Cardiac Safety Parameters of Olanzapine: Comparison With Other Atypical and Typical Antipsychotics

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Alterations of electrocardiogram results and cases of sudden cardiac death have been reported since the beginning of neuroleptic treatment. In particular, a temporal association exists between some antipsychotics and prolongation of the heart rate–corrected QT interval (QTc), an event that may increase the risk for developing a potentially fatal ventricular tachycardia arrhythmia known as torsades de pointes if it significantly exceeds normal intraindividual and interindividual variation. Although the incidence of serious adverse cardiac events in response to antipsychotic medications is relatively low, any possibility for the occurrence of cardiotoxicity warrants continued study. The present article reviews important differences among antipsychotic drugs in the potential for, and occurrence of, serious adverse cardiac outcomes and suggests that olanzapine, as therapeutically administered to patients with schizophrenia and related psychoses, does not contribute significantly to a QTc prolongation that could result in potentially fatal ventricular arrhythmias.

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Alterations of electrocardiogram results and cases of sudden cardiac death have been reported since the beginning of neuroleptic treatment.[1,2] In particular, a temporal association exists between some antipsychotics and prolongation of the heart rate–corrected QT interval (QTc), an event that, if it significantly exceeds normal intraindividual and interindividual variation, may increase the risk for developing a potentially fatal ventricular tachycardia arrhythmia known as torsades de pointes.[3,4] Although the incidence of serious adverse cardiac events in response to antipsychotic medications is relatively low, any possibility for the occurrence of cardiotoxicity warrants continued study. The present article reviews published data illustrating important differences among antipsychotic drugs in the potential for, and occurrence of, serious adverse cardiac outcomes. These data suggest that olanzapine is an atypical antipsychotic that, as therapeutically administered to patients with schizophrenia and related psychoses, does not contribute significantly to a QTc prolongation that could result in potentially fatal ventricular arrhythmias.

MYOCARDIAL ACTION POTENTIAL, QTc PROLONGATION, AND MALIGNANT ARRHYTHMIAS

Recording of the surface electrocardiogram (ECG) reflects various phases of the myocardial action potential (Figure 1). In particular, the QT interval corresponds largely to the plateau phase of the myocardial action potential and is measured in milliseconds (ms) from the start of the QRS wave to the end of the T wave. The broad T wave of the ECG recording results from the rapid repolarization occurring nonsimultaneously throughout the ventricles of the heart. Because QT length shortens with increasing heart rate, the QT interval must be corrected for heart rate (QTc) using a regression formula (e.g., Bazett's formula [$QTcB = QT/RR^{1/2}$]).[5]

The length of the QTc interval can be influenced by numerous factors. For example, the QTc interval tends to be longer in females than in males[6] and increases in length as a person ages.[7] Considerable variation in the QTc interval has also been observed as a function of the time of day and even between ECG leads during testing,[8] a phenomenon known as QTc dispersion. Furthermore, some individuals are born with a prolonged QTc interval that is referred to as the hereditary long QT syndrome (LQTS), while others develop what has been called an acquired LQTS (reviewed in Tan et al.[9]). Of interest, a variety of drugs, implicated in the etiology of acquired LQTS, have been shown

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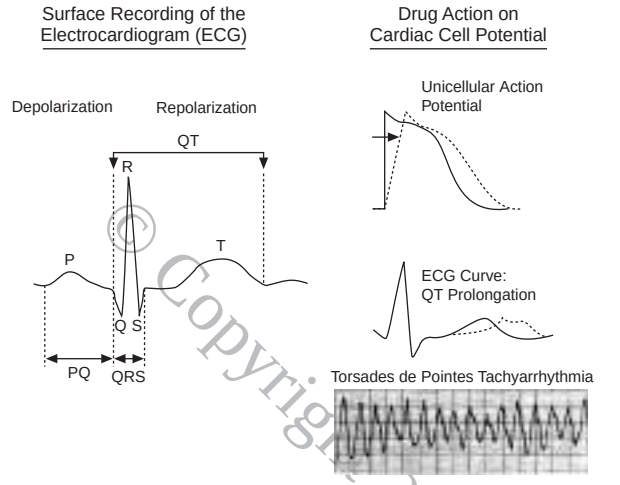
Figure 1. Effects of Antipsychotic Drugs on Cardiac Cells Can Prolong the QT Interval and Result in the Ventricular Arrhythmia Torsades de Pointes



to prolong the QTc interval, including certain antiarrhythmic drugs, antihypertensive drugs, anti-infective agents, tricyclic and tetracyclic antidepressants, and antipsychotic drugs (reviewed in Tan et al.[9]).

