Rate Dependence of Sotalol-Induced Prolongation of Ventricular Repolarization During Exercise in Humans

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Studies in animals have shown that drug-induced action potential prolongation with class III antiarrhythmic agents increases with slow pacing rates. We studied the physiological rate dependence of sotalol effects on ventricular repolarization, measured as QT interval duration on the surface electrocardiogram at rest and during a maximal exercise test, in 10 normal volunteers. In a randomized, crossover study, three dosages of sotalol (160 mg/24 hr, 320 mg/24 hr, and 640 mg/24 hr) were administered during 4 days to each subject. In a control period, no drug was administered. During each period, 50–100 QT intervals were measured over a wide range of RR intervals recorded at rest and during the course of a maximal exercise test. Plasma sotalol concentration and β-adrenoceptor blockade (percent reduction in peak exercise heart rate from control) were also measured. The QT-versus-RR relation was fitted to several formulas, and the overall best fit was used to calculate QT interval duration normalized for a heart rate of 60 beats/min (QTc) and to analyze the rate dependence of QT prolongation with sotalol. Sotalol-induced β-adrenoceptor blockade and QTc prolongation were dose and concentration dependent. Sotalol reduced peak exercise heart rate by 13.8±7% at the dosage of 320 mg/24 hr and by 25.4±8% at the dosage of 640 mg/24 hr (both p<0.01). Sotalol prolonged QTc interval by 5.8±3.7% and 11.8±3% at these respective dosages (both p<0.01). The concentration of sotalol required to produce minimal (mean QTc prolongation, 5.6%; confidence interval, 0–11.2%) QTc prolongation (680 ng/ml) tended to be lower than that required for minimal (mean percent reduction in maximal exercise heart rate, 13.9%; confidence interval, 0–27.8%) β-blockade (840 ng/ml). QT prolongation with sotalol increased with increasing RR intervals (i.e., decreasing heart rate) at all dosages. QT prolongation became statistically significant for RR of 800 msec or more at all dosages and for RR intervals of 600 msec or more at the dosage of 640 mg/24 hr. This rate dependence altered the relation between QT interval duration and sotalol plasma concentrations. These results suggest that sotalol prolongs QTc interval in humans at dosages and concentrations similar to those required to produce β-adrenoceptor blockade, QT prolongation with sotalol is more pronounced when heart rate decreases and is not apparent during exercise-induced tachycardia, and the relation between QT prolongation with sotalol and plasma concentrations of the drug depends on the heart rate at which measurements are made. (Circulation 1991;83:536–545)

Racemic sotalol is a nonselective β-adrenergic receptor antagonist that also prolongs action potential duration (class III activity) in several tissues and ventricular repolarization in humans, measured as QT interval duration on the surface electrocardiogram or as monophasic action potential duration during invasive electrophysiological studies. Sotalol has been used in the treatment of ventricular and supraventricular arrhythmias, and it has been suggested that its potentially useful antiarrhythmic activity was due, at least in part, to its effects on repolarization. Experimental as well as clinical data suggest that prolongation of repolarization can be both antiarrhythmic and arrhythmogenic,
and there is still a great deal of controversy about which factor determines which response.\textsuperscript{14−17} The possible occurrence of torsade de pointes arrhythmia is a major concern during treatment with all drugs that prolong repolarization.\textsuperscript{18} This rare but potentially lethal arrhythmia has been reported with almost all agents with class III activity, including sotalol.\textsuperscript{18−20} It appears that drug-induced QT prolongation per se may not be sufficient to cause torsade de pointes\textsuperscript{16,17} but that additional factors, such as hypokalemia, concomitant treatment with other QT-prolonging drugs, and/or bradycardia, contribute to this arrhythmia. Recent in vitro and animal studies have shown that action potential prolongation with quinidine, bretylium, disopyramide, or sotalol increased with slow pacing rates.\textsuperscript{21−31} This phenomenon could explain in part the favoring role of bradycardia in drug-induced torsade de pointes arrhythmias. The rate-dependent prolongation of action potential duration has not been extensively studied in humans. In a recent report, our group showed that bepridil-induced QT prolongation increased with bradycardia and was not apparent during exercise tachycardia in normal volunteers.\textsuperscript{32}

