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Factors Affecting the Degree of QT Prolongation with Drug Challenge in a Large Cohort of Normal Volunteers:

QT Prolongation with Drug Challenge in Normals

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Abstract

Background—The degree of QT prolongation by drug is highly variable and related to risk for polymorphic ventricular tachycardia due to drugs.

Objective—to determine factors that affect the degree of QT prolongation by drugs.

Methods—QT and QTc were measured before and after administration of the QT-prolonging drug ibutilide in 253 normal volunteers aged 18-40 years. Drug effect on QTc prolongation was defined as $\Delta\text{QTc} = \text{QTc after drug} - \text{QTc before drug}$.

Results—Ibutilide prolonged QT from 396 ± 31 ms to 418 ± 39 ms ($P < 0.001$) and QTc from 406 ± 15 ms to 446 ± 33 ms ($P < 0.001$). The ΔQTc did not correlate with baseline QTc (Pearson correlation 0.016, $P = 0.8$). Post-drug QTc was correlated weakly with pre-drug QTc (Pearson correlation 0.484, $p < 0.001$), and strongly with ΔQTc (Pearson correlation 0.882, $P < 0.001$). ΔQTc was identical for men and women (39 ± 29 ms vs. 39 ± 27 ms, $P = 0.9$), but displayed significant differences among body mass index categories ($P < 0.001$). Overweight (48 ± 27 ms) and obese (61 ± 31 ms) subjects had significantly more QT prolongation by drug than normal (31 ± 25 ms) or underweight (24 ± 12 ms) subjects.

Conclusions—QT prolongation by ibutilide does not correlate to baseline QTc, and does not differ between men and women. Overweight and obese subjects have greater drug effect on QTc than subjects with normal or low body mass index. These findings have implications for drug-induced long QT syndrome.

Keywords

Electrocardiography; Obesity; Ion channels; Pharmacology; QT interval

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Introduction

Prolongation of cardiac repolarization, as measured by the QT interval on the surface electrocardiogram (ECG), can be associated with the development of a potentially fatal polymorphic ventricular tachycardia termed Torsades de Pointes (TdP).^{1,2} QT prolongation occurs in the congenital long QT syndrome, and also as an “acquired” condition, most often due to drug administration.³ The risk for drug-induced long QT syndrome is one of the most common causes of withdrawal or restriction of drugs that have already been marketed.⁴ Unfortunately, the ability to predict this serious side effect is poor, both for individual patients and for populations of patients who are exposed to a given drug. While the degree of QT prolongation is imperfectly related to risk for ventricular arrhythmias, it remains a primary tool for evaluation of proarrhythmic risk of drugs, and guidelines regarding evaluation of QT prolongation in drug development have been endorsed by regulatory agencies.⁵

Several risk factors for drug-induced long QT syndrome have been identified, including hypokalemia, bradycardia, associated heart disease, female gender, and use of multiple drugs which prolong the QT interval or which interfere with metabolism or distribution of QT prolonging drugs.^{6,7,8,9} In addition, we have previously shown that dietary salt can affect QTc and its response to drug challenge.¹⁰ The purpose of this study was to investigate non-environmental factors which affect the degree of QT prolongation by drug. To minimize environmental effects on the QT interval, we chose to study young healthy subjects without heart disease or electrolyte abnormalities, and brought them into salt balance. We evaluated the effects on QT shortly after intravenous challenge with ibutilide, a drug known to prolong the QT and with risk for TdP,¹¹ to eliminate the confounding effects of variable drug metabolism.

Methods

Study population

The subjects for this study were healthy individuals, aged 18-40 years. Healthy was defined as no significant past medical history, no concurrent medications, normal physical exam, normal baseline electrocardiogram, and normal pre-study complete blood count, serum electrolytes, and liver function tests. Female subjects were required to have a negative urine pregnancy test. Subjects refrained from alcohol and caffeine during the study period. Subjects were brought into salt balance with 7 days of a diet containing 100 mEq/day of sodium and 100 mEq/day of potassium supplied by the Bionutrition Research Service of the Vanderbilt General Clinical Research Center.¹⁰ Salt balance is generally achieved on this diet in 4 days. After the 7-day dietary period, subjects came to the General Clinical Research Center after an overnight fast for the study protocol described below. All subjects gave written informed consent prior to entering the study. The protocol was approved by the Vanderbilt University Institutional Review Board.

Study protocol

Subjects were placed in a supine position and ECG leads and a peripheral intravenous line were placed. After a 10 minute rest period, a baseline ECG was obtained (pre-drug) and serum samples obtained for electrolyte analysis. Subjects then performed exercise on an electrically braked recumbent bicycle ergometer, using a staged 12 minute protocol; these data are not reported here. After recovery from exercise, when the heart rate had returned to within 5% of baseline, ibutilide 10 µg/kg (up to a maximal dose of 1 mg) was administered intravenously over 10 minutes. Ten minutes after the end of the infusion, the post-drug ECG

was obtained, serum drawn for electrolyte analysis, and the exercise protocol was repeated. Subjects were monitored continuously for any evidence of arrhythmia for 4 hours after the study.

