Analysis of the QTc Interval During Olanzapine Treatment of Patients With Schizophrenia and Related Psychosis

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Background: There may be a temporal association between some antipsychotics and prolongation of the heart-rate–corrected QT interval (QTc) representing a delay in ventricular repolarization. QTc prolongation significantly exceeding normal intraindividual and interindividual variation may increase the risk of ventricular tachydysrhythmias, especially torsade de pointes, and therefore, sudden cardiac death.

Method: Electrocardiogram recordings obtained as part of the safety assessment of olanzapine in 4 controlled, randomized clinical trials (N = 2700) were analyzed. These analyses were conducted to characterize any change in QTc temporally associated with olanzapine, compared with placebo, haloperidol, and risperidone, in acutely psychotic patients (DSM-III-R and DSM-IV) and to characterize variability and temporal course of the QTc in this patient population. Changes from baseline to minimum and maximum QTc were tested for significance, and baseline to acute-phase endpoint change in mean QTc was tested for significance within treatments and for differences between olanzapine and comparators. The possibility of a linear relationship between dose of olanzapine and mean change in QTc, as well as incidence of treatment-emergent prolongation of QTc (change from < 430 msec at baseline to ≥ 430 msec at endpoint), was tested.

Results: The incidence of maximum QTc ≥ 450 msec during treatment was approximately equal to the incidence of QTc ≥ 450 msec at baseline.

Conclusion: Results of these analyses suggest that olanzapine, as therapeutically administered to patients with schizophrenia and related psychoses, does not contribute to QTc prolongation resulting in potentially fatal ventricular arrhythmias.

(J Clin Psychiatry 2001;62:191–198)

Received March 28, 2000; accepted Feb. 1, 2001. From the Medical CNS Division, Lilly Deutschland, Bad Homburg, Germany (Dr. Czekalla); and Lilly Research Laboratories, Eli Lilly & Company, Lilly Corporate Center, Indianapolis, Ind. (Dr. Beasley, Mss. Dellva and Grundy, and Mr. Berg).

Sponsored by Eli Lilly and Company.

Appreciation is expressed to Suraja M. Roychowdhury, Ph.D., for technical assistance with the manuscript.

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The overall clinical experience with olanzapine, a novel antipsychotic effective in the treatment of psychosis, has been one of high tolerability with respect to extrapyramidal syndromes (EPS) as well as non-EPS adverse events.[1] Non-EPS adverse events, e.g., prolactin increase, sexual dysfunction, anticholinergic effects, or cardiovascular effects, can be associated in varying degrees with antipsychotics.[2]

Many antipsychotics have been associated with cardiovascular morbidity and mortality, including several of the first generation antipsychotics such as haloperidol, droperidol, pimozide, chlorpromazine, and thioridazine, as well as the novel (or second generation) antipsychotics such as risperidone and sertindole.[3–8] With some antipsychotics, changes in electrical activity of the myocardium, specifically prolongation of ventricular repolarization, reflected in prolongation of the heart-rate–corrected QT interval (QTc) of the electrocardiogram (ECG), have been observed.[9–11] Most reports refer to thioridazine, which has been associated with a potentially fatal polymorphic ventricular tachycardia termed *torsade de pointes*.[11] Sertindole was removed from the European market after reports of sudden death associated with a prolonged QTc interval (see Welch and Chue, for a recent review[12]).

The QT interval represents the ventricular repolarization time, and, because its length shortens with increasing heart rate, the QT interval corrected for heart rate (QTc) is determined (e.g., Bazett's formula [$QTc = QT/RR^{1/2}$][13]). QTc prolongation exceeding normal intraindividual and interindividual variation is thought to be due to alterations of ion channel functioning in the myocardium, at least in some cases, and might predispose patients to ventricular tachydysrhythmia.[14,15] Although there is no consensus as to a QTc value below which the risk of arrhythmia is minimal, some expert opinion has suggested a QTc of 500 msec as a lower limit for substantial risk of ventricular tachydysrhythmia.[16,17] However, the risk with most antipsychotics is considered to be less than with most tricyclic antidepressants.[18] Psychiatric illness itself, through alterations in parasympathetic and sympathetic autonomic activity, may contribute to alterations in QTc.[19] To evaluate the effect on QTc that might be temporally associated with olanzapine treatment, ECG recordings during treatment of patients with schizophrenia and related disor-

ders (DSM-III-R and DSM-IV), obtained as part of the safety assessment of olanzapine in controlled, randomized clinical trials, were analyzed.

