WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 16, 97-103. Research Article ISSN 2277–7105

THE EFFECT OF ORAL DOMPERIDONE ON QTC INTERVAL IN INFANTS AND CHILDREN

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Article Received on
10 Oct. 2017,

Revised on 30 Oct. 2017,
Accepted on 20 Nov. 2017,

DOI: 10.20959/wjpr201716-10185

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ABSTRACT

Domperidone is commonly used in pediatrics, it is accused to be one of the causes of long QT syndrome which can lead to death. Lot of studies have been done to evaluate its cardiac safety. The aim of this study was to evaluate the effect of domperidone on QT interval, this study is a prospective case control study which was done on 100 patients aged from 3 months to 5 years coming to Alexandria University Children's hospital, 50 cases received domperidone for 7 days or more while other 50 cases did not. Electrocardiogram was done to all patients and QTc interval was measured using Bazett's formula. The results showed that 8% of cases showed prolongation of QTc interval ≥ 0.45 ms, after one week of domperidone stoppage, QTc interval normalized. Overall, this study showed no statistically significant difference in QTc duration induced by domperidone. However, domperidone cardiac safety cannot be ensured.

KEYWORDS: Domperidone, Long QT Syndrome, Arrhythmia, Pediatric.

INTRODUCTION

Long QT syndrome is one of the most important causes of arrhythmia that can cause syncopal attacks and even death in pediatrics.[1] Long QT syndrome is considered if QTc interval measured is ≥ 0.45 sec.[2] A standard 12-lead ECG tracing at 25 mm/sec paper speed at 10 mm/mV amplitude is generally adequate for accurate measurement of QT-interval duration.[3,4] Lead II is generally the best single lead for measuring QT interval because the T wave ending is usually discrete and the QT interval obtained from lead II has a good correlation with the maximal QT measured from the 12-lead ECG.[5]

The normal values for the QT interval depend on the heart rate.[6] Numerous methodologies for correcting QT intervals for heart rate have been proposed, but the most universally utilized method is that described by Bazett in 1920. QTc interval is measured using Bazett formula which is obtained by dividing the actual QT interval by the square root of the RR interval, $QTc = QT / \sqrt{RR}$ where the QT interval is the interval from the beginning of the QRS complex to the end of the T wave and the R-R interval is the interval from the peak of QRS complex to the peak of the next one.[7-9]

Long QT syndrome can be congenital or acquired, it can be caused by many drugs, electrolyte disturbances, cardiac, metabolic, C.N.S causes and toxins.[10,11] Long QT syndrome can be asymptomatic or can come presenting with dizziness, syncope (60%), seizures (40%) and even up to sudden cardiac death.[12]

Domperidone was found to be one of the most important causes of long QT syndrome.[11] Experimental studies were carried out by Drolet et al[13] showed that Domperidone can prolong cardiac repolarization in a reverse rate-dependent manner by blocking the cardiac potassium current (IKr: rapidly activating delayed rectifier K^+ current). Excessive IKr block may lead to triggered tachyarrhythmia and sudden death, the study by Drolet et al. provided an explanation for QT prolongation and ventricular tachyarrhythmia during Domperidone treatment.[13,14]

So after this study, Domperidone was suggested to be associated with acquired long QT syndrome.[15] The aim of the work was to assess the effect of Domperidone on QTc interval in children receiving Domperidone at Alexandria University Children Hospital.

MATERIAL AND METHODS

A sample size of 50 patients was estimated enough required sample to detect a null value of 0.5 as statistically significant with 80% power. Sample size was calculated using MedCalc Statistical Software version 12.2.1.0.[16]

This was designed as a prospective case-control study including 100 cases, 50 cases were receiving domperidone at 0.3mg/ kg/ dose for at least 7 days, all patients who received other interacting drugs or electrolytes affecting ECG were excluded and any case with family history of prolonged QTc interval or any medical condition that causes prolongation of QTc

interval was again excluded. The other 50 cases did not receive domperidone. The sample was selected and allocated randomly using simple random sample technique.

All patients were subjected to ECG tracing within 6 hours from the last domperidone dosage received and QTc interval was calculated by using Bazett's formula. Those who had a positive first ECG (prolonged QT) were advised to stop the drug immediately and after one week another ECG was done to re-assess QT interval after stoppage of the drug.

RESULTS

This study showed that 8% of the cases (4 patients out of 50) showed prolongation of QTc interval after one week of Domperidone intake. According to Chi square test, there was no statistically significant difference between cases and control (p = 0.117). Moreover, these 4 cases when stopped domperidone and QT interval re- measured after one week, it was found normal. The Z-score for the primary outcome was calculated was 2.0412 using G Power version 3.1.9.2; the power of the study reached more than 80%, so the sample size was adequate.[17]

Table. (1): Comparison between the two studied groups according to demographic data.

