Tolerance to the repolarization effects of *rac*-sotalol during long-term treatment

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Aims To establish whether tolerance to the QT effect could ensue during maintenance treatment with *rac*-sotalol.

Methods The effect of *rac*-sotalol on QT interval duration was studied in 10 patients after single oral administration (160 mg) and after 6-day multiple oral dosing (80 mg two or three times daily). In order to separate the pure Class III effect from the bradycardia-related QT prolongation, heart rate/QT relationship was preliminarily assessed in each patient after the administration of a pure β -adrenoceptor blocker (propranolol, 80 mg orally). Repolarization changes were quantified as percent difference between the measured QT and the expected QT on the basis of the individual heart rate/QT relationship.

Results In all patients QT interval prolongation was linearly correlated with *rac*-sotalol log plasma concentration. The maximal QT prolongation and peak plasma concentration were not significantly different following acute and chronic administrations (QT effect: $+18.1 \pm 6.3\%$ *vs* $+14.2 \pm 3.3\%$; peak concentration: $1.64 \pm 0.49 \text{ mg l}^{-1}$ *vs* $1.83 \pm 0.66 \text{ mg l}^{-1}$). Line slopes were also unchanged following chronic treatment (21.8 ± 8.9 *vs* 21.1 ± 9.2). In four cases a significant rightward shift of the line occurred during repeated administrations, consistent with the appearance of pharmacodynamic tolerance. The inconstancy of this change in responsiveness may either be ascribed to a genetically determined individual susceptibility or to a variable interplay between Class III effect, gradual QT prolongation due to long-term β -adrenoceptor blockade and tolerance development.

Conclusions During maintenance treatment with *rac*-sotalol, partial loss of repolarization effects occurred in some patients suggesting pharmacological tolerance.

Keywords: *rac*-sotalol, QT interval, tolerance

Introduction

Rac-sotalol is a non selective β -adrenoceptor blocker which also blocks i_K current, thus prolonging action potential duration. Because of its mixed class II and class III properties, it is currently used for the treatment of a wide spectrum of cardiac arrhythmias [1]. A recent trial [2] reported that *rac*-sotalol was more effective than six other antiarrhythmic agents in preventing death and recurrences of ventricular tachyarrhythmias, while producing less adverse effects. Its class III electrophysiological properties are reflected on surface ECG by dose-dependent QT interval prolongation and a positive correlation has been found between drug plasma concentrations and QTc changes [3–9]. Two studies compared the concentration/QT effect relationship after single and multiple administration but produced conflicting results. Creamer *et al.* [4] demonstrated that, at equivalent plasma concentrations, *rac*-sotalol QT prolongation was more pronounced during long-term oral than acute intravenous administration. In contrast, Le Coz *et al.* [8] reported

that in 83% of cases QTc duration during *rac*-sotalol repeated oral administrations was below the value predicted from single administration and in 21% of cases the measured QTc fell outside the 95% confidence interval for the predicted QTc value. Since *rac*-sotalol is often administered to prevent life-threatening arrhythmias, the question of whether its effect is increased, maintained or decreased during chronic oral treatment is therapeutically relevant. Our study was planned to answer this question.

Methods

Study design

Ten inpatients, five males and five females, aged between 18 and 73 (mean $\pm$ s.d. age, 49 ± 17 years), took part in the study, after giving informed consent. They all had supraventricular or ventricular arrhythmias for which *rac*-sotalol treatment was indicated. A detailed clinical and laboratory examination excluded renal, hepatic or cardiac failure, atrio-ventricular conduction disturbances, long QT interval or T-wave abnormalities, peripheral vascular disease, bronchial asthma, diabetes and electrolyte disturbances. No one was

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taking drugs that could affect ECG intervals. Individual patient characteristics are shown in Table 1. The study protocol included three phases. In a preliminary phase, the frequency/QT relationship was assessed in each patient in order to predict the rate-dependent QT changes in the subsequent two phases. Heart rate changes were induced by giving a 80 mg oral dose of propranolol, a non-selective β -adrenoceptor blocker devoid of class III properties. In order to correlate heart rate with the QT interval duration, ECG traces were recorded at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 h after a morning (09.00 h) drug administration.