METHOD

ECG Databases and Assessments

ECG recordings from 4 major schizophrenia and related psychoses clinical trials with double-blind, acute treatment periods of 6 to 8 weeks and with different doses of olanzapine versus placebo and/or active comparator (haloperidol or risperidone) were analyzed. Prior to any patient entering any of the clinical trials, the study was explained to each patient and written informed consent was obtained. The studies were study HGAD,[20] study HGAP,[21] study HGAJ,[22] and study HGBG.[23] Studies HGAJ[22] and HGBG[23] were variable-dose studies; for the purposes of endpoint dose-response analyses, a patient's final dose was considered to be that patient's dose group. Study HGAD[20] had 3 arms of olanzapine treatment with specified doses. Study HGAP[21] had only 1 effective dose (i.e., 10 mg), precluding a dose-response relationship analysis with doses associated with relevant clinical effect.

For the majority of patients, baseline ECGs were obtained during a medication washout period of 2 to 9 days before beginning double-blind treatment. However, if a baseline ECG was obtained more than 42 days before beginning double-blind treatment, it was excluded from analyses. For patients with multiple baseline ECGs, the ECG obtained closest to the beginning of double-blind treatment was used in the analyses.

Postbaseline ECGs in the acute phase were required to have been obtained while the patient was taking olanzapine or active comparator or within the 24-hour day (midnight to midnight) after the last day on which olanzapine or active comparator was taken. This period was within the half-life of olanzapine (31 hours). For patients with multiple postbaseline ECGs, the last ECG obtained during the acute treatment period was used for endpoint analyses. Generally, only 1 postbaseline acute phase ECG was obtained, either at the completion of that phase or at discontinuation from the study. These criteria were chosen to provide a database of endpoint ECGs for which patients were actually on drug treatment and stood no risk of being influenced by possible withdrawal effects as well as minimal risk of being influenced by new antipsychotic therapy.

Postbaseline ECGs in the continuation phase were required to have been obtained within 5 days of the last day on which olanzapine was taken. Only studies HGAD, HGAJ, and HGBG had double-blind continuation phases after the acute phase.

ECG Recording and Measurement

Twelve-lead ECGs were recorded at each investigative site with site equipment, generally with paper speed of 25 mm/sec. For studies HGAD, HGAP, and HGAJ, all ECGs were manually read and interpreted by a centralized cardiology facility blinded to treatment. For study HGBG, the QTc was measured at the investigative site. Bazett's formula,[13] $QTc = QT/RR^{1/2}$, was used for calculation of QTc.

Postmarketing Surveillance

A careful review of overdose experience reported to the Pharmacovigilance Department of Eli Lilly and Company, Indianapolis, Ind., during the first 2 years of olanzapine marketing was undertaken as potentially relevant to cardiac safety. In addition, a literature search was conducted on MEDLINE (1966–September 2000) to search for published cases of olanzapine overdose.

Statistical Analyses

The distribution of baseline QTc for patients in all 4 studies combined is described with a histogram. For those patients who received olanzapine therapy, the minimum and maximum postbaseline QTc values are described with histograms. Also, for those patients, the distributions of QTc change from baseline to minimum and to maximum are described with histograms.

For the multiple-dose trials (HGAD, HGAJ, and HGBG), the baseline to acute phase endpoint change in mean QTc is tested for significance within treatment groups with Student t test. Differences between olanzapine treatment groups and comparative treatment groups are tested for significance with analysis of variance (ANOVA), with dose group and investigative site (geographic region in study HGAJ) included in the model. The possibility of a linear relationship between dose of olanzapine and mean change in QTc is tested with ANOVA.

Differences between olanzapine treatment groups and comparative treatment groups in the incidence of treatment-emergent prolongation of QTc during the acute phase (change from < 430 msec at baseline to ≥ 430 msec at endpoint) are analyzed with the chi-square test for the multiple-dose trials. A possible linear relationship between olanzapine dose and incidence of acute phase treatment-emergent QTc prolongation is tested with the Cochran-Armitage test.

Incidences and patterns of potentially clinically significant increases in QTc (defined as ≥ 30-msec increase from baseline) and of potentially clinically significant prolongations (described as ≥ 430 msec) are described for all 4 studies combined.