	Cases (n = 50)	Control (n = 50)	Test of Sig.	p
Sex				
Male n **(%)**	29 (58%)	31 (62%)	χ^2=0.167	0.683
Female **n (%)**	21 (42%)	19 (38%)		
Age (years)	1.30 (0.25 – 4.0)	1.48 (0.30 – 3.50)	U =1144.5	0.466
Dose (mg/kg/dose)	0.35 (0.30 – 0.50)	-	-	-
Duration of Domperidone intake (days)	8.0 (7.0 – 10.0)	-	-	-

Qualitative data were described using number and percent and was compared using Chi square. Abnormally distributed data was expressed using Median (Min. – Max.) and was compared using Mann Whitney test.

Table (2): Comparison between the two studied groups according to QTC interval.

QTC Interval	Cases (n = 50)	Control (n = 50)	Test Sig.	P_{FE}
mean ±SD	0.40 ± 0.04	0.40 ± 0.02	t = 0.228	0.820
<0.45 sec **n (%)**	46 (92%)	50 (100%)	χ^2= 4.167	0.117
≥0.45 sec n **(%)**	4 (8%)	0 (0%)		

Qualitative data were described using number and percent and was compared using Chi square. Normally quantitative data was expressed as Mean ± SD and compared using student t-test. FE: Fisher Exact test *: Statistically significant at p ≤ 0.05

Table. (3): Comparison between QTC interval before and after stoppage of Domperidone.

QTC interval	BEFORE	AFTER
First case	0.48	0.42
Second case	0.52	0.44
Third case	0.47	0.39
Fourth case	0.49	0.40
χ^2(p)	8.000*(0.029*)	
Mean ± SD.	0.49 ± 0.02	0.41 ± 0.02
t(p)	12.318*(0.001*)	

Qualitative data were described using number and percent and was compared using Chi square. Normally quantitative data was expressed as Mean ± SD and compared using student t-test. *: Statistically significant at $p \leq 0.05$

DISCUSSION

This study showed that Domperidone did not cause statistically significant prolongation of QT interval in infants and children. Even though, prolongation of the QT interval was reported in 8% of the cases and was reversed after stoppage of Domperidone. So, the drug could not be safely used in infants and children.

Ngoenmak T et al[18] found two out of twenty one cases with prolongation of QT interval after Domperidone intake which represented 10% of the studied cases and Vieira et al[19] who showed prolongation of QT interval in two out of forty five cases which represents 4.44% of the studied cases. Günlemez et al[20] who found two out of forty cases showed prolongation in QT interval after Domperidone intake which represents 5% of the studied cases. However, Hegar et al[21] showed zero out of ten cases with QT interval prolongation after Domperidone intake.

Over the last decade, a growing number of randomized trials were done to evaluate the cardiac safety of domperidone and evaluate its effect on QT interval. A literature review was done from 1980 to 2015, Study participants enrolled were between 2 days and 9 months of life. Although QTc interval prolongation was reported, none of the included studies reported infants with arrhythmias or sudden cardiac death. One of the studies included in this narrative review displayed a statistically significant change in the QTc interval, and a pathological QTc interval was consistently reported in 1 or 2 infants in most of the included studies. Although the incidence of the problem was low, there is a suggestion of an association between domperidone and QTc interval prolongation by this literature review.[22]

CONCLUSION AND RECOMMENDATIONS

From the current study, we concluded that Domperidone is one of the drugs that might cause prolongation of QTc interval in infants and children. Domperidone effect needs to be studied on a wider range of population and in a multi-center study to check its cardiac safety.

ACKNOWLEDGMENT

First of all I thank **Allah** the most gracious for helping me to accomplish this research and for providing me with such very encouraging and supportive supervisors.

I would like to express my deepest gratitude to my parents and sister who has always been an inspiration to me and they helped me a lot, without them this work would have never been accomplished.

I would like to express my deepest gratitude to **Prof. Dr. Aly Abd El Mohsen** Professor of Pediatrics, Faculty of medicine, University of Alexandria for helping me. I appreciate his unforgettable support as well as his generous efforts in the evaluation of this work. It is honorable to be supervised by him.

This work would have never been completed without the great help, offered by **Dr.Manal Abdel Malek Antonios,** Lecturer in Pediatrics, Faculty of Medicine, University of Alexandria, My deepest thanks and gratitude for her patience, hardworking, her friendly careful supervision, her valuable advice and support as well as her continuous encouragement and kind personality which made accomplishment of this work possible.

I'm also thankful to all staff members and to my colleagues in the Pediatrics Department for their help.

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