On the following day (phase 2), the relationship between plasma concentration and QT prolongation was determined after acute *rac*-sotalol administration. After an overnight fast, a single 160 mg oral dose of *rac*-sotalol was given at 09.00 h and blood was sampled at the following times 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8 h after administration in order to assay *rac*-sotalol plasma levels. ECG traces were recorded simultaneously to measure the corresponding changes in QT duration.

Chronic oral *rac*-sotalol treatment was then instituted (phase 3) with a daily dose of 160 mg (80 mg twice daily) in nine patients or 240 (80 mg three times daily) in one patient (number 4). At 09.00 h on the seventh day of continuous administration a *rac*-sotalol dose of 80 mg (five patients) or 160 mg (five patients) was given; blood samples and ECG traces were obtained at the times indicated for phase 2. The choice between 80 mg and 160 mg was essentially based on resting heart rate; when heart rate was lower than 50–55 beats min^{-1} the 80 mg dose was administered.

The study protocol was approved by the the local ethics committee.

QT interval measurement

After a 10 min bed rest, surface ECG was recorded in peripheral leads (paper speed: 50 mm s^{-1} ; amplitude: 1 mV=2 cm). ECG analysis was carried out in the lead where the T-wave voltage was maximal. Seven to ten

consecutive QT and RR intervals were measured manually by the same investigator (unaware of the recording time and of drug plasma concentrations), by means of a graded lens (resolution: 0.1 mm) and the mean QT and RR values were used for further analyses. Heart rate (HR) was then calculated from RR interval. The HR and QT pairs measured after propranolol administration were used to determine the linear regression line for each subject:

$$QT = QT_0 - \delta QT \times HR \quad (1)$$

This relationship was used to predict QT duration from frequency during *rac*-sotalol administration.

Rac-sotalol assay

Blood was sampled from an indwelling catheter (antecubital vein) and put in heparinized tubes. Plasma was separated within 15 min and frozen at -20°C until assayed by a specific and sensitive h.p.l.c. technique. In brief, 1 ml of plasma was alkalised with borate buffer (pH 9) and extracted with 8 ml ethyl acetate (internal standard: 0.2 mg l^{-1} metoprolol). The drug was back-extracted with 0.3 ml 0.2N HCl. A 50 μl aliquot was injected into an Ultrasphere (5 μm) octyl column (Beckman) eluted with a mobile phase composed of acetonitrile/1% NH_4 -acetate buffer, pH 4.7 (70:30). A fluorimetric detector was used (excit. λ =270; emiss. λ =310). The day-to-day coefficient of variation, at 1 mg l^{-1} , was 6%.

Pharmacokinetic calculations

A detailed compartmental analysis was beyond the scope of our study and was prevented by the relatively short sampling time. Nevertheless, the following model-independent parameters could be calculated after both acute and chronic *rac*-sotalol administration: peak concentration (C_{max}), time-to-peak concentration (t_{peak}) and area under the concentration-time curve from 0 to 8 h (AUC(0,8 h)).

Table 1 Patients' characteristics.

Patient	Age (years)	Gender	Weight (kg)	Disease	Arrhythmia	Maintenance regimen	Last dose (mg)
1	34	F	63	—	SVPT	80 mg twice daily	160
2	60	M	81	Diabetes	atrial flutter	80 mg twice daily	160
3	63	M	80	Mitral valve prolapse	PVB	80 mg twice daily	160
4	18	M	62	Mitral valve	SVPT	80 mg three times daily	80
5	61	M	80	Aortic valve stenosis	VT	80 mg twice daily	80
6	73	M	70	Mitral valve prolapse	PVB	80 mg twice daily	80
7	32	F	65	—	VT	80 mg twice daily	160
8	54	F	70	—	SVPT	80 mg twice daily	160
9	42	F	62	Hypertension	SVPT	80 mg twice daily	80
10	58	F	57	—	parox. atrial fibrillation	80 mg twice daily	80

SVPT=supra ventricular paroxysmal tachycardia; PVB=premature ventricular beats; VT=ventricular tachycardia.

