Effects of tedisamil, atenolol and their combination on heart and rate-dependent QT interval in healthy volunteers

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Aims Tedisamil is a new blocker of K^+ currents in cardiac tissues, exerts bradycardic effects and has shown clinical efficacy in angina pectoris. Theoretically, when coadministered with a β-adrenoceptor blocker the tedisamil combination could induce dangerous bradycardia and QT interval prolongation. Therefore, the aim of this study was to evaluate the effects of tedisamil and atenolol alone and in combination, on heart rate and QT interval duration at rest and during exercise tests.
Methods The effects of tedisamil (100 mg twice daily) and atenolol (50 mg twice daily) on heart rate and QT interval duration were analysed in a three-period crossover study in healthy male volunteers.
Results This study showed that tedisamil exerted a significant ($P<0.05$) bradycardic action at rest (-10 beats min^{-1}; 95% CI: -6 to -15 beats min^{-1}) similar to atenolol (-14 beats min^{-1}; -11 to -17) and drug combination (-9 beats min^{-1}; -6 to -12). During exercise, at the highest comparable workload, heart rate did not decrease significantly with tedisamil but decreased significantly with atenolol (-42 beats min^{-1}; -37 to -47) and combination (-47 beats min^{-1}; -41 to 52). Atenolol did not modify QT interval duration. Tedisamil alone and in combination with atenolol increased QT interval duration by 12% (95% CI: 7 to 17%) and 12% (8 to 16) respectively at RR = 1000ms, but not at RR < 700ms (combination). Tedisamil alone and in combination induced a reverse rate-dependent QT interval prolongation.
Conclusions These results indicate that the combination of tedisamil and atenolol is not associated with excessive bradycardia or excessive QT interval prolongation in healthy subjects.

Keywords: tedisamil, atenolol, bradycardic agents, QT interval, reverse rate-dependence

Introduction

Tedisamil is a new bradycardic agent that blocks both transient outward (Ito) and delayed rectifier potassium currents (Ik) in cardiac tissues [1, 2]. These effects result in a prolongation of the repolarization phase of the cardiac action potential [3]. In the sinoatrial pacemaker rabbit cells, this prolongation of the repolarization is responsible for a bradycardic action [4]. The class III actions of tedisamil exhibit reverse rate-dependence since prolongation of action potential duration decreases with faster heart rates [5]. Experimental and clinical data have suggested that prolongation of ventricular repolarization, as evidenced by QT interval prolongation on the surface ECG, can be associated with an increased risk of torsades de pointes when heart rate decreases [6–13].

Tedisamil is currently under investigation in the treatment of chronic stable angina pectoris. Because of its bradycardic action tedisamil could be recommended in this indication either alone or associated with other anti-anginal drugs such as β-adrenoceptor blockers. In contrast to β-adrenoreceptor antagonists, tedisamil does not reduce myocardial contractility [14, 15]. However the effects resulting from this association have not yet been investigated. Excessive bradycardia and prolongation of QT interval duration could increase the risk of potentially harmful arrhythmias. The rate-dependent QT interval duration has been currently investigated in humans using a standardized methodology [16, 17]. Therefore, the aim of this study was to evaluate the effects of tedisamil and atenolol alone and in combination at therapeutic dosages, on heart rate and QT interval duration in healthy volunteers at rest and during standardized exercise tests.

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Methods

Study design

The effects of tedisamil and atenolol on heart rate and QT interval duration were analysed in a three-period crossover study in healthy, nonsmoking male volunteers (mean ± s.d. age, 26 ± 3.6). Thirteen subjects were recruited, ten of them completed the study since three subjects had to be

