Assessment of the effect of a single oral dose of telithromycin on sotalol-induced QT interval prolongation in healthy women

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Aims

Telithromycin belongs to ketolides, a new class of macrolide antibiotics. Macrolides are known to have the potential to prolong QT interval duration. Previous studies have shown that telithromycin did not induce significant QT interval prolongation in healthy subjects compared with placebo. The main objective of this study was to demonstrate the absence of amplification of QT interval prolongation induced by sotalol, when telithromycin and sotalol were co-administered. The secondary objective was to correlate the QT interval changes induced by the study drugs to plasma concentrations during the elimination phase.

Methods

Twenty-four women received sotalol (160 mg) together with placebo or telithromycin (800 mg) in a two-period, double-blind, randomized study. Electrocardiograms were recorded at rest. Comparison of maximal corrected QT interval (QT_{Cmax}) with sotalol in the presence or absence of telithromycin was performed. The relation between sotalol concentration and QT_C was studied using linear regression.

Results

Mean difference (95% CI) between QT_{Cmax} with sotalol-placebo and QT_{Cmax} with sotalol-telithromycin was -15.5 ms (-27.7 to -3.2 ms). QT_{Cmax} interval prolongation was lower ($P < 0.05$) with sotalol-telithromycin than with sotalol-placebo, in relation to decreased sotalol plasma concentrations. Regression analysis showed that the relationship between sotalol plasma concentration and QT_C interval duration was not modified by telithromycin co-administration.

Conclusion

Our results do not support a potential synergistic effect on QT interval prolongation between sotalol and telithromycin. The decrease of mean QT_C interval in subjects taking telithromycin and sotalol may be explained by a decrease of sotalol concentration.

Introduction

Telithromycin (HMR 3647) belongs to the class of ketolides which are a new addition to the macrolide-lincosamide-streptogramin_B class of antimicrobials.

A review describes the main characteristics of telithromycin [1].

The QT interval encompasses the time from the earliest activation of the ventricular myocardium to the

latest ventricular repolarization. QT interval prolongation is associated with the risk of triggering a particular arrhythmia termed *torsades de pointes* [2]. The possible occurrence of torsades de pointes is a major concern during treatment with all drugs that prolong ventricular repolarization [3, 4]. These drugs share the ability to block the rapid component of the delayed rectifier potassium channel (I_{Kr}), resulting in inhomogeneous lengthening of action potential, T-wave morphological changes and QT interval prolongation [4].

Several antibiotic compounds such as quinolones [5–7] and macrolides [8, 9], are known to be associated with minimal increase of QTc interval. Since the ketolides represent a novel addition to the macrolide-lincosamide-streptogramin_B class of antimicrobials, a comprehensive assessment of their effects on cardiac repolarization is deemed necessary. In previous clinical study, where QT interval was measured and compared at fixed heart rate, no difference between placebo and telithromycin, up to 2400 mg, i.e. three times the clinical therapeutic dose was found [10]. *In vitro* data with telithromycin showed a significant increase in the duration of action potential (APD) in Purkinje fibre at high free concentrations (8 mg l⁻¹, i.e. approximately 10 times the therapeutic plasma concentration, taking into account a 70% protein binding). An *in vitro* study using Purkinje fibres showed a significant potentiation of prolongation telithromycin-induced APD in the presence of sotalol, a class III antiarrhythmic which prolongs the duration of ventricular repolarization [11, 12]. This synergistic effect was shown starting at 2.4 mg l⁻¹ of telithromycin (Hoechst Marion Roussel, report no. 99/10838). This might be clinically relevant in humans since previous clinical studies have shown a *C_{max}* value of 1.1 mg ml⁻¹ [10] to 2 mg l⁻¹ [1] during oral administration of 800 mg of telithromycin and *in vitro* studies in rats showed a heart : plasma ratio of about 3.8.

The main objective of the present study was to assess a potential interaction on QT interval when telithromycin and a QT interval-prolonging drug are co-administered. The secondary objective was to correlate the QT interval changes induced by the study drugs to sotalol plasma concentrations during the elimination phase.

