Sildenafil Citrate Does Not Affect QT Intervals and QT Dispersion: An Important Observation for Drug Safety

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Background: Sildenafil is an effective and widely used therapeutic agent for erectile dysfunction. Deaths have been reported due to sildenafil use and most of them are attributed to concurrent use of nitrates. However, the effects of sildenafil on QT intervals, QT dispersion, and the possible risk of ventricular arrhythmia have not been studied before. Our aim in this study was to evaluate the effect of sildenafil citrate on QT intervals and QT dispersion.

Methods: Thirty-six patients with erectile dysfunction were included in this study. Twenty-one patients had coronary artery disease whereas 12 of them also had accompanying diabetes mellitus. Standard 12-lead electrocardiograms (ECG) were recorded three times: before, and at the first and fourth hours of 50 mg sildenafil citrate ingestion. All QT parameters were corrected for heart rate.

Results: Mean age of the patients was 54 ± 12 years. The mean heart rate did not differ significantly between the three ECG examinations. The corrected and uncorrected maximum and minimum QT intervals were not significantly different between the three ECG examinations. The QT dispersion and corrected QT dispersion before and 1 hour and 4 hours after sildenafil ingestion were 31 ± 9 ms, 36 ± 10 ms; 32 ± 11 ms, 37 ± 14 ms; 27 ± 8 ms, 32 ± 9 ms, respectively ($P > 0.05$).

Conclusions: Sildenafil does not prolong QT intervals or increase QT dispersion in patients with erectile dysfunction. Our results suggest that the risk of ventricular arrhythmia does not increase with ingestion of 50 mg sildenafil.

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Erectile dysfunction is a relatively common problem in elderly males. Most patients with vasculogenic erectile dysfunction have one or more significant cardiovascular risk factors (hypertension, smoking, diabetes mellitus, high total cholesterol, low serum levels of high-density lipoprotein) and hence may have asymptomatic coronary artery disease.[1,2] According to the data from the Massachusetts Male Aging Study, the prevalence of erectile dysfunction is 39% in 40-year-old men, and 67% in 70-year-old men.[3]

Sildenafil is a cyclic guanosine monophosphate (c-GMP) specific phosphodiesterase type 5 (PDE5) inhibitor.[4–6] Phosphodiesterase type 5 degrades the c-GMP and is located mainly in the cavernous body, thrombocytes and vascular smooth muscle cells.[7] Thus, sildenafil selectively increases the levels of c-GMP.[4,5] It shows far less affinity to other isozymes of the phosphodiesterase, including PDE1 which is abundant in the ventricular myocytes.[8]

Sildenafil citrate is the first oral agent used for the treatment of erectile dysfunction and has been a major development in this field.[4,9] The most frequent side effects are associated with vasodilation, and include headache, facial flushing, and small decreases in blood pressure. In the presence of concurrent use of organic nitrates, significant hypotension may occur and may even result in death. Therefore, patients on nitrate therapy should avoid taking sildenafil. Sildenafil has also been reported to be potentially hazardous in patients with active coronary ischemia, congestive heart failure with

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low blood pressure, and in patients taking drugs that can slow down the elimination of sildenafil (drugs that are metabolized by or that inhibit cytochrome P450 3A4).[10]

After the worldwide prescription of sildenafil, deaths ascribed to its usage were reported. Hypotension is thought to be the most frequent mechanism of death in these patients. However, little is investigated about other possible aspects of cardiac involvement in sildenafil users. Ventricular arrhythmias may play a role in deaths due to sildenafil use. Indeed, the high frequency of erectile dysfunction among cardiac patients may further increase the risk of arrhythmias. QT interval prolongation and increased QT dispersion have been suggested as predictors of ventricular arrhythmias. However, QT interval prolongation and QT dispersion in patients taking sildenafil has not been studied before. Thus, our aim in this study was to investigate the effects of oral sildenafil citrate on QT intervals and QT dispersion.

