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The influence of propiverine hydrochloride on cardiac repolarization in healthy women and cardiac male patients

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Key words
propiverine – cardiac repolarization – torsades de pointes – drug safety – QTc-prolongation

Abstract. Objective: Two comprehensively designed mono-centric ECG studies were performed to investigate the influence of propiverine hydrochloride and its main metabolite propiverine-N-oxide on cardiac function with regard to QTc prolongation, QTc dispersion and T-wave shape. Methods: The first study was conducted on 24 healthy females, followed by a second study on 24 male patients with coronary heart disease (CHD) and a pathological Pardee-Q-wave in the ECG. Both studies were placebo-controlled and compared the effects of single (30 mg s.i.d.) and multiple dosing (15 mg t.i.d.) of propiverine hydrochloride in a crossover design over 6 and 13 days, respectively. In CHD patients, the ECG was recorded under standardized exercise stress conditions. Results: An effect of propiverine on cardiac safety in healthy women and male patients with CHD could not be determined by the evaluation of QTc intervals derived from ECG under the following conditions: (1) single dosage; (2) steady-state and elevated dosage; (3) healthy female volunteers and male CHD patients; (4) resting and stress conditions in CHD patients. Moreover, other ECG parameters like QT dispersion, T-wave shape, and U-wave occurrence were not affected by propiverine compared to placebo after single or repeated dosing to reach steady-state conditions. Conclusion: These results reflect and confirm preclinical data as well as clinical observations on hundreds of volunteers and numberless patients suffering from overactive bladder syndrome and neurogenic detrusor overactivity who were treated with propiverine hydrochloride over nearly three decades in Europe and Japan.

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Introduction

QT prolongation is a risk factor for ventricular arrhythmias not only in patients suffering from cardiovascular conditions, but also in otherwise healthy individuals. For years much attention was given to the prolongation of QTc as a sign of delayed ventricular repolarization; it is thus potentially associated with increased risk of cardiac rhythm disturbances such as "torsades de pointes".

Examples of drugs which pose a substantial clinical risk to provoke ventricular arrhythmias arise independently on pharmacological classes: sertindole, pimozide, haloperidole, terfenadine, astemizole, cisapride, halofantrine, erythromycin, sparfloxacin and some other non-cardiac drugs have been correlated with the ability to prolong ventricular repolarization [1]. In 1997 the European Agency for the Evaluation of Medicinal Products (EMEA) consequently issued a "Points to Consider" document addressing rigorous preclinical and clinical testing of new chemical entities to identify cardiac repolarization delay and to ensure safe clinical usage [2]. In 2001 the Health Canada published the "Therapeutic Products Directorate Guidance Document for assessment of the QT prolongation potential of non-antiarrhythmic drugs" [3] which served as the basis for the ICH guideline E14 [4].

Propiverine hydrochloride (in the following referred to as propiverine) is an anticholinergic and spasmolytic drug for the symptomatic treatment of urinary incontinence when accompanied by symptoms of urgency and frequency as may occur in patients with overactive bladder or neurogenic detrusor overactivity. It has been used in this indication for nearly three decades [5]. Among others, anticholinergic drugs are thought to cause arrhythmic events in humans. In the early 1990s, Terodiline, a drug of this class, was withdrawn from the market after only 5 years because of reported conduction disturbances, QT prolongation and "torsades de pointes" [6, 7].

Although propiverine has never been directly associated with cases of cardiac arrhythmia [5], propiverine blocks the human ether-à-go-go-related gene (hERG) channels in vitro that conduct the rapid component of the delayed rectifier K^+ current I_{Kr} [8]. Despite the action potential duration in several in-vitro models is rather shortened by propiverine, an influence on action potential duration and on the refractory period of the human myocardium under clinical conditions can thus not be excluded. In accordance with the "Therapeutic Products Directorate Guidance Document" [3] and before the guideline E14 [4] came into operation, two comprehensive ECG studies were conducted consecutively to determine the influence of propiverine on human cardiac function and to answer the question of whether propiverine influences repolarization processes in humans.

Gender-specific differences in the corrected QT interval have been reported since Bazett's initial description in the 1920s [9]. Several studies suggest that women are more susceptible than men to develop "torsades de pointes" during the administration of drugs that prolong cardiac repolarization (for review see: [10]). Based on these studies and following the recommendations of the "Therapeutic Products Directorate Guidance Document for assessment of the QT prolongation potential of non-antiarrhythmic drugs" [3] the first of the two studies was conducted on healthy women.

One of the predisposing factors for secondary forms of QT prolongation can be attributed to coronary heart disease manifested by myocardial ischemia or infarction [11, 12]. A consecutive study was thus planned in male cardiac post-infarct patients with increased risk for the development of rhythm disturbances [3, 13, 14].

Study objectives

Study I

Double blind, randomized, placebo-controlled, 2-way crossover study on healthy women to assess the effects of propiverine (P4) and its main metabolite propiverine-N-oxide (P4NO) on cardiac safety after single and multiple dosing under resting conditions

Study II

Double blind, randomized, placebo-controlled, two-way crossover study in high-risk cardiac male patients to assess the effects of propiverine and its main metabolite propiverine-N-oxide on cardiac safety after single and multiple dosing under resting and stress conditions

Both study protocols were approved by the Ethics Committee of the State Pharmacological Center of the Ukrainian Ministry of Health in Kiev, Ukraine.

Methods

Study I

The single center 2-way crossover study was conducted on healthy females, the most susceptible population for developing arrhythmias [15]. 24 Caucasians aged 40 – 65 years were informed in detail about the study and signed a written consent before starting study procedures. Females suffering from relevant diseases, particularly of the cardiac system, or from congenital long QT syndrome, or demonstrating QTc time above 450 ms at screening (corrected with Bazett formula), or with pathological potassium levels were not included in the study.

Since no reliable information on variability was available at time of trial planning, the standard deviation for the intra-subject difference between drug and placebo (SD_{diff}) of the maximum increase of QTc was assumed to be in the range of 20 – 30 ms as a conservative approach. 24 subjects were chosen as sample size in order to be able to detect a difference of about 15 ms (with an SD_{diff} of 25 ms) with significance level $\alpha = 5\%$ (2-sided) and a power of 80%.

