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Article · November 2015

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Drug-Induced QTc Interval Prolongation: A Multicenter Study to Detect Drugs and Clinical Factors Involved in Every Day Practice

Guillermo A. Keller^{1,2}, Paulino A. Alvarez^{1,3}, Marcelo L. Ponte^{1,4}, Waldo H. Belloso^{1,5}, Claudia Bagnes^{1,6}, Cecilia Sparanochia⁷, Claudio D. Gonzalez¹, M. Cecilia Villa Etchegoyen¹, Roberto A. Diez¹ and Guillermo Di Girolamo^{*,1}

¹Centro de Vigilancia y Seguridad de Medicamentos, Second Chair of Pharmacology, School of Medicine, Universidad de Buenos Aires, Buenos Aires, Argentina

²Emergency Department, Hospital General de Agudos Donación Francisco J. Santojanni, Buenos Aires, Argentina

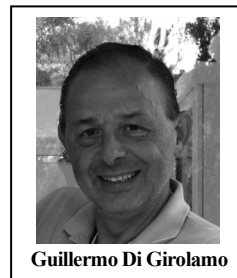
³Cardiology Division, Hospital de Clínicas José de San Martín, Buenos Aires, Argentina

⁴Internal Medicine Department, Hospital General de Agudos Cosme Argerich, Buenos Aires, Argentina

⁵Clinical Pharmacology Section, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

⁶Paliative Care Unit, Hospital General de Agudos Enrique Tornú, Buenos Aires, Argentina

⁷Cardiology Division, Hospital Militar Campo de Mayo, Buenos Aires, Argentina



Abstract: *Objective:* The actual prevalence of drug induced QTc prolongation in clinical practice is unknown. Our objective was to determine the occurrence and characteristics of drug-induced QT prolongation in several common clinical practices. Additionally, a subgroup of patients treated with dextropropoxyphene of particular interest for the regulatory authority was analysed.

Research Design and Methods: Medical history and comorbidities predisposing to QT interval prolongation were registered for 1270 patient requiring medical assistance that involved drug administration. Three ionograms and ECGs were performed: baseline, intra- and after treatment; QT interval was corrected with Bazget formula.

Results: Among patients, 9.9% presented QTc >450/470 ms, 3% QTc > 500 ms, 12.7% ΔQTc >30 ms and 5.2% ΔQTc >60 ms. QTc prolongation associated with congestive heart failure, ischemic cardiopathy, diabetes, renal failure, arrhythmias, hypothyroidism, and bradycardia. At univariate analysis, clarithromycin, haloperidol, tramadol, amiodarone, glyceryl trinitrate, amoxicillin + clavulanic acid, amoxicillin + sulbactam, ampicillin + sulbactam, fentanyl, piperacillin + tazobactam, and diazepam prolonged QTc. Prolongation remained significantly associated with furosemide, clarithromycin, glyceryl trinitrate and betalactamase inhibitors after multivariate analysis.

Conclusion: QT interval prolongation in everyday practice is frequent, in association to clinical factors and drugs that can be easily identified for monitoring and prevention strategies.

Keywords: Adverse drug reaction, QT-Interval prolongation, torsade des Pointes, arrhythmia.

INTRODUCTION

Torsades de Pointes (TdP) is a potentially life-threatening arrhythmia, consisting of a polymorphic ventricular tachycardia associated with prolongation of the QT interval [1, 2]. The acquired form of drug-induced long QT syndrome occurs in 1% to 10% of patients receiving QT-prolonging cardiovascular drugs, and much more rarely (at an undefined rate) in patients receiving non-cardiovascular drugs [3].

The actual prevalence of drug-induced QTc interval prolongation in clinical practice is unknown but a large

number of drugs have the potential to induce prolonged QTc interval and/or TdP [4]. In addition, prolonged QT interval-related arrhythmias are an uncommon but catastrophic event in hospitalized patients [5]. The probability of suffering drug-induced TdP may be greater in hospitalized patients than in outpatient populations, because inpatients are more likely to have risk factors, such as underlying heart disease, advanced age, electrolyte abnormalities, bradycardia, kidney or liver disease and drugs administered by intravenous route [6].

The frequency of drug-induced long QT syndrome and our inability to predict the risk for a given individual makes long QT syndrome, its frequency and related drugs an important issue for clinicians. In July 2010 we began a pharmaco-epidemiological study to assess the rate of QTc prolongation in common clinical practice in Buenos Aires, in

*Address correspondence to this author at the University of Buenos Aires, Argentina; Tel: ++54 11 59509500, Ext. 2212; Fax: ++54 11 59610943; E-mail: gdirolamo@fimed.uba.ar

association with frequently prescribed drugs at different settings: out- and inpatients, under pharmacological treatment that enabled the drug to reach the plasma steady state. Shortly thereafter, by February 2011, the Argentine drug regulatory agency, National Administration of Medicines, Food and Medical Technology (ANMAT), alerted about the potential cardiotoxic effect of dextropropoxyphene -ATC code N02AC04, an opiate very frequently used as a painkiller in Argentina- as revealed by its QTc interval prolonging effect. Besides, ANMAT required the different pharmacovigilance centres in Argentina to intensify the efforts for detecting signals associated with drug-induced QTc prolongation in general, with special focus on dextropropoxyphene and related agents. In response to ANMAT proposal, our Pharmacovigilance Unit adapted the activities then under way to increase focusing on opiates and dextropropoxyphene.

The objectives of this report are to determine the effect of drugs used in common clinical practice on QT interval duration, to identify the drugs most commonly involved in the detected cases of QT prolongation and to estimate the relative risk added by each drug and / or clinical factor to the risk of an individual in the analyzed clinical settings. Additionally, the frequency and risk factors associated with QT interval prolongations were studied in a subgroup of patients treated with dextropropoxyphene; this objective was included to comply with a specific requirement of the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), the drug regulatory agency of Argentina.

PATIENTS AND METHODS

Population and Sample

The study population corresponds to Argentina inhabitants requiring medical attention at different clinics in five hospitals of metropolitan Buenos Aires. The selection of the hospital and clinics was not at random, but aimed to span different and common clinical settings, and also, to guarantee the collection of appropriate clinical data and blood samples through the participation of well-trained medical staff, committed with pharmacovigilance activities.

This was a prospective, non-interventional, observational, longitudinal cohort study, that evaluated ECG changes induced by medicines prescribed for different clinical conditions, in order to determine the frequency of drug-induced QT interval prolongation in the current clinical settings in medical centers of metropolitan Buenos Aires. All cases corresponded to inpatients. The five centers are general hospital and they do not receive psychiatric patients.

The protocol and the corresponding informed consent were approved by the Ethics Committee of the School of Medicine of the Universidad de Buenos Aires and the Institutional Review Board at each hospital. The study was performed in agreement with the Declaration of Helsinki (revised, Korea 2008) and the Good Clinical Practice guidelines.

Initially, all patients were included consecutively if they met the following criteria: (1) Age over 18 years, both sexes; (2) treated exclusively at the participating health centres; (3),

Receiving the indication of one or more drugs for a limited period of time (with known start and end dates) that allows for the electrocardiographic monitoring of QTc interval before, in the meantime, and after the end of the indicated treatment. Subjects were excluded if the administration conditions did not allow for the intra-treatment electrocardiographic monitoring during the period along which the drug concentration were assumed as at steady state (for example, following a single unique dose or any treatment to be concluded within 5 half-lives). After February 2011, as a specific request was made by our national regulatory agency (ANMAT) to our pharmacovigilance unit, we asked the different researchers to specifically search for a subgroup of patients under treatment with dextropropoxyphene, who were included into the program. All patients were asked for medical history, registering data for age, vital signs, gender, weight, height, body mass index, comorbidities predisposing to QT interval prolongation (obesity [6, 7], hypothyroidism [8, 9], central nervous system disease, renal and/or liver failure, diabetes, arrhythmias of ventricular origin, amyloidosis and other conditions that may predispose to QT prolongation [10]), other drugs that patients were receiving (with special attention to drugs that could have pharmacokinetic interactions with QT prolonging drugs) and other diseases.

All data for each case were recorded on a numbered form, specially designed for this study, attached to each patient's clinical record.

DRUG REGISTRY

Since the study was initially designed to describe association of drug use with QT duration, no specific attempt was performed to select any particular drug or dose. As already mentioned, this criterion changed to satisfy a regulatory requirement arisen during the study, concerning the need to determine the risk of dextropropoxyphene, resulting in a biased inclusion of patients treated with this drug. For the final analysis, two subsets of data were analysed: the first comprising every drug other than dextropropoxyphene administered to patients, and a second one corresponding to patients under treatment with dextropropoxyphene.

Although the drug effect over QT we were looking for requires the drug to be in the heart, we did not try to measure drug exposure and consequently, we simply registered every drug the patient was receiving. This resulted in a long list of different drugs, which includes a few cases whose theoretical systemic exposure is minimal or null (such as oral nystatin, see Results), as well as the corresponding risk. However, we preferred to include these drugs in the analysis, since we had no clear quantitative criterion to exclude a particular drug. All drugs were used at the appropriate dose, according to the indication. On the other hand, some types of drugs, such as anti-psychotics or pediatric medication, are under-represented due to the characteristics of the participating centres.

Electrocardiographic Controls

Three electrocardiographic controls, designated as (1) baseline, (2) intra-treatment, and (3) after-treatment were carried out to all patients included in the study.