It has been suggested that the concentrations of sotalol required to produce minimal β-adrenoceptor blockade are lower than those required to produce minimal heart rate–corrected QT (QTc) prolongation.\textsuperscript{3} However, this result was based on correction of QT interval using Bazett’s formula. Recent studies have suggested that a monoexponential formula best fit the QT-versus-RR relation in humans.\textsuperscript{33,34} Thus, the use of Bazett’s formula might have biased the analysis of Wang et al.\textsuperscript{3}

The present study was designed to assess the rate and concentration dependence of QT prolongation with three different dosages of sotalol in normal volunteers. Two other objectives were to confirm that a monoexponential formula fits the QT-versus-RR relation better than Bazett’s formula and to determine whether QT prolongation and β-blockade occur within the same range of sotalol plasma concentrations in humans.

**Methods**

**Study Design**

The rate and concentration dependence of sotalol-induced QT prolongation was studied in an open, randomized, four-period crossover study in 10 healthy, nonsmoking male volunteers (mean±SD age, 22.6±1.6 years). All subjects showed no abnormalities on routine medical examinations, 12-lead electrocardiograms, chest radiographs, and standard laboratory tests, and they gave their informed written consent to participate in the study. The protocol was approved by the Committee for the Protection of Human Subjects in Biomedical Research at Saint-Antoine University.

Each subject received sotalol (160 mg/24 hr, 320 mg/24 hr, and 640 mg/24 hr) on three different occasions and no drug (control) during another study period. The order of the four periods was randomized. During each sotalol period, subjects were asked to take the drug while ambulatory at 9:00 AM and 9:00 PM during 4 days (eight doses) to ensure that pharmacokinetic steady state had been reached.\textsuperscript{2} On the morning of the fifth day (i.e., 12 hours after taking the last dose), subjects came to the Clinical Pharmacology Unit at Saint-Antoine University Hospital to have several electrocardiographic recordings for measurement of QT interval duration. These recordings were first obtained during a 30-minute supine rest in a quiet room and then during a short period in the sitting and the standing positions. Additional recordings were obtained during the course of a maximal exercise test performed on a bicycle ergometer. A blood sample for the determination of plasma sotalol concentration was drawn just before the exercise test. During the control period, the same tests were performed, but no drug was administered and no blood sample was drawn. A washout phase of at least 1 week was observed between each study period.

**Assessment of β-Adrenoceptor Blockade**

Maximal exercise tests were performed on a programmable bicycle ergometer (Siemens, Paris) according to the protocol of Bailey et al.\textsuperscript{35} To familiarize each subject with the procedure, one training exercise test was performed within 1 week of the first study period. The work load was increased until the subject was physically unable to pursue the test. Maximal heart rate was measured using the mean RR interval calculated from the shortest five consecutive RR intervals recorded at the peak of exercise. Maximal heart rate measurements were made, without knowledge of the treatment received, from the electrocardiograms used for QT measurements. Sotalol-induced β-adrenoceptor blockade was calculated as the percent reduction in maximal heart rate during sotalol compared with the control period.

**Measurement of QT Intervals**

All electrocardiographic recordings were made simultaneously in leads aVF, V$_2$, and V$_5$ at a paper speed of 50 mm/sec (amplitude, 1 mV=2 cm) using a Procom 503F recorder (Fukuda, Tokyo) with filtering at 0.05–60 Hz. The lead at which the T wave had the greatest amplitude was selected for QT interval measurement; this lead was V$_5$ in all subjects. QT interval was measured from the onset of the QRS complex to the end of the T wave, which was defined according to the criteria of Lepeschkin and Surawicz.\textsuperscript{36} To relate QT interval duration to the heart rate at which it was measured, each QT interval value was associated with the preceding RR interval. All intervals were measured manually, using a digitizing pad (True Grid 1017, Houston, Dijon, France) connected to a microcomputer, by the same investigator (who was unaware of the treatment received). The coefficient of variation of
QT interval measurements with this technique is less than 3%. For each subject and each period, a set of 50–100 QT-RR pairs was obtained from all recordings (resting supine, sitting, standing, and exercise). Data were then fit to different formulas using least-squares nonlinear regression.