RESULTS

Study Population

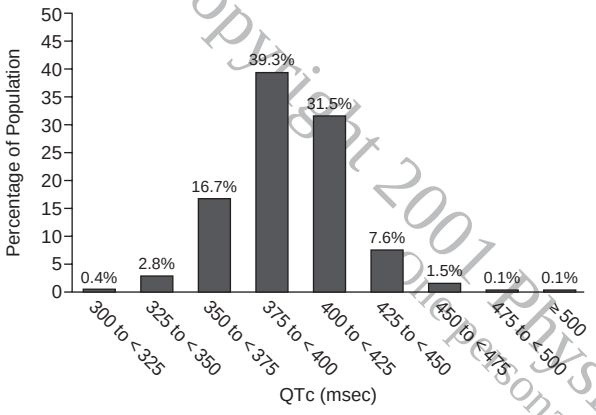
A total of 2700 patients were included in the baseline analyses for this study. Of these, 1342 were subsequently randomly assigned to olanzapine therapy. The baseline population was 32% female and 77% white. Other ethnic

Table 1. Percentiles for Baseline QTc Distribution in Acutely Psychotic Patients[a]

Percentile	QTc (msec)
1st	337.59
2.5th	347.09
50th	392.23
97.5th	444.50
99th	456.52

[a]N = 2700; includes patients from studies HGAD,[20] HGAP,[21] HGAJ,[22] and HGBG.[23]

Figure 1. Baseline QTc Distribution in Acutely Psychotic Patients[a]



[a]N = 2700; includes patients from studies HGAD,[20] HGAP,[21] HGAJ,[22] and HGBG.[23]

groups represented were African descent (14%), Hispanic (5%), east/southeast Asian (1%), and western Asian (1%). The mean ± SD age was 38 ± 11 years, the median age was 37 years, and the ages ranged from 18 to 86 years.

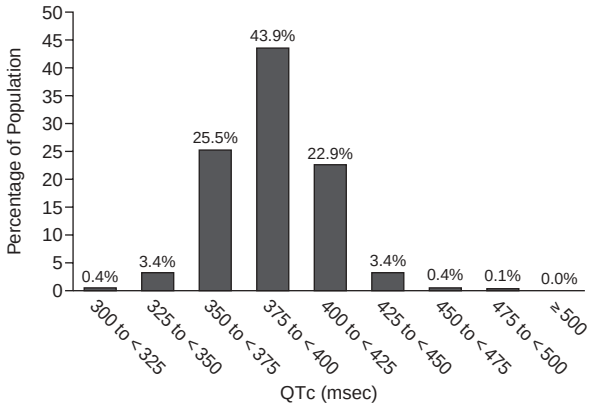
Baseline Distribution

For these analyses, 430 milliseconds was prospectively set as the threshold value defining a prolonged QTc. The validity of this limit was assessed through consideration of the distribution of baseline QTc values for the population of acutely psychotic patients in all 4 studies (total N = 2700). Table 1 displays a summary of the numerical descriptive findings, and Figure 1 provides a graphical representation. Using the 97.5th percentile to define the upper limit of a normal reference range[24] results in an upper limit of 444 msec for the population with schizophrenia. Use of the 99th percentile, which is sometimes used,[25] would extend this limit even higher (456 msec). Thus, 430 msec appears to be a conservative upper limit for a normal reference range in this psychotic patient population.

Minimum and Maximum Distributions

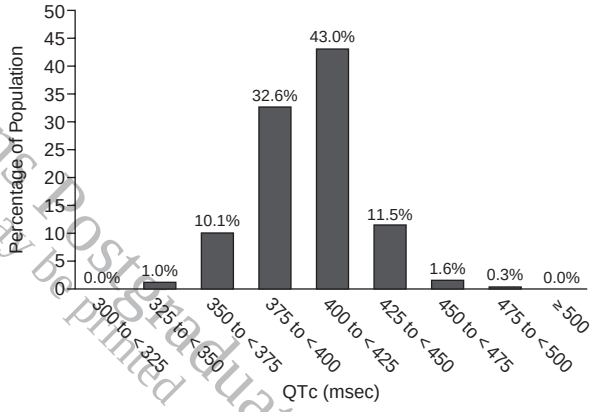
Figures 2 and 3 display the distributions of absolute minimum and maximum QTc values in 25-msec increments during olanzapine treatment for patients in all 4 studies combined who had a baseline and at least 1 post-baseline measurement (N = 1342). The percentage of patients with absolute maximum values ≥ 450 msec is comparable to the percentage of patients with baseline values ≥ 450 msec. In Figure 3, one can observe that 1.9% of olanzapine-treated patients had a QTc ≥ 450 msec based on their longest QTc during olanzapine treatment as compared to 1.7% of patients at baseline shown in Figure 1. These findings suggest that observed changes to maximum do not yield a distribution of values of potential clinical significance different from that observed at baseline. Additionally, no patient had a QTc ≥ 500 msec during olanzapine treatment.[16,17]