Pharmacodynamic calculations

The effect of *rac*-sotalol on the QT interval duration was calculated as percent difference of the QT actually measured from the QT obtained by substituting heart rate value in equation (1). The percentage QT change was correlated with the logarithm of the corresponding *rac*-sotalol plasma concentration (C), according to the equation:

$$QT(\%) = a + b \times \log(C) \quad (2)$$

Y-intercept (a), slope (b) and coefficient of correlation (r) were calculated by means of linear regression analysis. The threshold *rac*-sotalol concentration for the QT effect was calculated as the X-intercept (i.e., the concentration corresponding to zero effect). The logarithmic transformation was chosen for both theoretical and empirical reasons. Furthermore, logarithmic transformation made it possible to evaluate whether any rightward displacement of concentration/effect curves occurred during chronic treatment.

A separate analysis was carried out to compare the results of the method described above with those obtained with other widely used methods, such as the correction of the QT interval by the square root of the RR interval (Bazett's formula) and the cubic root of the RR interval (Fridericia's formula). The comparison was made at the maximum QT increase during acute and chronic administration.

Table 2 Intercepts, slopes and *r* values of the linear correlation between heart rate and QT interval.

Patient	QT ₀ (ms)	ΔQT(ms/beat)	r
1	477	1.22	0.70
2	447	1.19	0.72
3	637	3.43	0.93
4	571	2.71	0.88
5	554	1.92	0.83
6	462	0.73	0.36
7	533	1.46	0.70
8	588	2.71	0.70
9	516	1.91	0.90
10	499	1.57	0.82
Mean ± s.d.	528 ± 60	1.88 ± 0.84	0.75 ± 0.16

Table 3 Pharmacokinetic parameters after acute and chronic *rac*-sotalol treatment.

Patient	Acute treatment			Chronic treatment		
	AUC(0,8 h) (mg l ⁻¹ h)	C _{max} (mg l ⁻¹)	t _{peak} (h)	AUC(0,8 h) (mg l ⁻¹ h)	C _{max} (mg l ⁻¹)	t _{peak} (h)
1	11.39	1.94	3	14.30	2.63	3
2	8.60	2.04	2	8.57	1.55	2.5
3	4.50	0.84	4	10.80	1.92	4
4	11.85	2.49	4	8.07	1.32	3
5	7.24	1.47	3	6.01	0.91	3
6	8.93	1.80	1.5	9.05	1.36	1
7	5.26	0.81	3	15.35	2.88	4
8	9.54	1.78	4	11.35	1.70	4
9	8.37	1.50	4	13.05	2.75	3
10	9.65	1.77	4	8.29	1.25	3
Mean ± s.d.	8.43 ± 2.13	1.64 ± 0.49	3.25 ± 0.87	10.50 ± 2.89	1.83 ± 0.66	3.05 ± 0.85

Statistical analysis

Data are expressed as mean ± s.d. The null hypothesis that the log-concentration-effect lines obtained after acute and chronic treatment were coincident was tested with the method described by Bowman & Rand [10]. First, slopes were compared and, if lines were parallel, the coincidence of the two lines was tested. All the comparisons were carried out by means of the two-tail *t*-test, with a cut-off significance level of *P* < 0.05.

The comparison between the maximal QT effects obtained with different methods was performed by means of one-way ANOVA, followed by the Scheffé test.

Results

The maximal decrease in heart rate induced by the test dose of propranolol was 16.0 ± 3.0 beats min⁻¹, from 68 ± 5.8 beats min⁻¹ to 52.1 ± 6.3 beats min⁻¹. As expected, an inverse linear correlation was found between HR and QT duration. The results of the regression analyses (slopes, intercepts and coefficient of correlations) in the individual patient are shown in Table 2. A wide interpatient variability was observed, with slope ranging from -0.73 to -3.43 ms/beat (-1.88 ± 0.84 ms/beat) and intercept from 447 to 637 ms (528 ± 60 ms). The baseline QT duration extrapolated at 60 beats min⁻¹ was 416 ± 19 ms. The corresponding QT_c value calculated by means of the formulas of Bazett and Fridericia were 424 ± 22 ms and 418 ± 20 ms, respectively.