All electrocardiograms were performed with 3-channel ECG equipment and consisted of 12-lead registries with additional long DII record (ECG strip performed on DII lead for at least 10 seconds) for rhythm assessment. The first electrocardiogram registry (baseline) had to be taken after the inclusion of each subject into the study and recording the personal data, and before the administration of indicated treatment. To determine the appropriate time to perform the second and third electrocardiogram, the theoretical half-life of the indicated drug was taken into account. The second electrocardiogram (intra-treatment) was carried out after at least five elimination half-lives following the initiation of treatment (assuming that after this period the candidate drug had reached its steady state concentration). The third electrocardiogram (after-treatment) was performed on at least five half-lives after the end of treatment (last administration of the tested drug). For drugs with a long half-life and a loading dose, the second ECG was performed after the loading period and the third electrocardiogram one week after the treatment termination, although this does not constitute a real washout of the drug from the body. Indeed, the only drug presenting this problem was amiodarone, for which the ideal drug washout (greater than 150 days) was not reachable; therefore, in this case, the third control was performed even when sub-therapeutic (but potentially QTc-prolonging) plasma drug concentrations theoretically persisted. While amiodarone's pharmacokinetics hindered the assessment of causality criteria (dechallenge and rechallenge), such assessment seems to be of minor importance since amiodarone QTc prolongation is well known.

Electrocardiograph Measures

Two independent observers (both physicians trained in QT interval measurement), blinded about the clinical details of each case, carried out all the measurements manually; the corresponding intra and inter-observer variability coefficients were calculated.

The QT interval was determined as a mean value derived from at least 3 cardiac cycles, measured from the beginning of the earliest onset of the QRS complex to the end of the T wave. The QT measurement was performed in all leads and the longest value was used for calculations. We identified the end of the T wave when its descending limb returned to the TP baseline. When T-wave deflections of equal or near-equal amplitude resulted in a biphasic T wave, the QT interval measurement included the time until the return to baseline.

The RR' interval was measured between the peak of R-wave of one heart-cycle and the peak of R-wave of the next heart cycle. The heart rate (HR) was calculated in each electrocardiogram as: $HR = 60 \times 1000 / RR'$.

Given the apparent differences between correction formulas, the QT interval was corrected by heart rate using the following formulas [11]:

$$\text{Bazzet (QTcB)} = QT / RR'^{(1/2)}$$

$$\text{Fridericia (QTcFri)} = QT / RR'^{(1/3)}$$

$$\text{Framingham (QTcFra)} = QT + 154 \times [1 - (60 / HR)]$$

$$\text{Hogdes (QTcH)} = QT + 1.75 \times (HR - 60)$$

All interval durations were expressed in milliseconds. The additional variable "ΔQTc" was calculated as the absolute difference between QTc values obtained in the intra-treatment period and the value obtained at the baseline period.

QTc Interval Prolongation Criteria

Given the discrepancies about how to define QTc prolongation, we assessed four independent criteria [12]. QTc prolongation was defined as: (1) Absolute value of QTc interval greater than 450 ms (males) or 470 ms (women); (2) ΔQTc greater than 30 ms; (3) Absolute value of QTc interval greater than 500 ms; and / or (4) ΔQTc greater than 60 ms.

When the data analysis was performed, many patients with shortened QT were found. For the correct description of these cases, patients that met the criterion 1: "QTc < 350 ms in males or < 360 ms in women" or criterion 2 "QTc < 330 ms in males or < 340 ms in women" were considered as possible Short QT Syndrome cases [13].

Laboratory Controls

A blood sample was collected from all included individuals at each time an electrocardiogram was performed (baseline, intra-treatment and after-treatment). Those blood samples were used to determine the serum concentration of sodium, potassium, chloride, calcium and magnesium.

End of Participation and Data Confidentiality

The participation of the subjects was considered concluded when the after-treatment electrocardiogram was recorded and blood sample were collected. It was verified that all data were transcribed to the ad hoc numbered forms attached to the medical records. Then, the forms were separated from the medical records and sent to the principal investigator for analysis not including personal data that allow for patient identification (to ensure anonymity of patients).

Statistical Analysis

Categorical variables are presented as percentage. Continuous variables are characterized by mean ± standard deviation and analyzed by Student's t test. The drugs prescribed to each individual were classified and their frequency of prescription was expressed as a percentage of the total sample. Association between electrocardiographic parameters and numerical variables (age, weight, height, body mass index, laboratory results, and ECG parameters) was analyzed by correlation. Drug association with QTc prolongation was studied: (1) Numerical approach, QTc interval was compared between patients receiving and not each drug through Student's test; (2) Categorical approach, the relative risk of each drug was calculated for each prolonged QTc criteria. Chi2 test was used to assess the significance of these associations.

Multiple logistic regression models (Quasi Newton; maximum likelihood) were performed to explore the multivariate association between QTc prolongation greater than 450/470 ms and several covariates (age, gender, BMI,

sodium, potassium, chloremia, renal function, personal history of cardiac failure, ischemic heart disease and diabetes), including the exposure to drugs. The number of subjects exposed to a drug to be included into multivariate analysis was 38 (3% of the total number of patients). Beta-lactamase inhibitors were pooled as a class. The other covariates included clinical factors previously associated with QT-prolongation.

All the statistical analyses were performed with Statistica v.6 (StatSoft, Inc. Tulsa, OK USA). p values below 0.05 (two tailed) were considered as significant.

RESULTS

Anthropometric and Clinical Characteristics of the Sample

Between September 2010 and June 2012, 1270 patients were studied, including 623 (49.1%) women and 647 (50.1%) men. The age was 55 ± 21 years, (18-98), whereas the weight was 73 ± 15 kg (40-120), and height, 167 ± 9 cm (131-192).

The subset not receiving dextropropoxyphene (n = 828) was highly heterogeneous, reflecting the high diversity of diseases requiring hospitalization. Most common indications included infections, complication of cardiovascular diseases and inflammatory conditions, including asthma. The subset that received dextropropoxyphene (n = 442) included mainly cases of post-surgical pain (most cases corresponded to programmed surgery, including hernioplasty and abdominal surgery) as well as colic pain of different origins,

As to clinical risk factors for QTc prolongation, we found cases (presented as number and percentage in the whole mainly included sample) of obesity (326, 25.7%), arrhythmias (112, 8.8%), diabetes (103, 8.1%), ischemic cardiopathy (79, 6.2%), congestive heart failure (71, 5.6%), hypothyroidism (55, 4.3%), central nervous system disease (55, 4.3%), hypertrophic cardiopathy (54, 4.3%), hypoglycaemia (47, 3.7%), renal failure (42, 3.3%), liver failure (28, 2.2%), and bradycardia (17, 1.3%). No cases of amyloidosis or hypothermia were detected. Most of the population (663 patients, 52.2 %) had at least one of the above factors.

Electrolyte Analysis

Ion concentrations, in mEq/L, were at baseline: sodium 138 ± 5 (129-146), potassium 4.2 ± 0.8 (3.0-5.7), ionized

calcium 4.8 ± 0.5 (4.0-5.7), and magnesium 1.9 ± 0.5 (0.5-3.6). Corresponding values at intra-treatment evaluation were: sodium 138 ± 5 (130-146), potassium 4.4 ± 0.8 (3.0-5.7), ionized calcium 4.9 ± 0.8 (4.0-5.7), magnesium 2.0 ± 0.5 (0.8-3.6). Finally, at the after-treatment assessment, values were sodium 138 ± 5 (129-146), potassium 4.3 ± 0.8 (3.0-5.5), ionized calcium 4.8 ± 0.8 (4.1-5.6), and magnesium 1.9 ± 0.3 (1.3-2.3).

Electrocardiographic Parameters

Tables 1 and 2 show the electrocardiographic parameters. The sample had higher heart rates during the basal period and decreased in the treatment and post-treatment period. The uncorrected QT interval showed no significant changes, which only become apparent when correction formulas and basal-treatment differences were used. Intra and inter-observer variability were <6% and <7% respectively. Figure 1 shows the distribution histogram of Δ QTc, which is leptokurtic when Bazzet correction is compared with other corrections, resulting in a lower detection of QTc prolongation cases when Δ QTc is calculated by the Bazzet's formula.

In the total sample, gender did not affect any electrocardiographic parameter. A sub-analysis of individuals younger than 50 years (n = 542, 42.67% of the sample) showed significant between-gender differences at baseline and intra-treatment QTc for all the correction formulas, but not among individuals over 50 yr-old. Other anthropometric variables and the values of electrolytes did not correlate with ECG parameters.

Prescribed Drugs

Drugs prescribed to more than 5 patients are listed in Table 3 by drug name, number of patients receiving that drug and the percentage over the whole sample (N=1270). Most commonly prescribed drugs correspond to antimicrobials (47.09%), followed by NSAIDs (46.43%), cardiovascular agents (29.76%), central nervous system drugs (8.66%), digestive (8.34%), respiratory medicines (5.20%) and glucocorticoids (3.7%).