Electrocardiographic analysis

Electrocardiograms were obtained using an analog system at 25-mm/sec paper speed, 10-mm/mV gain and 40-Hz low pass filter setting without a notch filter (Marquette MAC 5000, GE Medical Systems, Milwaukee, WI). QT interval measurements were performed automatically, and with manual inspection and over-reading by a single observer. The start of the QT interval was defined as the earliest deflection of the QRS complex and the end was defined as the point at which the maximal downward slope of the T wave crossed the isoelectric point (tangent method)^{12,13}; U waves were considered an element of the T wave complex if the U wave amplitude was greater than half of the total TU complex amplitude. QT intervals were corrected for heart rate using Bazett's formula. The drug-induced change in QTc was calculated as: $\Delta QTc = \text{post-ibutilide QTc} - \text{baseline QTc}$.

Statistics

Normally distributed data are reported as mean $\pm$ 1 S.D. Body mass index (BMI) was calculated as weight in kilograms divided by the height in meters squared. Subjects were categorized as underweight (BMI < 18.5), normal (BMI 18.5-25), overweight (BMI 25-30) or obese (BMI > 30).¹⁴ Comparisons of normally-distributed data were accomplished with a Student's or paired *t*-test as appropriate, or with one-way ANOVA with least significant difference used for post-hoc analysis. Categorical values were compared with χ^2 . Pearson's correlation was used for continuous variables. A two-tailed P-value $\leq$ 0.05 was considered statistically significant. Data were analyzed using the statistical software SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Study Subjects

A total of 317 subjects consented to the study protocol, 64 subjects are not included for either non-compliance with the week-long prescribed diet, abnormal serum potassium (> 5.5 mEq/L), or abnormal baseline QTc (> 450 ms in males, > 470 ms in females), thus 253 subjects are included in the analysis. In all subjects who received ibutilide, there were no adverse events or arrhythmias. Serum potassium was 3.9 ± 0.3 mEq/L at baseline, and 4.0 ± 0.3 mEq/L after ibutilide. Study subjects had a mean age of 27 ± 5 years, and 153 (60%) were women. The BMI categories had the following distribution: 3% underweight; 58% normal BMI, 26% overweight and 12% obese. There was no significant gender imbalance among BMI groups ($P=0.58$).

Ibutilide effects on QTc

In the entire cohort, the baseline heart rate was 64 ± 11 bpm, baseline QT 396 ± 31 ms, and baseline QTc 406 ± 15 ms. As expected, ibutilide prolonged both the absolute QT (418 ± 39 ms, $P < 0.001$) and the QTc (446 ± 33 ms $P < 0.001$). The post-ibutilide heart rate was slightly faster (69 ± 11 bpm) than baseline heart rate, so QTc is used for subsequent comparisons. The drug effect on QTc (ΔQTc) had no correlation to baseline QTc (Pearson correlation 0.016, $P = 0.8$, see Figure 1). The post-drug QTc was significantly correlated with the pre-drug QTc (Pearson correlation 0.484, $p < 0.001$), but correlated very strongly with ΔQTc (Pearson correlation 0.882, $P < 0.001$). In other words, variability in post-drug QTc was influenced predominantly by the degree of QTc prolongation by drug (77%) rather than by baseline QTc (23%).

The Effect of Gender and Body Mass Index on Δ QTc

Prior to ibutilide infusion, women had significantly longer QTc than men (411 ± 15 ms vs. 399 ± 13 ms, $P < 0.001$). After ibutilide, QTc remained significantly longer in women compared to men (450 ± 33 ms vs. 439 ± 31 ms, $P = 0.01$), however, the Δ QTc was nearly identical (39 ± 29 ms for women vs. 39 ± 27 ms for men, $P = 0.9$, see Table 1). There was a significant difference in baseline QTc among BMI groups ($P=0.01$) with obese subjects having a significantly longer QTc (414 ± 18 ms) compared to normal (406 ± 4 ms, $P=0.041$) and overweight subjects (404 ± 13 ms, $P=0.02$). After ibutilide, there was a significant difference in QTc among BMI groups ($P<0.001$) with obese subjects having significantly longer QTc (475 ± 38 ms) than all 3 other groups (normal subjects 437 ± 29 ms, $P<0.001$; underweight subjects 437 ± 19 ms, $P=0.01$; overweight subjects 453 ± 29 ms, $P=0.01$). Overweight subjects also had significantly longer QTc compared to normal subjects, $P=0.01$. There was no significant difference in QTc between normal and underweight subjects either before or after ibutilide. The Δ QTc also displayed significant differences among BMI categories ($P<0.001$, see Figure 2). There was no significant difference in Δ QTc between underweight (24 ± 12 ms) and normal subjects (31 ± 25 ms), but overweight (48 ± 27 ms) and obese (61 ± 31 ms) subjects had significantly more QT prolongation by drug.