withdrawn, one for a non-study drug related side effect and two for non interpretable ECG recordings. All subjects were considered healthy, based on routine medical examination, 12-lead electrocardiograms (ECG) and standard laboratory tests. They gave their written informed consent to participate in the study and the protocol was approved by the Committee for the protection of Human Subjects in Biomedical Research of Pitié-Salpétrière University Hospital, (Paris, France). During the first two periods of the study, which were performed in a randomized double-blind cross-over design, subjects received either tedisamil (100 mg twice daily) or atenolol (50 mg twice daily) from the second to the sixth day of period. The first day of each period was a single-blind placebo administration. During the third period of the study, both drugs were co-administered twice daily in a single-blind manner at the same dosages as in the monotherapy from the second to the sixth day of treatment. A wash-out phase of at least 1 week was placed between each of the three study periods. Dosages of tedisamil and atenolol were those currently tested in phase III clinical trials (tedisamil) or prescribed in patients with coronary artery disease (atenolol). Treatment was given in the hospital every day. Subjects were outpatients during the two first periods up to the 6th day when they were hospitalized for 24 h at the Clinical Pharmacology Unit at Saint-Antoine University Hospital. They were also hospitalized during the entire duration of the third period.

Tedisamil and atenolol concentrations

Blood samples were drawn on the 6th day of each period, before and after the morning dose administration from 0 to 48 h (0, 0.5, 1, 2, 4, 8, 12, 24, 28, 36, and 48 h). A 10 ml blood sample was collected in a heparinized tube from an antecubital vein for each sample and each treatment. Blood was immediatly centrifuged and separated. Plasma samples were stored in screw-capped polypropylene tubes at -20°C. Tedisamil samples were quantified using a high performance liquid chromatography (h.p.l.c.) with electrochemical detection, the lower limit of quantification was 0.5 ng ml^{-1}. Atenolol samples were quantified using h.p.l.c. with fluorescence detection, the lower limit of quantification was 5.0 ng ml^{-1} (Solvay Pharma, Hannover, Germany).

Exercise tolerance tests

On the morning of the 1st and 6th days of each study period, subjects performed an exercise tolerance test (ETT) on a bicycle ergometer (Siemens, Model EM 840, Paris, France), 2 h after the morning placebo (1st day) or drug (6th day) administration at presumed maximal drug plasma concentration. The exercise test of the first day involved successive load levels of 3 min each, beginning at 60 watts and increasing by 30 watts until a heart rate of 180 beats min^{-1} was reached. On the sixth day, the exercise test was performed according to the same protocol and up the same workload as was individually reached during the ETT under placebo of the particular period. ECG recordings were obtained before the test after a 10 min supine rest in a quiet room. 12-lead ECG tracings were recorded every 30 s during the test.

Measurement of QT interval duration and cardiac cycle length

All electrocardiographic recordings were made simultaneously in 12 leads at a paper speed of 50 mm s^{-1} (amplitude, 1 mv = 2cm) using a Case 15 recorder (Marquette Electronics, Inc; Milwaukee, WI, USA). The tracings were recorded as 'Median-linked complexes' performed by the Case 15 machine, in order to obtain the best possible tracing quality (especially during exercise). The ECG recordings were read by the same blinded investigator at the end of the three treatment periods. QT intervals and corresponding cardiac cycle lengths (RR intervals) were measured manually in anterior leads V3 or V4 using a digitizing pad (SummaSketch II Professional MMII 1812-Summagraphics, Seymour, CT, USA) connected to a microcomputer. The QT interval duration was measured from the onset of the QRS complex to the end of the T wave, as defined according to the criteria of Lepeschkin & Surawicz [18].

Data analysis

Steady state On the 6th day of each treatment period, the plasma concentrations of tedisamil, atenolol, and each drug in combination at trough morning levels were compared with the drug concentrations 12 h later (dosing interval duration) in order to verify that steady state had been reached.

Treatment induced changes in heart rate The analyses of the effects of placebo, and of each drug and their combination on heart rate were performed at rest and at peak exercise during the ETT at 2 h after placebo or drug administration. Resting and exercising heart rates were then compared for each period between placebo (1st day) and drug (6th day) administration.