Prolongation of the QTc interval can predispose some patients to develop a polymorphic ventricular tachycardia known as torsades de pointes[9,10] (see Figure 1). Torsades de pointes (twisting of points) is a unique ventricular tachycardia arrhythmia in which the mean electrical axis of the QRS complex appears to twist around the isoelectric line.[11] Torsades de pointes may serve as a transitional state between ventricular tachycardia and ventricular fibrillation, the latter representing a condition that if untreated can result in cardiac arrest. Although there is no consensus as to the length of the QTc interval below which the risk of arrhythmia is minimal, some expert opinion has suggested that a QTc of 500 ms is the lower limit for substantial risk of developing torsades de pointes.[6,8]

Although a number of theories have been proposed, the occurrence of early afterdepolarizations within the myocardium is thought to be the main mechanism involved in QTc prolongation and development of ventricular arrhythmias (reviewed in Tan et al.[9]). Early afterdepolarizations can be triggered by various agents or conditions that reduce the magnitude of outward repolarizing K^+ currents or enhance inward depolarizing Na^+ or Ca^{2+} currents, leading to a delay of cardiac repolarization and the initiation of tachyarrhythmia. Drugs that significantly prolong the QTc interval or induce torsades de pointes have been found in in vitro experiments to alter these ion channel conductances.[12]

Antipsychotic Drugs and Cardiac Dysfunction

Antipsychotic drugs have been categorized into 2 main groups based primarily on differences in the appearance of extrapyramidal symptoms (EPS). The majority of typical antipsychotic drugs are older drugs that fall into 3 main classes based on chemical structure: (1) phenothiazine derivatives (thioridazine, chlorpromazine, fluphenazine), (2) diphenylbutylpiperidine derivative (pimozide), and (3) butyrophenones (haloperidol, droperidol). As a group, the typical antipsychotics have been shown to be effective in treating the positive symptoms of schizophrenia (i.e., hallucinations and delusions), although with a fairly high incidence of EPS. In contrast, the newer atypical antipsychotics are as effective as the typical agents in treating positive symptoms of schizophrenia, apparently more effective in treating negative symptomatology as well as anxious and depressive symptoms accompanying schizophrenia, and have a superior EPS profile.[13] Clinical availability of the atypical antipsychotics began with clozapine, to which risperidone, olanzapine, sertindole, quetiapine, and most recently ziprasidone (which is currently under review in several countries) were added subsequently.

Some antipsychotics have been shown to prolong the QTc interval, and as a consequence, their role in the development of torsades de pointes and sudden death has been suggested. However, recent data are beginning to suggest that there may be important differences among antipsychotics in their potential to cause cardiotoxicity. The reported effects of typical and atypical antipsychotics on electrocardiac function including mean QTc change, threshold QTc changes associated with torsades de pointes, and other cardiac safety reports are provided in Tables 1 and 2, respectively.

Typical Antipsychotics

Drugs within each class of the typical antipsychotics have been temporally associated with prolongation of the QTc interval, although to varying degrees. The largest mean increase in the QTc interval was observed for thioridazine (35.6 ms)[14,70] and droperidol (59 ms, intravenous [i.v.] application),[17] while the lowest increase was reported for haloperidol (range, 4.0–7.1 ms),[15,16,70] with intermediate values reported for chlorpromazine[15] and pimozide.[16] Although only limited data have been provided for threshold change in QTc associated with torsades de pointes, one report[18] shows that approximately 2% of patients treated with i.v. haloperidol show a QTc interval greater than 500 ms. Furthermore, numerous reports have indicated that each typical antipsychotic has been temporally associated with one or more serious cardiac events, with the majority of such events, including torsades de pointes, being observed after administration of the phenothiazine derivatives thioridazine and chlorpromazine (see Table 1).

