ORIGINAL ARTICLE

Dextrophropoxyphene effects on QTc-interval prolongation: Frequency and characteristics in relation to plasma levels

Guillermo Alberto Keller, MD, PhD; Cecilia Villa Etchegoyen, MD; Nicolás Fernandez, PharmD, PhD; Nancy Mónica Olivera, PharmD, PhD; Patricia Noemí Quiroga, PharmD, PhD; Roberto Alejandro Diez, PhD; Guillermo Di Girolamo, MD, PhD

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ABSTRACT

Objective: *To evaluate frequency and risk factors for dextropropoxyphene-induced QT-interval prolongation in the clinical setting.*

Design: *Prospective, noninterventional, observational, longitudinal cohort approach. Electrocardiograms were blindly evaluated by independent professionals.*

Setting: *General ward of a public hospital of metropolitan Buenos Aires.*

Patients, Participants: *Ninety-two patients with indication of receiving dextropropoxyphene for analgesic purposes were included consecutively. All patients finished the study.*

Interventions: *All patients were monitored with electrocardiographic controls (previous to drug administration and during steady state) to diagnose and quantify changes in the duration of the QTc interval.*

Main Outcome Measure: *Frequency of drug-induced QTc interval prolongation, QTc interval correlation with plasma drug, and metabolite levels.*

Results: *Ninety-two patients were studied (50 percent males). All patients received a (mean ± SD [range]) dextropropoxyphene dose of 125 ± 25[100-150] mg/d. Dextropropoxyphene and norpropoxyphene concentrations were 112 ± 38[45-199] and 65 ± 33[13-129] ng/mL, respectively. The intra-treatment QTc interval was >450 ms in only one patient (only with the Hodge correction). There were no cases of QTc > 500 ms, and there were no significant differences in the results considering different correction formulas (Bazzet, Fridericia, Framingham, Hodges). Dextropropoxyphene concentrations correlated with QTc (R > 0.45) interval and ΔQTc (R 0.52-0.87), whereas norpropoxyphene correlation was even greater for QTc (R > 0.40-0.64) and ΔQTc (R > 0.47-0.92). Depending on the QTc correction formula, eight patients presented ΔQTc > 30 ms and one patient with ΔQTc > 60 ms. No patient presented arrhythmia during the study.*

Conclusions: *The authors did not observe a relationship between dextropropoxyphene and QTc interval prolongation at the therapeutic doses used in Argentina.*

INTRODUCTION

Drug-induced QT interval prolongation and *torsade de pointes* (TdP) are common causes for the withdrawal or restriction of the use of drugs.[1] Many opioid drugs lengthen cardiac repolarization (QT-interval prolongation) in clinical reports or in vitro studies. QT-interval prolongation or TdP has been reported with L-α-acetylmethadol,[2] methadone,[3-8] dextropropoxyphene (DXP),[9] meperidine,[10] and oxycodone.[11] Human ether-a-go-go related gene (hERG) potassium channels blockade studies suggest a QT-prolongation risk for codeine, buprenorphine, and fentanyl.[12] These data led us to consider

QT prolongation could be a class problem with several opiates[13,14] or even other analgesic drugs.[15,16]

Propoxyphene is a synthetic diphenyl heptane analgesic with structural similarity to methadone. D-propoxyphene isomer possesses analgesic activity,[17] whereas the L-propoxyphene isomer possesses antitussive activity.[18] The analgesic effects of (DXP) were considered "weak," but the benefit/risk ratio was considered appropriate for several years since it also lacked strong addictive properties. Propoxyphene has a half-life of 6-12 hours.[19] The toxicity of propoxyphene is attributed to its major metabolite, norpropoxyphene (NPX),[20] produced through CYP3A4 and to a lesser extent by CYP2D6.[21-23] NPX lacks any opioid activity and presents a slightly greater local anesthetic effect.[20,24] It is subjected to renal and biliary excretion with a half-life of 30-36 hours.[19,20] It has been proposed that the accumulation of NPX contributes to central nervous system (CNS) depression, cardiac arrest, and respiratory depression and death[25] after propoxyphene administration. Regarding the mechanism of action,[26] the affinity to μ and δ receptors is similar to codeine and lesser than morphine and L-methadone, with no κ activity. Propoxyphene is not only an opiate receptor ligand, but also a sodium channel blocker, potassium channel modulator (involved in cardiac repolarization), noncompetitive antagonist for nicotinic receptor ($\alpha 3\beta 4$), and a noncompetitive antagonist for *N*-methyl-D-aspartate receptor.[24]