Study conduct

After thorough screening procedures and confirmation of eligibility, volunteers were placed randomly into one of two treatment groups, starting either with placebo or with propiverine in the first treatment period and vice versa in the second treatment period. The evening before treatment (Day –1) and on Days 5 and 12 of both periods, the volun-

teers were admitted to the clinical pharmacology unit (CPU) for 36 consecutive hours. The wash-out period between treatments lasted 2 weeks and the follow-up phase after the second treatment period was 7 days.

After overnight fasting volunteers were administered 2 tablets orally next morning which corresponded to either a single dose of 30 mg propiverine or to placebo. Pharmacokinetic blood samples (PK sampling) were taken at regular intervals over the next 24 h.

On the following 4 consecutive days, all volunteers received 15 mg propiverine t.i.d. The morning doses of Days 2 – 5 were administered in the CPU. The noon and evening doses of these days were taken by the subject at home. Intake was monitored by phone. After readmission and overnight fasting, the volunteers received 30 mg propiverine the morning of Day 6. Plasma concentrations were recorded for the next 24 h by PK-sampling.

Selection of doses

The recommended daily dose for adults is 15 mg propiverine immediate release (IR) 2 times daily, which can be increased to 3 times daily (t.i.d.), or 30 mg extended release (ER) once a day [16, 17]. In order to follow the most sensitive approach for investigating cardiac safety of propiverine in this study, the volunteers received the highest recommended dose: 30 mg (2 tablets propiverine IR) as single dose when starting treatment and, for repeated dosing, 15 mg t.i.d. over 4 days.

ECG measurement

For pharmacodynamic assessments the ECG was performed on Days 1, 6 and 13 of each period, starting before daily treatment. Additionally, 2, 4, 6, 8, 10, 12, 16 and 24 h after the morning dose of propiverine or placebo (Days 1 and 6) or for equivalent time points on Day 13, ECGs were recorded using the internationally recognized 12 leads [18]. Standard ECGs were printed at 25 mm/s using the Vetter-PC-ECG-ergo-system (Dr. Vetter GmbH, Baden-Baden, Germany). Heart rate (HR) and the following ECG intervals were determined: RR, PQ, QRS and QT. The QT interval was corrected for heart rate according to Bazett [9]:

$$QTcorrected = \frac{QTobserved\ (sec)}{\sqrt{60/RR(sec)}}$$

The positions of the electrodes on the skin were marked to ensure identical placement in both study periods. During the 24 h post-dose interval, the ECG was recorded while subjects remained in supine position. ECGs were evaluated twice by two independent cardiologists in a blinded manner. The first assessor and co-investigator also screened and assessed the ECG from a clinical point of view in a blinded manner.

Blood sampling

Pharmacokinetic blood samples for determination of propiverine (P4) and its main metabolite propiverine-N-oxide (P4NO) were collected in parallel with blood samples for determination of potassium concentration immediately following each ECG record. Serum levels of P4 and P4NO were determined using a validated HPLC method [19].

Safety assessments

All adverse events (AE) during the study were rated regarding onset, end, severity, seriousness, relationship to the study medication, outcome and actions taken. Safety laboratory examinations were performed before, during and after the end of study conduct.

Statistical analysis

The following descriptive statistics were calculated for ECG intervals, PQ, QRS, QT, QTc for heart rate and QT dispersion: n (number of non-missing values), arithmetic mean, standard deviation and minimum, maximum, median. Additionally, differences to baseline were considered. Baseline was defined as mean of measurements on Day –1 and Day 1 (pre-dose) in each period.

The following parameters were derived for QTc interval:

– Maximum increase: post-dose maximum (2 – 12 h) value minus baseline

- Maximum value: post-dose maximum value during ECG profile (2 – 12 h)
- Mean value: mean QTc interval of ECG profile on therapy (2 – 12 h)
- Baseline: mean measurements on Day –1 and Day 1 (pre-dose)

Two separate ratings of QTc post-dose maximum value and maximum increase during ECG profile were determined as shown in Table 1.

Frequency tables for the rating of QTc maximum and maximum increase and for T-wave shape and U-wave occurrence were provided. The QTc parameters maximum increase, AUC_{0-12}, maximum and mean value were submitted to separate analysis of variance including sequence, subject (sequence), period and treatment as class effects. Point estimates and 95% confidence intervals were constructed for the difference "propiverine minus placebo" using the residual variance. Distributional assumptions of analysis-of-variance were checked by inspection of residual plots of studentized residuals versus normal order scores to check normality and studentized residuals versus predicted values to check homogeneity of variance.

The following parameters were derived from QT-dispersion:

- Maximum increase: post-dose maximum (2 – 12 h) value minus pre-dose
- Maximum decrease: pre-dose minus post-dose minimum value (2 – 12 h)

Study II

After finishing and reporting Study I the following single center 2-way crossover study was performed in 24 male patients with coronary heart disease (CHD) and with a pathological Pardee wave in the ECG indicating a previous myocardial infarction.

As a QTc prolongation induced by propiverine or its metabolites may only be observed at higher heart rates and/or in patients suffering from CHD, the study was performed on post-infarct patients with CHD and pathological Q-wave (Pardee wave at least in one of the ECG leads) under resting as well as under standardized exercise stress conditions.

Table 1. Ratings of QTc post dose values.

	Maximum value	Maximum increase
Normal	< 450 msec	< 30 msec
Borderline	450 – 470 msec	30 – 60 msec
Prolonged	> 470 msec	> 60 msec

The primary aim of this study was to demonstrate that compared to placebo, repeated dosing of propiverine does not significantly increase the QTc interval in patients with high cardiac risk. For study inclusion patients had to meet all of the following requirements:

- Male Caucasians aged ≥ 45 years
- Written informed consent
- Pathological Q wave in at least 1 of the 12 standard ECG leads
- Ability to perform a standard exercise test on a bicycle

In Study I in healthy women the standard deviation for the intra-subject difference between drug and placebo (SD_{diff}) of the maximum increase in QTc was found as about 15 ms after repeated dosing (and only 7 ms after single dosing). But since patients with an increased cardiac risk were to be included, the SD_{diff} was assumed to be up to about 30 ms as a conservative approach. From the clinical point of view, differences between the drug and placebo below 30 ms were considered as equivalent. Taking into account that the true difference could be up to 5 ms, sample size calculation yielded a number of 18 patients with significance level $\alpha = 2.5\%$ (1-sided) and a power of 90%. 24 patients were included in the trial to take account for dropouts.

