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Antipsychotic Medication and Risk of QTc Prolongation: Focus on Multiple Medication and Role of Cytochrome P450 Isoforms

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Abstract

Objective: To identify the effects of antipsychotics on QTc prolongation in light of age, gender, antipsychotic combination pattern, antipsychotic doses and cytochrome P450 (CYP) mediation, using large database describing the antipsychotic treatment of patients with schizophrenia in Japan. Methods: Using database of 4176 patients with schizophrenia discharged between April 2004 and March 2005 and receiving outpatient treatment from 526 psychiatric hospitals in Japan. Of the patients, 1437 were included for the analysis. These patients were classified into three groups according to the antipsychotic CPZ-equivalent doses that they received (low, 1 - 299 mg; middle, 300 - 999 mg; and high, ≥1000 mg). QTc intervals ≥ 440 msec were considered prolonged. We reviewed all the package inserts of the antipsychotics used from the website of Pharmaceuticals and Medical Devices Agency. Results: The mean QTc interval of the total patient group was 410.4 ± 23.3 msec. The females had significantly higher QTc values than the males (414.5 ± 24.0 vs. 406.8 ± 22.2 msec, respectively; $p < 0.05$). Logistic regression analysis revealed that female gender (odds ratio [OR] = 1.83; 95% CI: 1.28 - 2.56), CYP3A4-metabolized drugs (OR 1.56; 95% CI: 1.05 - 2.30) were associated with an increased risk of QTc prolongation. Conclusion: The co-prescription of CYP3A4-mediated antipsychotic drugs should be carefully considered in females due to potential risk of QTc prolongation. Further studies of the cardiovascular safety of antipsychotics are warranted in patients receiving multiple medications.

Keywords

Antipsychotics, CYP, Drug Interaction, QTc Prolongation, Schizophrenia

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1. Introduction

Concern about cardiac safety is a leading cause for the withdrawal of several marketed drugs. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed guidelines (E14) to assess corrected QT (QTc) prolongation, which can lead to life-threatening cardiac arrhythmia or torsade de pointes [1]. The QTc interval represents the duration of ventricular depolarization and subsequent repolarization, and a delay in cardiac repolarization can be measured as prolongation of the QTc interval by electrocardiography (ECG). The QTc interval is used as a surrogate marker for the prediction of serious adverse drug effects, syncope, or death due to torsade de pointes [2].

Drugs that cause prolongation of the QTc interval have been extensively studied in the past decade [3]-[13]. Antipsychotics have been known to be associated with QTc prolongation, as have drugs such as antidysrhythmics and antibiotics [6] [9]. The use of antipsychotics is a first-line treatment for psychotic disorders such as schizophrenia. Some of the typical antipsychotics that are in use today have been available since the 1950s, and atypical antipsychotics have been used since the 1990s as the second-generation medications for psychotic disorders [4]. Thioridazine (a typical antipsychotic) and ziprasidone (an atypical antipsychotic) were withdrawn from the market due to the increased risk of QTc prolongation and sudden death that they presented [14] [15]. Antipsychotic medications are commonly prescribed off-label for conditions such as delirium and autism spectrum disorder, in populations including the elderly and children [16]. The increased risk of death in elderly patients has been reported regarding both typical and atypical antipsychotics [17].

In clinical practice, more than one drug is often prescribed concurrently, and combination-drug treatment is a common prescription pattern of antipsychotics in psychiatry [18]-[20]. Although co-prescribing can be appropriate, the interaction of multiple drugs may increase the risk of adverse effects by pharmacokinetic and pharmacodynamic interactions. One drug may alter the other's absorption, distribution, metabolism, and/or excretion with a pharmacokinetic interaction, and two drugs may have additive, synergistic, and/or antagonistic effects with a pharmacodynamic interaction [21].

In efforts to predict clinically relevant drug interactions, the cytochrome P450 (CYP) system is important; the system's six enzymes (CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) metabolize more than 90% of the existing drugs [22]. When two drugs sharing the same metabolic pathway compete for the same enzyme receptor site, enzyme inhibition occurs, and the plasma level of the unmetabolized drug is enhanced because the predominant inhibitor decreases the metabolism of the competing drug, leading to a greater potential for toxicity [23].