Propoxyphene and NPX (greater for the metabolite) produce dose-dependent negative inotropic effects in vitro.[27,28] Additionally, an inhibition of muscle tension was also demonstrated.[28] US label allows a maximal daily dose of 390-600 mg, whereas death cases have been reported within the therapeutic range, with no identifiable lethal threshold.[29]

In Xenopus oocytes transfected with human ether-a-go-go-related gene (hERG) K^+ channels,[30] low concentrations (5 μmol/L) of propoxyphene and NPX facilitated hERG currents, while higher drug concentrations blocked hERG currents (IC50 ~40 μmol/L). Based on human case reports, QRS widening is more common than QT prolongation; consistent with this interpretation, in a prospective, observational, longitudinal cohort study, we found only scarce cases of QT prolongation among patients administered with DXP.[31] A multiple ascending dose (MAD) study to evaluate the effects on cardiac electrophysiology among healthy volunteers[32] revealed that both 600 and 900 mg doses were associated with significant QTc interval prolongation with a dose-dependent prolongation of PR and QRS intervals. Based on these findings, the FDA advisory committee voted by a narrow margin (14 to 12) against the continued marketing of propoxyphene products in 2010.[33] Similar decision was adopted by other countries (Australia, Canada, European Union, New Zealand, and the United Kingdom)[32,34,35] based on its implication in overdose-related deaths, its impact on cardiovascular electrophysiology, and concerns regarding its analgesic efficacy.

However, the decision to withdraw DXP has received some criticism[36,37] as evidence to support withdrawal is limited and the relationship between the overdose-related deaths and the shift to other drugs has not been extensively studied. Following DXP ban, a major reduction in poisoning deaths has been reported in some countries,[38] as was the number of deaths associated with DXP/acetaminophen combination poisoning, with no compensatory rise in mortality from poisonings by other common analgesics,[39] though the lack of a control group hinders appropriate comparison. Also, fatal toxicity index has been reported to be inappropriate.[36] Additionally, the withdrawal failed to lower overall mortality due to suicides despite a reduction of DPX related suicide rate.[40,41]

After FDA and EMA regulatory measures, the Argentine regulatory agency (Administración Nacional de Medicamentos Alimentos y Tecnología Médica) decided to initiate a specific surveillance program but did not withdraw DXP products. The rationale for this measure included the absence of reports of adverse cardiovascular effects in Argentina, the absence of recorded cases of poisoning, and the recommended maximum dose in the country (200 mg/d below the 600 mg maximum dosage granted in other countries and to the 600-900 mg used in the MAD study[42] in which were detected cases of about 29.8-38.2 ms of QTc interval prolongation). The condition of sale for propoxyphene in Argentina is "prescription-only medicine": the product is considered a narcotic; commercial presentations may not contain units for more than 10 days of treatment (except hospital presentations) and is not allowed to supply free commercial samples.

The aim of our study was (i) to evaluate the effect of propoxyphene on QT interval in our clinical practice, (ii) to describe the relationship between plasma concentration of propoxyphene and NPX (its metabolite) with the QT-interval duration, and (iii) to elucidate the mechanism (including medical

history, laboratory, or other circumstances) leading to QT prolongation associated to propoxyphene administration.

MATERIALS AND METHODS

Population and sample

The study population corresponds to Argentinean patients receiving intravenous DXP treatment at a public hospital of metropolitan Buenos Aires. This study used a prospective, noninterventional, observational, longitudinal cohort approach to evaluate DXP-induced QTc interval prolongation prevalence, risk factors, and characteristics in the common clinical settings of metropolitan Buenos Aires medical centers. All cases corresponded to inpatients. 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 of the hospital, in agreement with the Declaration of Helsinki (revised, Fortaleza 2013) and the Good Clinical Practice guidelines.