A major concern that has been raised with the administration of typical antipsychotics is the clinical observation of a relationship between drug dose and QTc interval prolongation. In a recently published analysis (logistic

Table 1. Cardiac Safety Parameters Reported With Typical Antipsychotic Drugs[a]

Typical Antipsychotic	Mean QTc Change[b]	Threshold QTc Changes Associated With Torsades de Pointes (% patients with QTc > 500 ms)	Cardiac Safety Reports
Thioridazine	33–35.8 ms[14,70] (oral)	Not reported	Clinical ECG data available since 1966[2] Reports of torsades de pointes,[19,20] malignant arrhythmia,[21] and sudden death[1,22] Greater increase in QTc with higher dose[4,14] Overdose was reported with cardiotoxicity[23]
Chlorpromazine	14 ms[15]	Not reported	Clinical ECG data available since 1966[2] Reports of torsades de pointes[24,25] Greater increase in QTc with higher dose[4] Overdose (phenothiazines) was reported with cardiotoxicity[23]
Fluphenazine	Not reported	Not reported	Clinical ECG data available since 1965[26] Reports of T-ST wave abnormalities, supraventricular extrasystoles and broad QRS,[27] and sudden death[28] Greater risk of QTc prolongation with higher dose[4]
Pimozide	19 ms[16]	Not reported	Clinical ECG data available since 1987[16] Reports of T-U wave abnormalities,[15] ECG changes in Tourette's disorder,[16] and sudden cardiac death in young adults[29] Greater risk of QTc prolongation with higher dose[4] Overdose was reported with torsades de pointes[30]
Droperidol	59 ms[17] (iv)	Not reported	Clinical ECG data available since 1978[31] Greater increase in QTc with higher dose[4,17] Overdose was reported with conduction disturbances and torsades de pointes[32,33]
Haloperidol	4.0–7.1 ms[15,16,70] (oral)	2% of patients QTc > 500 ms[18] (iv)	Clinical ECG data available since 1987[16] Reports of torsades de pointes[18,34,35,36] and heart failure[37] Greater increase in QTc with higher dose[32] Overdose was reported with QTc prolongation, life-threatening ventricular arrhythmia, and torsades de pointes[38–42]

[a]Abbreviations: ECG = electrocardiogram, iv = intravenous, QTc = corrected QT interval.
[b]Range of maximum mean QTc changes reported in different studies.

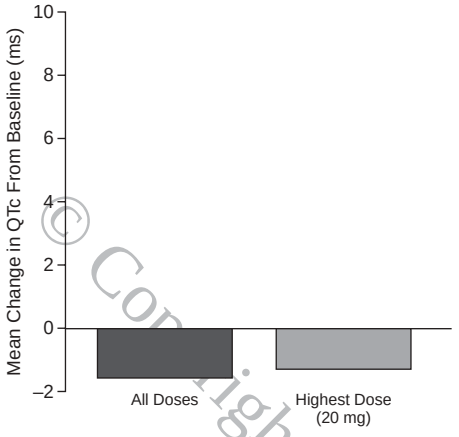
Table 2. Cardiac Safety Parameters Reported With Atypical Antipsychotic Drugs[a]