QT interval prolongation The QT *vs* RR relationship was analysed at rest and during each exercise test and was fitted to the monoexponentiel formula $QT = A\text{-}B^{\star} \exp(\text{-}C^{\star}RR)$ where QT and RR are the observed data and A, B, C are the regression parameters [19]. This formula has been shown to be optimal for describing the QT *vs* RR relationship during exercise [20–22]. The three regression parameters were used to calculate the QT interval of each subject during each exercise test corresponding to predetermined RR intervals of 1000 ms, 900 ms, 800 ms, 700 ms, 600 ms, 500 ms, and 400 ms. No difference was observed between QT-RR relationship during the three placebo ETTs on the first day of each period (Figure 1). One referential placebo QT-RR relationship was then selected at random for each subject. The variations (Δ) of QT interval duration during tedisamil, atenolol and bitherapy were calculated as the ratio $\Delta\ (\%) = 100^{\star}$ (value treatment—value placebo)/value placebo.

Statistical analysis

Differences were considered to be statistically significant at $P < 0.05$. Results throughout the text are expressed as the arithmetic mean with standard deviation for normal parameters, as the geometric mean with 95% confidence interval

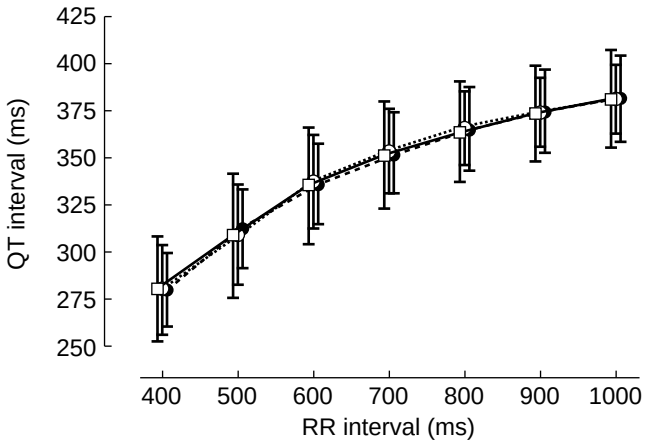

Figure 1 Reproducibility of exercise-induced changes in QT interval duration during administration of placebo on day 1 of each study period (○ 1, □ 2, ● 3) mean ± s.d. values are reported.

(95% CI) for log-normal pharmacokinetic parameters or as the median with 95% confidence interval for non parametric parameters.

Analysis of pharmacokinetic parameters In order to show that steady-state was achieved on day 5 of each period, the trough plasma concentrations of each drug were compared with trough concentrations measured 12 h later using a Student's *t*-test.

The area under the plasma concentration *vs* time curve (AUC) was determined by the trapezoidal rule. The following pharmacokinetic parameters were calculated by a monocompartment model: elimination half-life ($t_{1/2}$) associated with the terminal slope of the semilogarithmic concentration-time curve, time to reach peak concentration after administration (t_{max}), peak plasma concentration after administration (C_{max}), AUC from 0 to 12 h (AUC(0, 12h)). Differences in pharmacokinetic parameters between study periods were calculated by geometric means based on logarithmic transformation of the intraindividual ratios of log-normal parameters AUC, C_{max} and $t_{1/2}$. The differences between study periods and the standard deviations for the 95% confidence limits were calculated by ANOVA and Dunnett-test. Experimental t_{max} was compared by using the sign test.

Analysis of heart rate variation Comparisons of heart rate variations were made by 95% confidence intervals testing for differences between treatments. Differences in mean heart rate were compared with Student's paired *t*-test, at rest and during exercise at the same highest comparable workload.

Analysis of QT interval prolongation Treatment comparisons were made with three-factor repeated ANOVA (factors = treatment, subject and period). If this analysis indicated a significant difference, a Student's paired *t*-test was performed to compare the difference in mean QT interval durations between the active treatments and the placebo.

Analysis of rate dependency For each treatment period, variations of QT prolongation were compared by using 2-factor ANOVA (factors = RR interval and subject). If the analysis indicated a significant difference, a Student-Newman-Keuls post hoc test was performed to compare the variations of QT interval prolongation between the different RR intervals.

Results

Pharmacokinetics

Pharmacokinetic steady-state was reached on the last day of each study period as evidenced by the absence of significant difference between plasma concentration of tedisamil or atenolol measured immediately before the last drug intake and one dosing interval, i.e. 12 h, thereafter.

The effects of the tedisamil-atenolol combination on the pharmacokinetic parameters are summarized in Table 1.