Methods

A dose of 160 mg of sotalol was chosen because it is one of the recommended doses and because corrected QT interval prolongation using Bazett [13] or Fridericia [14] formula is known to be in the 40–50 ms range [12, 15]. The telithromycin 800 mg dose was chosen because at the time of the protocol writing, it was already known that this would be the recommended dose. A single dose

of both study drugs was administered at the same time since both the *t_{max}* are in the 2–4 h range. The study drugs were administered in the fasting state, the subjects received 800 mg of telithromycin or placebo and 160 mg of sotalol in standing position with 240 ml of mineral water.

The influence of telithromycin on QT interval prolongation induced by sotalol was studied in a two-period, randomized, placebo-controlled, double-blind, cross-over study. There was a washout phase of at least 1 week between each study period. Twenty-four female subjects were included. Women were chosen since they have a longer QT interval and are more prone to develop torsade de pointes than males [16–19]. This was not considered a safety issue since we had previously shown that no QT interval prolongation was found in women after single oral administration of telithromycin doses up to 2400 mg [10]. Subjects were nonsmokers, judged healthy from medical history, physical examination, routine laboratory investigations and 12-lead electrocardiogram (ECG). They were not allowed to take any drug other than study drugs for 3 months before inclusion and throughout the duration of their participation to the study. They gave their written informed consent to participate in the study and the protocols were approved by the Committee for the Protection of Human Subjects in Biomedical Research of Pitié-Salpêtrière University Hospital (Paris, France).

Sample size was calculated to test the equivalence between treatment with telithromycin and sotalol vs. treatment with placebo and sotalol. The equivalence limit of difference of mean QTc interval was set at 15 ms. With a one-sided test, a significance level of 5%, a power of 90% and a standard deviation of 24 ms, 24 subjects were needed to show the equivalence of the treatments.

Subjects were hospitalized for 24 h at the Clinical Investigation Centre (Centre d'Investigation Clinique) at Saint-Antoine University Hospital during each study day. Resting electrocardiograms (ECG) were recorded over the 24 h following each study drug administration at the time each plasma sample was drawn. ECG recordings were made simultaneously in 12 leads at a paper speed of 50 mm s⁻¹ (amplitude of 2 cm mV⁻¹) with the use of a Case 15 recorder (Marquette Electronics Inc, Milwaukee, Wisconsin). The ECG recordings were read by the same investigator who was blinded to the treatment at the end of the two treatment periods. The QT intervals were measured manually with a digitizing pad (SummaSketch II Professional MM II 1812, SummaGraphics, Seymour, Connecticut) connected to a micro-computer. The anterior ECG lead where the T wave had

the largest amplitude was selected for QT interval measurement in each subject. QT interval was measured from the onset of the QRS complex to the end of the T wave, which was defined as the intersection of the tangent to the steepest downslope of the T wave with the isoelectric line. A U wave, if present, was considered as augmented and was included in the QT measurement if it was >25% of the T-wave amplitude [20]. Several consecutive beats (at least three RR and corresponding QT intervals) were measured in each ECG lead and the result of these measurements was averaged to determine QTc (Bazett/Fridericia) value.

After oral administration, blood samples (~5 ml each) were drawn from 0 to 24 h (0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 h).

Sotalol was assayed in plasma by a validated liquid chromatography with tandem mass spectrometry (LC/MS-MS) method. Thawed plasma samples (50 µl) were mixed with 20 µl of internal standard solution and vortex-mixed. After proteins precipitation, the clean supernatant was evaporated to dryness at 40°C under nitrogen stream. The dry residue was taken up in 200 µl of injection solvent and 20 µl were injected in the LC/MS-MS system. The method has a standard curve range of 10–3000 ng ml⁻¹. The limit of quantification was 10 ng ml⁻¹. The interbatch per cent coefficient of variation for the quality control samples was between 4.8 and 10.1%. (SGS Biopharma, Wavre, Belgium)

Telithromycin was assayed in plasma by a high performance liquid chromatography/mass spectrometric (LC/MS) method. Plasma proteins were precipitated with acetonitrile, and the supernatant was analysed directly by LC/MS. The method has a standard curve range of 0.005–3 mg l⁻¹ telithromycin using 100 µl of plasma. The limit of quantification was 0.005 mg l⁻¹. The interbatch per cent coefficient of variation for the quality control samples was between 4.8 and 11.8% (Quintiles Inc., Kansas City, Missouri).