Because of ANMAT requirement, the search for patients under dextropropoxyphene treatment was stimulated and resulted in a relevant subgroup of the sample: grouping the two dextropropoxyphene associations available into the Argentine

Table 1. Statistical parameters for electrocardiographic measures of each period.

| Variable | Basal | Intra-Treatment | After-Treatment |
|-------------|--------------------------|--------------------------|--------------------------|
| RR' (ms) | 797 \pm 202 (320-2200) | 784 \pm 154 (360-2400) | 805 \pm 141 (520-2080) |
| HR (bpm) | 80 \pm 20 (27-188) | 79 \pm 15 (25-167) | 77 \pm 13 (29-115) |
| QT (ms) | 378 \pm 51 (200-600) | 383 \pm 43 (200-720) | 383 \pm 39 (320-800) |
| QTcB (ms) | 427 \pm 30 (280 - 793) | 434 \pm 29 (283 - 611) | 428 \pm 21 (320 - 730) |
| QTcFri (ms) | 409 \pm 31 (261 - 689) | 416 \pm 29 (252 - 601) | 413 \pm 24 (320 - 753) |
| QTcFra (ms) | 409 \pm 29 (259 - 608) | 416 \pm 28 (277 - 595) | 413 \pm 23 (320 - 769) |
| QTcH (ms) | 413 \pm 28 (290 - 659) | 417 \pm 28 (299 - 659) | 413 \pm 24 (320 - 783) |

market (228 plus metamizole and 214 plus ibuprofen), a total of 442 cases were treated with dextropropoxyphene, representing 34.8% of the total patients included into the study.

Table 2. Statistical parameters for electrocardiographic measures representing changes between periods (Δ QTc).

| Variable | Mean \pm SD (Range) |
|-----------------|----------------------------|
| Δ QTcB | +7 \pm 34 (-328 to +194) |
| Δ QTcFri | +7 \pm 36 (-262 to +203) |
| Δ QTcFra | +7 \pm 33 (-186 to +220) |
| Δ QTcH | +4 \pm 33 (-229 to +220) |

QTc Interval Prolongation

As shown in Table 4, the analysis for the presence of at least one of the four criteria of QTc interval prolongation was repeated for each QTc correction formula. The prolonged QTc interval frequency was between 5 and 10% for QTc > 450/470 ms, 1 to 3% for QTc > 500 ms, 12 to 19% for Δ QTc > 30 ms and about 5% for Δ QTc > 60 ms. No significant difference was found among the four correction formulas.

QTc Interval Prolongation for Different Clinical Risk Factors

Table 5 presents the relative risk (95% confidence interval) for each criterion of QTc prolongation among

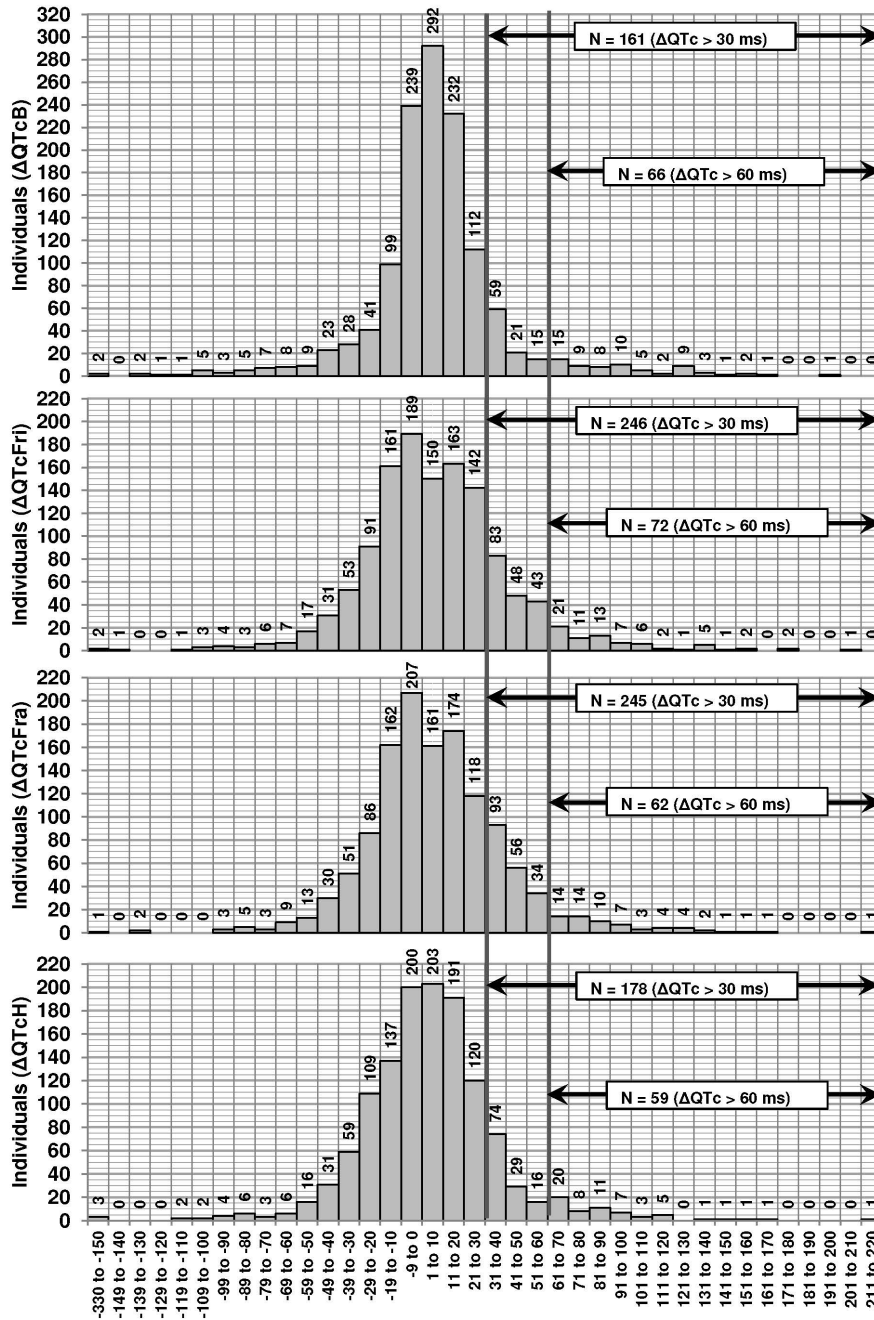


Figure 1. Δ QTc observed histogram for all analyzed individuals (dashed lines show Δ QTc 30 and 60 ms cut-offs).

Table 3. Drugs prescribed in more than 5 patients in the analyzed sample.

| Drug | N | % |
|---------------------------------|-----|--------|
| Dextropropoxyphene + Metamizole | 228 | 17.95% |
| Dextropropoxyphene + Ibuprofen | 214 | 16.85% |
| Ceftriaxone | 134 | 10.55% |
| Enoxaparin | 112 | 11.40% |
| Ciprofloxacin | 103 | 12.33% |
| Ibuprofen | 85 | 6.69% |
| Omeprazole | 80 | 6.30% |
| Furosemide | 69 | 5.43 % |
| Clarithromycin | 55 | 4.33% |
| Piperacillin + Tazobactam | 51 | 4.01% |
| Haloperidol | 40 | 3.15% |
| Cephalothin | 39 | 3.10% |
| Spironolactone | 38 | 2.99 % |
| Glyceryl trinitrate | 38 | 2.99% |
| Aspirin | 36 | 2.83% |
| Doxycycline | 35 | 2.75% |
| Phenytoin | 33 | 2.60% |
| Vancomycin | 32 | 2.52 % |
| Amoxicillin + Clavulanic acid | 32 | 2.52% |
| Salbutamol | 30 | 2.36% |
| Diazepam | 30 | 2.36% |
| Ipratropium | 29 | 2.28% |
| Clindamycin | 29 | 2.28% |
| Amoxicillin + Sulbactam | 29 | 2.28% |
| Paracetamol | 26 | 2.05% |
| Clopidogrel | 25 | 1.96% |
| Atorvastatin | 25 | 1.96% |
| Hydrocortisone | 21 | 1.65% |
| Ranitidine | 19 | 1.49% |
| Tramadol | 16 | 1.26% |
| Meprednisone | 15 | 1.18% |
| Diclofenac | 13 | 1.02% |

(Table 3) continuation

| Drug | N | % |
|--------------------------|----|-------|
| Clotrimazole | 13 | 1.02% |
| Amiodarone | 12 | 0.94% |
| Dexamethasone | 11 | 0.87% |
| Ampicillin + Sulbactam | 10 | 0.79% |
| Potassium chloride | 10 | 0.79% |
| Amikacin | 10 | 0.79% |
| Ketorolac | 10 | 0.79% |
| Imipenem | 10 | 0.79% |
| Enalapril | 9 | 0.71% |
| Nystatin | 9 | 0.71% |
| Fentanyl | 8 | 0.63% |
| Dopamine | 8 | 0.63% |
| Salbutamol + Ipratropium | 7 | 0.55% |
| Clonazepam | 7 | 0.55% |
| Metoclopramide | 7 | 0.55% |
| Ceftazidime | 7 | 0.55% |
| Atenolol | 6 | 0.47% |

different medical history factors. Statistically significant risk is marked as filled cells. History of arrhythmias, congestive heart failure, ischemic cardiopathy, renal failure and diabetes were associated with a significant risk of QTc prolongation using the diagnostic criterion $QTc > 450$ in males and 470 ms in women independently of the QTc correction formula, while the history of bradycardia exhibited a significant risk increase with the Fridericia, Framingham and Hodges corrections, but not with the Bazett's one. Antecedents of arrhythmias, congestive heart failure, ischemic cardiopathy, hypothyroidism and diabetes were associated with a significant risk of QTc prolongation using $QTc > 500$ ms differently depending on the correction used. The history of congestive heart failure, ischemic cardiopathy, renal failure, hypothyroidism, and diabetes were associated with a significantly increased risk of QTc prolongation using $\Delta QTc > 30$ ms. A history of bradycardia, congestive heart failure, ischemic cardiopathy, renal failure, hypothyroidism and diabetes were associated with a significant risk of QTc prolongation using the diagnostic criterion $\Delta QTc > 60$ ms. The antecedents of hypertrophic cardiopathy, liver failure, central nervous system diseases, hypoglycaemia, and obesity