When tedisamil was administered alone, the C_{max} and t_{max} were 532 ng ml^{-1} (95% CI: 411 to 689) and 1.5 h (1 to 2) respectively. The AUC (0, 12 h) of tedisamil was 2448 ng ml^{-1} h (1852 to 3238) and its apparent elimination half-life was 11.7 h (9.8 to 14.0). In association with atenolol, the pharmacokinetic parameters of tedisamil were not significantly modified: C_{max} 494 ng ml^{-1} (381 to 639), t_{max} 1.5 h (1 to 2), AUC (0, 12 h) 2436 ng ml^{-1} h (1854 to 3200) and half-life 9.8 h (8.3 to 11.6).

The combination of both drugs resulted in significant but limited changes in the AUC (0, 12 h) and C_{max} of atenolol with an increase of 20% (95% CI: 10 to 31) and 15% (4 to 28) respectively, t_{max} was not significantly modified.

Heart rate variations

At rest, tedisamil significantly decreased heart rate by -10 beats min^{-1} (95% CI: -6 to -15 beats min^{-1}), as compared with placebo. This effect was not significantly different from the effects of atenolol, -14 beats min^{-1} (−11 to -17 beats min^{-1}) and drug combination, -9 beats min^{-1} (−6 to -12 beats min^{-1}) (Table 2, Figure 2).

At peak exercise, heart rate did not decrease significantly with tedisamil as compared with placebo, -7 beats min^{-1} (0 to -13 beats min^{-1}). Atenolol significantly decreased heart rate by -42 beats min^{-1} (−37 to -47 beats min^{-1}) ($P<0.01$) alone, and in combination -47 beats min^{-1} (−41 ± 52 beats min^{-1}) ($P<0.01$). At comparable peak workload, the bradycardic action of drug combination was greater than that observed with atenolol alone. (Table 2, Figure 2).

QT interval prolongation and reverse rate-dependence

After 5 days of repeated administration, tedisamil significantly prolonged QT interval duration at rest (i.e. RR = 1000 ms). QT interval significantly increased from 383 ± 23 ms with placebo to 427 ± 39 ms with tedisamil alone ($P<0.01$ *vs* placebo) and to 428 ± 27 ms with tedisamil in combination with atenolol ($P<0.01$ *vs* placebo). These effects corresponded to an increase of 12% (7 to 17%) and 12% (8 to 16%) respectively (Figure 3). Atenolol did not significantly modify QT interval duration.

During exercise, the tedisamil-induced increase of QT

Table 1 Comparison of pharmacokinetic parameters of drugs alone and in combination.

Parameter	*Alone*	*In combination*	*Ratio % [95% CI]*
Tedisamil			
C_{max}	532 [411 to 689] (ng ml^{-1})	494 [381 to 639] (ng ml^{-1})	92.8 [73 to 118]
AUC (0, 12 h)	2448 [1852 to 3238] (ng ml^{-1} h)	2436 [1854 to 3200] (ng ml^{-1} h)	99.5 [80 to 124]
$t_{1/2}$	11.7 [9.8 to 14.0] (h)	9.8 [8.3 to 11.6] (h)	83.8 [68 to 103]
t_{max}	1.5 [1 to 2] (h)	1.5 [1 to 2] (h)	
Atenolol			
C_{max}	347 [317 to 380] (ng ml^{-1})	400 [358 to 448] (ng ml^{-1})	115.5 [102 to 130]★
AUC (0, 12 h)	2621 [2291 to 2998] (ng ml^{-1} h)	3149 [2725 to 3638] (ng ml^{-1} h)	120.1 [109 to 133]★
$t_{1/2}$	11.7 [9.8 to 13.9] (h)	10.1 [8.2 to 12.4] (h)	86.1 [70 to 107]
t_{max}	2 [2 to 4] (h)	2 [2 to 4] (h)	

Values are geometric mean with 95% confidence intervals (log-normal parameters: C_{max}, AUC and $t_{1/2}$).
Ratio in the means of the two groups with 95% confidence intervals.
Values are median with 95% confidence intervals (non parametric parameter: t_{max}).
★$P<0.05$.