On the basis of individual plasma concentration-time data, the following pharmacokinetic parameters were determined: area under the plasma concentration–time curve from 0 to 24 h (AUC_{0–24}) and from 0 to infinity (AUC_{0–inf}), peak plasma concentration after single oral dose administration (C_{max}), time to reach the peak concentration after oral drug administration (t_{max}), elimination half-life associated with the terminal slope λ_z of a semi logarithmic concentration time-curve ($t_{1/2}$). The pharmacokinetic parameters were calculated with a noncompartmental model with the use of the WinNonLin® software 3.0 (Pharsight Corporation, Mountain View, California) by Aventis Pharma, Romainville, France.

Plasma concentrations of sotalol, telithromycin and their respective pharmacokinetic parameters were presented as descriptive statistics. The effect of telithromycin on sotalol pharmacokinetics when sotalol was administered with telithromycin or with placebo was analysed using a three way analysis of variance (ANOVA) with treatment, period and subject as main effects in the model for lognormal parameters, i.e. logarithmic transformed C_{max} , AUC_{0–24} and AUC_{0–inf}. For t_{max} , a nonparametric parameter, a Wilcoxon test was used.

The primary pharmacodynamic parameter was the maximum corrected QT interval (QTc_{max} using Bazett's formula) obtained between 1 and 4 h after drug administration in 24 evaluable subjects.

Descriptive statistics were calculated for QTc intervals. ANOVA was used to compare QTc_{max} change from baseline (Δ QTc_{max}) between treatment, and an analysis of covariance (ANCOVA) was used to compare QTc_{max} between treatment. The model used for ANOVA contained the factors subject, treatment and period, the factor subject was used as a random factor in the model. For ANCOVA the model contained the factors included in ANOVA model and the covariate was the QTc at baseline.

The QTc interval analyses were done using Bazett's formula (QTcb, main analysis) and Fridericia's formula (QTcf).

To study the relation between QTc interval and sotalol plasma concentration during both treatments for each individual, regression analysis was used. Only data collected from t_{max} to 24 h were used in the regression analysis. For each treatment and each subject, regression analysis was performed and regression parameters were obtained. Regression parameters (slope and intercept) for both treatments were compared in each subject. The comparison was made by calculating the difference between slopes and its 95% confidence interval (95% CI). If the difference between the slopes was not significantly different from zero at an alpha level of significance of 5%, then the difference between adjusted intercepts was calculated with its 95% CI.

Safety variables for this study included adverse events, laboratory (haematology, blood chemistry and urinalysis) data, physical examinations, vital signs measurements (blood pressure, heart rate), 12-lead ECG recordings and Holter monitoring. All subjects who received at least one dose of study medication were included in the safety analysis.

Statistical analyses were performed using the SAS® software 6.12 (SAS Institute Inc, Cary, North Carolina) by the Drug Metabolism and Pharmacokinetics Department, Aventis Pharma.

Results

A total of 25 subjects were enrolled in the study, 24 subjects completed the study, one of the subjects did not participate to the second study period. All subjects were Caucasian women with a mean age of 26.3 ± 4.6 years (range: 19–36 years). The means of weight and height were 60.3 ± 6.8 kg (range: 48–76 kg) and 165.9 ± 6.4 cm (range: 153–178 cm), respectively. All the parameters measured in the physical examination and in the laboratory tests were normal at prestudy screening.

Pharmacokinetic results are presented in Table 1 and Figure 1. In the presence of telithromycin, sotalol C_{max} , AUC_{0-24} and AUC_{0-inf} decreased (34%, 27% and 20%, respectively. Median sotalol t_{max} decreased from 3 to 2 h and sotalol $t_{1/2}$ increased 1.3-fold. These changes were statistically significant (Table 1).

The QTc_{max} for each subject was reached between 2 and 5 h after administration of sotalol + placebo (sot/pL) and between 2 and 4 h after co-administration of sotalol and telithromycin (sot/teli). Arithmetic means of QTc_{max} and ΔQTc_{max} intervals are summarized in Table 2. Evolution of QTcb interval over time is presented in Figure 1.