Figure 2. Distribution of Minimum QTc Values During Olanzapine Treatment[a]



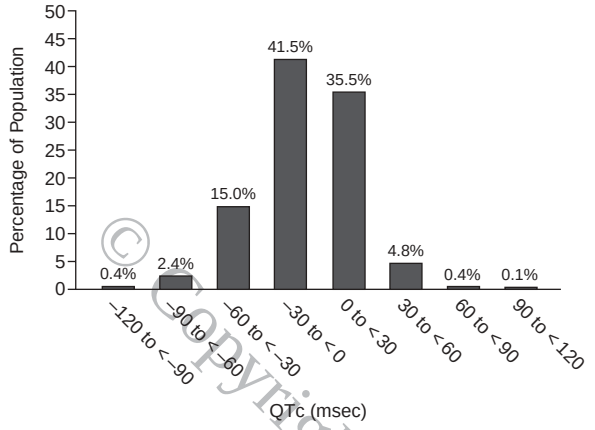
[a]N = 1342; includes olanzapine-treated patients from studies HGAD,[20] HGAP,[21] HGAJ,[22] and HGBG.[23]

Figure 3. Distribution of Maximum QTc Values During Olanzapine Treatment[a]



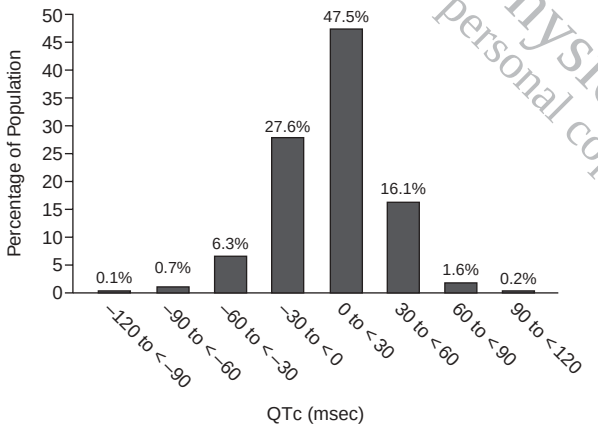
[a]N = 1342; includes olanzapine-treated patients from studies HGAD,[20] HGAP,[21] HGAJ,[22] and HGBG.[23]

Figure 4. Distribution of Change From Baseline to Minimum QTc Value During Olanzapine Treatment[a]



[a]N = 1342; includes olanzapine-treated patients from studies HGAD,[20] HGAP,[21] HGAJ,[22] and HGBG.[23]

Figure 5. Distribution of Change From Baseline to Maximum QTc Value During Olanzapine Treatment[a]



[a]N = 1342; includes olanzapine-treated patients from studies HGAD,[20] HGAP,[21] HGAJ,[22] and HGBG.[23]

Change From Baseline to Minimum and Maximum

Figures 4 and 5 illustrate the distribution of changes from baseline to minimum and maximum QTc, in 30-msec increments, during olanzapine treatment for all 4 studies combined. Changes in QTc were highly variable and symmetric around 0. A 30-msec or greater change in QTc may be considered potentially clinically significant.[26] The percentage of patients with changes to maximum ≥ 30 msec (17.9%) observed in Figure 5 is comparable to the percentage of patients with changes to minimum < –30 msec (17.8%) observed in Figure 4. This again emphasizes that QTc change values are highly variable over time during olanzapine treatment, but, importantly, this variability is symmetric around 0.

Table 2. Mean Change From Baseline to Endpoint in QTc Interval: Study HGAD,[20] Acute Phase

Therapy/ Dose Group	N[a]	Mean Change	SD	Within-Group p Value[b]	Vs Placebo p Value[c]	Vs Haloperidol p Value[c]	Linear Dose Response p Value[d]
Olanzapine							
5 ± 2.5 mg/day	44	–4.55	22.74	.191	.963	.156	.010
10 ± 2.5 mg/day	43	–6.51	23.61	.078	.899	.111	
15 ± 2.5 mg/day	47	8.44	27.12	.038	.004	.150	
Haloperidol							
15 ± 5.0 mg/day	44	0.97	26.07	.806	.144		
Placebo	42	–4.71	18.75	.111			

[a]N = patients with a baseline and at least 1 postbaseline ECG.
[b]p Value from Student t test.
[c]p Value from ANOVA.
[d]p Value from the linear contrast [–1 0 1] specified in the ANOVA.