Table 2 Effect on heart rate 2 h after administration of tedisamil and atenolol and 2 h after administration of tedisamil and atenolol in combination.

Heart rate (beats min^{-1})	*Tedisamil*	*Atenolol*	*Difference*
At rest	56.8 ± 7.8	54.0 ± 6.2	2.8 (−1.9 to 7.5) NS
After effort	155.9 ± 10.9	123.7 ± 8.7	32.2 (26.7 to 37.7)★
	Tedisamil	*Tedisamil + atenolol*	*Difference*
At rest	56.8 ± 7.8	52.5 ± 7.0	4.3 (−0.5 to 9.1) NS
After effort	155.9 ± 10.9	113.3 ± 8.4	42.6 (36.8 to 48.4)★
	Atenolol	*Tedisamil + atenolol*	*Difference*
At rest	54.0 ± 6.2	52.5 ± 7.0	1.5 (−2.9 to 5.9) NS
After effort	123.7 ± 8.7	113.3 ± 8.4	10.4 (4.9 to 15.9)★
Heart rate (beats min^{-1})	*Placebo*	*Tedisamil*	*Difference*
At rest	67.2 ± 6.5	56.8 ± 7.8	10.4 (6.0 to 14.9)★
After effort	162.4 ± 10.2	155.9 ± 10.9	6.5 (−0.1 to 13.1) NS
	Placebo	*Atenolol*	*Difference*
At rest	67.7 ± 6.5	54.0 ± 6.2	13.7 (10.6 to 16.8)★
After effort	165.9 ± 11.2	123.7 ± 8.7	42.2 (37.4 to 47.0)★
	Placebo	*Tedisamil + atenolol*	*Difference*
At rest	61.4 ± 5.9	52.5 ± 7.0	8.9 (5.6 to 12.1)★
After effort	159.8 ± 7.6	113.3 ± 8.4	46.5 (41.2 to 51.8)★

Heart rate values: mean ± s.d. at rest and at highest comparable workload.
Different in mean heart rate (95% CI). ★$P<0.01$.

interval duration remained significant at cardiac cycle lengths ranging from 1000 ms to 400 ms when tedisamil was administered alone and from 1000 ms to 700 ms when tedisamil was administered with atenolol. However reverse rate-dependence of QT interval duration was observed with both regimens of tedisamil. Indeed, compared with placebo, QT interval prolongation decreased from 12% (7 to 17%) at RR = 1000 ms (HR = 60 beats min^{-1}) to 5% (3 to 7%) at RR = 400 ms (HR = 150 beats min^{-1}) during administration of tedisamil alone. Similarly, compared with placebo, QT interval prolongation during combination of tedisamil and atenolol decreased from +12% (8 to 16%) at RR = 1000 ms to −2.2% (−7 to 3%) at RR = 500 ms (HR = 120 beats min^{-1}) (Figure 3).

Side effects

Adverse events were analyzed in all 13 volunteers included. Twelve subjects completed the three treatment periods, and one was withdrawn after the first tedisamil period (patellar fracture unrelated to the study).

The most frequent adverse event during administration of tedisamil alone was diarrhoea, which occurred in three subjects. Two subjects complained of asthenia and headache. After administration of atenolol alone, asthenia and headache occurred in three and two subjects respectively, while two subjects had diarrhoea and one nausea.

Combination of tedisamil and atenolol was associated with an increase in the frequency of adverse events with nine volunteers complaining of at least one adverse event. All of them reported diarrhoea and three subjects had also abdominal pain. Three subjects complained of headache and two of them also had asthenia. Two subjects had a mild vagal syncope at the end of exercise test.

No arrhythmia was detected on ECG recordings and monitorings during the study.