Study conduct

The patients were confined from the morning of Day –1 until the afternoon of Day 2, from the evening of Day 13 until the afternoon of Day 15, and additionally from the evening of Day 20 until the afternoon of Day 22 of each period. A follow-up visit took place on Day 22 of the second treatment period.

In the morning of Days 1 and 14 patients received 30 mg propiverine or placebo, and from Days 2 – 13 three times daily 15 mg

propiverine or placebo. Basic medication for the treatment of CHD or associated risk factors (e.g. hyperlipoproteinemia, diabetes mellitus, and hypertension) was continued throughout the study. Drugs which could prolong the QT interval were not permitted.

ECG recording under resting conditions and blood sampling were performed at Days 1, 14 and 21 (during washout) of each study period in the same manner as in the first study. Additionally, on these days an ECG under stress conditions was performed 8 h after the administration of study medication. On Days 7, 9, 11 and 13 of each treatment period trough levels of propiverine were collected to verify the correct intake of study medication.

Exercise ECG

A 12-lead ECG was recorded under standardized stress conditions with the patients on an ergometric bicycle. The procedure started with an ECG under resting conditions after at least 5 min in sitting position. Afterwards, load steps were increased every 3 min in intervals of 25 Watt starting with 50 Watt until an individual maximum heart rate was achieved. The individual maximum heart rate was defined in beats per minute (bpm) as 200 minus the age of the patient. ECG and blood pressure were recorded during the last minute of each load step. 2 and 3 min after termination of maximum load, an ECG under resting conditions was recorded to document the patient's recovery. For the ECG under stress conditions, pre-defined criteria for termination included reaching maximum pulse rate, exhaustion or angina pectoris.

Primary endpoint

The primary endpoint of this study was defined as the maximum increase in QTc interval: post-dose maximum of QTc on Day 14 minus baseline (mean of Day –1 and Day 1 with regard to 12-lead ECG at rest).

The following hypotheses were tested:

H_0: $\mu_{prop} - \mu_{plac} \geq 30$ msec versus H_1: $\mu_{prop} - \mu_{plac} < 30$ msec,

where μ_{prop} and μ_{plac} corresponded to the true maximum increase in QTc interval at rest between 0 and 12 h after propiverine and placebo administration, respectively, as defined above. Increases in QTc intervals up to 30 msec were generally considered as normal [14].

Secondary endpoints were: maximum increase in QTc interval (0 – 12 h post dosing) on Day 1 at rest; AUC_{0-12}, maximum value, mean value in QTc interval on Days 1, 14 and 21 at rest; QTc minimum value at rest; QTc maximum value at rest; QTc interval at the maximum workload (exercise ECG); plasma concentrations of propiverine and propiverine-N-oxide; plasma concentrations for potassium; shape of T-wave; occurrence of U-wave.

The handling of samples and the recording of adverse events were comparable to the procedures as described above for Study I.

Statistical analysis

For statistical analysis, nearly the same methods were applied as described for Study I. The QTc interval at the maximum workload on Days 1, 14 and 21 was submitted to separate analysis of variance in order to assess the effect of propiverine under exercise conditions.

Results

24 female subjects took part in Study I and finished the study according to protocol.

24 male post-infarct patients with CHD took part in Study II, 23 of them completed the study according to protocol. One patient terminated the study prematurely due to a serious adverse event (placebo arm). Demographic data of all volunteers are displayed in Table 2.

Maximum increase of QTc (msec)

Table 3 shows descriptive statistics concerning the maximum increase of QTc up to 12 h after dosing in comparison with placebo in healthy women. Over the whole observational period, and independently from the mode of study medication administration, the maximum increase of QTc differed statistically not significant between treatments. In contrast, a slight tendency for decrease of

Table 2. Main demographic data for both studies (AM/SD* (range)).

	Study I: n = 24	Study II: n = 24
Age (years)	51.1/4.2 (45 – 58)	51.1/4.5 (45 – 60)
Height (cm)	162.1/6.4 (151 – 176)	174.2/6.6 (162 – 188)
Weight (kg)	70.8/10.4 (50 – 96)	87.7/11.8 (66 – 107)

*AM = arithmetic mean; SD = standard deviation.

maximum increase of QTc under propiverine could be observed. This tendency increased after single-dose administration of propiverine in cardiac patients (Table 4) and tapered off after multiple dosing of propiverine. Nevertheless, a statistically significant difference between treatments could not be observed.

Based on this exploratory analysis it can be concluded that propiverine neither after single nor after repeated administration leads to a prolongation of the QTc interval in healthy women and male cardiac patients.

QTc maximum value

Table 5 and Table 6 show descriptive statistics for the QTc maximum values during the post-dose interval 2 – 12 h after treatment with propiverine or placebo in healthy women and in male cardiac patients respectively.

A relevant effect of propiverine on the maximum value of QTc interval in healthy females as well as in cardiac patients was not determined by the descriptive statistical analysis.

Shape of T-wave

In all healthy female volunteers no abnormal T-waves were detected at any point of assessment.

In Study II, except for 1 subject, all ECGs showed abnormal T-waves at every point of measurement during study including screening. At screening and pre-dose in the ECG negative, isoelectric, diphasic and coronaric T-waves occurred. The frequencies of change in T-wave shapes related to the screening and pre-dose findings appear comparable after the different treatments with placebo or propiverine.

Occurrence of U-waves

No U-waves occurred in the ECG in healthy women.

