Dextropropoxyphene induced QTc interval prolongation: A multicenter trial to study his prevalence and clinical relevance of the usual doses approved in Argentina

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Introduction: QT interval prolongation by dextropropoxyphene is a topic of current debate. Recently, the European Medicines Agency and the Federal Food & Drug Administration not recommended its use. This has resulted in the market recall in some countries. In Argentina, the national agency database does not have any notification of adverse effects with dextropropoxyphene associations. The purpose of this study was to determine the prevalence and importance in daily clinical practice of the usual doses approved in our country in the QTc prolongation by dextropropoxyphene.

Patients and Methods: Patients from 4 hospitals, carriers of acute pain consulting in guard and those from the immediate postoperative of abdominal or trauma surgery were enroled. All patients underwent an electrocardiogram (ECG) in three times: basal, after at least 24 hours following the start of intravenous infusion of dextropropoxyphene and after at least 24 hours of the end of the infusion. The QT was quantified in ms and corrected by Bazett's formula.

Results: We evaluated 354 patients (56.5% male) with a mean (range) age of 46 (15-93) years. All patients received dextropropoxyphene with an average dose of 107 mg (50-392) per day for an average of 3 days (1-8 days). In the study population, risk factors for QT interval prolongation were identified such as: [predisposing factor, number of patients (percentage of the population presented)]: Obesity 95 (26.83%), arrhythmias 22 (6.21%), diabetes 19 (05.36%), ischemic cardiomyopathy 14 (3.95%), congestive heart failure 7 (1.97%), central nervous system diseases 12 (3.38%), hypertrophic cardiomyopathy 10 (2.82%), hypothyroidism 6 (1.69%), hypoglycemia 13 (3.67%), renal failure 10 (2.82%), liver failure, 7 (1.97%), and bradycardia 5 (1.41%).

Before the start of treatment they have mean values (SD, range) of R-R' 823 (174, 320-1400) ms, heart rate (HR) 76 (18, 43-188) bpm, QT 377 (43, 260-460) ms, and QTc 418 (26; 306-509) ms. After the start of the drug the following mean values were observed: RR' 811 (190, 320-1120) ms, HR 78 (21, 53-188) bpm, QT 385 (48, 260-460) ms, and QTc 430 (17, 379-508) ms. Following the suspension of the drug: RR' 829 (166, 500-1400) ms, HR 75 (16, 43-120) bpm, QT 373, 39 (280-460) ms, QTc 413 (28, 306-509) ms. The mean (SD; range) change in QTc between treatment and baseline period (ΔQTc) were +4 ms (23, -107 to 124).

Taking into account the absolute value of QTc, 117 (33%) patients had prolonged QTc (greater than 450 ms in men or 430 women), including 2 cases (0.56%) of QTc greater than 500 ms . Considering the ΔQTc, 74 individuals (20.90%) had ΔQTc greater than 20 ms dQTc, being only 8 cases (2.26%) greater than 50 ms.

In all cases the QT prolongation was completely asymptomatic, mild, without evidence of seriousness and resolved spontaneously. No patient had symptoms related to arrhythmias or other clinically significant result.

An analysis of the background history and complementary studies of the enrolled individuals for risk factors of QTc interval prolongation was done. Obesity (RR 1.4, CI 1.06-1.86), diabetes (1.59, 1.02-2.49), ischemic cardiomyopathy (1.73, 1.08-2.78), central nervous system diseases (1.76, 1.07-2.90), and liver failure (2.16; 1.33-3.52) were identified as risk factors for QTc prolongation detected as an absolute value greater than 430 ms in men and 450 ms in womens. Heart failure (25.29, 1.75-364.74) and renal failure (17.70, 1.19-263.27) were identified as risk factors for a QTc greater than 500 msec. A history of diabetes was associated with a higher risk (4.66, 1.01-21.56) of delta QTc greater than 50 msec. We identified no statistically significant risk factors for presenting delta QTc greater than 20 msec.

Conclusion: These results support that although the dextropropoxyphene has a very slight tendency (not significant from a statistical point of view) to prolong the QTc (+4 ms), this effect has no clinical relevance at the doses used in everyday clinical practice in Argentina.