Discussion

This study shows that tedisamil significantly decreases heart rate at rest but not during exercise, while atenolol slows heart rate at rest and during exercise. Tedisamil, but not

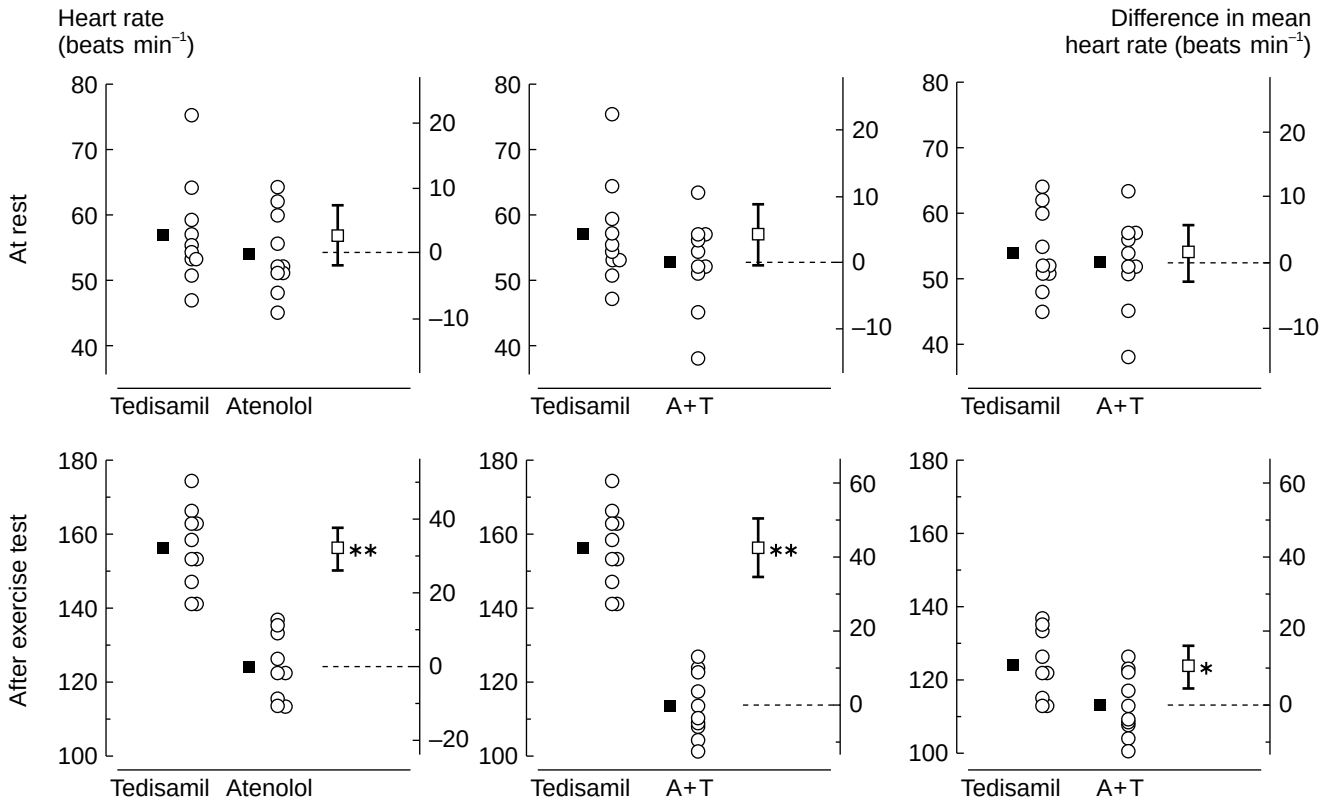

Figure 2 Heart rate values (○) at rest and after exercise test, with mean levels (■) after study drugs: tedisamil, atenolol and their combination (A + T). The differences between the means (□) are shown on the right together with their 95% confidence interval. $\star P<0.05$, $\star\star P<0.01$.

atenolol, prolonged the ventricular repolarization time as measured by QT intervals. A reverse rate-dependence was observed with tedisamil since QT interval prolongation was significantly less pronounced at higher than at lower heart rates. This phenomenon of reverse rate-dependence was also found during combination of tedisamil with atenolol, since QT interval prolongation was not significantly different from placebo at cardiac cycle lengths shorter or equal to 600 ms (i.e. heart rate less than 100 beats min^{-1}). The combination of drugs did not significantly modify the steady state pharmacokinetics of tedisamil and the difference in AUC (0, 12 h) and C_{max} of atenolol were limited. The exercise tests were performed 2 h after administration, this corresponded to the observed t_{max} (between 1 and 2 h).