In comparison with the sot/pL administration, the $QTcb_{max}$ interval was lower after sot/teli, 469 ± 44 ms and 453 ± 26 ms, respectively. The $QTcb_{max}$ interval mean difference, -15.5 ms (95% CI, -27.7 to -3.2), was statistically significant ($P < 0.05$). The $QTcb_{max}$ interval

variation ($\Delta QTcb_{max}$ from baseline), was also less pronounced after sot/teli co-administration than after sot/pL. The difference between the means was statistically significant, $P < 0.01$ (Table 2).

Similar results were found by use of Fridericia's correction: $QTcf_{max}$ and $\Delta QTcf_{max}$ (Table 2).

Individual relations between sotalol plasma concentration and QTc intervals were studied for the 24 subjects. A mild hysteresis was observed in subjects #1, #3, and #17. This phenomenon was taken into account and the analysis was studied during the elimination phase, i.e. after C_{max} was reached. For all subjects, sotalol C_{max} were higher after sot/pL treatment than after sot/teli co-administration.

For each subject regression parameters (slope and intercept) for both treatments were compared. There were no statistically significant differences between the slopes for 22 subjects out of 24 (representative subject #6, Figure 2 top panel). Slopes were statistically different in subjects #4 and #9. In subject #4, there was a slight potentiation of sotalol-induced QTcb prolongation in the presence of telithromycin (Figure 2 middle panel). However QTcb values obtained with sot/teli were within the 95% CI for predicted individual values of sot/pL (Figure 2 middle). In subject #9, the slope differences were due to low values at the beginning of the slope (intercept difference was statistically different, $P < 0.05$) and the QTcb values obtained with sot/teli were within the 95% CI for predicted individual values

Table 1

Telithromycin and sotalol pharmacokinetic parameters

Parameter	Telithromycin disposition kinetics (in the presence of sotalol) (n = 24)	Sotalol disposition kinetics (alone) (n = 25)	Sotalol disposition kinetics (in the presence of telithromycin) (n = 24)	PE* (n = 24)	P-value from ANOVA
C_{max} (mg l ⁻¹)	1.24 ± 0.34 (0.77–2.13)	1.49 ± 0.26 (1.13–2.30)	1.00 ± 0.23 (0.47–1.51)	0.66 (1.26) (0.62–0.73)	<0.001
$AUC_{(0-24)}$ (mg h ⁻¹ l ⁻¹)	5.80 ± 2.10 (3.34–10.37)	14.15 ± 1.90 (10.65–19.11)	10.41 ± 1.50 (6.90–13.54)	0.73 (1.15) (0.70–0.79)	<0.001
$AUC_{(0-inf)}$ (mg h ⁻¹ l ⁻¹)	†	15.94 ± 2.10 (11.80–21.10)	12.78 ± 1.80 (9.77–17.75)	0.80 (1.12) (0.77–0.85)	<0.001
$t_{1/2}$ (h)	†	7.32 ± 0.60 (6.44–8.61)	9.80 ± 1.5 (7.77–14.28)	1.33 (1.17) (1.25–1.44)	<0.001
t_{max} (h)	2.0 (2.0–3.0) (0.5–4.0)	3.0 (2.5–4.0) (1.0–5.0)	2.0 (1.5–2.5) (1.0–4.0)	–	<0.01

Mean $\pm$ SD (range), except t_{max} : Median, (95% CI) and (range). *PE: point estimate = geometric mean (geometric SD) and (95% CI) of the individual ratios of each parameter taking into account the parameters of sotalol + placebo as reference. †It was not possible to determine telithromycin terminal half-life and $AUC_{(0-inf)}$ due to the sampling schedule.

Figure 1

Evolution over time of QTcb interval (top), and study drugs plasma concentrations, Cp (bottom); sotalol mean ($\pm$ SD) values after single oral administration of 160 mg of sotalol + placebo (open squares) or co-administered with 800 mg of telithromycin (closed squares); telithromycin mean ($\pm$ SD) values (closed circles)

of sot/pL (Figure 2, bottom panel). The same results were found when using QTcf data.