AUC(0,8 h), C_{max} and t_{peak} did not significantly differ between acute and chronic administrations. Means and individual patient values are shown in Table 3.

Rac-sotalol slowed heart rate and prolonged QT interval in all the patients, without appreciably changing the T wave amplitude and morphology. At the peak of *rac*-sotalol effect mean heart rate was 48.8 ± 5.5 beat min⁻¹ during acute treatment and 47.3 ± 7.7 beats min⁻¹ during chronic treatment, while the maximal QT increase was 18.1 ± 6.3% during acute treatment and 14.2 ± 3.3% during chronic treatment, the differences being nonsignificant.

To test whether the method used to correct QT interval by heart rate could influence the results we also calculated

the maximum % QT prolongation after acute and chronic administration with the formulas of Bazett and Fridericia. A comparison between the results (Figure 1) indicates that both Bazett's and Fridericia's formulas underestimate the QT change obtained with the individualized method. The maximum QT prolongation was, on average, $16.1 \pm 5.5\%$ with the individualised method, $11.3 \pm 5.6\%$ with Bazett's formula ($P=0.029$) and $13.7 \pm 5.1\%$ with Fridericia's formula (NS).

The analysis of the log-concentration-effect lines revealed that the threshold *rac*-sotalol concentration for the appearance of repolarisation effects (X-intercept) was widely variable among patients (range: $0.12\text{--}0.76\text{ mg l}^{-1}$; mean: $0.39 \pm 0.15\text{ mg l}^{-1}$). In one case (number 7) threshold concentration was not reached with the first dose and the QT interval was increased only during chronic treatment (Figure 2). Since no comparison could be made between

Figure 1 Correlation between the maximal percent QT increases measured with the individualized method (abscissa) and the corresponding values obtained with Bazett's formula (open triangles and dotted-dashed line) and with Fridericia's formula (solid triangles and dashed line). The identity line is indicated with a solid trace.

Figure 2 Correlation between log plasma *rac*-sotalol concentration and percent QT change in patient 7, after the first administration (open circles and dashed line) and a 6-day continuous treatment (solid circles and solid line). The first dose did not elicit any detectable QT effect.

acute and chronic effect, this case was not included in the following analysis.

The slopes, Y-intercepts and X-intercepts of the log-concentration/effect lines found in each patient, after single and multiple dosing, are shown in Table 4. In no patient did the slope of the line significantly change after 6-day treatment (mean values: 21.8 ± 8.9 vs 21.1 ± 9.2). Furthermore, in five out of nine subjects no significant displacement of the line was demonstrable during chronic treatment, so that acute and chronic lines must be considered coincident (Figure 3). In the remaining four cases a rightward shift occurred during chronic treatment (Figure 4), which was significant ($P<0.05$) in patients 5, 6 and 8 and approached the significance level in patient number 4 ($P=0.063$). $Auc(0,8\text{ h})$ and $C_{\max}$ were not significantly different from those of non-tolerant patients. Likewise, no consistent association was observed in this group with other factors such as age, underlying disease and type of arrhythmia.

All patients completed the study without experiencing side effects. In particular, no patient developed typical β -adrenoceptor blockade symptoms or proarrhythmic effects.