All patients were included consecutively if they met the inclusion criteria: (1) older than 18 years; (2) treated exclusively at the participating health center; (3) having an indication of repetitive administration of DXP for pain, during a time that allows reaching the steady state (3 d); (4) Be admitted during a time that allows for the electrocardiographic monitoring of QTc interval before and during the treatment (at steady state: ~3 d).

Exclusion criteria were (1) indication of any concomitant drug treatment; (2) lack of conditions allowing monitoring during the steady state (five half-lives, ~3 d); (3) Basal QTc interval >450 ms (males) or >470 ms (women). All patients were interviewed, registering age, vital signs, gender, weight, height, body mass index, comorbidities predisposing to QT-interval prolongation (obesity,[42,43] hypothyroidism,[44,45] CNS disease, renal and/or liver failure, diabetes, arrhythmias of ventricular origin, amyloidosis, and other conditions that may predispose to QT prolongation[46]), other drugs that patients were receiving (with special attention to drugs that could have pharmacokinetic interactions with DXP), 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.

Electrocardiographic controls

Two electrocardiographic controls, at (1) baseline and (2) intra-treatment, were carried out to all patients included in the study. All electrocardiograms were performed with three-channel ECG equipment and consisted of 12-lead registries with additional long DII record (ECG strip performed on DII lead for at least 10 s) 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 the first dose of DXP. The second electrocardiogram was performed after 3 days of the first DXP administration, taking into account the theoretical half-life (t1/2 β) of the indicated drug to reach plasma steady state. All electrocardiograms were performed on morning hours (8:00-10:00 AM) to ensure equal conditions of the QTc-interval respect to the circadian cycle.

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 three 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 (R′). The heart rate (HR) was calculated in each electrocardiogram as: $HR = 60 \times 1{,}000/RR'$. Given the apparent differences between correction formulas, the QT interval was corrected by HR using[47]: (1) Bazzet (QTcB) = $QT/RR'^{(1/2)}$; (2) Fridericia (QTcFri) = $QT/RR'^{(1/3)}$; (3) Framingham (QTcFra) = $QT + 154 \times [1 - (60/HR)]$; and (4) 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.

QTc interval prolongation criteria

Given the discrepancies about how to define QTc prolongation, we assessed four independent criteria.[48] QTc prolongation was defined as: (1) absolute value of QTc interval >450 ms (males) or >470 ms (women); (2) ΔQTc >30 ms; (3) absolute value of QTc interval >500 ms; and/or (4) ΔQTc >60 ms.

Laboratory controls

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

DXP and NPX quantification

Analytical standards of propoxyphene (PXP), NPX, and their deuterated analogs (DPX-d5, NPX-d5) were purchased from Cerilliant Analytical Reference Standards (Round Rock, TX) in solution at 1 mg/mL. Solid phase extraction cartridges Clean Screen® (CSDAU 303) were obtained from United Chemical Technologies (Bristol, PA) and vacuum manifolds was obtained from Varian (Lake Forrest, CA). Chromatographic analysis was performed using an HP6890N gas chromatograph (Hewlett-Packard), equipped with a model 5973 mass-selective detector (GC Hewlett-Packard 6890-MS Agilent Technologies 5973 Network, Palo Alto, CA). Chromatographic separation was achieved on an HP-5MS fused-silica capillary column (5 percent-phenyl-methylpolysiloxane, 30 m × 0.25 mm × 0.25 µm film thickness) (J&W Scientific, Folsom, CA). Plasma samples (500 µL) were treated with a strong alkali hydroxide to form NPX amide and extracted using solid phase extraction. The recovery of the procedure was >81 percent. Quantitation was done in the selected ion monitoring (SIM) mode, the ions were monitored at m/z 178,193, and 250 for propoxyphene and at m/z 220, 234, and 235 for norpropoxiphene amide, (quantitation ions are underlined). For the internal standards, only one ion was monitored for each compound, at m/z 255 propoxyphene -*d5* and at m/z 240 for norpropoxiphene amide -*d5*. Calibration curves were prepared by spiking blank plasma with corresponding analytical solution to obtain calibration concentration of 25, 100, 200, 400, 600, 800, and 1,000 ng/mL. Limits of quantification was 25 ng/mL, with linear response over the range 25-1,000 ng/mL and correlation coefficients >0.999. Data were acquired and analyzed using Agilent Enhanced ChemStation G1701DA software. Each specified ion was automatically selected and peak abundances determined. The acceptance criteria for compound identification were according to the World Anti-Doping Agency (WADA 2011).[49]