At screening, 19 cardiac patients showed a U-wave in the ECG under resting conditions, 9 patients showed a U-wave at all time points for the duration of study. U-waves occurred at several time points with comparable frequencies under propiverine and placebo treatment in 11 patients.

QT dispersion maximum increase

QT dispersion was assessed in healthy women only (Study I). Table 7 shows descriptive statistics for the QT dispersion maximum increase from 2 to 12 h after dosing.

An effect of propiverine on the maximum increase of QT dispersion was not indicated by statistical analysis. A further analysis of the maximum decrease of QT dispersion also revealed no differences between treatments.

Exercise ECG

Table 8 displays the effects of propiverine or placebo on QTc interval at maximum workload in cardiac patients under stress conditions (Study II only). Maximum workload was reached 8 h after single dose of 30 mg propiverine after 125 W (4 patients), 100 W (7 patients), 75 W (9 patients) or 50 W (3 patients). Similar responses were observed in all other exercises.

An effect of propiverine on QTc interval at maximum workload was not determined by statistical analysis.

Central QTc tendency

Figure 1 displays the central tendency of QTc development over time in healthy women after administration of propiverine and placebo respectively. In healthy women the baseline before single dose administration of placebo as well as of propiverine seems to be lower compared to baselines at multiple dose and washout. No difference could be determined when comparing placebo to propiverine under the respective administration conditions.

Table 3. Maximum increase of QTc (msec) in healthy women (AM/SD (range)) and mean differences propiverine minus placebo (AM (2-sided CI))*.

Study Day	Propiverine	Placebo	Mean difference (95% CI)
1	5.8/5.3 (–3.0, 17.0)	8.0/5.6 (0, 23.0)	–2.2 (–5.4, 0.9)
6	10.3/8.8 (–9.0, 23.0)	12.1/9.3 (–5.5, 28.0)	–1.8 (–8.0, 4.4)
13	8.4/7.4 (–2.0, 26.0)	8.3/8.6 (–3.5, 31.0)	0.1 (–5.8, 5.9)

*AM = arithmetic mean; SD = standard deviation; CI = confidence interval.

Table 4. Maximum increase of QTc (msec) in male cardiac patients (AM/SD (range)) and mean differences propiverine minus placebo (AM (1-sided CI))*.

Study Day	Propiverine	Placebo	Mean difference (97.5% CI)
1	5.4/6.4 (–9, 17.5)	8.9/10.0 (–1.5, 38.0)	–3.6 (–∞, –0.5)
14	9.1/10.5 (–13.0, 26.0)	4.9/12.0 (–14.5, 46.0)	4.3 (–∞, 9.3)
21	9.1/8.7 (–5.5, 23.5)	4.9/7.7 (–15.0, 17.0)	4.2 (–∞, 8.4)

*AM = arithmetic mean; SD = standard deviation; CI = confidence interval.

Table 5. Maximum values of QTc (msec) in healthy women (AM/SD (range)) and mean differences propiverine minus placebo (AM (2-sided CI))*.

Study Day	Propiverine	Placebo	Mean difference (95% CI)
1	443/8.9 (428, 456)	445/11.8 (424, 473)	–1.5 (–5.2, 2.2)
6	448/10.5 (434, 470)	449/12.6 (416, 478)	–1.1 (–6.2, 4.0)
13	446/9.7 (430, 474)	445/9.0 (427, 463)	0.8 (–3.7, 5.2)

*AM = arithmetic mean; SD = standard deviation; CI = confidence interval.

Table 6. Maximum values of QTc (msec) in male cardiac patients (AM/SD (range)) and mean differences propiverine minus placebo (AM (one-sided CI))*.

Study Day	Propiverine	Placebo	Mean difference (97.5% CI)
1	451/13.2 (425, 478)	455/16.0 (427, 510)	–4.7 (–∞, –0.5)
14	455/16.2 (419, 490)	451/17.3 (419, 498)	3.1 (–∞, 7.0)
21	455/12.7 (429, 477)	452/13.3 (419, 472)	3.1 (–∞, 5.9)

*AM = arithmetic mean; SD = standard deviation; CI = confidence interval.

Table 7. QT dispersion (msec) in healthy women (AM/SD (range)) and mean differences propiverine minus placebo (AM (2-sided CI))*.

Study Day	Propiverine	Placebo	Mean difference (95% CI)
1	6.7/8.9 (–7, 34)	5.1/8.3 (–9, 23)	1.6 (–3.6, 6.7)
6	6.3/7.5 (–3, 25)	7.4/9.1 (–9, 28)	–1.1 (5.3, 3.2)
13	6.8/7.2 (–1, 27)	6.8/9.2 (–21, 19)	–0.1 (–4.4, 4.2)

*AM = arithmetic mean; SD = standard deviation; CI = confidence interval.

Table 8. QTc intervals (msec) at maximum workload in male cardiac patients (AM/SD (range)) and mean differences propiverine minus placebo (AM (1-sided CI))*.

Study Day	Propiverine	Placebo	Mean difference (97.5% CI)
1	471/25.3 (444, 574)	472/24.7 (437, 569)	–1.4 (–∞, 4.5)
14	470/17.9 (449, 535)	467/16.7 (440, 529)	2.6 (–∞, 7.6)
21	470/20.3 (432, 542)	466/11.1 (438, 486)	4.7 (–∞, 10.6)

*AM = arithmetic mean; SD = standard deviation; CI = confidence interval.

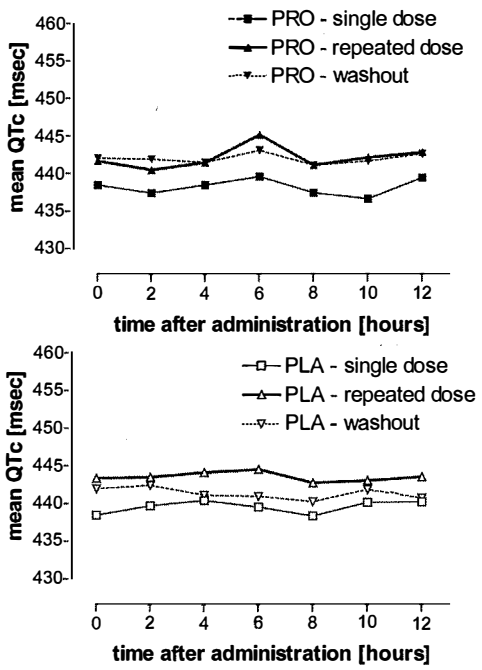

Figure 1. Central tendency of QTc after administration of propiverine (upper diagram, PRO) or placebo (lower diagram, PLA) in healthy women.