METHODS

Study Subjects

Thirty-six patients (mean age 54 ± 12, range 32–71 years) participated in this study. Drugs that can prolong the QT interval resulting in polymorphic ventricular tachycardia (torsade de pointes) are well known.[11] None of our subjects were taking any medicine that could affect the QT interval, including beta-adrenergic receptor blockers and antiarrhythmic drugs. The patients did not take any medication that could alter serum levels of electrolytes. Twenty-one of the patients had known coronary artery disease, among which four patients also had previous myocardial infarction. In the remaining 15 patients, the presence of coronary artery disease was excluded by the absence of any symptoms or signs typical for coronary artery disease. Twelve patients had diabetes mellitus. Among the medications of the patients were low dose aspirin (300 mg/day), amlodipine, isosorbide-5-mononitrate, acarbose, gliclazide, and glimepiride.

Study Design

Erectile dysfunction patients who were eligible for sildenafil treatment were informed about the risks of sildenafil use. They were advised to ingest the first dose of sildenafil citrate (50 mg) at the hospital. All patients gave oral informed consent. Standard 12-lead electrocardiograms (ECG) were recorded three times: before sildenafil ingestion, one hour after sildenafil ingestion and 4 hours after sildenafil ingestion. The ECG was recorded at the first hour of sildenafil ingestion, because the drug achieves its peak effect at approximately one hour after ingestion. The serum levels of sodium, potassium, and chloride were measured within 48 hours of the ECG recordings.

Electrocardiographic Evaluation

QT intervals and QT dispersion were analyzed from standard 12-lead surface ECGs. The ECGs were recorded by a Hewlett Packard Pagewriter 300pi HP M1770A Cardiograph (Hewlett Packard, Andover, MA, USA) at a paper speed of 50 mm/s. QT interval was manually measured by a cardiologist blinded to the clinical diagnosis of the subjects. The onset of Q wave was considered as the onset of the QT interval. The point where T wave returned to the isoelectric TP segment was regarded as the end of QT interval. ECGs were accepted if at least eight leads could be analyzed. QT intervals of two QRS complexes from each lead were measured and the average value was noted as the QT interval of that particular lead. QT_d was calculated as the difference between maximum QT (QT_{max}) and minimum QT (QT_{min}) intervals. The QT intervals were corrected for heart rate according to the Bazzet's formula: QT_c interval = QT interval/square root of the RR interval.[12] QT_d was defined as the difference between QT_{max} and QT_{min}. Similarly, corrected QT_d (QTcd) was calculated as the difference between corrected QT_{max} (QTcmax) and corrected QT_{min} (QTcmin).

Statistical Analysis

Data were presented as mean ± SD. Because the ECG examinations formed three related groups of samples, the mean values of QT parameters were compared with the nonparametric Friedman test. A P value < 0.05 was accepted as statistically significant. ECGs of ten randomly selected subjects were reanalyzed by the same cardiologist on a different day to determine the intraobserver variability. These ECG recordings were also analyzed by another cardiologist (E.O.) to determine the interobserver variability. We have calculated the inter- and intraobserver variabilities (of QT_{max} and QT_{min}) by

Table 1. The Clinical and Biochemical Characteristics of Subjects

Age (years)	54 ± 12
Body mass index (kg/m^2)	24.3 ± 5.1
Serum creatinine (mg/dL)	0.8 ± 0.4
Systolic blood pressure (mmHg)	115 ± 21
Diastolic blood pressure (mmHg)	72 ± 9
Glucose (mg/dL)	144 ± 63
Total cholesterol (mg/dL)	214 ± 44
Triglycerides (mg/dL)	201 ± 82
LDL cholesterol (mg/dL)	132 ± 41
HDL cholesterol (mg/dL)	42 ± 8
VLDL (mg/dL)	40 ± 17

Data are expressed as mean ± SD.

coefficient of variation according to the following formula: $[S \times 100/(\times)]\%$, where S is the observer error (SD of the mean difference/$\sqrt{2}$) multiplied by 100 divided by the pooled mean values.

