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Primary research

Gender difference in QTc prolongation of people with mental disorders

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Abstract

Background: We examined gender difference in QTc interval distribution and its related factors in people with mental disorders.

Methods: We retrospectively reviewed medical charts of patients discharged from a university psychiatric unit between November 1997 and December 2000. Subjects were 328 patients (145 males and 183 females) taking psychotropics at their admission. We examined patient characteristics, medical history, diagnosis, and medication before admission.

Results: Mean QTc interval was 0.408 (SD = 0.036). QTc intervals in females were significantly longer than those in males. QTc of females without comorbidity was significantly longer than that of males.

Conclusion: The influence of gender difference on QTc prolongation in people with mental disorders merits further research.

Background

QT interval prolongation is regarded as an indicator of potential for malignant ventricular arrhythmia [1]. Many antiarryhythmic drugs are known to prolong ventricular repolarisation, and result in the QT interval prolongation. Since prolonged ventricular repolarisation may provoke torsades de pointes and sudden death, measurement of QT interval prolongation is important to identify the high-risk patients and prevent avoidable negative outcomes.

Female gender is regarded as a high-risk group of QTc interval prolongation. QTc interval has been reported to be longer in females than in males [2]. A meta-analysis of 332 published cases of torsades de pointes associated with cardiovascular drugs [3] suggested that female were more prone than male to prolong cardiac repolarization. Although females appear to be more protected from coronary heart diseases than males in general population [4], gender differences in QTc interval prolongation and cardiovascular diseases for people with mental disorders are still unknown.

In addition to cardiac drugs, there are recently many reports on non-cardiac drugs' effects on QT interval prolongation [5-10]. Such drugs include some antihistamines, antibiotics, antimalarials, antifungal agents, and psychotropic drugs [4]. As to psychotropic drugs for people with mental disorders, some tricyclic antidepressants and antipsychotics including thioridazine are reported to

be associated with QT interval prolongation [5-7]. A survey of medico-legal autopsies performed revealed that phenothiazine derivative was present in 46 of all 49 sudden unexpected deaths associated with the use of antipsychotic or antidepressant drugs during the study period in Finland [8]. Moderate-dose antipsychotic users (>100 mg in thioridazine equivlalents) was reported to be in a 2.39 times greater risk of sudden cardiac death than non-users [9]. Reilly et al. [10] estimated the point prevalence of QTc prolongation in psychiatric patients in various inpatient and community settings and found that age over 65 years, use of tricyclic antidepressants, thioridazine, and droperidol were predictors of QTc prolongation.

Although Reilly et al. [10] examined the effect of gender differences, it was not strongly related to QTc prolongation as age and psychotropic drugs. To our knowledge, there were no specific studies on related factors to QTc prolongation by gender. We hypothesized that female gender in people with mental disorders could be a risk factor of QTc prolongation. In this research, we focused on gender difference in QTc interval distribution and examined related factors of the QTc prolongation of people with mental disorders.

Methods

Subjects

We retrospectively reviewed the medical charts of patients with history of previous psychiatric treatment, discharged from a psychiatric unit of a university hospital between November 1997 and December 2000. In this unit, electrocardiograms (ECGs) of all admitted patients were examined within several days from the admission as one of physical checks to consult other professionals such as cardiologists if necessary. Since 4 patients were excluded for missing values, we analyzed 328 patients (145 males and 183 females).

The mean age (SD) of the subjects was 41.1 (17.4) years old. As to psychiatric diagnosis using Diagnostic Statistical Manual, 4th edition (DSM-IV), 94 (28.7%) patients were diagnosed as suffering from schizophrenia, 95 (29.0%) from mood disorders, and 139 (42.4%) from other.

The mean duration (SD) of taking psychotropic drugs in years was 7.90 (9.38). Of the subjects, 232 (70.7%) and 90 (27.4%) were taking antipsychotics and antidepressants, respectively. The mean doses (SDs) of antipsychotics (chlorpromazine equivalent / day) and antidepressants (maprotiline equivalent / day) among patients taking each cluster of psychotropics were 435 (545) mg and 73.9 (75.1) mg, respectively. Since atypical antipsychotics (AAPs) were approved in 1996 by the Ministry of Health, Labour and Welfare, Japan, only 36 patients received AAPs in the study period. Regarding antidepressants, 25 patients were taking selective serotonin reuptake inhibitors (SSRIs) while 45 patients were taking tricyclic antidepressants (TCAs).

There were 204 (62.2%) patients with some physical comorbidities. These included 70 (21.3%) hepatic failures, 51 (15.5%) cardiovascular diseases, 25 (7.6%) diabetes, and 10 (3.0%) cerebrovascular diseases.