Twenty-four of the 25 subjects enrolled were treated with single oral doses of sotalol (160 mg) + telithromycin (800 mg) or sotalol (160 mg) + placebo and completed the study. One subject (#7) treated with sot/pL during Period 1 did not participate in Period 2 because of QTc interval prolongation greater than 500 ms (see below). All 25 subjects were evaluable in the safety analysis.

There was no serious adverse event during this study. Eight and 10 subjects complained of adverse event after sot/pL and sot/teli, respectively. The observed adverse events were diarrhoea (4 and 10), nausea (3 and 2), QTcb interval prolongation >470 ms (3 and 1), vomiting (0 and 1) and abdominal pain (1 and 1) after drug administrations (sot/pL and sot/teli). All adverse events were mild or moderate in intensity except for one case of diarrhoea (sot/pL) which was considered as severe. This

Figure 2

Relationship between QTcb interval and sotalol plasma concentration (mg L⁻¹) with regression line in the presence (closed circles, dashed line) and absence (open squares, solid line) of telithromycin in three representative subjects (see text); dashed curves represent the 95% confidence interval for individual predicted values for QTcb of sotalol + placebo treatment

subject (#24) experienced 10 episodes of diarrhoea on days 2 and 3. She recovered without sequel.

Subject #7 was withdrawn because of a QTc interval prolongation greater than 500 ms during four consecutive measurements (exclusion criterion was three consecutive QTcb measurements >500 ms). This event was asymptomatic, QTcb interval varied between 521 and 538 ms (QTcf: 507 and 528 ms) from 3 to 5 h after sot/

Table 2Statistical comparison between treatments for corrected QT_{max} parameters (*n* = 24 in both groups)

	Parameter/Treatment	Mean ± SD (range)(ms)	Difference between means(95% CI) (ms)	P-value
Bazett	QT _{max} interval			
	Sotalol + placebo	469 ± 44 (413–636)	–15.5 (–27.7 to –3.2)	<0.05
	Sotalol + telithromycin	453 ± 26 (416–537)		
	ΔQT _{max} interval			
Fridericia	Sotalol + placebo	74 ± 31 (39–195)	–15.7 (–26.2 to –5.1)	<0.01
	Sotalol + telithromycin	59 ± 16 (35–103)		
	QT _{max} interval			
	Sotalol + placebo	471 ± 44 (418–633)	–23.5 (–34.9 to –12.1)	<0.001
	Sotalol + telithromycin	448 ± 31 (406–547)		
	ΔQT _{max}			
	Sotalol + placebo	79 ± 30 (44–193)	–22.3 (–31.5 to –13.0)	<0.001
	Sotalol + telithromycin	56 ± 18 (25–106)		

pL administration. A notched T wave was noted on the ECG at the time of this event. A blood sample for genotyping of ion channels (LQT2 and LQT5) was performed, but no anomaly was detected. Subject #17 had an increase of QTc interval greater than 500 ms in Period 1 (sot/teli), but she was not withdrawn from the study (isolated QTcb prolongations at 3 and 10 h, 537 and 506 ms, respectively). During Period 2, notched T waves and humps with a slow downsloping portion of the end of the T wave were found in only lead V3, with an associated significant prolongation of QTc in this lead but not in any other (QTcb varied between 510 and 596 ms, from 2.5 to 8 h, with a peak at 5 h up to 636 ms). This morphological change was more pronounced during Period 2 (sot/pL) than during Period 1 (sot/teli). This event was asymptomatic and a blood sample for genotyping of ion channels (LQT2 and LQT5) was performed, but no anomaly was detected. Three additional subjects experienced isolated QTcb interval prolongations >500 ms, subject #3 (511 ms, sot/pL, T +5 h), subject #5 (523 and 524 ms, sot/pL, T +2 and T +3 h), subject #11 (505 ms, sot/pL, T +3 h).

None of the subjects had any repetitive arrhythmia during Holter monitoring.

There were no clinically significant abnormal values for the subjects during the study.

