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ECG Changes After Parenteral Ondansetron Administration in Children with Vomiting

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ABSTRACT

Background: The potential for ondansetron to cause ECG changes as QT prolongation is well-reported.
Objectives: The aim of this study was to evaluate the effect of parenteral ondansetron on the PR interval, QRS duration and QTc interval of ECG at peak effect and at post peak effect in pediatric patients with vomiting in PED.
Patients and methods: The study was conducted in the Pediatric Emergency Department, Sohag University Hospital. ECG was done for 110 patients before and after injection of ondansetron 0.15 mg/ kg for vomiting. 60 Patients received ondansetron by intravenous injection and 50 patients received ondansetron by intramuscular injection.
Results: IV ondansetron administration resulted in a significant increase in QTc interval after 15 minutes and 45 minutes p= 0.03 and p= 0.0003 respectively, significant decrease in PR interval after 15 minutes p= 0.02 and there was a significant decrease in QRS duration at 15 minutes after injection of ondansetron p= 0.02. IM ondansetron administration resulted in a significant increase in QTc interval after 30 minutes and 60 minutes p= 0.04, p= 0.0001 respectively, significant decrease in PR interval after 30 minutes and 60 minutes p<0.0001, p= 0.04 respectively and a statistically significant decrease between QRS duration before and after 30 minutes of ondansetron injection p<0.0001.
Conclusion: It could be concluded that significant ECG changes occurred in children receiving a single dose of parenteral Ondansetron 0.15 mg/ kg. None of the patients had an ondansetron related cardiac adverse events.
Keywords: Ondansetron, Vomiting, ECG, QTc

INTRODUCTION

Ondansetron is a potent and highly specific antagonist of the 5HT3 receptor. Its method of action in controlling vomiting is unknown, however it might be linked to antagonism of 5HT3 receptors on peripheral and central nervous system neurons [(1)].

A single dose of oral ondansetron lowers vomiting and allows oral rehydration in children with gastroenteritis (GE) and dehydration, making it ideally suited for usage in the emergency room [(2)].

Although ondansetron is a widely accepted treatment for vomiting with gastroenteritis in children, ondansetron is being used for a broader spectrum of primary diagnoses. Ondansetron improves the success of oral rehydration in children with gastroenteritis. The potential for Ondansetron to cause ECG changes as QT prolongation is well-reported, few clinical trials evaluating ECG changes after ondansetron administration in the PED setting exist [(3)].

The aim of this study was to evaluate the effect of parenteral ondansetron on the PR interval, QRS duration and QTc interval of ECG at peak effect and at post peak effect in pediatric patients with vomiting in PED.

PATIENTS AND METHODS

This cross-sectional hospital-based study conducted for 6 months period between August 2020 to February 2021in Pediatric Emergency Department at Sohag University Hospital included a total of 110 patients aged from one month to 12 years complaining of vomiting.

We excluded from the study, patients who did not give consent. Also, we excluded patients with known cardiac disease or dysrhythmias.

ECG was done for the 110 patients before and after injection of ondansetron 0.15 mg/ kg for vomiting. 60 Patients received ondansetron by intravenous injection and 50 patients received ondansetron by intramuscular injection.

Data collection:

For all the patients enrolled in the study checklist was filled by the investigators. The checklist included data of the patients concerning age, sex, duration of vomiting, previous treatment and previous illnesses. Blood samples were collected from the patients. They were analyzed for complete blood count, liver function tests, serum creatinine and serum electrolytes (Na, k, and Ca).

ECG: 12 leads ECG was performed for all children with vomiting before and after 15 min, 45 min in children received ondansetron 0.15 mg/ kg by IV route injection and 30 min, 60 min in children received ondansetron 0.15 mg/ kg by IM route using (Fukuda Denshi CardiMax ECG device model FCP-7101 with a 25 mm/s paper speed, gain 10 mm/mV).

Location of chest electrodes was not changed before and after ondansetron administration. The electrocardiograms were reviewed through the creation

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of descriptive reports and determination of the following variables: heart rate, PR interval and QRS duration. The QT interval was measured from the onset of the QRS complex to the end of the T wave, defined by the return of the terminal T wave to the isoelectric T-P baseline. Then QT interval was corrected for heart rate using Bazett's formula. Interpretation of every ECG paper was done using specific centile tables for normal values of ECG waves and intervals according to age. [4]

***Ethical Consideration*:**

This study was ethically approved by Sohag University's Research Ethics Committee. Written informed consent of all the participants' parents was obtained. This work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Data analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P value < 0.05 was considered significant.

