respect to drugs already identified in the initial analysis, no patient was taking high-dose or very-high-dose thioridazine, so to assess dose relations for this drug, high dose was defined as more than 600 mg/day. Using logistic regression analysis with the three dose levels for all antipsychotic drugs as additional variables, we found a relation only for high-dose depot fluphenazine (11·3 [1·9–69·3], p=0·009) and high-dose thioridazine (22·5 [2·8–181·1], p=0·003). Of the four patients in the study taking at least 600 mg thioridazine, two had QTc lengthening. No significant dose association was found for droperidol.

Specific interactions between the predictive variables were compared by cross-tabulation. Numbers were too small to allow investigation in the full regression model, although interaction between age and use of thioridazine, droperidol, or tricyclic antidepressants was not significant. Only three of ten elderly patients who were also on thioridazine had QTc lengthening. Thioridazine and age over 65 years are independent predictors of QTc lengthening; thus, the thioridazine effect in this study is unlikely to be a consequence of preferential use of thioridazine in elderly patients.

Risk factor	Total number exposed	Exposed cases (QTc >456 ms)	Missing data	AOR (95% CI) from full model	p	AOR (95% CI) via backwards stepwise regression*	p
Demography							
Age >65 years	52	10	8	3·6 (1·4–9·4)	0·01	4·1 (1·7–9·9)	0·002
Sex (male)	298	17	. .	0·59 (0·27–1·3)	0·21	0·48 (0·24–0·96)	0·039
Drug therapy							
Tricyclic	97	13	6	3·0 (1·2–7·7)	0·02	2·6 (1·2–5·6)	0·012
Antipsychotic							
Low dose	280	20	19	1·4 (0·53–3·6)	0·52	. .	. .
High dose	41	5	9	5·4 (1·1–24·4)	0·03	3·4 (1·2–10·1)	0·026
Very high dose	18	4	9	8·2 (1·5–43·6)	0·01	5·6 (1·6–19·3)	0·007

AOR=adjusted odds ratio. *Only significant odds ratios are shown.

Table 3: **Antipsychotic dose and risk of QTc lengthening**

By use of the same technique for calculating a cut-off value as for QTc lengthening, only eight psychiatric patients were confirmed as having abnormal QT dispersion (>152 ms), thus making logistic-regression analysis impossible. We therefore used a revised cut-off value of 100 ms,[15] which allowed us to identify 51 patients with QT dispersion longer than 100 ms. By backward stepwise regression, the significant predictive variables were age over 65 years (odds ratio 2·7 [95% CI 1·2–6·1], p=0·013) and lithium use (2·9 [1·5–5·5], p=0·001). For T-wave abnormality, backward regression showed predictive factors to be age over 65 years (2·2 [1·1–4·4], p=0·027), female sex (male sex 0·47 [0·29–0·76], p=0·002), cardiovascular disease (2·3 [1·2–4·2], p=0·011), heart rate more than 99 beats/min (3·0 [1·6–5·6], p<0·001), and lithium use (1·9 [1·1–3·4], p=0·032). For both outcome variables, forward stepwise regression analyses showed similar results. No effect was found for antipsychotic use or other psychiatric disorders.

Discussion

Our study shows an association between QTc lengthening and increasing antipsychotic dose. Use of tricyclic antidepressants, droperidol, and thioridazine were robust predictors of QTc lengthening in a logistic regression model, but there was no relation with any other drugs or risk factors apart from age. Differences between drugs are as important as the link with antipsychotic dose and are not explained by confounding for age or differential prescribing of some drugs in higher doses. Lithium was the only drug therapy associated with QT dispersion and non-specific T-wave abnormality, but no significant association was found between lithium therapy and QTc lengthening.

One limitation of studies of QTc lengthening is the variation in cut-off values for abnormality—from 420 ms to 470 ms. We sought to establish a threshold via a reference group and confirm an abnormal QTc group via repeated analysis. We have also shown reliability between and within observers. Our prevalence of QTc lengthening in the patient group was 8%. This is lower than the value of 23% found previously[10] and may be explained by the lower cut-off value (420 ms) used in that study and by differing characteristics of patients.