As the dose of ibutilide was based on weight, one possible explanation for the exaggerated drug effect in overweight and obese subjects is the higher absolute dose received. In a subset of subjects > 100 kg ($n=15$; 2 overweight, 13 obese), all received the maximum dose (1 mg) of ibutilide, allowing an investigation of the relationship between BMI and Δ QTc in subjects receiving the same absolute dose of drug. In this subset, Δ QTc was 34 ± 45 ms in the 2 overweight subjects, and 75 ± 25 ms in the 13 obese subjects ($p=0.07$). When treated as a continuous variable, BMI correlated strongly with Δ QTc in the entire cohort of 253 subjects (Pearson correlation 0.436, $p<0.001$). When limited to the subjects > 100 kg, a similar trend was observed (Pearson correlation 0.406, $p=0.13$), with greater drug effect in those with higher BMI, despite the same absolute ibutilide dose (and a smaller per kilogram dose). While the comparisons within the small subset did not have adequate power to reach statistical significance, the consistently observed trends suggest that the greater drug effect in overweight and obese subjects in the entire cohort is not strictly due to ibutilide dose.

Discussion

Prolongation of the QT interval by drugs can be associated with potentially fatal ventricular arrhythmias, and multiple factors which associate with excessive prolongation and torsades de pointes have been identified.^{15,7} In order to investigate non-environmental factors that affect the degree of QT prolongation by drug, we challenged subjects with ibutilide in a tightly controlled setting. Our subjects were healthy, in a relatively narrow age range, underwent dietary modification to achieve salt balance, and we excluded those with abnormal serum electrolytes or abnormal baseline QTc. Among our major findings, the first is that the degree of QT prolongation by drug (Δ QTc) had no correlation to baseline QT interval. The QTc after ibutilide correlated with baseline QTc, but much more tightly with Δ QTc. Thus, in our study, post-drug QTc was more strongly influenced by Δ QTc than by baseline QTc. If this were true in other populations as well, it would suggest that risk of TdP is more strongly influenced by Δ QTc than by baseline QTc. Indeed, this is consistent with the prior observation that patients with drug-induced long QT syndrome with TdP had higher Δ QTc, but not pre-drug QTc, than those without TdP.¹⁶ Similarly, Kaab et al performed acute intravenous sotalol challenge in patients with a history of drug-induced TdP and compared the QT response to control subjects. Those with a history of drug-induced TdP had greater Δ QTc and post-drug QTc, while baseline QTc did not differ.¹⁷

Secondly, despite a known increased risk for drug-induced long QT syndrome in women, we found no gender difference in Δ QTc. While women had a longer QTc than men at baseline and after drug, the change in QTc with drug was identical. This and the above findings are in contrast to those reported by Lehman et al,¹⁸ who observed that with chronic sotalol therapy, Δ QTc was inversely related to baseline QTc, and women were found to have greater Δ QTc compared to men. Of note, those subjects were patients enrolled in various clinical trials, and differed significantly from our normal, young cohort in several ways including older age (56-60 years of age) and presence of associated heart disease (35-63% with ischemic heart disease, 16-19% with heart failure, and 21-42% with sustained ventricular tachycardia). Furthermore changes in QTc in that study were assessed over the course of days to months, allowing the possibility of additional factors which modify QT prolongation (e.g. salt balance, electrolyte abnormalities). Our study of acute (10 minute) effects of ibutilide in young, healthy subjects in salt balance likely minimize these environmental factors. Furthermore, variability in drug absorption, metabolism, and elimination are minimized by our study design. The acute sotalol challenge performed by Kaab et al is comparable to the present study design and yielded results consistent with our findings.¹⁷