Discussion

Our results indicate that after 6-days' oral treatment with *rac*-sotalol, partial loss of the repolarization effects can occur in some patients, substantially confirming the findings of Le Coz *et al.* [8]. However, before comparing our data with previous reports, some relevant methodological aspects concerning measurement of drug effect on repolarization need to be discussed briefly. In general, QT prolongation induced by *rac*-sotalol results from several independent mechanisms: 1) specific blockade of the delayed outward potassium current (i_K) in ventricular myocytes [11, 12]; 2) non-specific QT prolongation due to the bradycardic effect; 3) an interaction between mechanism 1) and 2), consisting in the potentiation of Class III effect induced by low frequencies [7] (reverse use-dependence); 4) long-term β -adrenoceptor blockade, which by itself gradually prolongs repolarization through an unknown mechanism [13–15]. Bazett's formula has been used frequently, despite its well known limitations [16, 17] to separate the genuine Class III effect from the bradycardia-dependent QT prolongation. In fact, this popular formula proved to be mathematically inadequate to model the RR/QT relationship, which varies not only between subjects but also within subject [18–20] in relation to different physiological situations (exercise, vagal tone, etc.). Fridericia's formula has been claimed to be more reliable than Bazett's [21], but when a Class III drug is administered, neither method takes into account the reverse use-dependence of the effect. The alternative approach followed by us and by others [22–24], consists in determining the frequency/QT relation in each subject and using it to extrapolate the drug-free QT duration during drug administration. With this procedure no QT correction is actually made, but the QT interval duration is compared, at the same frequency, in the presence and in the absence of the drug. This method, besides being physiologically correct, measures also the amount of QT prolongation due to *rac*-sotalol reverse use-dependence. It may, therefore, be expected that QT prolongation obtained in this way is

Table 4 Pharmacodynamic parameters after acute and chronic *rac*-sotalol treatment.

Patient	Acute treatment				Chronic treatment			
	Y-intercept	X-intercept	Slope	r	Y-intercept	X-intercept	Slope	r
1	9.1	0.30	17.5	0.90	8.7	0.31	17.2	0.92
2	11.3	0.39	27.3	0.88	11.6	0.38	27.6	0.75
3	9.7	0.25	16.1	0.75	10.6	0.33	21.9	0.92
4	8.5	0.32	17.2	0.85	5.3	0.47	16.3	0.66
5	16.6	0.32	30.3	0.87	12.1	0.46	36.0	0.74
6	10.2	0.55	38.8	0.76	4.0	0.76	34	0.70
7	—	—	—	—	5.0	0.50	16.8	0.90
8	6.0	0.47	18.2	0.82	3.3	0.63	16.4	0.92
9	9.7	0.23	15.0	0.83	8.6	0.27	15.3	0.84
10	3.3	0.37	7.7	0.73	5.4	0.12	5.9	0.41
Mean $\pm$ s.d.	9.4 $\pm$ 3.6	0.36 $\pm$ 0.10	21.8 $\pm$ 8.9	0.82 $\pm$ 0.06	7.4 $\pm$ 3.4	0.43 $\pm$ 0.18	21.1 $\pm$ 9.2	0.77 $\pm$ 0.16

Figure 3 Correlation between log plasma *rac*-sotalol concentration and percent QT change in five patients, who did not show any significant change in the concentration-response line during continuous treatment. Open circles and dashed line: first drug administration; solid circles and solid lines: 6-day continuous treatment.

Figure 4 Correlation between log plasma *rac*-sotalol concentration and percent QT change in four patients, who showed a rightward shift of the concentration-response line during continuous treatment. Open circles and dashed line: first drug administration; solid circles and solid lines: 6-day continuous treatment.

greater than the one calculated with the conventional formulas. Indeed, the maximal percent QT prolongations we calculated with the formulas of Bazett and Fridericia were smaller than that we found with the individualised approach, the difference being larger using Bazett's correction. This observation may partly explain the discrepancy in the literature regarding the plasma concentration of *rac*-sotalol required to prolong the QT interval. Wang *et al.*, [5] who used Bazett's method, reported that significant QT prolongation occurred at concentrations higher than 2.5 mg l^{-1} . In contrast, other authors [6, 8] who did not correct QT but kept frequency constant with atrial pacing ($100 \text{ beats min}^{-1}$) or used the more reliable Fridericia's formula, found a Class III effect at substantially lower concentrations ($\approx 0.8\text{--}1.4 \text{ mg l}^{-1}$). Our data indicate that the threshold concentration for the appearance of QT effect is, on average, 0.39 mg l^{-1} . In a recent paper [7], *rac*-sotalol chronic effect was evaluated in healthy volunteers after 4-day oral treatment and QT correction was carried out determining the RR versus QT relation experimentally. We used the concentration-effect relation reported in Figure 3 (p. 541) of the cited paper to calculate the QT prolongation corresponding to the mean C_{max} we measured during chronic *rac*-sotalol treatment (1.64 mg l^{-1}): the percent QT change obtained (+14.4%) was practically coincident with that experimentally found by us (+14.2%). Thus, in summary, the individualized method to predict QT duration from heart rate seems to give reproducible results, while the other commonly used methods underestimate *rac*-sotalol effect to various extent.