Table 3. Mean Change From Baseline to Endpoint in QTc Interval: Study HGAJ,[22] Acute Phase

Therapy/ Dose Group	N[a]	Mean Change	SD	Within-Group p Value[b]	Vs Haloperidol p Value[c]	Linear Dose Response p Value[d]
Olanzapine						
5 mg/day	115	–3.47	24.80	.136	.149	.588
10 mg/day	152	–2.93	23.30	.123	.067	
15 mg/day	185	–0.58	22.45	.725	.002	
20 mg/day	319	–1.24	25.58	.388	.009	
Haloperidol						
5–20 mg/day	282	–7.34	23.53	< .001		

[a]N = patients with a baseline and at least 1 postbaseline ECG.
[b]p Value from the within-dose group Student t test.
[c]p Value from ANOVA.
[d]p Value from the linear contrast [–3 –1 1 3] specified in the ANOVA model.

Mean Change From Baseline to Endpoint

Mean change in QTc data and analyses for studies HGAD, HGAJ, and HGBG are displayed in Tables 2 through 4. As can be seen in Table 2, in study HGAD, the change in QTc for the olanzapine 15 ± 2.5 mg/day dose group was 8.44 msec and was statistically significant (p = .038). This increase associated with olanzapine 15 ± 2.5 mg/day differed from the 4.71 msec decrease in QTc associated with placebo (p = .004). The 0.97 msec increase within the haloperidol treatment group was not statistically significant. The haloperidol treatment group did not differ significantly from the placebo treatment group. None of the 3 olanzapine treatment groups differed significantly from the haloperidol treatment group. There was a significant linear relationship between olanzapine dose and change in QTc (p = .010).

As can be seen in Table 3, in study HGAJ, the within-olanzapine-dose-group changes in QTc were all decreases, and none were statistically significant. There was no linear relationship between dose and change in QTc. The 7.34-msec decrease observed with haloperidol treatment

Table 4. Mean Change From Baseline to Endpoint in QTc Interval: Study HGBG,[23] Acute Phase

Therapy/ Dose Group	N[a]	Mean Change	SD	Within-Group p Value[b]	Vs Risperidone p Value[c]	Linear Dose Response p Value[d]
Olanzapine						
10 mg/day	13	6.12	22.15	.339	.253	.342
15 mg/day	36	–7.83	23.09	.049	.129	
20 mg/day	85	3.46	27.91	.257	.972	
Risperidone						
4–12 mg/day	140	2.04	31.02	.437		

[a]N = patients with a baseline and at least 1 postbaseline ECG.
[b]p Value from the within-dose group Student t test.
[c]p Value from ANOVA.
[d]p Value from the linear contrast [–1 0 1] specified in the ANOVA model.

Table 5. Treatment-Emergent Prolonged QTc Interval (≥ 430 msec) at Endpoint: Study HGAD,[20] Acute Phase

Therapy/ Dose Group	N[a]	n[b]	%[c]	Vs Placebo p Value[d]	Vs Haloperidol p Value[d]	Linear Dose Response p Value[e]
Olanzapine						
5 ± 2.5 mg/day	42	0	0.0	n/a	> .999	.036
10 ± 2.5 mg/day	39	1	2.6	.494	> .999	
15 ± 2.5 mg/day	46	4	8.7	.120	.363	
Haloperidol						
15 ± 5.0 mg/day	42	1	2.4	> .999		
Placebo	40	0	0.0			

[a]N = number of patients with baseline QTc < 430 msec.
[b]n = number with prolonged QTc (≥ 430 msec) at endpoint.
[c]% = percentage of patients with prolonged QTc at endpoint.
[d]p Value from Fisher exact test.
[e]p Value from the Cochran-Armitage test.

Table 6. Treatment-Emergent Prolonged QTc Interval (≥ 430 msec) at Endpoint: Study HGAJ,[22] Acute Phase

Therapy/ Dose Group	N[a]	n[b]	%[c]	Vs Haloperidol p Value[d]	Linear Dose Response p Value[e]
Olanzapine					
5 mg/day	108	2	1.9	> .999	.539
10 mg/day	143	4	2.8	.727	
15 mg/day	169	9	5.3	.092	
20 mg/day	292	9	3.1	.430	
Haloperidol					
5–20 mg/day	259	5	1.9		

[a]N = number of patients with baseline QTc < 430 msec.
[b]n = number with prolonged QTc (≥ 430 msec) at endpoint.
[c]% = percentage of patients with prolonged QTc at endpoint.
[d]p Value from Fisher exact test.
[e]p Value from the Cochran-Armitage test.