Another major finding is that Δ QTc was significantly longer in overweight and obese subjects compared to underweight subjects and those with normal BMI. At baseline, obese subjects had longer QTc than normal or overweight subjects, which is consistent with previous studies.^{19,20,21} The degree of QT prolongation by drug was similar in underweight and normal subjects, but longer in overweight subjects and markedly longer (61 ± 31 ms) in obese subjects. Thus, obese subjects appear to be at highest risk for drug-induced long QT syndrome, given the longer QTc at baseline and larger drug effect. The mechanisms underlying the greater Δ QTc in obese subjects are uncertain, but several lines of evidence suggest that obesity-induced changes in autonomic function may contribute. It is known that among obese subjects, QTc correlates tightly with plasma free-fatty acid levels,²² and that elevating free-fatty acid levels in normal and obese subjects stimulates cardiac sympathetic nervous activity, increases serum catecholamines, and prolongs the QT.²³ Thus, autonomic dysfunction has been implicated as the mechanism of QT prolongation associated with obesity.²⁴ We have previously shown that sympathetic activation increases the degree of QT prolongation by quinidine,¹⁰ and that autonomic tone affects the degree of QT prolongation by ibutilide.²⁵ Although not investigated in this study, autonomic dysfunction may underlie the greater Δ QTc in obese subjects as well. Previous studies have shown that weight loss reduces QTc, free-fatty acids, and serum catecholamines in obese subjects;²⁶ it is unknown if drug effects would normalize as well. As we did not measure drug levels in our study, it is possible that serum levels were higher in obese subjects, which could underlie the greater drug effect in obese subjects. The consistent trends observed in the subgroup > 100 kg who received the same 1 mg dose suggests that the greater drug effect in heavier subjects is not simply dose-related.

One limitation of our study is that the findings in normal volunteers may not be applicable to patients exposed to QT-prolonging drugs. We chose to study these subjects to eliminate potential environmental effects on the QT interval; nevertheless these effects are important in clinical practice. It is possible that exercise performed prior to the administration of ibutilide affected the QTc, but we attempted to minimize such effects by postponing drug infusion until the heart rate had returned to within 5% of the baseline heart rate. Another limitation is that we studied the intermediate phenotype of QT prolongation, rather than the actual clinical outcome of interest, TdP, for obvious safety reasons. While QT prolongation is not perfectly related to the risk of TdP, it remains a primary tool for evaluation of proarrhythmic risk of drugs. We did not observe any arrhythmias in our study sample, while ibutilide is associated with a roughly 4% risk of TdP in patients.¹¹ The impact of associated heart disease, electrolyte abnormalities, and concomitant drug use in patients, and their

absence in our study sample likely accounts for this observation. Another possibility is that the major indication for ibutilide use in patients is to convert atrial fibrillation, and recent conversion from atrial fibrillation is a newly recognized risk factor for TdP.²⁷ While most drugs that prolong the QT interval share the same mechanism (potent I_{Kr} block) as ibutilide, the results we observed may not be applicable to all QT-prolonging drugs. We used Bazett's rate correction for QTc due to its widespread clinical use however any rate correction formula has limitations. Finally, we did not measure drug levels in our study.

Conclusion

In conclusion, QT prolongation by ibutilide does not correlate to baseline QT, and does not differ between men and women. The degree of QT prolongation by drug may be more relevant to risk for TdP than baseline QT. Overweight and obese subjects have greater drug effect on QTc than subjects with normal or low body mass index. These findings have implications for drug-induced long QT syndrome, with obese subjects at particularly high risk due to QT prolongation at baseline, and greater QT prolongation by drug.

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Abbreviations

BMI	body mass index
ECG	electrocardiogram
TdP	torsades de pointes

Figure 1. Scatterplots of baseline QTc, post-drug QTc, and Δ QTc

The Δ QTc shows no correlation to baseline QTc ($P=0.8$, top left panel). The post-drug QTc correlates significantly, but weakly, with baseline QTc ($P<0.001$, $R^2=.23$, right panel), and strongly with Δ QTc ($P<0.001$, $R^2=.77$, bottom left panel).

Figure 2. Body Mass Index affects ΔQT_c

The ΔQT_c (mean + 1 SEM) is plotted for all subjects by BMI category. There is no significant difference in ΔQT_c between underweight and normal subjects, but overweight and obese subjects have significantly more QT prolongation by drug.

Table 1

QTc before and after ibutilide.

	Baseline QTc	Post-ibutilide QTc	Δ QTc
All subjects (N=253)	406 $\pm$ 15	446 $\pm$ 33	39 $\pm$ 28
Women (N=153)	411 $\pm$ 15	450 $\pm$ 33	39 $\pm$ 29
Men (N=100)	399 $\pm$ 13	439 $\pm$ 31	39 $\pm$ 27
Underweight (N=8)	413 $\pm$ 15	437 $\pm$ 19	24 $\pm$ 12
Normal BMI (N=147)	406 $\pm$ 15	437 $\pm$ 29	31 $\pm$ 25
Overweight (N=66)	404 $\pm$ 13	453 $\pm$ 29	48 $\pm$ 27
Obese (N=32)	414 $\pm$ 18	475 $\pm$ 38	61 $\pm$ 31

BMI = body mass index. Underweight = BMI < 18.5, normal = BMI 18.5-25, Overweight = BMI 25-30, Obese = BMI > 30.