Confidentiality and end of participation

The participation of the subjects was considered as concluded when the electrocardiogram was recorded and blood samples were collected during the treatment. 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 without personal data that allow for patient identification (to ensure anonymity of patients).

Statistical analysis

Categorical variables (gender, presence of a clinical factor for QTc prolongation) are presented as percentage. Normality of variables was determined by using normal probability plots. Continuous variables (age, weight, height, body mass index, laboratory results, and ECG parameters) were characterized by mean ± SD and range (minimum-maximum) and analyzed by Student's *t* test. Association between electrocardiographic parameters and numerical variables (age, weight, height, body mass index, laboratory results, and ECG parameters) was analyzed by Pearson correlation. All the statistical analyses were performed with Statistica v.6 (StatSoft, Inc. Tulsa, OK). $p < 0.05$ (two tailed) were considered as significant.

RESULTS

Clinical characteristics of the sample

Between August 2013 and January 2014, 92 patients were studied, including 46 (50.0 percent) females and 46 (50.0 percent) males. The age, expressed as mean ± SD (min-max), was 67 ± 13 years, (41-89), whereas the weight was 71 ± 14 kg

(51-99), and height, 168 ± 8 cm (151-182). The body mass index was 25.10 ± 4.00 kg/m^2 (17.71-33.56).

Patients presented a history of obesity in 30 cases (62.0 percent of the whole sample), congestive heart failure (11, 12.0 percent), renal failure (11, 12.0 percent), arrhythmia (10, 10.9 percent), ischemic cardiomyopathy (8, 8.7 percent), diabetes (7, 7.6 percent), CNS diseases (6, 6.5 percent), hypertrophic cardiomyopathy (4, 4.3 percent), and hypothyroidism (3, 3.3 percent). No cases of amyloidosis, bradycardia, liver failure, or hypothermia were detected. Since clinical factors have independent distribution, one or more factors were simultaneously present in 57 patients (62.0 percent); on the other hand, 35 patients (38.0 percent) had no clinical factors for QTc prolongation.

At intra-treatment controls (electrocardiogram, electrolyte analysis, and plasma drug level) all patient had received DXP at a total dose of 125 ± 25 (100-150) mg/d during 8.5 ± 4.4 (3.0-25.0) days. The dose corrected by body mass was 1.83 ± 0.55 (1.01-2.88) mg/kg. DXP indications included cases of post-polytrauma and/or fracture pain (most cases corresponded to traumatology inpatients).

Electrolyte analysis and plasma drug levels

At baseline, ion concentrations, in mEq/L, were sodium 137 ± 5 (130-146), potassium 4.4 ± 0.8 (3.0-5.7), and ionized calcium 4.8 ± 0.6 (4.0-5.7). Corresponding values at intra-treatment evaluation were sodium 139 ± 5 (130-146), potassium 4.2 ± 0.8 (3.0-5.7), and ionized calcium 4.9 ± 0.5 (4.0-5.7).

Plasma concentrations of DXP and NPX were 112 ± 38 (45-199) ng/mL and 65 ± 33 (13-129) ng/mL, respectively. DXP and NPX concentrations were slightly superior in subjects with renal failure history, but these differences did not reach statistical signification (p = 0.10 for DXP and p = 0.24 for NPX).