Table 7. Treatment-Emergent Prolonged QTc Interval (≥ 430 msec) at Endpoint: Study HGBG,[23] Acute Phase

Therapy/ Dose Group	N[a]	n[b]	%[c]	Vs Risperidone p Value[d]	Linear Dose Response p Value[e]
Olanzapine					
10 mg/day	11	0	0.0	.613	.143
15 mg/day	31	1	3.2	.195	
20 mg/day	74	7	9.5	.644	
Risperidone					
4–12 mg/day	121	15	12.4		

[a]N = number of patients with baseline QTc < 430 msec.
[b]n = number with prolonged QTc (≥ 430 msec) at endpoint.
[c]% = percentage of patients with prolonged QTc at endpoint.
[d]p Value from Fisher exact test.
[e]p Value from the Cochran-Armitage test.

was statistically significantly different from the slight decreases observed in the olanzapine 15 mg/day and olanzapine 20 mg/day treatment groups.

As can be seen in Table 4, in study HGBG, there was a statistically significant (p = .049) within-treatment decrease in QTc observed in the olanzapine 15 mg/day treatment group (–7.83 msec) and nonsignificant increases observed in the olanzapine 10 mg/day and olanzapine 20 mg/day treatment groups. There was no significant linear relationship. The 2.04 msec increase observed with risperidone was not significant, and none of the 3 olanzapine treatment groups differed statistically significantly from risperidone.

Treatment-Emergent Prolongation at Endpoint

Treatment-emergent prolongation of QTc data and analyses for studies HGAD, HGAJ, and HGBG are displayed in Tables 5 through 7. As can be seen in Table 5, in study HGAD, the difference in the incidence of treatment-emergent prolongation of QTc did not reach significance with any of the olanzapine treatment groups compared with the placebo treatment group. However, as with the mean change data, there was a significant linear relationship between olanzapine dose and the incidence of QTc prolongation.

As can be seen in Table 6, in study HGAJ, the analysis of treatment-emergent prolongation of QTc yielded results similar to those seen in the mean change analysis, except that no olanzapine group differed significantly from the haloperidol group.

As can be seen in Table 7, in study HGBG, the results of the analysis of treatment-emergent prolongation of QTc were similar to the analyses of the mean change data.

Potentially Clinically Significant Measurements

On an individual basis, the sequential pattern of ECGs for patients who showed a potentially clinically significant increase in QTc (predefined as ≥ 30 msec) or an absolute prolonged QTc (≥ 430 msec, per definition) at any time during or within 5 days of last treatment with olanzapine fell into the following patterns:

- 245 patients (of 1555 patients with a baseline and at least 1 postbaseline ECG) with endpoint ECG obtained within 5 days of the last dose of olanzapine had a QTc increase ≥ 30 msec at any time after randomization. Their sequential ECGs fall into the patterns described in Table 8.

- Analysis of multiple and consistent QTc increases of ≥ 30 msec over baseline revealed only 2 patients (of 1555 patients) with an endpoint QTc increased by ≥ 70 msec (70 msec and 73.3 msec).
- 125 patients (of 1424 patients with a baseline ECG with QTc < 430 msec and at least 1 postbaseline ECG) with endpoint ECG obtained within 5 days of last dose of olanzapine had a QTc ≥ 430 msec. Their sequential ECGs fall into several patterns as shown in Table 9.
- Only 8 patients (of 1424 patients) showed multiple and consistent postbaseline and endpoint QTc values ≥ 430 msec, with 4 of these having values ≥ 450 msec and the greatest value being 462 msec.

Table 8. Number of Patients With a QTc Increase ≥ 30 msec at Any Time After Randomization

Endpoint QTc not increased ≥ 30 msec over baseline	77
Endpoint QTc increased ≥ 30 msec over baseline but other postbaseline QTc values not increased ≥ 30 msec over baseline	96
Only 1 postbaseline QTc and that QTc increased ≥ 30 msec over baseline	45
Multiple postbaseline QTc values and all increased ≥ 30 msec over baseline	27
TOTAL	245

Table 9. Number of Patients With a Baseline QTc < 430 msec and a QTc ≥ 430 msec at Any Time After Randomization

Endpoint QTc < 430 msec	41
Endpoint QTc ≥ 430 msec but other postbaseline QTc values < 430 msec	55
Only 1 postbaseline QTc and that QTc ≥ 430 msec	21
Multiple postbaseline QTc values and all ≥ 430 msec	8
TOTAL	125