RESULTS

Biochemical characteristics of the patients are presented in Table 1. Electrocardiographic data are depicted in Table 2. Mean heart rate of patients did not differ significantly between the three ECG examinations. Both corrected and uncorrected QT intervals did not differ significantly between the three ECG examinations ($P > 0.05$). Similarly, the QT_d and QT_c were also not significantly different ($P > 0.05$). Electrocardiographic interpretation was suggestive of old myocardial infarction in four patients. Electrolyte imbalance was not detected in any of the subjects.

Inter- and intraobserver variabilities (coefficients of variation) were <5% for QT_{max} and QT_{min} measurements.

DISCUSSION

The results of the present study demonstrate that QT intervals and QT dispersion do not increase after 50 mg sildenafil citrate ingestion.

Increased QT dispersion reflects inhomogeneity of regional ventricular repolarization. QT dispersion has been proposed as a marker for ventricular arrhythmias and sudden death in several disease states, including congestive heart failure, congenital long QT syndrome, mitral valve prolapse, hypertensive heart disease, hypertrophic cardiomyopathy, and end-stage renal failure patients undergoing hemodialysis.[13–17]

The interaction of sildenafil with nitrates is well known and is potentially lethal. Because sildenafil is prescribed commonly, possible interaction of this drug with QT prolonging drugs had to be evaluated. Some drugs (antibacterials, psychotropic drugs, antihistamines, and antiarrhythmic drugs) are known to prolong the QT interval, predisposing to ventricular arrhythmias.[18–22] It is well known that these drugs should not be ingested concomitantly in order to decrease the risk of arrhythmia. Because patients with erectile dysfunction may have concomitant cardiac disease, they may already be on antiarrhythmic therapy.

Therefore, evaluation of the effect of sildenafil on QT intervals and QT dispersion is an important aspect for drug safety. The results of the present study suggest that 50 mg of sildenafil citrate may be safely administered to patients with increased QT dispersion. Our results also suggest that sudden deaths occurring after the ingestion of sildenafil citrate are probably not due to ventricular arrhythmias.

Recently, it has been reported that QT dispersion after exercise was a more powerful predictor of coronary artery disease than QT dispersion at

Table 2. Electrocardiographic Measurements of the Patients Before and After Sildenafil Citrate Ingestion

	Before Sildenafil	1 Hour After Sildenafil	4 Hours After Sildenafil
Heart rate (per minute)	81 ± 11	83 ± 11	83 ± 9
RR interval (s)	0.75 ± 0.10	0.74 ± 0.10	0.73 ± 0.08
Maximum QT (ms)	379 ± 30	378 ± 23	375 ± 25
Minimum QT (ms)	348 ± 25	346 ± 23	348 ± 24
Maximum QT_c (ms)	437 ± 24	441 ± 16	440 ± 14
Minimum QT_c (ms)	401 ± 21	404 ± 16	408 ± 16
QT dispersion (ms)	31 ± 9	32 ± 11	27 ± 8
QT_c dispersion (ms)	36 ± 10	37 ± 14	32 ± 9

Data are mean ±"SD. QT_c: Corrected QT interval. $P > 0.05$ for all of the above parameters.

rest.[23,24] In this study, we did not aim to identify coronary artery disease patients by measuring QT_d. Our aim was to evaluate the effect of sildenafil on QT_d. Therefore, we have not performed exercise test after ingesting sildenafil citrate.

The amount of sildenafil ingested may be a limitation of this study. We have given 50 mg of sildenafil citrate to our subjects. Some patients with erectile dysfunction may need 100 mg of sildenafil for the alleviation of their symptoms. However, we have not evaluated the effect of 100 mg of sildenafil citrate on the electrocardiographic parameters.

CONCLUSION

In the present study, we did not observe significant prolongation of the QT intervals or increase in QT_c dispersion after the ingestion of 50 mg sildenafil citrate. To the best of our knowledge, this is the first study to investigate QT interval prolongation and QT dispersion in sildenafil citrate users. These observations suggest that sildenafil use does not increase the risk of ventricular arrhythmias. Although we observed no effect of sildenafil citrate ingestion on QT intervals and QT dispersion, further research is needed to rule out the possibility of adverse interactions between sildenafil and various QT prolonging drugs when used concomitantly.

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