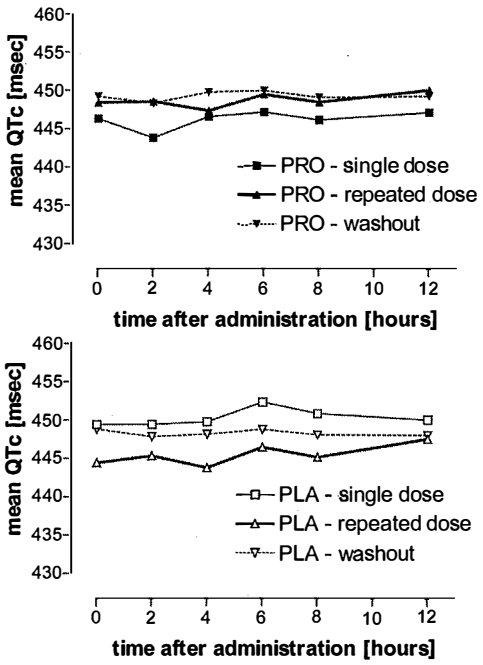

Figure 2. Central tendency of QTc after administration of propiverine (upper diagram, PRO) or placebo (lower diagram, PLA) in male cardiac patients.

Figure 2 displays the central tendency for QTc development over time in male cardiac patients after administration of propiverine and placebo respectively. Summarizing the data, differences in QTc tendency between propiverine and placebo could not be determined.

Potassium serum concentration

In both studies the concentration-time curves for potassium were similar after the different treatments. All measured values were within normal ranges. No effect of propiverine on the potassium concentration in healthy women or in male cardiac patients could be determined.

Pharmacokinetic parameters

The maximum plasma concentration of both propiverine and propiverine-N-oxide (P4NO) in healthy women after administration of a single dose of 30 mg propiverine as well as after repeated dosing of 15 mg propiverine t.i.d. was comparable to those found in other studies on healthy volunteers [20, 21]. Mean terminal half-life after single dose were found to be 18.0 h for propiverine and 9.1 h for P4NO, after repeated dosing 18.6 h for propiverine and 12.1 h for P4NO, respectively.

The maximum plasma concentration of propiverine and P4NO after administration of a single dose of 30 mg propiverine in male cardiac patients were slightly increased compared to healthy females. Mean terminal half life after single dose was found to be 13.8 h for propiverine, and 9.0 h for P4NO, after repeated dosing 17.4 h for propiverine and 13.3 h for P4NO, respectively.

The corresponding PK parameters and descriptive statistics are listed in Table 9.

Adverse events

In total, 11/24 female subjects reported 29 adverse events (10 with propiverine, 1 with placebo). All of them were treatment emergent and non-serious (25 of mild intensity, 4 of moderate intensity). Blurred vision, dry mouth or nausea were most frequently reported.

During the study on male cardiac patients 88 adverse events (56 with propiver-

Table 9. Descriptive statistics for PK parameters obtained from Study I and Study II (extract).

Parameter (Unit)	Propiverine, geometric mean/SD (range)	Propiverine-N-oxide (P4NO), geometric mean/SD (range)
Single dose, Study I		
$AUC_{(0-24)}$ (ng × h/ml)	864/1.5 (475; 2,408)	6,358/1.5 (2,918; 15,493)
C_{max} (ng/ml)	88.8/1.6 (40; 206)	731/1.4 (366; 1,291)
$t_{1/2}$ (h)	18.0/1.4 (9.3; 34.7)	9.1/1.6 (5.0; 29.9)
Single dose, Study II		
$AUC_{(0-24)}$ (ng × h/ml)	1,200/1.5 (703; 2,584)	6,493/1.3 (3,470; 9,598)
C_{max} (ng/ml)	119.8/1.5 (74; 287)	661.8/1.4 (285; 1,221)
$t_{1/2}$ (h)	13.8/2.0 (6.3; 156,3)	9.0/1.3 (5.6; 20.7)
Multiple dose, Study I		
$AUC_{(0-24)}$ (ng × h/ml)	2,160/1.6 (1,148; 5,911)	10,939/1.6 (5,917; 31,789)
C_{max} (ng/ml)	166/1.6 (79.0; 410)	946/1.5 (418; 2,313)
$t_{1/2}$ (h)	18.6/1.4 (11.4; 30.5)	12.2/1.7 (6.4; 48.9)
Multiple dose, Study II		
$AUC_{(0-24)}$ (ng × h/ml)	3,511/1.4 (1,998; 6,592)	15,272/1.4 (6,592; 25,269)
C_{max} (ng/ml)	273.1/1.4 (134; 525)	1140/1.4 (552; 1,777)
$t_{1/2}$ (h)	17.4/1.9 (5.1; 82.8)	13.3/1.6 (6.4; 41.8)

ine, 23 with placebo, 9 prior to medication) were reported. Except for 1 case of angina pectoris, all AEs were non-serious. This SAE in a placebo-treated patient was judged as "unlikely related" to study medication. 21 adverse events were of severe intensity, but all of them were assessed as "unrelated" to the study medication. The most frequent AE was dry mouth, complained in 70% under propiverine and 33% under placebo.

Discussion

Nowadays the regulatory authorities expect in almost all drugs at least one clinical pharmacology study assessing a medication's effect on the ECG, even when non-clinical safety pharmacology studies, which also assess the potential for delayed ventricular repolarization, do not provide cause for concern [22].