Atypical Antipsychotic	Mean QTc Change[b]	Threshold QTc Changes Associated With Torsades de Pointes (% patients with QTc > 500 ms)	Cardiac Safety Reports
Clozapine	Not reported	Not reported	Clinical ECG data available since 1985[50] Reports of cardiomyopathy,[51] atrial fibrillation,[52] and sudden cardiac death[53] Overdose was reported with decreased heart rate variability[54]
Risperidone	4.4–10.0 ms[43,70]	Not reported	Clinical ECG data available since 1997[43] Reports of cardiac arrest and QRS and QTc prolongation[55] Overdose was reported with adverse cardiac effects[56]
Sertindole	24–30 ms[44,70]	3.1%–4.0% of patients QTc > 500 ms[48]	Clinical ECG data available since 1997[48] Reports of QTc prolongation and 3.5% arrhythmia vs 1.3% in reference group[57] Greater increase in QTc with higher dose[48] Overdose was reported with torsades de pointes[58–60]
Olanzapine	–4.9 to 6.8 ms[43,45,70]	None[69]	Clinical ECG data available since 1997[61] Overdose was reported with sinus tachycardia[62–64]
Quetiapine	8–14.5 ms[46,70]	Not reported	Clinical ECG data available since 1997[46] Reports of ECG changes[15,65] Overdose was reported with prolonged QTc and tachycardia[66–68]
Ziprasidone (not yet approved in all countries)	4.7–20.6 ms[47,70]	0.06%–1.2% of patients QTc > 500 ms[49,70]	Clinical ECG investigations performed in comparison to marketed atypical antipsychotics[70] Reports of QT prolongation have led to delays in approval by the FDA[29]

[a]Abbreviations: ECG = electrocardiogram, FDA = U.S. Food and Drug Administration, QTc = corrected QT interval.
[b]Range of maximum mean QTc changes reported in different studies.

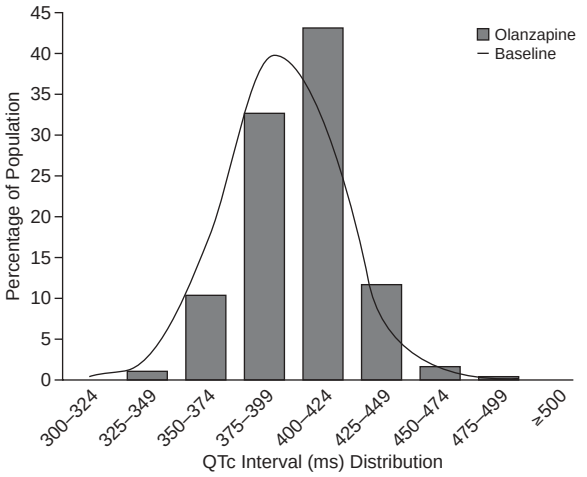
regression) of ECGs obtained from 495 psychiatric patients, robust predictors of QTc lengthening (defined from a healthy reference group as > 456 ms) included not only treatment with typical antipsychotics but also dose of antipsychotic.[4] Indeed, the majority of reported cases of serious cardiac events or sudden death occurred in patients prescribed more than 50 mg/day of either haloperidol or droperidol and after an overdose with drugs in each class (phenothiazine derivatives, diphenylbutylpiperidine derivatives, butyrophenones).

Figure 2. Mean Change in QTc From Baseline Following Olanzapine Treatment at All Doses (N = 955) or at the Highest Dose (N = 319) in Acutely Psychotic Patients[a]



[a]Data from Czekalla et al.[69] Abbreviation: QTc = corrected QT interval.

Figure 3. Distribution of All Corrected QT (QTc) Intervals at Baseline (N = 2700) and Maximum QTc Intervals With Olanzapine Treatment (N = 1342) in Acutely Psychotic Patients[a]



[a]Data from Czekalla et al.[69] Note that approximately 0.1% of patients at baseline showed QTc intervals > 500 ms, while no patient in the olanzapine-treated group had a QTc interval > 500 ms.