**Sotalol Plasma Concentrations**

A 10-ml blood sample was drawn from an antecubital vein before each exercise test. Blood was immediately centrifuged and separated. Plasma samples were stored at −20°C until assayed, which was usually within 2 weeks. Sotalol plasma concentration was determined by high-performance liquid chromatography using a previously described method.37

**Data and Statistical Analyses**

Dose versus effect and concentration versus effect relations. The relation between the dose of sotalol and β-adrenoceptor blockade or QT prolongation was plotted and analyzed using Spearman’s coefficient of rank correlation. The relation between sotalol plasma concentration and β-adrenoceptor blockade or QT prolongation was plotted, and data were fit to a linear model and an E\textsubscript{max} (Hill’s equation) model\textsuperscript{38} using least-squares regression techniques.\textsuperscript{39} The Akaike information criterion (AIC; see below) was used to define the best of these two fits.\textsuperscript{40} For these analyses, the QT interval normalized for a heart rate of 60 beats/min (QTc) was used in each subject. This QTc was calculated from the best fit obtained during the QT-versus-RR analysis (see below). QTc prolongation was measured as the percent increase in QTc interval duration with sotalol compared with control.

**QT versus RR relation.** For each subject and each period, the set of 50–100 QT-RR pairs obtained from all electrocardiographic recordings (resting supine, sitting, standing, and exercise) was fit to four different formulas using least-squares nonlinear regression:\textsuperscript{39}

\[
\begin{align*}
\text{QT} &= A_1 \cdot \frac{1}{RR} \text{ (Fridericia’s formula)} \\
\text{QT} &= A_2 + (B2/RR) \text{ (Kovacs’ formula)} \\
\text{QT} &= A_3 + (B3 \cdot \exp^{-C3 \cdot RR}) \text{ (monoexponential formula)} \\
\text{QT} &= A_4 \cdot \frac{1}{RR} \text{ (Bazett’s formula)}
\end{align*}
\]

where \(A_1, B_2, C_3\) are regression parameters. The first three formulas were selected on the basis of their previously demonstrated ability to adequately describe the QT-versus-RR relation.\textsuperscript{41} Bazett’s formula\textsuperscript{42} was used because it remains a widely applied standard.\textsuperscript{43} The AIC was used to define the best of these four fits\textsuperscript{40} for a given period in a given subject:

\[
\text{AIC} = N \cdot \ln(\text{RSS}) + 2P
\]

where \(N\) is the number of observations (QT-RR pairs), \(\ln\) is the natural logarithm, RSS is the residual sum of squares, and \(P\) is the number of parameters in the equation used. The equation with the minimum AIC is regarded as the best representation of a given plot of data. AIC has no unit and is used only to compare different models. For this reason and for the sake of clarity, results of AICs are presented in the text after normalization of AICs using 0 as the AIC of the best fit.

A \(\chi^2\) test was used to compare the number of fits for which a given formula best described the QT-versus-RR relation. The overall best formula was then used to examine the rate dependence of sotalol-induced QT prolongation. For this purpose, individual QT intervals were calculated in each subject at seven predetermined RR interval values: 375, 400, 500, 600, 700, 800, and 1,000 msec. These QT intervals were obtained using each subject’s fit and setting RR to each of the seven predetermined values. In each subject, this calculation of a fitted QT interval was performed only for those predetermined RR intervals that had actually been observed and for which QT interval measurement was technically feasible (i.e., no extrapolation was made). The QT interval durations at these seven predetermined RR values were then compared during the four study periods using general linear model analysis of variance and, if the null hypothesis of no difference could be rejected, Duncan’s multiple comparison test.\textsuperscript{44} Finally, the influence of heart rate on the QT-versus-sotalol plasma concentration was plotted.

A difference was considered significant when the probability of a type I error was less than 0.05. Results are reported as mean±SD in the text and as mean±SEM in the figures.