Table 4. Number of individuals presenting each QTc prolongation criterion according the different QTc correction formulae.

| Parameter | QTc | | | | ΔQTc | | |
|-----------------|--------------|--------------|--------------|--------------|-------------|---------------|-------------|
| | < 330/340 ms | < 350/360 ms | > 450/470 ms | > 500 ms | > 30 ms | > 60 ms | |
| Number of cases | QTcB | 8 (0.63%) | 18 (1.42 %) | 126 (9.92 %) | 38 (2.99 %) | 161 (12.68 %) | 66 (5.20 %) |
| | QTcFri | 12 (0.94%) | 34 (2.68 %) | 67 (5.28 %) | 17 (1.34 %) | 246 (19.37 %) | 72 (5.67 %) |
| | QTcFra | 9 (0.71%) | 55 (4.33 %) | 55 (4.33 %) | 16 (1.26 %) | 245 (19.29 %) | 62 (4.88 %) |
| | QTcH | 8 (0.63%) | 25 (1.97 %) | 63 (4.96 %) | 19 (1.50 %) | 178 (14.02 %) | 59 (4.65 %) |

Table 5. Relative risk for QTc interval prolongation related to different clinical history factors (shaded cells indicate p <0.05).

| | | QTc > 450/470 ms | QTc > 500 ms | ΔQTc > 30 ms | ΔQTc > 60 ms |
|--------------------------------|--------|-------------------|-------------------|------------------|-------------------|
| Arrhythmias | QTcB | 1.98 (1.31-3.00) | 2.09 (0.94-4.63) | 1.27 (0.81-1.99) | 1.20 (0.56-2.57) |
| | QTcFri | 2.03 (1.12-3.68) | 4.00 (1.51-10.62) | 1.15 (0.80-1.66) | 1.10 (0.52-2.35) |
| | QTcFra | 2.27 (1.21-4.26) | 4.25 (1.57-11.48) | 1.30 (0.92-1.82) | 1.28 (0.60-2.74) |
| | QTcH | 1.98 (1.06-3.68) | 3.58 (1.39-9.24) | 1.08 (0.68-1.72) | 0.96 (0.39-2.35) |
| Bradycardia | QTcB | 2.37 (0.99-5.68) | 1.97 (0.29-13.51) | 1.39 (0.49-3.93) | 3.40 (1.18-9.75) |
| | QTcFri | 4.46 (1.83-10.86) | 4.39 (0.62-31.29) | 1.21 (0.51-2.88) | 2.08 (0.55-7.78) |
| | QTcFra | 5.43 (2.21-13.34) | 4.67 (0.65-33.38) | 1.52 (0.72-3.21) | 3.61 (1.26-10.40) |
| | QTcH | 4.74 (1.94-11.58) | 3.93 (0.56-27.80) | 1.68 (0.70-4.00) | 2.53 (0.67-9.54) |
| Congestive Cardiac Failure | QTcB | 2.70 (1.76-4.12) | 3.30 (1.50-7.22) | 2.00 (1.30-3.07) | 2.71 (1.45-5.08) |
| | QTcFri | 2.94 (1.61-5.35) | 5.26 (1.91-14.52) | 1.45 (0.99-2.14) | 2.48 (1.33-4.63) |
| | QTcFra | 2.93 (1.49-5.74) | 4.47 (1.48-13.51) | 1.46 (0.99-2.15) | 2.31 (1.14-4.66) |
| | QTcH | 2.56 (1.32-4.96) | 4.71 (1.74-12.70) | 1.71 (1.10-2.65) | 2.12 (1.00-4.50) |
| Hypertrophic Cardiomyopathy | QTcB | 0.75 (0.29-1.95) | No cases | 0.15 (0.02-1.02) | 0.36 (0.05-2.52) |
| | QTcFri | 0.35 (0.05-2.48) | No cases | 0.57 (0.27-1.23) | 0.33 (0.05-2.31) |
| | QTcFra | 0.43 (0.06-3.03) | No cases | 0.58 (0.27-1.23) | 0.38 (0.05-2.69) |
| | QTcH | 0.37 (0.05-2.64) | No cases | 0.40 (0.13-1.20) | 0.40 (0.06-2.82) |
| Ischemic Cardiomyopathy | QTcB | 2.55 (1.68-3.88) | 2.96 (1.35-6.51) | 1.70 (1.08-2.66) | 2.44 (1.29-4.59) |
| | QTcFri | 2.88 (1.61-5.15) | 6.62 (2.59-16.92) | 1.31 (0.88-1.94) | 2.01 (1.04-3.89) |
| | QTcFra | 3.51 (1.93-6.38) | 6.03 (2.25-16.16) | 1.38 (0.94-2.02) | 2.07 (1.02-4.20) |
| | QTcH | 3.06 (1.70-5.50) | 5.08 (1.98-13.00) | 1.72 (1.13-2.60) | 2.18 (1.07-4.43) |
| Renal Failure | QTcB | 2.64 (1.54-4.51) | 2.39 (0.76-7.45) | 2.63 (1.67-4.14) | 4.12 (2.19-7.76) |
| | QTcFri | 3.16 (1.54-6.49) | 3.56 (0.84-15.06) | 1.97 (1.32-2.94) | 2.94 (1.44-6.02) |
| | QTcFra | 3.85 (1.85-7.99) | 3.78 (0.89-16.10) | 2.22 (1.54-3.21) | 3.41 (1.66-7.04) |
| | QTcH | 2.88 (1.32-6.30) | 3.18 (0.76-13.33) | 2.55 (1.66-3.92) | 3.08 (1.40-6.75) |
| Liver Failure | QTcB | 1.08 (0.37-3.19) | 2.39 (0.60-9.43) | 0.28 (0.04-1.94) | No cases |
| | QTcFri | 1.35 (0.35-5.26) | No cases | 0.37 (0.10-1.41) | No cases |
| | QTcFra | 1.65 (0.42-6.43) | No cases | 0.37 (0.10-1.41) | No cases |
| | QTcH | 1.44 (0.37-5.60) | No cases | 0.25 (0.04-1.75) | No cases |
| Hypothyroidism | QTcB | 1.65 (0.89-3.07) | 2.43 (0.89-6.61) | 1.86 (1.13-3.07) | 1.75 (0.73-4.18) |
| | QTcFri | 2.07 (0.93-4.57) | 4.07 (1.21-13.77) | 1.31 (0.82-2.09) | 2.24 (1.08-4.66) |
| | QTcFra | 2.10 (0.87-5.05) | 4.33 (1.27-14.75) | 1.32 (0.83-2.10) | 2.61 (1.25-5.46) |
| | QTcH | 2.20 (0.99-4.88) | 3.65 (1.09-12.14) | 1.69 (1.03-2.77) | 2.35 (1.06-5.22) |
| Central Nervous System Disease | QTcB | 0.73 (0.28-1.91) | 0.61 (0.08-4.35) | 0.72 (0.31-1.67) | 1.05 (0.34-3.24) |
| | QTcFri | 1.03 (0.34-3.19) | No cases | 0.94 (0.53-1.66) | 0.96 (0.31-2.96) |
| | QTcFra | 1.26 (0.41-3.91) | No cases | 1.04 (0.60-1.78) | 0.74 (0.19-2.97) |
| | QTcH | 1.10 (0.36-3.40) | No cases | 0.78 (0.36-1.68) | 1.57 (0.59-4.16) |
| Diabetes | QTcB | 2.25 (1.50-3.37) | 2.60 (1.22-5.51) | 1.76 (1.19-2.61) | 2.06 (1.11-3.80) |
| | QTcFri | 2.58 (1.48-4.48) | 2.90 (0.96-8.74) | 1.20 (0.83-1.74) | 1.54 (0.79-3.01) |
| | QTcFra | 2.91 (1.62-5.25) | 2.31 (0.67-7.98) | 1.11 (0.75-1.63) | 1.39 (0.65-2.98) |
| | QTcH | 2.35 (1.29-4.26) | 1.95 (0.58-6.57) | 1.73 (1.19-2.51) | 1.04 (0.43-2.55) |
| Hypoglycemia | QTcB | 0.43 (0.11-1.68) | No cases | 0.17 (0.02-1.17) | No cases |
| | QTcFri | 0.40 (0.06-2.84) | No cases | 0.33 (0.11-0.99) | No cases |
| | QTcFra | 0.49 (0.07-3.48) | No cases | 0.22 (0.06-0.86) | No cases |
| | QTcH | No cases | No cases | 0.15 (0.02-1.06) | No cases |
| Obesity | QTcB | 0.43 (0.25-0.74) | 0.10 (0.01-0.74) | 0.41 (0.25-0.67) | 0.35 (0.15-0.81) |
| | QTcFri | 0.29 (0.12-0.72) | 0.23 (0.03-1.72) | 0.81 (0.61-1.07) | 0.65 (0.35-1.19) |
| | QTcFra | 0.35 (0.14-0.88) | 0.24 (0.03-1.84) | 0.83 (0.63-1.09) | 0.63 (0.32-1.22) |
| | QTcH | 0.31 (0.13-0.76) | 0.21 (0.03-1.53) | 0.57 (0.38-0.85) | 0.40 (0.17-0.91) |

did not show any significant increase of the risk of QTc interval prolongation, independently of the QTc correction formula and/or criteria utilized for this purpose.