Variables

Variables included into the analyses were gender, age at admission, diagnosis, daily doses of psychotropic drugs, comorbidities, and QTc interval.

Diagnosis was categorized into schizophrenia, mood disorders, and others according to DSM-IV. Daily doses of psychotropics were calculated as to antipsychotics (in chlorpromazine equivalents) and antidepressants (in maprotiline equivalents) prescribed as regular medication at the point of ECGs. As distributions of doses of antipsychotics and antidepressants did not follow the normal distribution, they were categorized into four levels. Dose of antipsychotics in mg (AP) was divided as following; $AP = 0$, $0 < AP < 100$, $100 \leq AP < 500$, and $500 \leq AP$. Dose of antidepressants in mg (AD) was divided as following; $AD = 0$, $0 < AD < 50$, $50 \leq AD < 100$, and $100 \leq AD$. As to comorbidities, we examined whether patients had cardiovascular disease, cerebrovascular disease, hepatic failure and diabetes at admission or not.

QTc interval measurements were calculated automatically by a computer algorithm using Bazett's formula (QTc = QT / square root of RR).

All variables used are provided in Table 1, with values and their coding for qualitative variables, as well as analysis which each variable was used by.

Analyses

First, we calculated a mean QTc interval for all subjects, and compared QTc intervals between males and females with t-test. We also made a histogram of QTc interval with a class interval of 0.02 second in each gender.

Second, we carried out two-way analyses of covariance (ANCOVAs) to examine considerably related factors with QTc prolongation. We used QTc interval as a dependent variable, and age at admission as a covariate. As to the two factors, gender was included as one of them, and each of seven variables (diagnosis, daily doses of antidepressants and antipsychotics, and existences of cardiovascular disease, cerebrovascular disease, hepatic failure, and diabetes) as the other. We also calculated means (SDs) of QTc interval in each category of each factor other than gender. If the factor other than gender was significant, we

Table 1: Variables used in the study and their locations in the statistical model of each analysis.

Variable (with values and their codes for qualitative variables)		t-test	two-way ANCOVAs[1)]	one-way ANCOVAs
gender		indep.var.	factor[a)]	factor
	0 male			
	1 female			
age at admission			covariate	covariate
diagnosis			factor[b)]	
	0 others			
	1 schizoperenia			
	2 mood disorders			
antipsychotics[2)]			factor[b)]	
	0 0 mg			
	1 0–100 mg			
	2 100–500 mg			
	3 500 mg +			
antidepressants[3)]			factor[b)]	
	0 0 mg			
	1 0–50 mg			
	2 50–100 mg			
	3 100 mg +			
cardiovascular disease			factor[b)]	
	0 absent			
	1 present			
cardiovascular disease			factor[b)]	
	0 absent			
	1 present			
hepatic failure			factor[b)]	
	0 absent			
	1 present			
diabetes			factor[b)]	
	0 absent			
	1 present			
QTc interval		dep.var.	dep.var.	dep.var.

indep.var. = independent variable dep.var. = dependent variable 1) We included gender (marked with 'a') as one factor, and one of the other qualitative variables (marked with 'b') as the other, therefore we carried out 7 two-way ANCOVAs in total. 2) Dose of antipsychotics was estimated in chlorpromazine equivalents. 3) Dose of antidepressants was estimated in maprotiline equivalents.

compared QTc intervals between the categories of the factor. We used Bonferroni correction for multiple comparisons.

Finally, we carried out one-way ANCOVAs in cases that the factor other than gender was significant in a two-way ANCOVA. To exclude the effect of the factor, we applied one-way ANCOVAs to every subgroup in which the factor belongs to the same category, using QTc interval as a dependent variable, gender as a factor, and age at admission as a covariate. We also calculated means (SDs) of QTc interval in each gender in every subgroup.

All statistical analyses were performed with the SPSS 11.0 J for Windows. All tests were two-tailed.

Results

The QTc interval was 0.408 ± 0.036 seconds. The QTc interval in females (0.413 ± 0.036) was significantly longer than that in males (0.401 ± 0.035; $t(326) = 2.861$, $p < 0.01$). Figure 1 shows the histogram of QTc intervals in each gender. There were three males and one female whose QTc intervals were longer than 0.5 seconds.

The results of 7 two-way ANCOVAs are shown in Table 2. There were no significant interaction effects in any test. Gender was a singnificant factor in three tests (when diagnosis, antipsychotics, and hepatic failure were included as the other factor). Cardiovascular disease was the only factor other than gender that was significant. The mean QTc interval in those with cardiovascular disease was significantly longer than that in those without it.