**Results**

**Relation Between Sotalol Dosage or Concentration and β-Adrenoceptor Blockade**

Sotalol significantly reduced peak exercise heart rate by 13.8±7% at 320 mg/24 hr and by 25.4±8% at 640 mg/24 hr (both \(p<0.01\)). The small reduction (4.5±4%) found with the 160-mg/24 hr dosage was not statistically significant. There was a positive relation between the dosage of sotalol administered and the percent reduction in peak exercise heart rate (Spearman’s \(p=0.835; \ p<0.001\)). There was also a significant correlation between the percent reduction in peak exercise heart rate and sotalol plasma concentration (Figure 1). The lower 95% confidence interval increased above baseline for a sotalol plasma concentration of 840 ng/ml (mean percent reduction in peak exercise heart rate, 13.9%; confidence interval, 0–27.8%). A linear fit described the relation better than an \(E_{\text{max}}\) model (normalized AIC, 0.2).

**Best Fit for QT-Versus-RR Relation**

Of the 40 individual (10 subjects and four periods) analyses of the QT-versus-RR data, 27 (67.5%); five control, eight sotalol 160 mg/day, seven sotalol 320 mg/day, and seven sotalol 640 mg/day) showed the monoexponential formula to describe the relation
better than the other three formulas ($p<0.001$) (Table 1). The best fit was given by Kovacs’ formula in 11 cases (27.5%; four control, two sotalol 160 mg/day, three sotalol 320 mg/day, and two sotalol 640 mg/day), Fridericia’s formula in two cases (5%; one control and one sotalol 640 mg/day), and Bazett’s in none. Examples of fits given by the four different formulas using the same set of QT-RR pairs are given in Figure 2. Because the monoexponential formula proved to describe the QT-versus-RR relation better overall and during each period than the other formulas, it was chosen to analyze the rate dependence of sotalol-induced QT prolongation. For the same reason, the QT interval for an RR interval of 1,000 msec (i.e., the QTc interval) was calculated using the individual monoexponential fit rather than Bazett’s formula in each subject during each period.

Relation Between Sotalol Dosage or Concentration and Prolongation of QTc Interval

QTc interval duration was 368±20 msec for the control period, 383±17 msec for sotalol 160 mg/24 hr ($p=0.05$), 389±19 msec for sotalol 320 mg/24 hr ($p<0.01$), and 411±20 msec for sotalol 640 mg/24 hr ($p<0.05$ versus control and sotalol 320 mg/24 hr). Sotalol significantly prolonged QTc interval duration by 5.8±3.7% at 320 mg/24 hr and by 11.8±3.3% at 640 mg/24 hr (both $p<0.01$). The small prolongation (4.3±3.4%) found with the 160-mg/24 hr dosage was not statistically significant. There was a positive relation between the dose of sotalol administered and the percent prolongation in QTc interval from control values (Spearman’s $\rho=0.693$; $p<0.001$). There was also a significant correlation between the percent QTc prolongation and sotalol plasma concentration (Figure 3). The lower 95% confidence interval increased above baseline for a sotalol plasma concentration of 680 ng/ml (mean QTc prolongation, 5.6%; confidence interval, 0–11.2%). A linear fit described the relation better than an $E_{\text{max}}$ model (normalized AIC, 2.1). In addition, the percent QTc prolongation with sotalol was linearly related to the percent reduction in peak exercise heart rate (slope [95% confidence interval], 0.23 [0.09–0.37]; $r=0.532$; $n=30$; $p<0.002$).