Atypical Antipsychotics

Similar to the typical antipsychotics, QTc prolongation has been reported for all atypical antipsychotics studied to date. However, differences among these drugs have been reported for the mean QTc increase and the percentage of patients showing QTc values > 500 ms. The largest mean increase in the QTc interval (range, 24–30 ms) was observed for sertindole,[44,70] whereas olanzapine[43,45,70] was temporally associated with the smallest change (range, –4.9 to 6.8) (see Table 2). In fact, in a large clinical trial comparing treatment efficacies of haloperidol with those of olanzapine, changes in mean QTc among the olanzapine dose groups were all decreases (range, –0.58 to –3.47 ms), and none were statistically different from control (Figure 2).[69] A review of baseline QTc values and change during olanzapine treatment in this trial and 2 other schizophrenia trials suggested normal random variability rather than a consistent drug effect.[69] Similarly, in a large clinical trial[43] comparing treatment efficacies of risperidone and olanzapine, risperidone-treated patients demonstrated a significant increase in QTc interval prolongation (4.4 ms) in comparison to olanzapine-treated patients who again showed a decrease (–4.9 ms). Very recently, a randomized study[70] in psychotic patients (N = 183) compared the effects of atypical and typical antipsychotics on the QTc interval at their estimated peak concentrations (T_{max}) following oral administration. The largest mean QTc prolongation was reported with thioridazine (35.8 ms), the next largest increase was caused by ziprasidone (20.6 ms), followed sequentially by quetiapine (14.5 ms), risperidone (10.0 ms), olanzapine (6.4 ms), and haloperidol (4.7 ms).[70] Only thioridazine and ziprasidone increased QTc by 75 ms or more in at least one study patient.[70]

An increased risk of developing malignant arrhythmias has also been associated with elevations in the QTc interval > 500 ms. Among the atypical antipsychotics, sertindole was associated with the greatest percentage of patients possessing a QTc interval > 500 ms (3.1%–4.0%).[48] A lower incidence (0.06%–1.2%) has been reported with treatment with ziprasidone.[49,70] Of interest, a recent clinical trial analysis of the distribution of QTc values in acutely psychotic patients revealed no evidence for QTc intervals > 500 ms in schizophrenia spectrum patients treated with olanzapine (Figure 3).[69] Furthermore, in the treatment of acute mania, no significant differences were noted between olanzapine- and placebo-treated patients with respect to the incidence of treatment-emergent QTc interval prolongation.[71] Most recently, comparative analyses of cardiac function following treatment with several atypical antipsychotics have revealed no pathologic effects of olanzapine in regard to heart rate variability or QTc intervals > 500 ms.[72]

Sertindole, which had the highest mean QTc increase and the greatest percentage of patients with a QTc interval > 500 ms, has been linked to torsades de pointes after overdose.[58–60] Olanzapine and risperidone were suggested to have a favorable overdose profile in comparison to the phenothiazines and butyrophenones.[64] Other reports of cardiac events temporally associated with an overdose of the atypical drugs include tachycardia, ECG changes, and a decrease in heart rate variability (see Table 2).

Other Variables Affecting Cardiotoxicity

Determining the role that antipsychotic drugs may play in clinical cardiotoxicity can be difficult in lieu of other factors that can increase the risk for cardiac dysfunction.

For example, the effect of a given drug on the QTc interval may be exacerbated by an interaction with other drugs or by the presence of other conditions that can increase QTc prolongation including severe bradycardia, electrolyte disturbances, and cardiac, nutritional, endocrine, and central nervous system disorders (reviewed in Tan et al.[9]). Furthermore, cardiac safety concerns may increase with the treatment of patients who possess an inherited form of LQTS (e.g., Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome; reviewed in Tan et al.[9]). Interestingly, even psychiatric illness itself, through alterations in parasympathetic and sympathetic autonomic regulation of heart rate variability, can contribute to cardiac liability.[73]

CONCLUSION

The precise etiology of sudden death in patients receiving antipsychotic medication is uncertain, but prolongation of the QTc interval and its association with cardiac arrhythmias like torsades de pointes is a possible cause. Reports of serious adverse cardiac events temporally associated with parenteral application, overdose, and higher dosages of phenothiazines (thioridazine, fluphenazine, chlorpromazine), pimozide, and butyrophenones (haloperidol, droperidol) have been frequently observed, although such events are typically fewer in number, and less severe, in patients treated with atypical agents. The available data do not suggest that olanzapine, as therapeutically administered to schizophrenia spectrum patients, contributes significantly to a QTc prolongation that could result in malignant arrhythmias.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

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