Discussion

This study was undertaken to analyse the possible interactions between telithromycin and sotalol, a representative class III antiarrhythmic drug, since *in vitro* studies had shown a synergistic effect between the two compounds on the duration of ventricular repolarization in

rabbit Purkinje fibres. In this study the effects of a single dose of sotalol on QT interval were assessed in the presence of placebo or telithromycin in a crossover study. ECG were simultaneously recorded with plasma collection for sotalol and telithromycin concentration determination. Compared with sotalol alone, mean QTc interval decreased in subjects taking the combination of telithromycin and sotalol. This was due to an unanticipated decrease of sotalol plasma concentrations in the presence of telithromycin since the relationship between sotalol plasma concentration and QTc interval was not modified by telithromycin co-administration.

After single oral administration of 160 mg of sotalol and placebo in healthy female subjects, plasma pharmacokinetics of sotalol was similar to that obtained in previous studies at the same dose [21, 22]. In the presence of telithromycin, unexpected modifications of sotalol pharmacokinetics parameters were observed. *C*_{max}, AUC_{0–24} and AUC_{0–inf} significantly decreased (34%, 27% and 20%, respectively), associated with a significant decrease in *t*_{max} (3–2 h).

Sotalol given alone is known to be nearly completely absorbed (absolute bioavailability is 90–100%), without any first-pass metabolism and no significant biotransformation [23]. Any potential intestinal secretion by active transporters is not documented in the literature [23], and there is no suggestion for a decrease in drug absorption caused by telithromycin from various interaction studies. We therefore have no explanation for the increase in sotalol apparent elimination half-life in the presence of telithromycin. The 1.3-fold increase in sotalol apparent elimination half-life could be an artefact due to the lack of precision of calculation at low sotalol plasma

concentrations. The most likely explanation for the pharmacokinetic interaction between sotalol and telithromycin is a decrease in sotalol absorption in the presence of telithromycin. Unfortunately, urine was not collected during the study since the main objective targeted the pharmacodynamic interaction and this explanation remains uncertain.

Telithromycin pharmacokinetic parameters observed in presence of sotalol were in the range of those obtained in other studies after administration of a single dose of 800 mg.

As expected, sotalol increased QTc interval in female subjects. The mean 74 ms QTc_{b_{max}} interval prolongation we found in our female subjects was greater than the 44 ms we found in a previous study we performed in male subjects at the same dose [15] and highlights the higher susceptibility of female subjects to QT interval prolonging drugs. However in presence of telithromycin, QTc prolongation was less pronounced since sotalol plasma concentrations decreased.

In order to investigate whether telithromycin interacted with sotalol-induced QTc interval prolongation despite the decrease of sotalol concentration during co-administration, the relationship between sotalol plasma concentrations and QTc interval duration was assessed in each subject. Telithromycin did not significantly alter the relationship between QTc and sotalol plasma concentration. Thus, we could not confirm the clinical relevance of the preclinical data showing a synergistic effect of telithromycin and sotalol in Purkinje fibres.

The most frequently observed adverse events were nausea and diarrhoea with both treatments. These effects were more frequent with the combination, but these effects are expected with telithromycin [1] but also with sotalol [24]. All were mild to moderate except for one severe diarrhoea observed with sotalol and placebo. Only one subject was withdrawn from the study during sotalol + placebo administration because of a QTc interval prolongation reaching the level of an exclusion criterion.

Results obtained in this study do not support a synergistic effect of sotalol and telithromycin on QT interval prolongation since the relationship between sotalol plasma concentration and QTc interval was not modified by telithromycin co-administration. The decreased mean QTc interval in subjects taking telithromycin + sotalol may be explained by a decrease of sotalol plasma concentrations in the presence of telithromycin.