Rate Dependence of Sotalol-Induced QT Prolongation

In addition to the dose-dependent prolongation of QT interval by sotalol, a clear rate dependence of this effect was found. Figure 4 shows this dose and rate dependence in one subject, and Figure 5 shows the mean±SEM effects of sotalol on QT prolongation at the three dosages used in our study for seven predetermined RR intervals. RR intervals between 500 and 1,000 msec were reached by all subjects during each period. QT interval could not be measured at shorter RR intervals in some subjects (400 msec: three control, no sotalol 160 mg/day, one sotalol 320 mg/day, and five sotalol 640 mg/day; 375 msec: three control, no sotalol 160 mg/day, two sotalol 320 mg/day, and six sotalol 640 mg/day). QT interval was significantly prolonged by sotalol at all dosages when RR interval was equal to or more than 800 msec (i.e., for a heart rate of 75 beats/min or less), and QT prolongation increased when RR interval increased (Figure 5). The 640-mg/24 hr dosage also increased QT intervals calculated for RR intervals of 600 and 700 msec (heart rates of 100 and 86 beats/min, respectively). Figure 6 shows the results when QT prolongation is expressed as the percent change from control value. The same pattern of rate dependence was found with this type of analysis. Thus, QT interval prolongation with sotalol increased with dosage, with concentration, and with decreasing heart rate. At short RR intervals, sotalol tended to shorten QT intervals (Figures 5 and 6), but the changes did not reach statistical significance.

Influence of Heart Rate on QT–Versus–Sotalol Plasma Concentration Relation

The rate dependence of sotalol-induced QT prolongation altered the relation of QT interval duration to sotalol plasma concentration (Figure 7). QT interval appeared to be prolonged in relation to increased sotalol plasma concentrations only when the relation was plotted using QT intervals obtained at RR intervals equal to or more than 700 or 800 msec. QT interval even tended to decrease with increasing sotalol plasma concentrations when the relation was plotted using QT intervals obtained at an RR interval of 400 msec.

Discussion

Our results confirm that sotalol prolongs ventricular repolarization as assessed by QTc interval duration on the surface electrocardiogram in relation to both dosage and concentration.2–5 The relation between dose or concentration and QT interval prolongation was carefully analyzed using a QT value normalized for a heart rate of 60 beats/min (i.e., the usual QTc interval). To limit biases associated with
TABLE 1. Normalized Akaike Information Criterion for the QT-Versus-RR Relations

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C, control; S1, S2, S3, sotalol 160, 320, and 640 mg/day, respectively.

correction of the QT interval using Bazett’s formula, QTc was obtained from the best nonlinear fit to several QT-RR pairs, the monoexponential fit (Figure 2). Further analysis showed that sotalol-induced QT interval prolongation increased with bradycardia.

Relation Between QTc Prolongation and β-Adrenoceptor Blockade With Sotalol

Results of studies have suggested that β-adrenoceptor blockade prolongs QT interval in humans during chronic (5-week) administration but not during acute administration, although QT interval prolongation was found with acute propranolol administration in a recent study. In all cases, the extent of QT interval prolongation with β-adrenoceptor blockade, if any, was limited. It is therefore unlikely that the effects of sotalol on QTc interval observed in our study were due to its β-adrenoceptor-blocking properties. It has clearly been shown that the d or (+)-enantiomer of sotalol, which lacks β-blocking activity, prolongs QT and QTc intervals. Also, in a previous study, we found that
propranolol-induced β-adrenoceptor blockade does not alter the QT-RR relation during exercise testing.33 Wang et al3 and Nattel et al48 found that the concentrations of sotalol required for β-blockade were fourfold to ninefold less than those required for its class III effects. We (Figures 1 and 3) and others12 were unable to find such a difference. In the study of Wang et al,3 the β-adrenoceptor blockade versus sotalol plasma concentration was described in patients using an $E_{\text{max}}$ model, whereas the QTc prolongation versus sotalol plasma concentration was described using standard linear regression. In addition, QTc was calculated using Bazett’s formula. Thus, the comparison of the sotalol plasma concentrations required for β-blockade and QTc prolongation was based on two models and used a less-than-optimal mode of correction of QT interval. This might explain the difference with our results. In the study of Nattel et al,48 β-adrenoceptor blockade was assessed by isoproterenol tests in autonomically intact dogs, whereas the class III effects of sotalol were assessed as the sotalol-induced percent change in refractory periods in dogs with autonomic blockade. The possible influence of autonomic blockade on refractory periods together with the high pacing rate at which refractory periods were measured might explain the results. We determined the sotalol plasma concentrations for which β-adrenoceptor blockade or QTc interval prolongation occurred using the same technique, which was also used by Wang et al3 to examine sotalol-induced QTc prolongation. In our study, the Sotalol-Induced QT Prolongation