Postmarketing Experience

Sponsor's adverse event database. A review of all adverse event reports received by Eli Lilly and Company during the first 2 years of marketing of olanzapine was conducted to find cases of probable overdose of olanzapine alone. There were 178 cases identified, and, in the majority of these cases, the patients were taking multiple concomitant medications although probably overdosing on olanzapine alone. Fatalities were reported (N = 9; only 1 reported as not taking concomitant psychotropic medications), but the pathophysiologic cascade leading to death could have involved processes other than alterations in cardiac electrophysiologic activity, such as sedation and respiratory depression. The reporting of these deaths does not establish an etiologic link to olanzapine. The lowest dose reportedly associated with a fatal outcome was 450 mg, but a patient received an overdose with 1500 mg and survived.

Results of ECGs and/or cardiac monitoring were explicitly reported for 33 patients. No cases of ventricular tachycardia, including torsade de pointes, or ventricular fibrillation were reported. The only significant ECG findings reported included 1 patient with 2 episodes of sinus pause that spontaneously resolved and 2 patients with supraventricular arrhythmias; 1 patient recovered fully, while the second had persistent mild sinus tachycardia at 5 days after the overdose.

Published literature. A search on MEDLINE using the terms *olanzapine* and *overdose* between the years 1966 to Sept. 2000 yielded 16 reports of 20 cases of olanzapine overdose.[27–42] Of these, 4 cases resulted in fatalities.[36,39,42] No conduction abnormalities were reported in any of these cases; tachycardia without arrhythmia was observed in 2 patients. A recent review of the overdose profiles of antipsychotic drugs, specifically olanzapine, clozapine, risperidone, and sulpiride, was conducted by the National Poison Information Service, London, over a 7-month period.[43] No fatalities were reported from overdose with any agent. Patients who had ingested overdoses several times the highest recommended doses of olanzapine had fewer adverse events than expected, and only 33% of patients experienced adverse events after ingesting 17.2 times the maximum recommended dose of olanzapine (1400 mg) compared with 66% reporting adverse events after ingesting only 3 times the maximum recommended dose of clozapine. Maximum overdoses (in terms of maximum recommended doses) for the 3 comparators were as follows: clozapine, 3.3; risperidone, 5.8; and sulpiride, 2.2. The authors concluded that olanzapine and risperidone were safer in overdose than the phenothiazines and butyrophenones.

DISCUSSION

Results of these analyses suggest that olanzapine, as therapeutically administered to patients with schizophrenia and related psychoses, does not contribute to prolonged QTc, which can cause potentially fatal ventricular repolarization. In the 3 studies with more than 1 effective dose, with a total of 10 dose groups evaluated, only 1 (olanzapine 15 ± 2.5 mg/day, study HGAD) showed a statistically significant increase in QTc (8.44 ± 27.12 msec, p = .038) and 1 dose group (olanzapine 15 mg/day, study HGBG) showed a statistically significant decrease in QTc (–7.83 ± 23.09 msec, p = .049). Therefore, only 2 of 10 olanzapine dose groups showed a statistically significant within-group change in QTc, and 1 of these was an increase, while the other was a decrease. The olanzapine 15 ± 2.5 mg/day group in study HGAD did differ significantly from placebo with respect to mean change in QTc, where placebo was associated with a 4.71 ± 18.75 msec decrease (p = .004) contributing to the total difference between treatment groups. As only study HGAD allowed for olanzapine treatment groups to be compared with placebo, this constitutes 1 of 3 comparisons showing a statistically

significant difference from placebo. Importantly, the incidence of treatment-emergent prolongation of QTc, a more clinically relevant result than mean change, in study HGAD did not differ significantly between olanzapine 15 ± 2.5 mg/day and placebo. In both the mean change analysis and the categorical analysis of treatment-emergent prolongation, significant relationships were shown between dose and QTc. However, this represents only 2 of 6 analyses showing significant dose-response relationships. Additionally, in study HGAJ, the study that provided the greatest number of patients, the changes (mean decrease in QTc with all dose groups) and the incidence of prolongation were modest, and dose-response relationships were not observed.