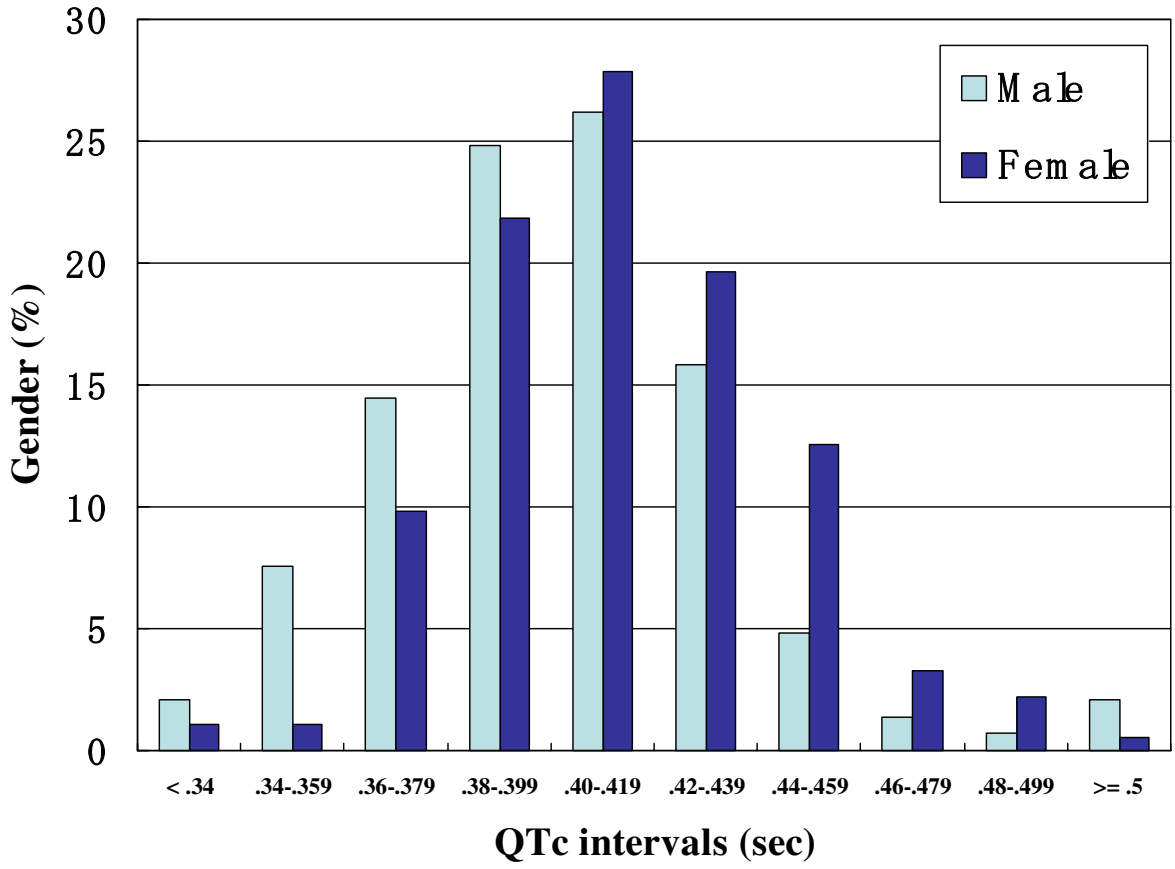

Figure 1
Histogram of QTc interval in each gender. The lower limit of each range is included in the range, while the upper limit is not.

Table 3 shows the results of one-way ANCOVAs. As cardiovascular disease was a significant factor in a two-way ANCOVA, we carried out one-way ANCOVAs individually in those with and without cardiovascular disease. The mean QTc interval was significantly different by gender when cardiovascular disease was absent (male < female), while it was not when present.

Discussion

According to the results of the current study, female gender is a contributing factor in QTc lengthening. Although the relationship between QTc prolongation and gender has been discussed in recent cardiovascular researches in general [4], it has not been well examined in people with mental disorders.

QTc intervals in females were significantly higher than in males among the mentally ill "without" cardiovascular comorbidity. This suggests that a gender difference still exists in QTc lengthening in persons with mental disorders after excluding effects of cardiovascular comorbidity.

No other factors were related to QTc lengthening in this study, though some other studies pointed out the influence of psychotropic drugs to QTc lengthening [2,5-10]. The possible reasons are that the institution in this study is a university hospital where psychiatrists try to avoid tricyclic antidepressants which reportedly put the patient at risk for QTc lengthening, and can easily consult with cardiologists if necessary. But the sample is small, and we need to study the psychotropic effects on QTc lengthening in a larger sample.