The main mechanism of propiverine effects on the bladder is based on muscarinic acetylcholine receptor antagonism which may involve calcium and potassium channels in smooth muscle cells. Furthermore, direct inhibition of L-Type Ca^{2+} currents in the urinary bladder may occur [23, 24, 25, 26] and thereby relax smooth muscles. As a consequence of the channel-blocking properties of propiverine, an influence on the cardiac repolarization may be expected. Moreover, it has been suggested that anticholinergics like terodiline [6, 7, 27] can cause polymorphic ventricular arrhythmias like "torsades de pointes" by blocking I_{Kr}. In a previously performed multicenter study, elderly patients with detrusor overactivity but no signs for cardiac dysfunction were given 45 mg propiverine daily for 4 weeks. At the end of treatment no evidence for the development of QT prolongation was detected [28]. Compared to placebo, differences in heart rate or in parameters characterizing conduction processes were not observed. In another previously performed study, patients with symptoms of overactive bladder were treated over 4 weeks with 30 mg propiverine (immediate- or extended-release) daily, or with placebo (395, 391 and 202 patients) [29]. The study demonstrated neither evidence for QTc-prolongation nor for significant changes from baseline in the QTc (Bazett) interval in all three treatment groups (mean (SD): 0.3 (23.3), –0.8 (22.5) and 0.1 (22.4) ms; corresponding p-values: 0.80, 0.49 and 0.95 (paired t-test)).

Anticholinergics, however, have been proven to increase heart rate by blocking the parasympathetic innervation of the heart. Increased heart rate seems to be correlated with an increased risk of morbidity and mortality [30, 31]. Terodiline is the only anticholinergic substance with a "torsade de points" potential reported so far [32, 33, 34, 35]. In a recently published study, Japanese patients suffering from overactive bladder were

treated over 12 weeks with propiverine, imidafenacin or placebo. A significant increase in the mean QTc by 7.56 ± 20.08 ms under propiverine (20 mg s.i.d.) and −1.35 ± 19.29 ms in the placebo group was reported, but no clinical signs of arrhythmia or arrhythmic events [36]. Maximal value in the QTc interval in the propiverine group was 486.6 ms. Since the heart rate was slightly increased by propiverine (4.4 ± 9.2 bpm, placebo: −1.0 ± 9.2 bpm), this result may rather be attributed to the QTc correction procedure as discussed below.

In 2002, the two ECG studies were performed to investigate the influence of propiverine and its main metabolite propiverine-N-oxide on cardiac function with special regard to QTc prolongation, QTc dispersion and T-wave shape.

In the first study, female volunteers received in each of the two treatment periods propiverine or placebo as previously described in detail. The resulting plasma concentrations of propiverine and P4NO and the extent of exposure were comparable with other existing data for young healthy volunteers receiving propiverine as single dose or under steady-state conditions [20, 21].

In the second study, male cardiac patients received in each of the two treatment periods propiverine or placebo in the previous described manner. The resulting plasma concentrations of propiverine, P4NO and the extent of exposure were slightly increased when compared to those of healthy women after a single dose of 30 mg propiverine as well as under steady-state conditions (15 mg propiverine t.i.d.). The concentrations were found to be in the range of exposure for patients with impaired hepatic or renal function [37, 38].

Furthermore, in both studies concentration-time curves for potassium were similar after propiverine or placebo treatment. As changes in electrolytes can be a confounder for development of torsades de points the influence on drugs on these parameters may be a predictor for the drug-related potential to provoke such hazardous sensations [39].

Neither the study on healthy women nor the study on CHD-patients provided any evidence for effects of propiverine on the ECG. There were no differences apparent between propiverine and placebo with regard to post-dose maximum of QTc, QTc AUC_{0-12}, average QTc (over post-dose assessment up to 12 h), rating of QTc maximum interval, T-wave shape, U-wave occurrence under resting conditions or QTc interval at the maximum workload in CHD patients.

In both study populations the actual standard deviation for the intra-subject difference between drug and placebo (SD_{diff}) of the maximum increase in QTc was found much smaller than anticipated at the planning stages with SD_{diff} of about 7 ms after single dosing in both trials, and SD_{diff} of 12 – 15 ms after repeated dosing.

According to the current ICH guideline E14 the upper bound of the 95% 1-sided confidence interval for the difference between drug and placebo should exclude 10 ms in order to allow for concluding that the drug has no relevant effect. Thus, 10 ms may also be considered as the acceptable equivalence boundary to be applied for these trials. A-posteriori power considerations based on the observed maximum SD_{diff} of 15 ms resulted in 22 subjects that would have been required for the cross-over trial to demonstrate "no effect" even with 90% power. In consequence, since at least 22 subjects were included in each of the QTc analyses, both trials can be considered as sufficiently powered and the results can be regarded as highly reliable and credible also in context of the requirements of the current guideline.

Despite the fact that these studies were planned and conducted before the ICH guideline E14 came into operation, the studies were performed according to recommendations existing at this time. Moreover, some criteria, differing from the actual recommendations described by ICHE14, tend to overestimate the potential risk of QTc prolongation caused by drug treatment. First, it is currently recommended to assess the ECG automatically rather than manually or by both methods. Depending on the conditions of the particular investigation, each procedure has advantages. In the cardiac patient population displaying a pathological ECG pattern with altered T-wave morphology the manual assessment of ECG has clear advantages [40]. In addition, the application of different automated measurement devices requires careful standardization [41].

Second, the application of any procedure which corrects the frequency-dependent

changes of QT may lead to overcorrection. In particular, Bazett's formula for frequency-based correction of QT leads to an overcorrection at elevated heart rates resulting in longer QTc intervals [42, 43, 44, 45]. Hence, the application of the Bazett's formula in such cases produces rather false positive than false negative results [46]. To avoid incidental findings, the two studies were designed in a cross-over manner and the QT/QTc intervals were compared intra-individually.

Another aspect, described in the above mentioned guideline, which has not been considered for these studies, was a positive control group. The disadvantage due to the absence of a positive control like moxifloxacine is partly compensated by the cross-over design of these two studies and the placebo controlled mono-centric setting. Additionally, in the study on cardiac patients physical exercise under tightly controlled conditions can serve as a positive control for QT-prolongation [47, 48].