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\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Plots of examples of QT-versus-RR relation fitted to the four different formulas in individual cases. Upper panel: Best fit with monoexponential formula (subject 6, sotalol 320 mg/day). Middle panel: Best fit with Kovacs’ formula (subject 2, sotalol 320 mg/day). Lower panel: Best fit with Fridericia’s formula (subject 4, sotalol 640 mg/day).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Plot of percent QTc prolongation as a function of sotalol plasma concentration. Linear fit and 95% confidence interval for prediction in an individual are shown.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Plot of QT-versus-RR relation fitted with monoexponential formula on each study period in one subject. There was a dose-dependent increase in QT interval with sotalol, which was more pronounced at long RR intervals.}
\end{figure}
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lack of an improved description of the β-blockade–
versus–plasma concentration relation by an $E_{\text{max}}$
model can be explained by the lower concentrations of
sotalol we observed compared with those of Wang
et al. 58 and Nattel et al. 59 In fact, the concentrations we
found in our subjects remained within the range of the
linear portion of the sigmoid $E_{\text{max}}$ relation they
both described. Nevertheless, the concentration of
840 ng/ml for which the lower 95% confidence interval
of the relation between β-blockade and plasma
concentration increased above baseline in our study
is similar to the value of 800 ng/ml they both found
for the concentration producing 50% of maximal
β-blockade. Using the same type of linear regression
analysis, we found that the plasma concentration of
sotalol required to produce minimal QTc prolonga-
tion was 680 ng/ml, a value that tends to be lower
than the value of 840 ng/ml required for minimal
β-blockade. In addition, there was a correlation
between the degree of QTc prolongation and the
degree of β-blockade produced by sotalol. In our
analysis, we calculated QTc using the best overall fit
to the QT-versus-RR relation. Thus, based on a
reliable mode of QT correction, our results indicate
that the concentrations of sotalol required to pro-
duce significant QT prolongation are not higher than
those required to produce significant β-adrenoceptor
blockade in humans.

Rate Dependence of Sotalol-Induced QT Prolongation

Numerous animal studies have shown that brady-
cardia, or a slow pacing rate, increases drug-induced
prolongation of action potential duration. 21–31 Our
study confirms these findings in humans with sotalol
(Figures 4–6). This rate dependence of a class III
effect is inverse of the rate dependence of sodium
channel blockade described for sodium channel
blockers. 49 It is generally recognized that drug-in-
duced prolongation of repolarization is due to block-
ade of various potassium currents, although other
mechanisms may exist. 50 It has been suggested that
action potential prolongation by sotalol is due to its
ability to block the time-dependent plateau outward
potassium current ($I_{\text{K}}$). 51 Roden et al. 52 have shown a
relation between the time spent at depolarized
potentials and the blockade of $I_{\text{K}}$ induced by quin-
dine in cardiac myocytes. The blockade of $I_{\text{K}}$
decreased with the time spent at depolarized potentials.
A similar mechanism could explain the relation be-
tween tachycardia (i.e., less time spent at negative
diastolic potentials due to shortening of electrical
diastole) and the decrease in sotalol-induced QT
prolongation we have found in humans. Such a
mechanism has been recently suggested to explain
the rate-dependent class III actions of UK68,798 in
guinea pig papillary muscle. 53 It has been postulated
that it could be due to an ability of most drugs with
class III activity to bind to $I_{\text{K}}$ channels in the closed
state. 54 Another explanation is that because tachycar-
dia is associated with decreased action potential

![Figure 5](image1)

**FIGURE 5.** Plot of mean ± SEM values of QT during each of
the four study periods calculated at seven predetermined RR
intervals. *p<0.05 versus control; †p<0.01 versus control,
sotalol 80 mg q 12hr, and 160 mg q 12hr.

![Figure 6](image2)

**FIGURE 6.** Plot of mean ± SEM QT prolongation with three
dosages of sotalol expressed as percent change from control
value. *p<0.002 versus sotalol 80 mg q 12hr and 160 mg q
12hr.