Adverse cardiovascular effects due to drug interactions are of great concern, but the effects of combined drugs on QTc prolongation have not been clarified. The objective of the present study was to identify the effects of antipsychotics on QTc prolongation in light of age, gender, antipsychotic combination pattern, antipsychotic doses and CYP mediation, using a large database of antipsychotic treatment of patients with schizophrenia in Japan.

2. Methods

2.1. Data Sources

A retrospective study was conducted using the database from a nationwide study conducted by the Japan Psychiatric Hospitals Association (JPHA) in 2007. Of the 1215 member hospitals of the JPHA, 526 hospitals (43.3%) participated in the original study to examine the effects of daycare services for patients with schizophrenia who were discharged between April 2004 and March 2005 and who continued to receive outpatient treatment at the hospitals [24] [25]. Using a systematic sampling technique, every fifth patient was selected from the medical records of the total 21,396 patients (n = 4176). QTc was measured during the patient's hospitalization at psychiatric hospitals. The database includes sociodemographics, diagnosis, and prescription drug and QTc information.

2.2. Study Population

In the present study, patients with following available data were included: 1) age, 2) gender, 3) QTc interval during hospitalization, and 4) prescription information of the antipsychotics used by the patients. Exclusion criteria were: 1) aged under 20 or over 99 years old, 2) history of myocardial infarction or angina, 3) patients whose QTc were monitored only at admission, 4) QTc under 360 msec or over 600 msec, 5) antipsychotic monotherapy, and 6) antipsychotics without any information on CYP. After 2598 patients were excluded based

on these criteria, 1437 patients were included for the analysis.

QTc-interval measurements were generated by a computer algorithm at each participating hospital. In the present study, QTc intervals ≥ 440 msec were considered prolonged [26] [27]. All antipsychotic doses were converted to chlorpromazine equivalent (CPZ-equivalent) [28]. In general, 300 mg to 999 mg is known as the recommended dose of an antipsychotic CPZ-equivalent drug [19] [29]. In the present study, the patients were classified into three groups according to the CPZ-equivalent antipsychotic dose they had been prescribed: 1 - 299 mg as the low-dose group (n = 119), 300 - 999 mg as the middle-dose group (n = 789), and ≥1000 mg as the high-dose group (n = 529). QTc intervals were studied by drug combination patterns (typical + typical, typical + atypical, and atypical + atypical antipsychotics).

We examined the cardiac effects of combined antipsychotics that were metabolized by the same CYP system. We reviewed all of the package inserts of antipsychotics from the website of Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and all of the relevant articles in scientific journals on CYP isoforms and QTc interval information of antipsychotics (**Table 1**) [3] [15] [22] [26] [30]-[50].

2.3. Statistical Analysis

Mean and standard deviation (SD) were used to represent distribution of continuous variables. We used Student's t-test and one-way analysis of variance (ANOVA) to compare QTc prolongation group (QTc ≥ 440 msec) and control group (QTc < 440 msec). Multiple logistic regression analysis was performed to assess factors that could contribute to QTc interval prolongation. Age, gender, and CYP groups (1A2, 2D6 and 3A4) were included in the forced entry method. Only the significant variables were included when comparing the dichotomized QTc intervals (≥ 440 msec vs. <440 msec). All statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). p-values < 0.05 were accepted as significant.

Table 1. CYP isoforms and QTc interval of antipsychotics.