QTc Interval Prolongation Risk Among Different Drugs

Table 6 lists the drugs that prolonged QTc length in the treatment period or Δ QTc. In the after-treatment period only amiodarone showed a QTc interval higher than the rest of the studied agents ($p = 0.0492$). As stated in Methods, for amiodarone, the third electrocardiogram was performed 1 week after the suspension of the drug. Due to the long elimination half-life of amiodarone, this time does not permit for a real washout of the drug from the body.

Table 7 summarizes the relative risk of presenting intra-treatment QTc interval prolongation for each drug and the four analyzed criteria.

QTc Interval Prolongation and Other Factors

In our sample, gender did not influence the heart rate, R-R', uncorrected QT, QTcB, QTcFri, QTcFra, QTcH, Δ QTcB, Δ QTcFri, Δ QTcFra or Δ QTcH (all variables were compared between genders without significant differences, $p=0.05$ to 0.12). Anthropometric variables (age, weight, height, body mass index) and the values of electrolytes (sodium, potassium, calcium and magnesium) showed no correlation with QTc interval duration or Δ QTc (for all correction formulas). Correlation analysis did not show significant association

between electrocardiographic parameters (RR', QT, QTc, Δ QTc) of any of the electrocardiograms (basal, intra-treatment, after-treatment) with the only exception of a strong (and expected) correlation of Δ QTc with basal QTc ($R = 0.57$, $p < 0.001$) and intra-treatment QTc ($R = 0.58$, $p < 0.001$).

We did not identify cases of significant pharmacokinetic interactions that may have modified the effect of the drug on the QTc interval.

Multivariate Analysis

Intra-treatment QTc prolongation $>450/470$ ms persisted significantly associated with the exposure to some drugs after a multivariate adjustment. This was the case for: furosemide (OR: 6.50; 95%CI: 1.56-27.05; $p < 0.01$), beta-lactamase inhibitors -considered as a group, that included clavulanic acid, tazobactam and sulbactam (OR: 4.14; 95%CI: 2.52-6.79; $p < 0.01$), glyceryl trinitrate (OR: 3.39; 95%CI: 1.61-7.76; $p < 0.01$) and clarithromycin (OR: 1.93; 95%CI: 1.34-3.62; $p < 0.05$). Potassium levels were also associated with QTc prolongation when furosemide was included into the logistic analysis ($p < 0.05$, no interaction between both variables detected); age was also associated with QTc prolongation for the model including clarithromycin ($p < 0.05$, no interaction between the drug and age detected). No other drugs were included into the diverse logistic models carried out to detect multivariate associations with QTc prolongation.

Table 6. Electrocardiographic parameters for drugs showing a greater QTc or Δ QTc value (shaded cells indicate $P < 0.05$).

| Drug | Intratreatment QTc as Mean \pm SD (ms) | | | | Δ QTc as Mean \pm SD (ms) | | | |
|---------------------------------|--|--------------|--------------|--------------|------------------------------------|-----------------|-----------------|---------------|
| | QTcB | QTcFri | QTcFra | QTcH | Δ QTcB | Δ QTcFri | Δ QTcFra | Δ QTcH |
| Dextropropoxyphene + Metamizole | 430 \pm 27 | 417 \pm 25 | 417 \pm 24 | 415 \pm 23 | 6 \pm 19 | 6 \pm 26 | 6 \pm 26 | 2 \pm 23 |
| Dextropropoxyphene + Ibuprofen | 429 \pm 26 | 411 \pm 25 | 411 \pm 24 | 411 \pm 24 | 6 \pm 33 | 6 \pm 34 | 6 \pm 31 | 2 \pm 33 |
| Fentanyl | 454 \pm 18 | 442 \pm 19 | 445 \pm 18 | 442 \pm 19 | 35 \pm 36 | 28 \pm 29 | 33 \pm 28 | 29 \pm 25 |
| Tramadol | 451 \pm 20 | 417 \pm 28 | 413 \pm 28 | 426 \pm 24 | 20 \pm 105 | 14 \pm 89 | 15 \pm 71 | 20 \pm 80 |
| Haloperidol | 445 \pm 31 | 436 \pm 40 | 435 \pm 39 | 439 \pm 44 | 15 \pm 30 | 17 \pm 43 | 17 \pm 43 | 19 \pm 46 |
| Diazepam | 446 \pm 11 | 427 \pm 13 | 426 \pm 13 | 425 \pm 10 | 18 \pm 8 | 13 \pm 23 | 12 \pm 24 | 9 \pm 18 |
| Phenytoin | 430 \pm 7 | 416 \pm 11 | 416 \pm 11 | 415 \pm 10 | 2 \pm 9 | 1 \pm 20 | 1 \pm 19 | -1 \pm 17 |
| Nitroglycerine | 450 \pm 46 | 443 \pm 45 | 442 \pm 45 | 443 \pm 46 | 28 \pm 57 | 33 \pm 57 | 33 \pm 58 | 30 \pm 56 |
| Amiodarone | 476 \pm 41 | 470 \pm 46 | 471 \pm 46 | 470 \pm 47 | 31 \pm 73 | 44 \pm 72 | 45 \pm 70 | 41 \pm 68 |
| Enoxaparin | 428 \pm 31 | 410 \pm 29 | 410 \pm 28 | 412 \pm 27 | 5 \pm 42 | 6 \pm 39 | 5 \pm 36 | 4 \pm 37 |
| Atorvastatin | 444 \pm 38 | 427 \pm 31 | 425 \pm 30 | 430 \pm 28 | 25 \pm 57 | 24 \pm 52 | 25 \pm 50 | 20 \pm 43 |
| Omeprazole | 426 \pm 40 | 404 \pm 39 | 405 \pm 34 | 406 \pm 33 | 4 \pm 52 | 5 \pm 52 | 5 \pm 46 | -1 \pm 42 |
| Clarithromycin | 449 \pm 36 | 424 \pm 30 | 422 \pm 25 | 426 \pm 28 | 19 \pm 30 | 16 \pm 25 | 14 \pm 23 | 14 \pm 26 |
| Piperacillin + Tazobactam | 443 \pm 15 | 420 \pm 14 | 419 \pm 14 | 422 \pm 14 | 20 \pm 32 | 17 \pm 35 | 15 \pm 34 | 14 \pm 32 |
| Ampicillin + Sulbactam | 467 \pm 38 | 444 \pm 47 | 442 \pm 47 | 448 \pm 40 | 37 \pm 44 | 32 \pm 35 | 30 \pm 36 | 31 \pm 32 |
| Amoxicillin + Clavulanic acid | 460 \pm 54 | 428 \pm 52 | 424 \pm 48 | 434 \pm 49 | 33 \pm 58 | 21 \pm 48 | 16 \pm 41 | 23 \pm 47 |
| Amoxicillin + Sulbactam | 452 \pm 40 | 424 \pm 43 | 422 \pm 41 | 428 \pm 38 | 16 \pm 77 | 14 \pm 67 | 14 \pm 54 | 14 \pm 58 |
| Cotrimoxazole | 422 \pm 34 | 395 \pm 25 | 394 \pm 22 | 401 \pm 23 | 7 \pm 37 | 5 \pm 29 | 4 \pm 26 | 7 \pm 26 |
| Vancomycin | 426 \pm 48 | 401 \pm 39 | 400 \pm 34 | 406 \pm 39 | 8 \pm 64 | 7 \pm 50 | 8 \pm 47 | 4 \pm 49 |

Table 7. Risk of QTc interval prolongation for each drug according to different criteria: QTc>450/470 ms (Panel A), QTc > 500 ms (Panel B), ΔQTc > 30 ms (Panel C) and ΔQTc > 60 ms (Panel D) (shaded cells indicate p < 0.05).