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References

- 1 Balfour JA, Figgitt DP. Telithromycin. *Drugs* 2001; 61: 815–29.
- 2 Singh BN. When is QT prolongation antiarrhythmic and when is it proarrhythmic? *Am J Cardiol* 1989; 63: 867–9.
- 3 De Ponti F, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of non-antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: an overview. *Drug Saf* 2002; 25: 263–86.
- 4 Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, Escande D, Franz M, Malik M, Moss A, Shar R. The potential for QT prolongation and pro-arrhythmia by non-antiarrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. *Cardiovasc Res* 2000; 47: 219–33.
- 5 Démolis JL, Charransol A, Funck-Brentano C, Jaillon P. Effects of a single oral dose of sparflaxacin on ventricular repolarization in healthy volunteers. *Br J Clin Pharmacol* 1996; 41: 499–503.
- 6 Stass H, Dalhoff A, Kubitz D, Schuhly U. Pharmacokinetics, safety, and tolerability of ascending single doses of moxifloxacin, a new 8-methoxy quinolone, administered to healthy subjects. *Antimicrob Agents Chemother* 1998; 42: 2060–5.
- 7 Démolis JL, Kubitz D, Tenneze L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. *Clin Pharmacol Ther* 2000; 68: 658–66.
- 8 Daleau P, Lessard E, Groleau MF, Turgeon J. Erythromycin blocks the rapid component of the delayed rectifier potassium current and lengthens repolarization of guinea pig ventricular myocytes. *Circulation* 1995; 9: 3010–6.
- 9 Tschida SJ, Guay DR, Straka RJ, Hoey LL, Johannig R, Vance-Bryan K. QTc-interval prolongation associated with slow intravenous erythromycin lactobionate infusions in critically ill patients: a prospective evaluation and review of the literature. *Pharmacotherapy* 1996; 16: 663–74.
- 10 Démolis JL, Vacheron F, Cardus S, Funck-Brentano C. Effect of a single and repeated oral doses of telithromycin on cardiac QT interval in healthy subjects. *Clin Pharmacol Ther* 2003; 73: 242–52.
- 11 Edvardsson N, Hirsch I, Emanuelsson H, Ponten J, Olsson SB. Sotalol-induced delayed ventricular repolarization in man. *Eur Heart J* 1980; 1: 335–43.
- 12 Funck-Brentano C, Kibleur Y, Le Coz F, Poirier JM, Mallet A, Jaillon P. Rate dependence of sotalol-induced prolongation of ventricular repolarization during exercise in humans. *Circulation* 1991; 83: 536–45.
- 13 Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920; 70: 353–70.

- 14 Fridericia LS. Die Sytoledauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 1920; 53: 522–34.
- 15 Le Coz F, Funck-Brentano C, Poirier JM, Kibleur Y, Mazoit FX, Jaillon P. Prediction of sotalol-induced maximum steady-state QTc prolongation from single-dose administration in healthy volunteers. *Clin Pharmacol Ther* 1992; 52: 417–26.
- 16 Makkar RR, Fromm BS, Steinman RT, Meissner MD, Lehmann MH. Female gender as a risk factor for torsade de pointes associated with cardiovascular drugs. *Jama* 1993; 270: 2590–7.
- 17 Lehmann MH, Hardy S, Archibald D, Quart B, MacNeil DJ. Sex difference in risk of torsade de pointes with d,l-sotalol. *Circulation* 1996; 94: 2535–41.
- 18 Stramba-Badiale M, Locati EH, Martinelli A, Courville J, Schwartz PJ. Gender and the relationship between ventricular repolarization and cardiac cycle length during 24-h Holter recordings. *Eur Heart J* 1997; 18: 1000–6.
- 19 Ebert SN, Liu XK, Woosley RL. Female gender as a risk factor for drug-induced cardiac arrhythmias: evaluation of clinical and experimental evidence. *J Womens Health* 1998; 7: 547–57.
- 20 Lepeschkin E, Surawicz B. The measurement of the QT interval of the electrocardiogram. *Circulation* 1952; 6: 378–88.
- 21 Anttila M, Arstila M, Pfeffer M, Tikkanen R, Vallinkoski V, Sundquist H. Human pharmacokinetics of sotalol. *Acta Pharmacol Toxicol (Copenh)* 1976; 39: 118–28.
- 22 Laer S, Neumann J, Scholz H. Interaction between sotalol and an antacid preparation. *Br J Clin Pharmacol* 1997; 43: 269–72.
- 23 Hanyok JJ. Clinical pharmacokinetics of sotalol. *Am J Cardiol* 1993; 72: 19A–26A.
- 24 Zanetti LA. Sotalol: a new class III antiarrhythmic agent. *Clin Pharm* 1993; 12: 883–91.