Drug name	Antipsychotic class	CYP[a] isoform
Known to prolong the QTc interval		
Bromperidol [51]	Typical	3A4 [47]
Chlorpromazine [26] [52]	Typical	2D6 [38]
Fluphenazine decanoate [53] [54]	Typical	2D6 [50]
Haloperidol [55] [56]	Typical	2D6 [50]
Haloperidol decanoate [52] [57]	Typical	2D6 [34] [48]
Levomepromazine [52] [58]	Typical	2D6 [49]
Nemonapride [59]	Typical	2D6 [30]
Olanzapine [60] [61]	Atypical	1A2, 2D6 [45]
Perphenazine [8] [40]	Typical	2D6 [45]
Pimozide [41] [62]	Typical	1A2, 2D6, 3A4 [33]
Quetiapine [42] [60]	Atypical	3A4 [4] [35]
Risperidone [60] [63]	Atypical	2D6 [32]
Trifluoperazine [64]	Typical	1A2 [44]
No available information on QTc interval		
Perospirone	Atypical	1A2, 2C8, 2D6, 3A4 [5]
Zotepine	Atypical	1A2, 2B6, 2C9, 2C19, 2D6, 3A4, 3A5 [5]

[a]CYP: cytochrome P450.

2.4. Ethical Considerations

The study protocol was approved by the Institutional Review Boards of the JPHA and National Center of Neurology and Psychiatry (NCNP). The study protocol has been registered in the UMIN Clinical Trials Registry (UMIN-CTR) in Japan (UMIN000010473).

3. Results

The mean QTc interval of the total group of patients was 410.4 ± 23.3 msec (**Table 2**). The females (n = 670) had significantly longer than QTc intervals compared to the males (n = 767) (414.5 ± 24.0 vs. 406.8 ± 22.2 msec, respectively; $p < 0.05$). There were no significant differences in QTc intervals among the three dose groups or among the different drug combination patterns.

The results of the logistic regression analysis examining the risk factors of QTc interval prolongation are presented in **Table 3**. Females were more susceptible to QTc prolongation than men (odds ratio [OR] = 1.83; 95% CI: 1.28 - 2.56). CYP3A4-mediated antipsychotics were more likely to prolong the QTc interval compared to non-CYP3A4-mediated antipsychotics (OR 1.56; 95% CI: 1.05 - 2.30). CYP1A2-mediated antipsychotics were less likely to prolong the QTc interval compared to non-CYP1A2-mediated antipsychotics (OR 0.65; 95% CI: 0.44 - 0.97).

4. Discussion

The present study revealed that patients receiving combined antipsychotics that were metabolized by the CYP3A4 had longer QTc intervals than those receiving drugs that were metabolized by different pathways. The female patients were significantly more susceptible to QTc prolongation than the males. Antipsychotic dosing and typical/atypical combination patterns were not associated with QTc prolongation.

Although a recent study demonstrated that the use of combined antipsychotics did not increase the risk of sudden cardiac death or ventricular arrhythmia [12], the present analysis indicates that combined CYP3A4-mediated antipsychotics may be a risk factor for QTc prolongation. The results showed that the QTc interval was

Table 2. Mean QTc interval and patient characteristics.

	n (%)	Mean QTc ± SD (msec)
Overall	1437 (100)	410.4 ± 23.3
Gender		
Male	767 (53.4)	406.8 ± 22.2
Female	670 (46.6)	414.5 ± 24.0*
Age (years)		
<65	1290 (89.8)	409.9 ± 23.1
>65	147 (10.2)	414.7 ± 25.3
CPZeq[a]		
1 mg - 299 mg	119 (8.3)	406.2 ± 24.0
300 mg - 999 mg	789 (54.9)	411.2 ± 22.1
≥1000 mg	529 (36.8)	410.1 ± 24.9
Combination pattern		
Typical + typical	451 (31.4)	408.4 ± 23.2
Typical + atypical	880 (61.2)	411.3 ± 23.5
Atypical + atypical	106 (7.4)	411.3 ± 21.6

[a]CPZeq: chlorpromazine equivalent. *$p < 0.05$.