Several tricyclic antidepressants have previously been linked with QTc lengthening[17] and ventricular arrhythmia, but risks are usually only perceived in overdose, or in those with pre-existing cardiac disease. Our results suggest that therapeutic doses of tricyclics lengthen the QT interval independently of the presence of cardiovascular disease. Droperidol is associated with QT lengthening and ventricular arrhythmia when used intravenously in critically ill patients,[18] but has not previously been reported to have a specific effect on QT interval when prescribed orally to psychiatric patients.

Of the specific drug relations, thioridazine has been most frequently linked in therapeutic doses to QT lengthening[19] and consequent ventricular arrhythmia.[20] The mechanism of this adverse effect is probably a blocking of the delayed rectifier potassium channel in the myocardium[21] and consequent abnormal repolarisation. 25% of patients prescribed thioridazine in our study had QTc lengthening. Only four patients were on thioridazine doses of 600 mg or above, but of these, two had QT lengthening. The possibility of a dose relation for thioridazine in a population of patients accords with studies in healthy volunteers[22] that show a dose-dependent increase in QTc with administration of thioridazine. However, most patients prescribed thioridazine who had QTc lengthening in our study were on doses of less than 300 mg/day, which is well within accepted ranges. The common practice of prescribing low-dose thioridazine is therefore an important risk factor. Thioridazine is perceived as having fewer adverse effects than more potent neuroleptics and is used symptomatically for treating insomnia or anxiety, despite there being little evidence for its efficacy.[23]

No significant relation was found between T-wave abnormalities and antipsychotic drugs. However, we found lithium to be significantly associated with T-wave abnormality and increased QT dispersion. T-wave changes have previously been reported with lithium,[24] which has also been associated with torsade de pointes in combination with thioridazine.[5] In other populations, QTc dispersion is a predictor of arrhythmia and sudden death,[25] but conclusions are conflicting and there is debate about its repeatability and reliability,[26] and also its value in the absence of underlying cardiac disease. That the numbers of patients with increased QT dispersion are small is reassuring. In fact, QT-dispersion abnormalities were so uncommon in patients that it was necessary to do a post-hoc logistic regression with the lower cut-off value of 100 ms, derived from patients with cardiac disease. No significant association between QT dispersion above this value and antipsychotic therapy was shown. However, drug-induced increases in QT dispersion may be largely confined to patients with pre-existing cardiovascular disease. These formed only a small proportion of the current study sample.

Several factors limit the applicability of these results to current practice. Despite the large size and wide heterogeneity of our sample, the possibility of selection bias remains, which will tend to exclude more severely ill inpatients who were unable to consent to participation. Over 30 different psychotropic drugs were being used, with many patients on more than one drug. Thus our

conclusions about the effects of individual drugs are limited because of the small numbers in which some drugs are prescribed. We cannot eliminate the possibility that some drugs may have proved to have significant effects had the numbers been larger. Differential prescribing to patients most likely to have QTc abnormalities might account for associations with drug therapy and cannot be ruled out completely. However, neither age nor cardiovascular disease seem to be confounding factors. An arbitrary age of 65 years was used to divide the patients into two groups. An alternative would have been to adjust for age with more age groups. This adjustment was not done because such an approach would have made the statistical model too complex. One potential confounding factor we were unable to examine was serum potassium; hypokalaemia is linked to QTc lengthening as well as other electrocardiographic abnormalities and may also increase the risk of arrhythmia.

The confirmation of a link between QT-interval abnormalities and high-dose prescribing supports current guidelines for electrocardiographic screening, but our results suggest that monitoring is also needed in patients taking tricyclic antidepressants, droperidol, and thioridazine, particularly if other risk factors are present. Caution may be needed in the use of combinations of these drugs with lithium, since increased QT dispersion may increase the risk of arrhythmia. However, QT-interval abnormalities are surrogate markers and the link between psychotropic drugs, arrhythmia, and sudden death should be examined.

Contributors

S H L Thomas and I N Ferrier designed the study and wrote the protocol with J G Reilly. J G Reilly and S J Jones collected and logged the data. Statistical analysis was done by S A Ayis. All investigators were involved in the analysis of the data and in the writing of the paper.

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