| | Drug | QTcB | QTcFri | QTcFra | QTcH |
|-----------|---------------------------------|-------------------|-------------------|-------------------|------------------|
| A | Clarithromycin | 1.90 (1.06-3.42) | 1.10 (0.51-2.39) | 0.91 (0.39-2.14) | 1.10 (0.51-2.39) |
| | Piperacillin + Tazobactam | 2.06 (1.15-3.69) | 0.19 (0.03-1.34) | 0.19 (0.03-1.34) | 0.19 (0.03-1.34) |
| | Haloperidol | 1.81 (0.90-3.62) | 2.94 (1.73-5.01) | 2.94 (1.73-5.01) | 2.94 (1.73-5.01) |
| | Nitroglycerine | 4.72 (3.12-7.13) | 3.41 (2.07-5.62) | 3.41 (2.07-5.62) | 3.10 (1.83-5.25) |
| | Amoxicillin + Clavulanic acid | 2.62 (1.41-4.89) | 1.60 (0.70-3.64) | 0.94 (0.32-2.81) | 1.60 (0.70-3.64) |
| | Tramadol | 3.92 (2.04-7.54) | 1.26 (0.34-4.67) | 1.26 (0.34-4.67) | 1.26 (0.34-4.67) |
| | Amiodarone | 8.06 (5.58-11.66) | 6.17 (3.71-10.24) | 6.17 (3.71-10.24) | 5.24 (2.90-9.46) |
| | Ampicillin + Sulbactam | 4.13 (1.90-8.99) | 3.07 (1.18-8.04) | 3.07 (1.18-8.04) | 3.07 (1.18-8.04) |
| | Fentanyl | 3.85 (1.55-9.56) | 2.54 (0.76-8.55) | 2.54 (0.76-8.55) | 1.26 (0.20-7.95) |
| | Aspirin | 3.28 (1.95-5.53) | 2.02 (1.02-4.00) | 1.42 (0.62-3.25) | 2.32 (1.23-4.38) |
| | Atorvastatin | 3.38 (1.86-6.13) | 1.63 (0.65-4.07) | 1.21 (0.41-3.56) | 2.06 (0.92-4.59) |
| | Ketorolac | 4.13 (1.90-8.99) | 3.07 (1.18-8.04) | 2.03 (0.58-7.10) | 3.07 (1.18-8.04) |
| | Vancomycin | 2.28 (1.16-4.48) | 0.62 (0.16-2.41) | No Cases | 0.62 (0.16-2.41) |
| | Furosemide | 2.71 (1.73-4.26) | 1.83 (1.06-3.15) | 1.18 (0.60-2.31) | 1.34 (0.71-2.52) |
| | Hydrocortisone | 2.46 (1.12-5.38) | 0.96 (0.25-3.62) | 0.96 (0.25-3.62) | 0.96 (0.25-3.62) |
| | Dexamethasone | 2.79 (1.05-7.43) | 0.92 (0.14-5.98) | 0.92 (0.14-5.98) | 1.85 (0.52-6.54) |
| | Amikacin | 3.07 (1.18-8.04) | 2.03 (0.58-7.10) | 2.03 (0.58-7.10) | 2.03 (0.58-7.10) |
| | Clopidogrel | 2.49 (1.21-5.10) | 0.80 (0.21-3.07) | 0.80 (0.21-3.07) | 1.21 (0.41-3.56) |
| | Potassium chloride | 3.07 (1.18-8.04) | 2.03 (0.58-7.10) | 2.03 (0.58-7.10) | 2.03 (0.58-7.10) |
| Enalapril | 3.42 (1.34-8.74) | 1.12 (0.18-7.17) | No Cases | 1.12 (0.18-7.17) | |
| B | Furosemide | 3.26 (1.41-7.54) | 2.21 (0.45-3.42) | 0.53 (0.41-6.45) | 1.62 (0.14-5.48) |
| C | Dextropropoxyphene + Metamizole | 0.21 (0.10-0.44) | 1.72 (1.25-2.35) | 1.77 (1.30-2.42) | 0.69 (0.44-1.06) |
| | Clarithromycin | 1.62 (0.94-2.81) | 2.27 (1.44-3.58) | 1.78 (1.06-3.00) | 1.78 (1.06-3.00) |
| | Piperacillin + Tazobactam | 2.28 (1.42-3.64) | 2.10 (1.28-3.44) | 1.92 (1.15-3.23) | 1.58 (0.89-2.81) |
| | Haloperidol | 1.40 (0.70-2.78) | 2.70 (1.69-4.33) | 2.48 (1.51-4.07) | 2.48 (1.51-4.07) |
| | Nitroglycerine | 3.58 (2.39-5.35) | 4.08 (2.82-5.90) | 4.08 (2.82-5.90) | 4.08 (2.82-5.90) |
| | Amoxicillin + Clavulanic acid | 3.68 (2.42-5.61) | 3.12 (1.94-4.99) | 2.56 (1.50-4.37) | 3.12 (1.94-4.99) |
| | Amoxicillin + Sulbactam | 3.14 (1.92-5.12) | 2.83 (1.68-4.78) | 2.53 (1.44-4.45) | 3.45 (2.18-5.45) |
| | Tramadol | 4.10 (2.46-6.84) | 3.03 (1.59-5.81) | 3.03 (1.59-5.81) | 3.56 (2.01-6.33) |
| | Amiodarone | 4.77 (2.89-7.86) | 5.48 (3.58-8.40) | 5.48 (3.58-8.40) | 5.48 (3.58-8.40) |
| | Ampicillin + Sulbactam | 4.04 (2.14-7.63) | 4.04 (2.14-7.63) | 4.04 (2.14-7.63) | 4.04 (2.14-7.63) |
| | Fentanyl | 5.06 (2.90-8.82) | 4.02 (1.98-8.16) | 5.06 (2.90-8.82) | 4.02 (1.98-8.16) |
| | Aspirin | 2.03 (1.13-3.64) | 2.76 (1.70-4.49) | 2.76 (1.70-4.49) | 2.76 (1.70-4.49) |
| | Atorvastatin | 1.93 (0.95-3.93) | 2.60 (1.44-4.70) | 2.60 (1.44-4.70) | 2.60 (1.44-4.70) |
| | Ketorolac | 4.88 (2.88-8.26) | 3.21 (1.48-6.95) | 4.04 (2.14-7.63) | 3.21 (1.48-6.95) |
| | Vancomycin | 2.84 (1.72-4.68) | 2.84 (1.72-4.68) | 2.84 (1.72-4.68) | 3.12 (1.94-4.99) |
| | Omeprazole | 1.87 (1.21-2.89) | 1.99 (1.31-3.03) | 1.99 (1.31-3.03) | 1.64 (1.03-2.61) |
| | Furosemide | 1.28 (0.73-2.24) | 2.33 (1.54-3.52) | 2.33 (1.54-3.52) | 1.53 (0.92-2.55) |
| | Hydrocortisone | 3.52 (2.10-5.90) | 3.94 (2.46-6.32) | 3.94 (2.46-6.32) | 3.94 (2.46-6.32) |
| | Dexamethasone | 3.67 (1.89-7.12) | 2.92 (1.32-6.46) | 2.92 (1.32-6.46) | 5.20 (3.25-8.33) |

(Table 7) continuation

| | Drug | QTcB | QTcFri | QTcFra | QTcH |
|------------|-------------------------------|------------------|-------------------|------------------|------------------|
| C | Amikacin | 4.88 (2.88-8.26) | 4.88 (2.88-8.26) | 4.88 (2.88-8.26) | 4.88 (2.88-8.26) |
| | Paracetamol | 2.83 (1.64-4.90) | 2.50 (1.38-4.54) | 2.50 (1.38-4.54) | 3.17 (1.91-5.27) |
| | Clopidogrel | 1.93 (0.95-3.93) | 2.26 (1.19-4.32) | 2.60 (1.44-4.70) | 2.60 (1.44-4.70) |
| | Nystatin | 2.66 (1.04-6.78) | 3.57 (1.70-7.52) | 2.66 (1.04-6.78) | 2.66 (1.04-6.78) |
| | Enoxaparin | 1.47 (0.96-2.24) | 1.55 (1.02-2.35) | 1.72 (1.16-2.56) | 1.64 (1.09-2.45) |
| | Ciprofloxacin | 1.43 (0.91-2.23) | 1.89 (1.28-2.80) | 1.70 (1.13-2.56) | 1.43 (0.91-2.23) |
| | Meprednisone | 3.24 (1.71-6.12) | 2.13 (0.91-5.00) | 1.59 (0.57-4.42) | 2.68 (1.29-5.57) |
| | Cotrimoxazole | 2.46 (1.08-5.64) | 1.84 (0.67-5.01) | 1.84 (0.67-5.01) | 1.22 (0.34-4.39) |
| | Ceftriaxone | 0.81 (0.48-1.35) | 1.63 (1.12-2.39) | 1.49 (1.00-2.20) | 0.87 (0.53-1.44) |
| | Ibuprofen | 0.73 (0.37-1.43) | 1.65 (1.05-2.58) | 1.54 (0.96-2.45) | 1.02 (0.58-1.81) |
| Dopamine | 1.98 (0.59-6.65) | 1.98 (0.59-6.65) | 1.98 (0.59-6.65) | 3.00 (1.21-7.41) | |
| D | Haloperidol | 1.46 (0.48-4.46) | 4.24 (2.17-8.28) | 4.24 (2.17-8.28) | 5.49 (3.03-9.95) |
| | Nitroglycerine | 5.12 (2.74-9.56) | 5.79 (3.21-10.45) | 5.12 (2.74-9.56) | 4.47 (2.30-8.69) |
| | Amoxicillin + Clavulanic acid | 4.59 (2.28-9.25) | 4.59 (2.28-9.25) | 1.21 (0.31-4.72) | 4.59 (2.28-9.25) |
| | Amoxicillin + Sulbactam | 4.28 (2.01-9.10) | 3.51 (1.52-8.08) | 2.76 (1.08-7.08) | 3.51 (1.52-8.08) |
| | Aspirin | 2.81 (1.20-6.57) | 4.07 (2.00-8.27) | 4.07 (2.00-8.27) | 3.43 (1.59-7.41) |
| | Atorvastatin | 4.08 (1.80-9.28) | 4.08 (1.80-9.28) | 4.08 (1.80-9.28) | 4.08 (1.80-9.28) |
| | Vancomycin | 3.17 (1.37-7.36) | 1.21 (0.31-4.72) | 1.21 (0.31-4.72) | 2.50 (0.97-6.44) |
| | Omeprazole | 2.66 (1.41-5.01) | 1.76 (0.83-3.74) | 1.76 (0.83-3.74) | 1.76 (0.83-3.74) |
| Ranitidine | 2.06 (0.54-7.80) | 3.14 (1.08-9.10) | 3.14 (1.08-9.10) | 2.06 (0.54-7.80) | |

Arrhythmias and Clinical Events

No patient had evidence of arrhythmia, ventricular tachycardia, *torsades de pointes* and / or sudden death during the present study. Therefore, arrhythmogenic risk associated with different factors and / or drugs could not be estimated.