Table 3. Risk factors of QTc prolongation by logistic regression.

	n (%)	QTc prolongation (%)[a]	Odds ratio (95% CI)	p value
Gender				
Female	670 (46.6)	89 (13.3)	1.83 (1.28 - 2.56)	0.001
Male	767 (53.4)	59 (7.7)	1.00	
Age (years)				
<65	1290 (89.8)	131 (10.2)	1.06 (0.61 - 1.83)	0.846
>65	147 (10.2)	17 (11.6)	1.00	
CYP 1A2				
CYP 1A2-mediated drugs	637 (44.3)	58 (9.1)	0.65 (0.44 - 0.97)	0.033
Non CYP 1A2-mediated drugs	800 (55.7)	90 (11.3)	1.00	
CYP 2D6				
CYP 2D6-mediated drugs	1414 (98.4)	145 (10.3)	0.94 (0.27 - 3.33)	0.925
Non CYP 2D6-mediated drugs	23 (1.6)	3 (13.0)	1.00	
CYP 3A4				
CYP 3A4-mediated drugs	574 (39.9)	68 (11.8)	1.56 (1.05 - 2.30)	0.026
Non CYP 3A4-mediated drugs	863 (60.1)	80 (9.3)	1.00	

[a]Number of patients with QTc ≥ 440 msec.

prolonged in patients receiving CYP3A4-mediated antipsychotic combinations. Ray *et al*. studied the potential relationship between macrolide antimicrobial agent and sudden death, and they concluded that the concurrent use of erythromycin and strong inhibitors of CYP3A4 should be avoided [43].

Several studies support the finding of a gender difference, *i.e*., that female patients are at greater risk of QTc prolongation [7] [12]. The gender difference in QTc prolongation may be related to sex hormones [65] [66]. The QTc interval is similar in children aged younger than 15 years before puberty, but the QTc interval in males decreases after puberty, resulting in longer QTc intervals in females [67]. Testosterone may be related to the difference, and gender-specific medication therapy should be considered [36].

Also, the antipsychotic dosing and typical/atypical combinations were not associated with QTc prolongation in the present study. Regarding the dosing, the results of previous studies have been contradictory; one study reported that high doses presented a risk of QTc prolongation [7], whereas another suggested there was no association [12]. Ozeki *et al*. reported that the first-generation antipsychotics partly contributed to QTc prolongation, and the second-generation antipsychotics presented a relatively low risk of fatal arrhythmia [52].

Despite the documented abnormal QTc, the rate of serious cardiovascular effects is low [31]. QTc prolongation in a schizophrenic population cannot directly address clinically relevant issues of cardiovascular adverse effects due to acceptable small extensions, and the risk of sudden death is likely to be small in these data. The definitions of the QTc prolongation vary, and QTc intervals are different in males and females. When the QTc interval exceeds 500 msec, it implies clinical significance in both males and females [14]. Because the subjects of the present study were not patients with pre-existing cardiovascular conditions, 440 msec was used as the cutoff point of the QTc prolongation for both the males and females.

However, caution is needed when a drug is known to prolong the QTc interval due to potential inhibition of its metabolism by another drug. In clinical practice, the avoidance or the minimum use of co-prescribed CYP3A4-metabolized antipsychotics should be considered.

There are several limitations to the present study. First, the database did not include information on predisposing factors including congenital long QTc syndrome and comorbidity, or for prescriptions for comorbidity such as for the presence of diabetes and the prescription of antidiabetic drugs. Second, the effects of potential confounders cannot be excluded. The CYP pathway of antipsychotic drugs have not all been revealed, and thus further studies are required before the present results could be generalized. Third, QTc may be considerably affected by blood concentration of the antipsychotic drugs. The time points of the daily administration of the drugs

and measurement of QTc was unknown because we used the secondary data from the multicenter study. More sophisticated study is needed. Fourth, context of the time the antipsychotics and the time of measurement of the QTc was prescribed is unknown. Fifth, the study design is a retrospective open cohort study, so the observed associations should be interpreted carefully. It is believed that the timing of the prescription blood levels to be involved, and further study. Despite these limitations, the present findings highlight the potential CYP-mediated drug-drug interactions in combined antipsychotics revealed by using a large database, and our results will contribute to the risk management of drug-induced QTc prolongation.

5. Conclusion

The co-prescription of CYP3A4-mediated antipsychotic drugs should be carefully considered in females due to potential risk of QTc prolongation. Further studies of the cardiovascular safety of antipsychotics are warranted in patients receiving multiple medications.

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Competing Interests

The authors declare that they have no competing interests.

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