Significant degrees of QT dispersion may have influenced the interpretation of results. 12-lead QT dispersion was not routinely measured because 6 out of the 10 patients had supraventricular arrhythmias and measurement of QT (ventricular) dispersion seemed inappropriate. Furthermore, while intra- and inter-observer reproducibility of the QT interval measurement was reported to be high (relative error <6%), that of QT dispersion was low (relative error 25–35%) [25]. Therefore QT dispersion did not seem an optimal parameter to correlate with plasma drug concentration.

Our finding of a rightward shift of the log-concentration/effect line during chronic *rac*-sotalol treatment, without a change in slope, is consistent with the development of pharmacodynamic tolerance. A study in rats [26] demonstrated that long-term treatment with mexiletine, a Na channel blocker, was associated with an increase in Na channel number, which was reversible on drug withdrawal. Analogously, it could be hypothesised that chronic treatment with *rac*-sotalol, a K channel blocker, may induce K channel up-regulation. An alternative explanation is that inhibition of i_K by *rac*-sotalol may be partly counterbalanced by the adaptive increase of other outward potassium currents. However, it is difficult to explain why only some patients became partially tolerant to *rac*-sotalol. A greater exposure to drug effect cannot be invoked because plasma concentrations were in the same range in the tolerant as in the non-tolerant group. Since ion channel expression is under genetic control and potassium channel abnormalities can be responsible for repolarization disturbances [27] (e.g.

congenital or drug-induced long QT syndrome), it may be hypothesized that some subjects have a genetic predisposition to develop tolerance. On the other hand, another explanation based on the known properties of *rac*-sotalol can be put forward. As stated above, Class III effect of *rac*-sotalol should not be considered as fully or exclusively responsible for the prolongation of QT interval, because also long-term β -adrenoceptor blocker treatment can induce a gradual prolongation of ventricular repolarization [13–15]. In this sense, the net effect of long-term *rac*-sotalol administration on QT interval should result from a variable interplay between Class III effect, prolonged β -adrenoceptor blocking activity and possible occurrence of tolerance. Finding no change in *rac*-sotalol chronic effect in some patients may derive from a balance between the two slowly developing repolarization changes, i.e. prolongation due to chronic β -adrenoceptor blockade and shortening due to tolerance. According to this interpretation, occurrence of tolerance is not genetically determined but is a constant feature of *rac*-sotalol action.

The results referred to by Creamer *et al.* [4] of a greater *rac*-sotalol QT prolongation during long-term oral treatment compared with the acute i.v. administration, might be theoretically ascribed to a prevalence of the chronic β -adrenoceptor blockade effect over the development of tolerance. However, since in this study the evaluation of the acute effect was done at the very end of an i.v. administration, it seems more likely that tissue distribution was not yet complete and the effect was measured in non-equilibrium conditions.

The clinical consequences of possible development of tolerance to repolarization effects of *rac*-sotalol cannot be easily predicted, because of the multiple mechanisms of action of the drug. In particular, the relative contribution of β -adrenoceptor blockade and Class III properties to therapeutic effect is not well established. A recent clinical study [28] found no difference in the incidence of ventricular arrhythmia recurrences and sudden death episodes between patients treated with a 'pure' β -adrenoceptor blocker, metoprolol, and those treated with *rac*-sotalol. Furthermore, no correlation has so far been demonstrated between *rac*-sotalol induced QTc prolongation and suppression of arrhythmias [29–31]. Nevertheless, in the light of Le Coz's study and ours, if therapeutic efficacy is lost during long-term *rac*-sotalol treatment of a patient with stable drug plasma levels, the possibility of onset of pharmacological tolerance should also be considered.

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