Other Considerations

Additionally, the occurrence of QTc shortening was analyzed. Table 4 presents the number of cases according to different criteria and corrections.

No drug showed a statistically significant relative risk for QTcB shortening below 350 ms (males) or 360 ms (women). Dextropropoxyphene + metamizole (but not dextropropoxyphene + ibuprofen) showed a significant relative risk increase (95%CI) for QTcFri, QTcFra and QTcH shortening of 2.49 (1.25-4.96), 2.96 (1.40-6.23) and 3.59 (1.65-7.81) respectively. Other drugs showed significant risk only when Framingham correction was applied: vancomycin 9.04 (3.22-25.34), paracetamol 10.14 (3.10-33.15) and imipenem 9.56 (1.38-66.30).

No drug was associated with QTcB, QTcFri or QTcH below 330 ms (males) or 340 ms (women), whereas only two drug associated with QTcFra shortening below 330 (males) or 340 ms (women): paracetamol 23.81 (4.56-124.26) and imipenem 41.73 (4.74-367.71).

DISCUSSION

In this report, we illustrate some characteristics of drug-induced QT interval prolongation in current clinical practice. We used standard electrocardiograms to estimate QTc-prolongation frequency associated with frequently prescribed drug and clinical factors [14]. The best HR correction should be estimated for each individual; unfortunately, this is unfeasible in the clinical setting [15]. Bazett is a commonly used and criticized correction, Fridericia (rarely criticized) is usually chosen by regulatory authorities, but unfriendly for clinical practice, Framingham, together with Fridericia, is considered superior to Bazett), whereas Hodges correction is less used. One report [16] criticized some formulas to be inaccurate in risk prediction. Our study confirms that the use of QTcB leads to case over-diagnosis (twice cases). However, there were no significant differences between QTcFri, QTcFra and QTcH.

The differences between correction formulas have not been studied when Δ QTc has been used. Our study suggests that using Δ QTc, errors with Bazett formula tend to disappear, diagnosing the same number of cases that the other formulas (Δ QTc > 60) or even slightly fewer (Δ QTc > 30ms). If confirmed, this finding would support the use of Δ QTcB in clinical situations where other approaches are difficult.

We analyzed a broad sample. Further, because the requisition by the Argentine Drug Regulatory Agency (ANMAT), we placed special emphasis on dextropropoxyphene use, resulting in over-representation of analgesic use. This bias hinders proper evaluation of prevalence, but still allows the analysis of the impact of many factors to prolong QT interval.

In addition, our ECG measuring procedure took into consideration the information from all leads, which is usually considered the gold standard procedure, nevertheless, it should be emphasized that by using this method, QT intervals can be slightly longer than single lead values [17].

With these caveats in mind, we found an association of QTc interval prolongation with female gender, but only in individuals younger than 50 years [1,14-18], probably linked to the shorter QTc in men due to testosterone [19, 20]. The lack of correlation with electrolyte imbalances was an unexpected finding that probably relates to the low number of significant ion disorders in our sample. Even so, potassium levels were associated with QTc length in the multivariate analysis. We estimated a 2 to 3 fold QTc prolongation risk with well-known clinical factors (congestive cardiac failure, ischemic cardiopathy or diabetes) [21, 22]. We confirmed the risk of prolonged QT (4-fold) in patients with kidney failure. Some previously reported factors [10] showed limited association to a single criterion: arrhythmias (QTc > 450 /470 ms), bradycardia (Δ QTc > 60 ms) and hypothyroidism (Δ QTc > 30 ms), whereas other factors (hypertrophic cardiopathy, liver failure, central nervous system disease, hypoglycemia and obesity) did not associate at all. Strikingly, obesity did not induce QT prolongation; on the contrary, it did decrease the risk as assessed by all criteria: The reason is unknown and probably reflects the confounding effect of other factors, such as a lower dose per body weight, with an expected lower effect on QT interval.

We found an increased QT duration with 9 drugs previously reported as risky: clarithromycin [23], haloperidol [24, 25], tramadol [26], glyceryl trinitrate [27], piperacillin + tazobactam [28], cotrimoxazole [28], two dextropropoxyphene associations (with ibuprofen and metamizole) [29] and amiodarone [21].

We also found an increased QT duration during treatment with some drugs previously not reported as risky:

- Fentanyl (previously reported as safety [30] or even a protective effect [31]). We found short QTc prolongations (<460 ms) with significant Δ QTc only when using Δ QTcFra and Δ QTcH. Such effect could correspond to complex actions on ionic currents, similar to amiodarone [32] and need further research.
- Phenytoin showed significant differences in QTcB and Δ QTcB with no risk by any diagnostic criteria [33]. The relevance of this finding is unknown and indeed phenytoin even has been used for prolonged QTc treatment.
- Diazepam, omeprazole, vancomycin and enoxaparin showed small prolongation of Δ QTc (<30 ms) that do not seem clinically significant.

- Atorvastatin: showed prolonged QTcH and risk for Δ QTc > 30 and 60 ms. We suppose this finding to be secondary to its associated indication, such as ischemic cardiopathy.
- Ampicillin + sulbactam, amoxicillin + clavulanic acid, amoxicillin + sulbactam: these drugs, and piperacillin + tazobactam (previously reported) [28] showed higher QTc and Δ QTc values, risk to produce Δ QTc > 30 and 60 ms, and all are members of the same ATC group. The association between QTc duration >450/470 ms and these agents persisted after the multivariate analysis. Further research on this potential association is required.

QTc prolongation induced by drugs was reversible and did not persist in the after-treatment period (except with amiodarone, which is probably explained by its multi-compartmental kinetics and prolonged half-life).

Unexpectedly, dextropropoxyphene combinations induced slightly shorter intra-treatment QTc, and no QTc prolongation was found (except the metamizole combination by Δ QTcFri and Δ QTcFra > 30 ms criteria).

FDA agreed to withdraw all dextropropoxyphene products based on the results MAD study [29], a clinical trial involving two cohorts of healthy subjects that received oral dextropropoxyphene (either 600 or 900 mg/day, for 11 days) concluding that such doses prolong the QTc > 20 ms. At least from the methodological point of view, such design seems striking, since the maximal dose approved by the FDA was 600 mg per day, that is, subjects had to receive an overdose (apparently selected to simulate the physiological impairment common in the elderly) for more than a week to determine whether such overdose could be toxic. Besides these considerations, that study was the base for a regulatory decision very soon imitated by several other authorities all over the world, without a clear evidence of actual risk at the dose level commonly used in clinical practice. In addition, the risk of most probable alternatives is also unknown. At least in Argentina, dextropropoxyphene is a common and relatively economic option for pain treatment and Argentine regulators decided to gather local information about actual risk before taking a decision.

Upon ANMAT requirement, we increased the search for dextropropoxyphene-receiving patients and consequently, a high proportion of the patients reported herein (34.8%) were treated with this drug. Such high proportion is an overrepresentation, resulting from that search bias. Our data shows the utilization pattern of dextropropoxyphene, in doses that did not exceed 200 mg/day for a mean duration of 3 days. From our findings, it is clear that the modality commonly used in Argentina did not induce QTc prolongation. The main reason for the discrepancy between our results and those reported for the MAD study is probably the difference in dose (200 mg/d IV vs 600 or 900 mg/d per os) and the duration of treatment (3 days vs 11 days). The use of low doses (up to 200 mg/d IV for short periods) still seems to be a safe and economic option for acute pain treatment, mainly in low or middle-income countries. After more than 40 years of use in Argentina, pharmacovigilance reports concerning dextropropoxyphene are almost non-existent and a search performed by ANMAT in Vigibase [29,

34] in 2012 only retrieved 120 reports among which none proved causality. While spontaneous reporting system for suspected ADRs represents the cornerstone of the pharmacovigilance, this system also suffers of several limitations, mainly related to under-reporting [35].

From a drug safety point of view, QT-shortening is also quite interesting. Short QT syndrome (SQTS) is an inherited channelopathy associated with sudden cardiac death (SCD) [36-38]. QTc <350 ms in males or 360 ms in women is used as diagnostic criterion [13]. However, a consensus has yet to be established [39, 40]. None of the studied drugs showed a constant effect of shortening the QTc interval. Rather, the shortening was observed with some combinations of drugs (dextropropoxyphene plus methimazole but not plus ibuprofen) and only with some corrections (Fridericia, Framingham, Hodges). This behaviour could be the result of specific drug interactions or be a bias originated by correction formulas that tend to decrease the length of the QTc interval. We suggest that this possibility requires further study.

Our study has some limitations. One refers to the assessment of causality which is a discursive process of conjecture and refutation where causality cannot be fully demonstrated.