The results of these two studies reflect recent preclinical findings: even though propiverine and some of its metabolites block in a concentration-dependent manner hERG channels expressed in HEK293 cells and native I_K current in ventricular myocytes of guinea pigs and $I_{Ca,L}$ in human atrial myocytes, the action potential duration was not prolonged in guinea-pig and human ventricular tissue [8]. Similar effects were observed in dog Purkinje fibres. Obviously, the concomitant block of hERG, I_{KS} and L type Ca^{2+} channels leads to a compensation of the respective effects of the action potential duration (APD) resulting in shortening rather than lengthening of APD. Furthermore, the safety margin for propiverine and its metabolites account for 30- to 70-fold higher propiverine or metabolite concentrations to block hERG channels in man [16, 25].

Conclusion

The results of these two Phase-I clinical studies investigating cardiac safety in healthy middle-aged women and male patients with coronary heart disease revealed no negative effect of propiverine on cardiac function in the evaluation of QTc intervals deriving from ECGs under resting as well as exercise conditions when compared to placebo. Repeated high doses of propiverine neither prolonged the QTc interval nor affected other ECG parameters like QT dispersion, T-wave shape, and U-wave occurrence. Potassium levels appeared unaffected by treatment.

Propiverine was tolerated well with respect to adverse events, clinical laboratory, and vital signs.

These results confirm nearly three decades of clinical observations on the effects of propiverine hydrochloride in the treatment of patients of both genders and of all age groups suffering from overactive bladder and urinary incontinence in Europe and Japan.

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References

[1] *Carlsson L.* Drug-induced torsade de pointes: the perspectives of industry. Eur Heart J. 2001; *3:* K114-K120.

[2] *CPMP.* Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products (CPMP/986/96). 17 Dec 1997.

[3] *Health Canada.* Assessment of the QT prolongation potential of non-antiarrhythmic drugs. 15 Mar 2001.

[4] *CHMP.* The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (CHMP/ICH/2/04, ICH-topic E14). Nov 2005.

[5] *Madersbacher H, Mürtz G.* Efficacy, tolerability and safety profile of propiverine in the treatment of the overactive bladder (non-neurogenic and neurogenic). World J Urol. 2001; *19:* 324-335.

[6] *Connolly MJ, Astridge PS, White EG, Morley CA, Cowan JC.* Torsades de pointes ventricular tachycardia and terodiline. Lancet. 1991; *338:* 344-345.

[7] *Stewart DA, Taylor J, Ghosh S, Macphee GJ, Abdullah I, McLenachan JM, Stott DJ.* Terodiline causes polymorphic ventricular tachycardia due to reduced heart rate and prolongation of QT interval. Eur J Clin Pharmacol. 1992; *42:* 577-580.

[8] *Christ T, Wettwer E, Wuest M, Braeter M, Donath F, Champeroux P, Richard S, Ravens U.* Electrophysiological profile of propiverine-relationship to cardiac risk. Naunyn Schmiedebergs Arch Pharmacol. 2008; *376:* 431-440.

[9] *Bazett HC.* An analysis of the time-relations of electrocardiograms. Heart. 1920; *7:* 353-370.

[10] *Hreiche R, Morissette P, Zakrzewski-Jakubiak H, Turgeon J.* Gender-related differences in drug-induced prolongation of cardiac repolarization in prepubertal guinea pigs. J Cardiovasc Pharmacol Ther. 2009; *14:* 28-37.

[11] *Haverkamp W, Mönnig G, Kirchhof P, Eckardt L, Borggrefe M, Breithardt G.* Torsade de pointes induced by ajmaline. Z Kardiol. 2001; *90:* 586-590.

[12] *Laakso M, Aberg A, Savola J, Pentikäinen PJ, Pyörälä K.* Diseases and drugs causing prolongation of the QT interval. Am J Cardiol. 1987; *59:* 862-865.

[13] *Krikler DM, Curry PV.* Torsade De Pointes, an atypical ventricular tachycardia. Br Heart J. 1976; *38:* 117-120.

[14] *Montanez A, Ruskin JN, Hebert PR, Lamas GA, Hennekens CH.* Prolonged QTc interval and risks of total and cardiovascular mortality and sudden death in the general population: a review and qualitative overview of the prospective cohort studies. Arch Intern Med. 2004; *164:* 943-948.

[15] *Furukawa T, Kurokawa J.* Regulation of cardiac ion channels via non-genomic action of sex steroid hormones: implication for the gender difference in cardiac arrhythmias. Pharmacol Ther. 2007; *115:* 106-115.

[16] *APOGEPHA.* Mictonorm® 15 mg Coated Tablets (Summary of Product Characteristics). 27 Oct 2005.

[17] *MHRA.* Public Assessment Report: Mictonorm XL 30 mg Modified Release Capsules, Propinorm XL 30 mg Modified Release Capsules (PL 15072/0006, PL 15072/0007). 13 Feb 2008.

[18] *Gertsch M.* Das EKG. Berlin-Heidelberg: Springer; 2009. p. 569-588.

[19] *Richter K, Scheithauer S, Thümmler D.* High-performance liquid chromatographic determination of propiverine and its N-oxide in human serum. J Chromatogr B Biomed Sci Appl. 1998; *708:* 325-329.

[20] *May K, Westphal K, Giessmann T, Wegner D, Adam U, Lerch MM, Oertel R, Warzok RW, Weitschies W, Braeter M, Siegmund W.* Disposition and antimuscarinic effects of the urinary bladder spasmolytics propiverine: influence of dosage forms and circadian-time rhythms. J Clin Pharmacol. 2008; *48:* 570-579.

[21] *May K, Giessmann T, Wegner D, Oertel R, Modess C, Oswald S, Braeter M, Siegmund W.* Oral absorption of propiverine solution and of the immediate and extended release dosage forms: influence of regioselective intestinal elimination. Eur J Clin Pharmacol. 2008; *64:* 1085-1092.

[22] *Health Canada.* Release of final Health Canada document: Health Canada Question and Answer Document Regarding the ICH S7B and E14 Guidances. 30 Nov 2006.