Table 2: The effects of gender and other related factors on QTc interval.

Factor other than gender	Term in the statistical model	Mean (SD) of QTc interval	F-value
diagnosis	gender		8.559**
	diagnosis		1.870
	others (n = 139)	0.402 (0.040)	
	schizophrenia (n = 94)	0.407 (0.033)	
	mood disorders (n = 95)	0.415 (0.032)	
	gender • diagnosis		0.253
antipsychotics	gender		7.952**
	antipsychotics		1.035
	0 mg (n = 96)	0.406 (0.036)	
	0–100 mg (n = 66)	0.405 (0.031)	
	100–500 mg (n = 103)	0.410 (0.039)	
	500 mg + (n = 63)	0.409 (0.035)	
	gender • antipsychotics		1.526
antidepressants	gender		1.359
	antidepressants		1.036
	0 mg (n = 238)	0.405 (0.038)	
	0–50 mg (n = 26)	0.416 (0.030)	
	50–100 mg (n = 39)	0.413 (0.031)	
	100 mg + (n = 25)	0.417 (0.026)	
	gender • antidepressants		1.752
cardiovascular disease	gender		1.114
	cardiovascular disease		5.483*
	absent (n = 277)	0.405 (0.036)[1)]	
	present (n = 51)	0.420 (0.035)[1)]	
	gender • cardiovascular disease		2.180
cerebrovascular disease	gender		2.048
	cerebrovascular disease		0.014
	absent (n = 318)	0.407 (0.036)	
	present (n = 10)	0.414 (0.029)	
	gender • cerebrovascular disease		0.267
hepatic failure	gender		4.694*
	hepatic failure		0.024
	absent (n = 258)	0.408 (0.037)	
	present (n = 70)	0.407 (0.034)	
	gender • hepatic failure		0.062
diabetes	gender		0.065
	diabetes		0.103
	absent (n = 303)	0.408 (0.033)	
	present (n = 25)	0.408 (0.063)	
	gender • diabetes		2.125

Two-way ANCOVA (analysis of covariance): Gender and each of the 7 variables in the most left column were included as two factors, QTc interval as a dependent variable, and age at admission as a covariate. 7 tests were performed in total. *$p < 0.05$, **$p < 0.01$. 1) As this variable has only two categories, it is manifest without post-hoc analysis that there is a significant difference between these values.

The results of this study cannot lead directly to the conclusion that females without comorbidity having QTc lengthening are at high risk for cardiovascular diseases. This is partly because factors related to female gender such as steroid hormone receptors and ion channels may possess cardioprotective properties [4]. In fact, there was only one female with QTc interval of more than 0.5 second, a threshold of higher occurrence of torsades de pointes, while there were 3 males [10]. Different life styles by gender such as smoking [11] may also decrease the risks for cardiovascular diseases in females.

The current study has several limitations. Since we did not examine the QTc effects on cardiovascular diseases in this retrospective study, we could not clarify the relationship between cardiovascular diseases and gender. Potential influential factors on QTc interval such as body weight and history of smoking [6] were not included in this retrospective study design. Since persons with mental disor-

Table 3: Gender difference in QTc interval when the factor significant in two-way ANCOVA is fixed.

Factor significant in two-way ANCOVA	Mean (SD) of QTc interval	F-value
	cardiovascular disease	
absent (n = 277)		10.251**
Male (n = 122)	0.398 (0.035)	
Female (n = 155)	0.411 (0.036)	
present (n = 51)		0.353
Male (n = 23)	0.421 (0.034)	
Female (n = 28)	0.420 (0.037)	

One-way ANCOVA (analysis of covariance): Gender was included as a factor, QTc interval as a dependent variable, and age at admission as a covariate. There was only one factor significant in two-way ANCOVAs (cardiovascular disease), and it has two categories (absent, and present), therefore 2 tests were performed in total. **$p < 0.01$.

ders are about twice as likely to smoke as other people [11] and men smoke more frequently than females in Japan [12], a further prospective study is needed.

Conclusions

Our results suggest the presence of QTc prolongation in female patients with mental disorders and this group could be at high risk of cardiovascular diseases. Gender difference should be considered in combination with the effect of psychotropic drugs on cardiovascular system.

Competing interests

None declared.

Authors' contributions

HI conceived and designed the study and drafted the manuscript. TK participated in the design of and carried out the study, and performed the statistical analysis. SI participated in the design of, carried out, and coordinated the study. HM participated in its design and coordination. All authors read and approved the final manuscript.

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