Bradycardic effect

At rest In animal studies, tedisamil showed a dose-dependent bradycardic effect [4, 23, 24]. In humans, Bargheer *et al.*, in 10 resting patients with coronary artery disease, observed that tedisamil (0.3 mg kg^{-1} i.v.) decreased heart rate significantly from 67 ± 9 beats min^{-1} to 59 ± 8 beats min^{-1} (−12%) [5]. Mitrovic *et al.* also found at rest a dose-dependent decrease in heart rate in 24 patients with ischaemic heart disease [25]. Thormann *et al.* found a decrease of 17% in heart rate after an i.v. infusion of tedisamil 0.3 mg kg^{-1} i.v. [15]. These results are consistent with the bradycardic effect we have found with tedisamil at rest (−15 ± 9%). Bargheer *et al.* showed that left ventricular monophasic action potentials were prolonged in all patients in parallel with a reduction of heart rate [5]. Tedisamil blocks potassium channels and prolongs repolarization in the ventricle [1] and in the sinus node [3, 26]. Prolongation of repolarization in the sinus node is known to be a mechanism of bradycardia [27]. Since tedisamil does not modify the conductance of other sodium or calcium channels in myocardial cells at therapeutic doses, its bradycardic effect is very likely due to prolongation of action potential duration in nodal cells. These class III effects have also been found with *d*-(+)-sotalol, the enantiomer of sotalol which is devoid of β-adrenoceptor blocking properties. It has been suggested that the bradycardic effects of *d*-sotalol are due to its class III actions in the sinus node [28, 29] and that the amplitude of these effects correlate with the degree of QT prolongation.

During exercise The lack of bradycardic action of tedisamil during exercise could be explained by a reverse rate dependence in the sinus node. In fact, tedisamil exerted minimal and no significant bradycardic effect at the submaximal workload during exercise, while atenolol and the drug combination exerted significant bradycardic effects. Mitrovic found a significant bradycardic effect of 7.7% with tedisamil in patients with coronary heart disease during application of a symptom-limited maximal workload [25]. However, these effects were observed after an i.v. tedisamil dose of 0.3 mg kg^{-1} corresponding to a C_{max} of 1611 ± 437 ng ml^{-1}. At the lower i.v. dose of tedisamil (0.1 mg kg^{-1}), resulting in a C_{max} = 405 ± 160 ng ml^{-1}, in the range of that found in our study, no significant effect on heart rate was observed. Therefore our study indicates that the bradycardic effects of tedisamil during exercise