This study involved only five medical centres and we used non-continuous electrocardiograms to calculate the QTc interval at only three specific moments through a non-continuous approach. In addition, the exposure to some drugs may be under-reported.

In addition, the possibility of an effect of non-indicated drugs (such as medication used by patients at home and non-mentioned in the clinical record, or inadvertently administered to the patients) cannot be excluded, though the weight of such mistakes, if any, should be minimal, non-systematic and very unlikely to affect the analysis.

In conclusion, we found that QT interval prolongation in everyday practice is a frequent event (5-19%). We confirmed drugs frequently associated with QTc prolongation (clarithromycin, haloperidol, tramadol, glyceryl trinitrate, piperacillin + tazobactam, cotrimoxazole, two dextropropoxyphene associations and amiodarone) and identified other drugs that have not been previously reported (particularly beta-lactamase inhibitors). Further research on their potential risk and clinical implications is required

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This clinical and multicenter research was conducted by members of the "Centro de Vigilancia y Seguridad de Medicamentos" of the second chair of pharmacology of the school of medicine at the Universidad de Buenos Aires. The research was funded by grant from the Universidad de Buenos Aires (UBACYT No. 20020090200610).

PATIENT'S CONSENT

Declared none.

REFERENCES

- [1] Gupta A, Lawrence AT, Krishnan K. Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes. *Am Heart J* 2007; 153: 891-9.
- [2] Bauman JL, Bauernfeind RA, Hoff JV. Torsade de pointes due to quinidine: observations in 31 patients. *Am Heart J* 1984; 107: 425-30.
- [3] Zipes DP, Camm AJ, Borggreffe M, *et al.* ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006; 114: e385-e484.
- [4] Tisdale JE, Wroblewski HA, Overholser BR, Kingery JR, Trujillo TN, Kovacs RJ. Prevalence of QT interval prolongation in patients admitted to cardiac care units and frequency of subsequent administration of QT interval-prolonging drugs: a prospective, observational study in a large urban academic medical center in the US. *Drug Saf* 2012; 35(6): 459-70.
- [5] Drew BJ, Ackerman MJ, Funk M. On behalf of the American Heart Association acute cardiac care committee of the council on clinical cardiology, the council on cardiovascular nursing, and the American College of Cardiology Foundation. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* 2010; 21: 1047-60.
- [6] Mizia-Steć K, Mandecki T, Zahorska-Markiewicz B, Szulc A, Jastrzebska-Maj E, Szymański L. QT interval dispersion and the type of obesity in women. *Pol Arch Med Wewn* 1999; 101: 391-6.
- [7] Arslan E, Yiğiner O, Yavaşoğlu I, Özçelik F, Kardeşoğlu E, Nalbant S. Effect of uncomplicated obesity on QT interval in young men. *Pol Arch Med Wewn* 2010; 120: 209-13.
- [8] Galetta F, Franzoni F, Fallahi P, *et al.* Heart rate variability and QT dispersion in patients with subclinical hypothyroidism. *Biomed Pharmacother* 2006; 60: 425-30.
- [9] Shojaie M, Eshraghian A. Primary hypothyroidism presenting with Torsades de pointes type tachycardia: a case report. *Cases J* 2008; 1: 298.
- [10] Ponte ML, Keller GA, Di Girolamo G. Mechanisms of drug induced QT interval prolongation. *Curr Drug Saf* 2010; 5: 44-53.
- [11] Lou S, Michler K, Johnston P. A comparison of commonly used QT correction formulae: the effect of heart rate on the QTc of normal ECGs. *J Electrocardiol* 2004; 37: 81-90.
- [12] Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MC. QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Intern Med* 2007; 167: 2469-75.
- [13] Patel C, Yan GX, Antzelevitch C. Short QT syndrome: from bench to bedside. *Circ Arrhythm Electrophysiol* 2010; 3: 401-8.
- [14] Litwin JS, Kleiman RB, Gussak I. Acquired (drug-induced) long QT syndrome. In: electrical diseases of the heart genetics, mechanisms, treatment, prevention. Gussak I, Antzelevitch C (Eds). London, Springer-Verlag, 2008, 705-18.
- [15] Batchvarov VN, Ghuran A, Smetana P, *et al.* QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. *Am J Physiol Heart Circ Physiol* 2002; 282: H2356-63.
- [16] Stratmann HG, Kennedy HL. Torsades de pointes associated with drugs and toxins: recognition and management. *Am Heart J* 1987; 113: 1470-82.
- [17] Rautaharju PM, Surawicz B, Gettes LS, *et al.* AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part IV: The ST segment, T and U waves, and the QT interval: A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of

- Cardiology Foundation; and the Heart Rhythm Society: Endorsed by the International Society for Computerized Electrocardiology. *Circulation* 2009; 119: e241-50.
- [18] Hreiche R, Plante I, David LP, Simard C, Turgeon J, Drolet B. Impact of glucose concentration on cardiac ventricular repolarization under I Kr/I Ks blocking agents. *J Mol Cell Cardiol* 2009; 47: 210 -20.
- [19] James AF, Choisy SC, Hancox JC. Recent advances in understanding sex differences in cardiac repolarization. *Prog Biophys Mol Biol* 2007; 94(3): 265-319.
- [20] Charbit B, Christin-Maître S, Démolis JL, Soustre E, Young J, Funck-Brentano C. Effects of testosterone on ventricular repolarization in hypogonadic men. *Am J Cardiol*. 2009; 103(6): 887-90.
- [21] Taira CA, Opezzo JA, Mayer, Höcht C. Cardiovascular drugs inducing QT prolongation: facts and evidence. *Curr Drug Saf* 2010; 5: 65-72.
- [22] Burkett E, Keijzers G, Lind J. The relationship between blood glucose level and QTc duration in the critically ill. *Crit Care Resusc* 2009; 11: 8-13.
- [23] Cetin M, Yıldırım M, Ozen S, *et al.* Clarithromycin-Induced long QT syndrome: a case Report. *Case Rep Med* 2012; 2012: 634-52.
- [24] Beach SR, Celano CM, Noseworthy PA, *et al.* QTc prolongation, torsades de pointes, and psychotropic medications. *Psychosomatics* 2013; 54: 1-13.
- [25] Alvarez PA, Pahissa J. QT alterations in psychopharmacology: proven candidates and suspects. *Curr Drug Saf* 2010; 5: 97-104.
- [26] Emamhadi M, Sanaei-Zadeh H, Nikniya M, Zamani N, Dart RC. Electrocardiographic manifestations of tramadol toxicity with special reference to their ability for prediction of seizures. *Am J Emerg Med* 2012; 30: 1481-5.
- [27] Berger E, Patel K, Anwar S, Davies W, Sheridan DJ. Investigation of the effects of physiological and vasodilation-induced autonomic activation on the QTc Interval in healthy male subjects. *Br J Clin Pharmacol* 2005; 60: 17-23.
- [28] Poluzzi E, Raschi E, Motola D, Moretti U, De Ponti F. Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the US FDA Adverse Event Reporting System. *Drug Saf* 2010; 33: 303-14.
- [29] Food and Drug Administration [homepage on the Internet]. Multiple Ascending Dose (MAD) Study Review [updated 2011 Feb 01; cited 2011 Jul 07]. Available from: <http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientandproviders/ucm234330.pdf/>
- [30] Cafiero T, Di Minno RM, Di Iorio C. QT interval and QT dispersion during the induction of anesthesia and tracheal intubation: a comparison of remifentanyl and fentanyl. *Minerva Anestesiol* 2011; 77: 160-5.
- [31] Chang DJ, Kweon TD, Nam SB, *et al.* Effects of fentanyl pretreatment on the QTc interval during propofol induction. *Anaesthesia* 2008; 63: 1056-60.
- [32] Ponte ML, Keller GA, Di Girolamo G. Mechanisms of drug induced QT interval prolongation. *Curr Drug Saf* 2010; 5: 44-53.
- [33] Khan IA, Gowda RM. Novel therapeutics for treatment of long-QT syndrome and torsade de pointes. *Int J Cardiol* 2004; 95: 1-6.
- [34] ANMAT [homepage on the Internet]. Comunicado Acerca del principio Activo Dextropropoxifeno (in Spanish) [updated 2014 Jun 01; cited 2014 Jul 14]. Available from: <http://www.anmat.gov.ar/webanmat/Comunicados/2010/Dextropropoxifeno.pdf>.
- [35] Palleria C, Leporini C, Chimirri S, *et al.* Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. *J Pharmacol Pharmacother* 2013; 4: S66-72.
- [36] Gussak I, Brugada P, Brugada J, *et al.* Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 2000; 94: 99-102.
- [37] Gussak I, Antzelevitch C, Goodman D, *et al.* Short QT interval: ECG phenomenon and clinical syndrome. In: Gussak I, Antzelevitch C, eds. *Cardiac Repolarization. Bridging Basic and Clinical Sciences*. Totowa, NJ: Humana Press; 2003: 497-506.
- [38] Gussak I, Bjerregaard P. Short QT syndrome: 5 years of progress. *J Electrocardiol* 2005; 38: 375-7.
- [39] Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: proposed diagnostic criteria. *J Am Coll Cardiol* 2011; 57: 802-12.
- [40] Bjerregaard P. Proposed diagnostic criteria for short QT syndrome are badly founded. *J Am Coll Cardiol* 2011; 58: 549-50.

Received: July 7, 2015

Revised: October 17, 2015

Accepted: November 2, 2015