A few methodological issues need to be addressed. For the majority of patients, baseline ECGs were obtained during a medication washout period of 2 to 9 days before double-blind treatment. Thus, it is possible that the previously administered drug had not washed out completely, since most of the patients had been treated for a significant period of time with antipsychotic drugs. Under these circumstances, the change in the QTc interval may have been affected by a previous antipsychotic drug effect. In study HGAD, placebo treatment did result in a reduction in the QTc interval (see Table 2). However, as mentioned above, treatment-emergent changes in the QTc interval during olanzapine therapy were inconsistent, with one study showing an increase and another a decrease in the QTc interval.

The pooled data considering both acute and continuation therapy with olanzapine also serve to suggest that olanzapine does not have a clinically significant influence on QTc. The incidence of maximum QTc ≥ 450 msec during treatment was approximately equal to the incidence of QTc ≥ 450 msec at baseline.

These clinical findings are consistent with recent preclinical results. In a perfused feline heart model, olanzapine at a concentration of 1 μM (310 ng/mL) produced an approximately 7% increase in QT interval; at a higher concentration of 10 μM (3100 ng/mL), an approximately 26% increase in QT interval was observed.[44] The mean plasma concentration observed for olanzapine in 10,519 samples from patients administered between 5 and 20 mg/day in clinical trials was 24.5 ng/mL, with the median being 18.85 ng/mL, the 99th percentile being 95.5 ng/mL, and the maximum being 211.3 ng/mL (data on file, Eli Lilly and Company, Indianapolis, Ind.). Further, in the patient, olanzapine is approximately 93% plasma protein bound, reducing the effective free concentration to approximately 7% of the total circulating concentration. These preclinical data suggest that olanzapine, as administered in a dose range of 5–20 mg/day, would have no clinically significant adverse effect on QTc.

The data presented here can assist in defining a reference range for QTc in an acutely psychotic population with schizophrenia, schizophreniform disorder, and schizoaffective disorder. Although the upper limit of normal for QTc has traditionally been defined as < 440 msec,[26,45,46] a limit of < 430 msec was used in these analyses, consistent with the regulatory submission analyses for olanzapine.[47] Recent literature[48] has suggested that in normal males a QTc < 450 msec should not be considered prolonged, whereas in females a QTc < 470 msec should not be considered prolonged. Dekker and colleagues[49] have reported data in which the 97.5th percentile for QTc is 437.5 for middle-aged men. De Bruyne and colleagues[50] reported the 75th percentile for QTc to be 437 msec for males and 446 msec for females in an older population. Although there is no consensus as to a QTc value below which the risk of a malignant ventricular tachydysrhythmia is minimal, some expert opinion has suggested a QTc of ≥ 500 msec as a lower limit,[16,17] and some authors have extended this to ≥ 550 msec.[51]

The baseline data presented here for patients with schizophrenia or related psychoses suggest an upper limit of 444 msec using the 97.5th percentile and 456 msec using the 99th percentile, as upper limits for a reference range.

Several authors have suggested substantial normal intraindividual variation in QTc. Morganroth and colleagues[26] reported the mean within-subject variability in QTc over 7 ECGs obtained up to 12 hours after placebo administration to be 12 msec in normal volunteers and 2 standard deviations to be ± 24 msec, and 15 msec in cardiac patients and 2 standard deviations to be ± 30 msec. An average variability of 56 msec was observed with 40 ECGs obtained during placebo administration.[51] Taking a conservative approach, Pratt and colleagues[51] calculated that an increase in QTc of 35 msec while receiving drug therapy is likely to represent a drug effect at the 95% confidence interval. Morganroth and colleagues,[16] based on 24 hour Holter monitoring in healthy men, found the mean diurnal variation in QTc to be 76 ± 19 msec, with 1 patient showing a maximum of 102 msec diurnal variation. Therefore, the incidence of shifts in QTc of ≥ 30 msec, rather than reflecting drug effect, may reflect, to a great extent, normal intrasubject variability.

Funck-Brentano and Jaillon[52] cite literature indicating that although the QT shortens in the QRST cycle after an abrupt increase in heart rate, steady-state adjustment may not be achieved for 2 to 3 minutes and that the commonly used Bazett formula for calculating QTc ($QTc = QT/RR^{1/2}$) may not be optimal. These considerations further influence the interpretation of the QTc in a severely disturbed psychiatric population with increased liability for marked and rapid fluctuations in autonomic tone. In conclusion, and particularly when considering the fact that 430 msec is a rather low threshold for the predefined reference range limit, change during olanzapine treatment might represent normal random variability rather than a consistent drug

effect. The consideration of cardiovascular safety for an individual patient should always include consideration of existing cardiovascular risk factors, concomitant medications, and changes in the status of the psychiatric disorder.

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

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