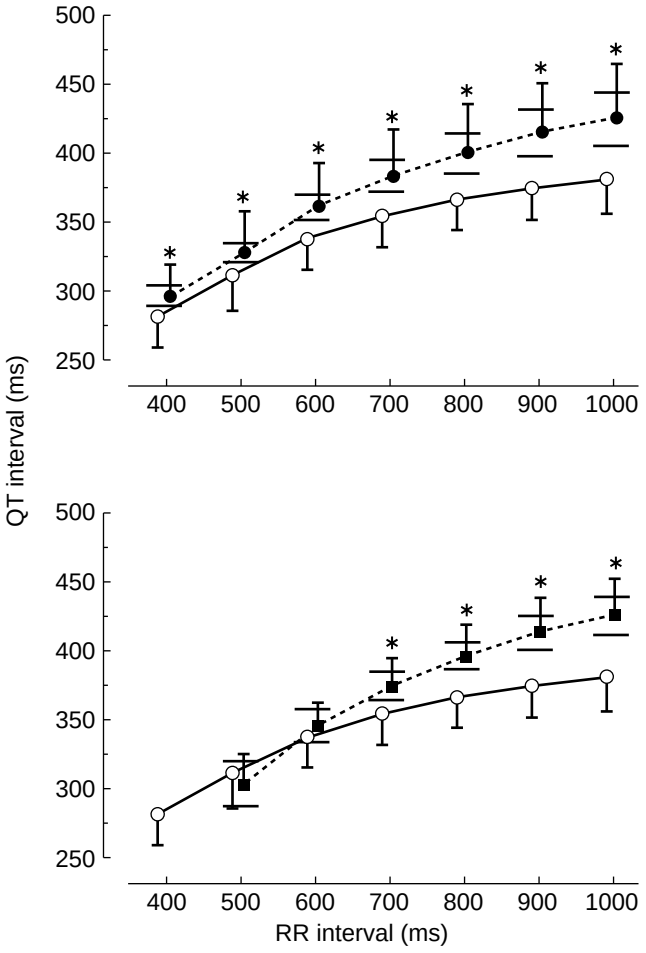

Figure 3 Effects of placebo (○), tedisamil alone (●) and tedisamil in combination with atenolol (■) on QT interval. The horizontal lines represent the 95% confidence interval for the mean differences centred on treatment mean values. Exercise test was performed 2 h after administration. $\star P < 0.01$.

remains very limited at the oral dosage of 100 mg twice daily. The lack of a significant effect of tedisamil on exercise-induced tachycardia probably reflects the fact this drug has no anti-adrenergic property. If the drug exerts anti-anginal effect it could be related to other pharmacodynamic properties [25].

QT prolongation and reverse rate-dependence

An increase in action potential duration and a dose-dependent QT interval prolongation have been shown during administration of tedisamil in animals studies [3, 4, 23, 24]. In patients with coronary artery disease, Bargheer *et al.* observed a prolongation of the action potential duration and the ventricular effective refractory period [5]. Prolongation of repolarization decreased as heart rate increased (12.2% at RR = 600 ms, and 8.9% at RR = 400 ms). However, prolongation of repolarization remained significant even at the shortest cardiac cycle length of 400 ms tested and corrected QT interval (Bazett's formula) was prolonged by about 9.7% [5]. After administration of the same dose of tedisamil (0.3 mg kg^{-1} i.v.), Mitrovic *et al.* [25] and Thormann *et al.* [15] found a QTc interval prolongation of 12 and 14% respectively. In our study, tedisamil administration was associated with a significant QT interval prolongation of 11.6 ± 7.1% at RR = 1000 ms, and a reverse rate-dependence of this effect which is in accordance with the results of electrophysiologic studies performed during pacing [5]. There was no QT interval prolongation with atenolol as was expected [20, 21, 30, 31]. However, drug combination resulted in a QT interval prolongation with a persistent reverse rate-dependence similar to the effects of tedisamil alone. This study was performed in male subjects and women were not included in this phase I study in order to limit the gender-related possible source in QT interval duration [32]. Therefore our results may not be extrapolatable to female subjects.

Pharmacokinetics

The association with atenolol did not significantly modify the steady state pharmacokinetics of tedisamil. AUC (0, 12 h) and C_{max} of atenolol increased by 20.1% and 15.5% respectively during administration of tedisamil and there was no change of t_{max}. These differences in AUC (0, 12 h) and C_{max} of atenolol were small and without pharmacodynamic consequence since the effects of atenolol alone *vs* atenolol in combination were not significantly different (at rest and during exercise).

Tolerability

No proarrhythmic effect was observed during the study. However an increase in non serious-adverse adverse events, especially diarrhoea and asthenia, was observed during the combination of tedisamil with atenolol. The increase of side effects of combination may have been due to the fact that the volunteers were hospitalized throughout this period. All symptoms were moderate in intensity and disappeared spontaneously.

One serious adverse event (left patella fracture, leading to hospitalization of the volunteer and withdrawal from the study) not related to the study occurred in the tedisamil monotreatment period.

Conclusion

The combination of tedisamil and atenolol is not associated with an excessive bradycardia or with QT prolongation greater than that observed during administration of tedisamil alone. However, the results of this study in healthy subjects cannot be directly extrapolated to patients with ischaemic heart disease. Further clinical studies in patients with myocardial ischaemia should be performed to confirm that administration of tedisamil and a β-adrenoceptor blocker is not associated with an increase in unwanted cardiovascular responses. The results of the present study indicate that such studies can now be initiated in patients.

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