Electrocardiographic parameters and QTc interval prolongation

Electrocardiographic parameters are shown in Table 1. Cases of prolonged QTc-interval were detected by ΔQTc and listed in Table 2 according to the different correction formula and criteria for prolongation. A histogram of resulting ΔQTc according to each formula is shown in Figure 1. There were no cases of QTc >500 ms, and only one patient presented an intra-treatment QTc interval prolonged (a male with QTc = 450 ms only with Hodges correction).

No significant difference was found among the four correction formulas. While the use of Bazzet correction formula showed a mean QTc value

Table 1. Electrocardiographic parameters at baseline and intra-treatment period expressed in milliseconds

	Mean	SD	Range	
			Min	Max
Basal				
R-R′	841	173	520	1,120
QT	392	43	300	460
QTcB	429	6	416	440
QTcFri	416	17	373	446
QTcFra	416	17	374	445
QTcH	418	14	394	450
Intra-treatment				
R-R′	807	165	520	1,100
QT	384	42	300	460
QTcB	430	7	416	442
QTcFri	414	17	373	446
QTcFra	414	17	374	445
QTcH	415	13	396	450
ΔQTcB	0	10	–24	+22
ΔQTcFri	–2	24	–67	+64
ΔQTcFra	–2	24	–66	+63
ΔQTcH	–2	20	–46	+42

Table 2. Number of cases of prolonged ΔQTc according to diferent correction formula

	ΔQTc > 30		ΔQTc > 60	
	N	Percentage	N	Percentage
QTcB	0	0.00	0	0.00
QTcFri	8	8.70	1	1.09
QTcFra	7	7.61	1	1.09
QTcH	6	6.52	0	0.00