![Figure 7](image3)

**FIGURE 7.** Plot of mean±SEM QT interval duration–ver-
sus–mean sotalol plasma concentration relation during each
study period for different values of RR intervals.
duration, it could thus decrease the time during which sotalol interacts with potassium channels during the plateau phase. Such a mechanism has been proposed by Hafner et al\textsuperscript{27} to explain the rate-dependent effects of sotalol on action potential prolongation in guinea pig papillary muscles. However, further studies are required to clarify the mechanism of the rate-dependent effects of sotalol on QT prolongation we have found in humans.

The decrease in sotalol-induced QT prolongation with increased heart rate might contribute to the beneficial effect of heart rate acceleration in the treatment of torsade de pointes arrhythmias occasionally observed with this drug.\textsuperscript{18} One of the direct implications of our study relates to the determination of the effect--versus--plasma concentration relation in clinical pharmacological studies of drugs that prolong repolarization. As shown in Figure 7, the relation between sotalol plasma concentration and QT interval duration must consider the heart rate at which measurements are made; this might also apply to the newer drugs with class III activity. Our results suggest that a heart rate of more than 75 beats/min might conceal the effects of a drug on ventricular repolarization.

Study Limitations

Assessment of the relation between QT and RR intervals during the course of an exercise test does not fully take into account that the influence of a change in heart rate on QT interval may vary over time.\textsuperscript{55} Despite the fact that results similar to ours have been found in studies performed at steady state in vitro,\textsuperscript{27} it is possible that our results would have been different if each of the QT intervals had been measured after several minutes at a given heart rate.

Also, in our study, physiological heart rate changes were produced by an exercise test. Thus, QT interval changes were not due solely to shortening of heart rate per se but possibly also to exercise-induced \( \beta \)-adrenoceptor stimulation. Analysis of the rate dependence of sotalol's effects on QT interval in the absence of \( \beta \)-adrenoceptor stimulation requires further studies with atrial pacing. However, results from in vitro studies in paced guinea pig papillary muscle indicate that the rate dependence of action potential prolongation with sotalol is independent of \( \beta \)-adrenoceptor stimulation.\textsuperscript{27} Moreover, in a previous study, we found that the QT-RR relation during exercise was not altered by propranolol-induced \( \beta \)-adrenoceptor blockade.\textsuperscript{33}

In this noninvasive study, we did not analyze the rate dependence of sotalol effects on refractory periods. In vitro studies with bretylium, another drug with class III activity, have shown that the decrease in drug-induced prolongation of effective refractory periods at high pacing rates paralleled that of action potential prolongation.\textsuperscript{21} Opposite results have been found with drugs with class I activity for which high pacing rates result in more prolongation of refractory periods and less prolongation of action potential duration.\textsuperscript{21,28,29} The frequency dependence of sotalol effects on postrepolarization refractoriness in humans requires additional studies.

Finally, we analyzed the effects of heart rate on sotalol-induced QT prolongation in normal volunteers. Studies have shown that the class III actions of sotalol are more pronounced in ischemic tissue.\textsuperscript{56,57} It is therefore possible that the pattern of frequency dependence of sotalol effects on QT interval duration that we found in normal volunteers might differ in patients with heart disease.

Conclusions

Results of the present study indicate that bradycardia and exercise-induced tachycardia increases and decreases, respectively, the ability of sotalol to prolong QT interval. It also confirms that sotalol-induced QT prolongation is related to both the dosage and the plasma concentrations of the drug. However, in contrast with results of previous studies, results from the present study show that the concentrations of sotalol required to produce significant QTc interval prolongation in humans are not higher than those required for \( \beta \)-adrenoceptor blockade. The relation between QT prolongation and sotalol plasma concentration is influenced by heart rate.

References

5. Echt DS, Berte LE, Clusin WT, Samuelsson RG, Harrison DC, Mason JW: Prolongation of the human cardiac monophasic action potential by sotalol. \textit{Am J Cardiol} 1982;50:1082--1086
54. Honegedhem LM, Snyder JS: Class III antiarrhythmic agents have a lot of potential but a long way to go: Reduced


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C Funck-Brentano, Y Kibleur, F Le Coz, J M Poirier, A Mallet and P Jaillon

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