[23] *Michel MC, Hegde SS.* Treatment of the overactive bladder syndrome with muscarinic receptor antagonists: a matter of metabolites? Naunyn Schmiedebergs Arch Pharmacol. 2006; *374:* 79-85.

[24] *Wuest M, Hecht J, Christ T, Braeter M, Schoeberl C, Hakenberg OW, Wirth MP, Ravens U.* Pharmacodynamics of propiverine and three of its main metabolites on detrusor contraction. Br J Pharmacol. 2005; *145:* 608-619.

[25] *Wuest M, Weiss A, Waelbroeck M, Braeter M, Kelly LU, Hakenberg OW, Ravens U.* Propiverine and metabolites: differences in binding to muscarinic receptors and in functional models of detrusor contraction. Naunyn Schmiedebergs Arch Pharmacol. 2006; *374:* 87-97.

[26] *Zhu HL, Brain KL, Aishima M, Shibata A, Young JS, Sueishi K, Teramoto N.* Actions of two main metabolites of propiverine (M-1 and M-2) on voltage-dependent L-type Ca^{2+} currents and Ca^{2+} transients in murine urinary bladder myocytes. J Pharmacol Exp Ther. 2008; *324:* 118-127.

[27] *Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PK, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG.* Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. Cardiovasc Res. 2003; *58:* 32-45.

[28] *Dorschner W, Stolzenburg JU, Griebenow R, Halaška M, Schubert G, Mürtz G, Frank M, Wieners F.* Efficacy and cardiac safety of propiverine in elderly patients – a double-blind, placebo-controlled clinical study. Eur Urol. 2000; *37:* 702-708.

[29] *Jünemann KP, Hessdörfer E, Unamba-Oparah I, Berse M, Brünjes R, Madersbacher H, Gramatté T.* Propiverine hydrochloride immediate and extended release: comparison of efficacy and tolerability in patients with overactive bladder. Urol Int. 2006; *77:* 334-339.

[30] Habib G. Reappraisal of the importance of heart rate as a risk factor for cardiovascular morbidity and mortality. Clin Ther. 1997; *19 (Suppl A):* 39-52.

[31] *Lanza GA, Fox K, Crea F.* Heart rate: a risk factor for cardiac diseases and outcomes? Pathophysiology of cardiac diseases and the potential role of heart rate slowing. Adv Cardiol. 2006; *43:* 1-16.

[32] *Abrams P, Andersson KE.* Muscarinic receptor antagonists for overactive bladder. BJU Int. 2007; *100:* 987-1006.

[33] *Andersson KE, Olshansky B.* Treating patients with overactive bladder syndrome with antimuscarinics: heart rate considerations. BJU Int. 2007; *100:* 1007-1014.

[34] *Jones SE, Shuba LM, Zhabyeyev P, McCullough JR, McDonald TF.* Differences in the effects of urinary incontinence agents S-oxybutynin and terodiline on cardiac $K(^{+})$ currents and action potentials. Br J Pharmacol. 2000; *131:* 245-254.

[35] *Malhotra BK, Glue P, Sweeney K, Anziano R, Mancuso J, Wicker P.* Thorough QT study with recommended and supratherapeutic doses of tolterodine. Clin Pharmacol Ther. 2007; *81:* 377-385.

[36] *Homma Y, Yamaguchi O; Imidafenacin Study Group.* A randomized, double-blind, placebo- and propiverine-controlled trial of the novel antimuscarinic agent imidafenacin in Japanese patients with overactive bladder. Int J Urol. 2009; *16:* 499-506.

[37] *Blume H, Schug B, Wonnemann M, Donath F.* Safety and tolerability of propiverine hydrochloride (Mictonorm®) in patients with severe renal impairment (SRI). 8/31/05, 9/2/05 ICS 2005.

[38] *Siepmann M, Nokhodian A, Thümmler D, Kirch W.* Pharmacokinetics and safety of propiverine in patients with fatty liver disease. Eur J Clin Pharmacol. 1998; *54:* 767-771.

[39] *CHMP.* The nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (CHMP/ICH/423/02 S7B). 25 May 2005.

[40] *Malik M, Camm AJ.* Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. Drug Saf. 2001; *24:* 323-351.

[41] *Sarapa N, Morganroth J, Couderc JP, Francom SF, Darpo B, Fleishaker JC, McEnroe JD, Chen WT, Zareba W, Moss AJ.* Electrocardiographic identification of drug-induced QT prolongation: assessment by different recording and measurement methods. Ann Noninvasive Electrocardiol. 2004; *9:* 48-57.

[42] *Darpo B, Agin M, Kazierad DJ, Layton G, Muirhead G, Gray P, Jorkasky DK.* Man versus machine: is there an optimal method for QT measurements in thorough QT studies? J Clin Pharmacol. 2006; *46:* 598-612.

[43] *Malik M.* Problems of heart rate correction in assessment of drug-induced QT interval prolongation. J Cardiovasc Electrophysiol. 2001; *12:* 411-420.

[44] *Malik M, Färbom P, Batchvarov V, Hnatkova K, Camm AJ.* Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart. 2002; *87:* 220-228.

[45] *Milic M, Bao X, Rizos D, Liu F, Ziegler MG.* Literature review and pilot studies of the effect of QT correction formulas on reported beta2-agonist-induced QTc prolongation. Clin Ther. 2006; *28:* 582-590.

[46] *Piotrovsky V.* Pharmacokinetic-pharmacodynamic modeling in the data analysis and interpretation of drug-induced QT/QTc prolongation. AAPS J. 2005; *7:* E609-E624.

[47] *Démolis JL, Vacheron F, Cardus S, Funck-Brentano C.* Effect of single and repeated oral doses of telithromycin on cardiac QT interval in healthy subjects. Clin Pharmacol Ther. 2003; *73:* 242-252.

[48] *Nagy D, DeMeersman R, Gallagher D, Pietrobelli A, Zion AS, Daly D, Heymsfield SB.* QTc interval (cardiac repolarization): lengthening after meals. Obes Res. 1997; *5:* 531-537.