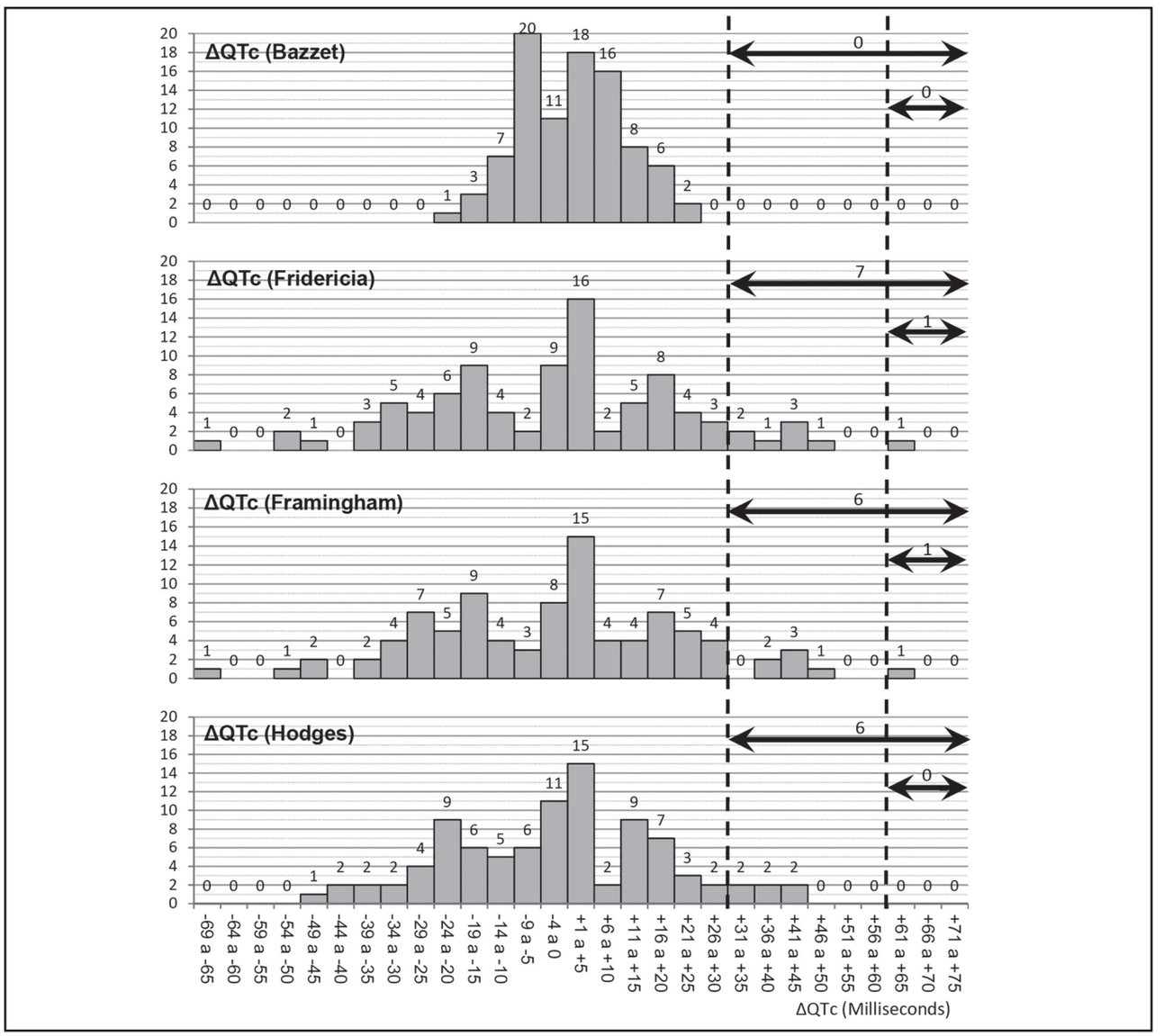

Figure 1. Histogram of ΔQTc distribution according to QTc correction formula employed.

slightly greater, with lower standard deviation and a more leptokurtic distribution, there were no statistically significant differences when compared with the other corrections like Fridericia (p = 0.21), Framingham (p = 0.22), and Hodges (p = 0.12).

QTc interval calculated with the four correction formulas presented low correlation with weight-adjusted dose (R < 0.10), but high correlation with plasma DXP (R[Bazzet] = 0.45, R[Fridericia] = 0.64, R[Framingham] = 0.64, R[Hodges] = 0.65) and NPX concentrations (R[Bazzet] = 0.40, R[Fridericia] = 0.62, R[Framingham] = 0.62, R[Hodges] = 0.64). ΔQTc interval showed a low correlation with weight-adjusted dose (R < 0.10), and very high correlation with plasma DXP (R[Bazzet] = 0.52, R[Fridericia] = 0.86, R[Framingham] = 0.85, R[Hodges] = 0.87) and NPX concentrations (R[Bazzet] = 0.47, R[Fridericia] = 0.92, R[Framingham] = 0.92, R[Hodges] = 0.91).

QTc interval prolongation for different clinical risk factors

The relative risk for presenting QTc prolongation among different parameters (age, vital signs, gender, weight, height, body mass index) and history factors (obesity, hypothyroidism, CNS disease, renal failure, liver failure, diabetes, cardiac arrhythmias of ventricular origin, amyloidosis, others concomitant

administered drugs) was analyzed. There was no significant risk of QTc prolongation independently of the QTc prolongation criteria and the chosen correction formula for all analyzed factors.

Causality assessment

All cases of ΔQTc prolongation were analyzed according to WHO–UMC causality assessment system as "possible," since all cases complied with: (1) event with reasonable time relationship to drug intake, (2) without any other explanation by disease or other drugs, and (3) information on drug withdrawal may be lacking (indeed there is no information regarding what has happened after stopping DPX). The use of Adverse Drug Reaction Probability Score (Naranjo Scale) showed a final score of [+6] corresponding to "probable" category ([+1] there are previous conclusive reports, [+2] the adverse event appear after the suspected drug was administered, [+2] there are no alternative causes, and [+1] the adverse event was confirmed by objective evidence).

Cardiac arrhythmias and clinical events

No patient had evidence of cardiac arrhythmia, ventricular tachycardia, TdP, and/or sudden death during the present study. Therefore, arrhythmogenic risk associated with different factors and/or drug administration could not be estimated.

Clinical outcomes of benefit of using dextrophropoxyphene

The evaluation of analgesic efficacy was not an objective of this study. However, it should be noted that all patients received similar doses of DXP, and there were no reports of lack of efficacy (pain) requiring additional doses, increase of regular dose, and/or additional medications. All included patients reported adequate pain management with the administered dose.

DISCUSSION

Despite the long discussion on the cardiovascular safety of dextrophropoxyphene and the postmarketing data suggesting cardiac toxicity risk, no clinical trial has been conducted in common clinical settings at therapeutic doses. Moreover, given that the recommended dose in Argentina was lower than in other countries, and that the MAD study[34] used much higher doses, the present study seems to be the first to evaluate the effects of DXP use in common clinical practice on QTc interval prolongation. We found a more complex association between QT interval and plasma concentrations of propoxyphene and its metabolite than the previously described. Our methodology is characterized by using standard electrocardiograms to estimate QTc prolongation and multiple QT interval correction: Bazzet (commonly used), Fridericia (preferred by regulatory authorities), Framingham, and Hodges, since various formulas have been reported to be inaccurate[50] or involved in biased correction-specific QT effects (ie, oxycodone and QTcF)[12]; however, the included patients had normal HRs, without extreme values where the sensitivity and specificity of correction formulas vary, and therefore, we found no significant differences between QTcB, QTcFri, QTcFra, and QTcH.

Although we did not find cases of arrhythmia, QT is only a surrogate for TdP, and the same QT prolongation induced under two different circumstances can bear a different risk of TdP.[51] Our population had no electrolyte disturbances or altered HR and was strictly controlled in the hospital.

Drug-induced QT prolongation is associated with blocking the hERG channel, which inhibits the rapidly activating delayed rectifier potassium current (Ikr).[52] Taking into account, its chemical structure seems plausible that DXP interact with the two aromatic amino acid side-chains in the pore region (Tyr652 and Phe656).[53] Basic[32] and clinic[32,34] evidences support this possibility. A VigiAccess search shows that 6552 propoxyphene-related adverse drug events have been reported. Among them, 3836 (59 percent) correspond to the MedDRA system and organ class (SOC) known as "cardiac disorders," including 978 cases of ventricular arrhythmias and cardiac arrest (183 cardiac arrest, 770 cardio-respiratory arrest, only one TdP, one ventricular arrhythmia, 13 ventricular extrasystoles, 13 ventricular fibrillations, and 13 ventricular tachycardia).[54]

The observed correlation between ΔQTc and plasma concentrations of propoxyphene and NPX not only maintains linearity at the upper segment (high concentrations lead to prolongation of the QTc interval), but also at the lower segment of concentrations (lower quantities of drug are accompanied by decrease of the QTc interval). This observation, which may initially appear disconcerting, are

consistent with a previous in vitro study in which low concentrations of propoxyphene and NPX facilitated hERG currents whereas higher drug concentrations blocked hERG currents.[32] Additionally, the FDA in its Recommendation on a Regulatory Decision for Propoxyphene-containing products used a complex model with ΔQTcF (in which QTc is compared with basal value and placebo treatment) showing cases of decreased QTc with the low concentrations.[34] However, the shortening of QTc interval, far from being able to have a "protective" role, has been linked also to risk of arrhythmia, like the prolongation of the QTc interval.[55] In the present study, there was only one case of QTc-interval prolongation diagnosed by an absolute QTc value prolongation (a value close to normal 450 ms in a male) and no QTc prolongation cases were detected using Bazzet correction, but we found a statistically significant difference between intra-treatment values and QTc at baseline, suggesting ΔQTcFri is the best diagnostic parameter.

Crude WHO–OMS causality-assessment resulted in a "possible" status, although cases appear to have a stronger evidence of causality when also considering some of the Bradford Hill criteria[56] biological gradient (ΔQT correlates with DPX and NPX plasma concentration), plausibility (previously demonstrated),[32-34] coherence (the observed effect of DXP on QT does not contradict current knowledge), and analogy (respect to opiates like morphine and heroine). This stronger evidence support going one step "higher" (eg, from "possible" to "probable"),[57] which is consistent with the result obtained with the Naranjo Scale. Strong ΔQTc/plasma drug concentration correlation suggests (in absence of other known causes) a typical cause-effect relationship.

Considering the low number of cases of prolonged QT interval detected in our study, the complex correlation between ΔQT concentrations (with even QT-interval shortening effect at low concentrations), and the frequency of different adverse reactions in VigiAccess, it seems correct that although propoxyphene is associated with a cardiovascular risk, this is not related to a classic effect of QTc prolongation. On the other hand, the local casuistry (low frequency of reports) and the effects observed at these concentrations could justify their lower risk at the doses suggested in Argentina (<200 mg/d), although the therapeutic benefit should still be assessed; this issue was not evaluated in the present study. All this information is important since reconsideration for propoxyphene ban has been proposed,[58] based on the low cost of this drug, an apparent lower risk of addiction, low incidence of adverse reactions in other countries, and absence of frequent use for suicide (except in United Kingdom and North America). Additionally, this drug is an old opioid and opioid access is a problem in developing countries, especially for strong opioids. Maintaining, in the pharmacopoeia, this agent that is familiar to physicians may allow more patients access to cancer pain treatment.

Our study has interesting characteristics such as evaluating real patients in a clinical setting with current recommended doses, after reaching steady state. This approach contrasts with the anecdotic toxicity reports, in which high plasma concentrations of any drug could induce unspecific blockade of several channels. Additionally, it shows a low frequency of prolongation of the QTc interval, which, when present, were small, and the absence of arrhythmias, at the therapeutic doses used in Argentina. Interestingly, this study is the first to find evidence of shortening the QTc interval with lower doses in the clinical settings, which is consistent with previous experimental evidence, providing additional information on the safety profile and correlation of the QTc interval with plasma concentrations.

Noteworthy, our study has also some limitations. We used noncontinuous electrocardiograms to calculate the QTc interval at only two specific moments through a noncontinuous approach. The lack of dechallenge and rechallenge data was a limitation in causality assessment.

CONCLUSIONS

The main conclusion is that we did not observe a relationship between DXP and QTc-interval prolongation at the therapeutic doses used in Argentina. Propoxyphene concentration correlates with QTc interval, with a complex relationship, best diagnosed using Fridericia correction and comparing QTc interval to basal ECG (ΔQT).

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Guillermo Alberto Keller, MD, PhD, Universidad de Buenos Aires, Facultad de Medicina, Departamento de Toxicología y Farmacología, Centro de Vigilancia y Seguridad de Medicamentos, Buenos Aires, Argentina; Emergency Department, Hospital General de Agudos Donación Francisco J. Santojanni, Buenos Aires, Argentina.

Cecilia Villa Etchegoyen, MD, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Toxicología y Química Legal, Centro de Asesoramiento Toxicológico Analítico (CENATOXA), Buenos Aires, Argentina.

Nicolás Fernandez, PharmD, PhD, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Toxicología y Química Legal, Centro de Asesoramiento Toxicológico Analítico (CENATOXA), Buenos Aires, Argentina.

Nancy Mónica Olivera, PharmD, PhD, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Toxicología y Química Legal, Centro de Asesoramiento Toxicológico Analítico (CENATOXA), Buenos Aires, Argentina.

Patricia Noemí Quiroga, PharmD, PhD, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Toxicología y Química Legal, Centro de Asesoramiento Toxicológico Analítico (CENATOXA), Buenos Aires, Argentina.

Roberto Alejandro Diez, PhD, Universidad de Buenos Aires, Facultad de Medicina, Departamento de Toxicología y Farmacología, Centro de Vigilancia y Seguridad de Medicamentos, Buenos Aires, Argentina.

Guillermo Di Girolamo, MD, PhD, Universidad de Buenos Aires, Facultad de Medicina, Departamento de Toxicología y Farmacología, Centro de Vigilancia y Seguridad de Medicamentos e Instituto de Investigaciones Cardiológicas "Prof. Dr. Alberto C. Taquini", Buenos Aires, Argentina.

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