RESULTS

ECG was done for 110 patients before and after injection of ondansetron 0.15 mg/ kg for vomiting. 60 Patients received ondansetron by intravenous injection and 50 patients received ondansetron by intramuscular injection. Age of studied patients ranged from 29 days to 12 years with mean age of 52.78 months. 68 (61.82%) males and 42 (38.18%) females were included.

Table (1): Patient demographics (n =110)

Variable	**Value**
Age/month	
Mean ± SD	52.78±44.57
Median (range)	45 (1.25:144)
Gender	
Female	42 (38.18%)
Male	68 (61.82%)
Cause of vomiting	**N (%)**
Gastroenteritis	37 (33.64%)
Pneumonia	30 (27.30%)
Metabolic causes	12 (10.90%)
CNS infection	8 (7.27%)
Acute tonsilitis	7 (6.36%)
Otitis media	6 (5.45%)
UTI	6 (5.45%)
Obstructive uropathy	4(3.37%)
Laboratory values,	**Median (IQR)**
WBCs (cells per cmm)	12.45 (1.6:33.9)
Hb (g/dl)	10.55 (1.5:14.8)
Hematocrit (%)	32 (4:64.5)
MCV (femtoliters)	75.85 (51.3:164)
PLTs (cells per cmm)	331.5 (10:905)
Na (mmol/L)	132 (110:175)
K (mmol/L)	3.5 (1.9:5)
Ionized Ca (mmol/L)	1.05 (0.45:1.84)
ALT (units per liter)	22 (10:1230)
AST (units per liter)	22 (10:1140)
Direct bilirubin (mg/dl)	0.2 (0.1:29.7)
Total protein (g/dl)	7.3 (4:9.6)
Albumin (g/dl)	3 (1.8:4)
Random blood sugar (mg/dl)	99.5 (60:412)
S. creatinine (mg/dl)	0.43 (0.1:2.97)

Sixty of studied patients received IV ondansetron. EGCs were obtained. QRS duration, PR and QTcB intervals was measured before and 15, and 45 after a 0.15mg/kg IV dose of ondansetron given for children with vomiting. The mean baseline QTc was 418.67±20.59 milliseconds. Mean difference (15 min after-before) (95%CI) =5.34 (0.64:10.05), p= 0.03. Mean difference (45 min after-before) (95%CI) =7.59

(3.69:11.48), p= 0.0003, Mean difference (45 min after-15 min after) (95%CI) =2.24 (-1.38:5.87), p= 0.22.

There was significant increase in QTc interval after 15 minutes and 45 minutes but there was no significant change between peak effect at 15 minutes and 45 minutes post peak. The mean baseline PR was 121.03±20.92 milliseconds. Mean difference (15 min after-before) (95%CI) = -7.12 (-13.21: -1.03), p= 0.02. Mean difference (45 min after-before) (95%CI) =-5.24 (-12.13:1.64), p= 0.13 and mean difference (45 min after-15 min after) (95%CI) =1.88 (-4.53:8.29), p= 0.56.

There was significant decrease in PR interval after 15 minutes but there is no significant change occurred in PR interval after 45 minutes or between peak effect at 15 min and 45 min post peak.

The mean baseline QRS duration was 75.53±12.50 milliseconds. Mean difference (15 min after-before) (95%CI) =-4.05 (-7.54: -0.57), p= 0.02. Mean difference (45 min after-before) (95%CI) =-1.98 (-5.81:1.85), p= 0.30, Mean difference (45 min after-15 min after) (95%CI) =2.07 (-1.08:5.21), p= 0.19. There was a significant decrease in QRS duration at 15 minutes after injection of ondansetron but there was no significant change at post peak effect of 45 minutes or between 15 minutes and 45 minutes post peak (Table 2).

Table (2): ECG changes in patients received ondansetron by IV injection (n=60)

	At 15 minutes after injection	**At 45 minutes after injection**
QTc interval		
418.67±20.59	424.02±16.33	426.26±16.21
Mean difference (15 min after-before) (95%CI) =5.34 (0.64:10.05), p= 0.03 Mean difference (45 min after-before) (95%CI) =7.59 (3.69:11.48), p= 0.0003 Mean difference (45 min after-15 min after) (95%CI) =2.24 (-1.38:5.87), p= 0.22		
PR interval		
121.03±20.92	113.91±18.12	115.79±18.28
Mean difference (15 min after-before) (95%CI) = -7.12 (-13.21: -1.03), p= 0.02 Mean difference (45 min after-before) (95%CI) =-5.24 (-12.13:1.64), p= 0.13 Mean difference (45 min after-15 min after) (95%CI) =1.88 (-4.53:8.29), p= 0.56		
QRS duration		
75.53±12.50	71.48±8.81	73.55±10.57
Mean difference (15 min after-before) (95%CI) =-4.05 (-7.54: -0.57), p= 0.02 Mean difference (45 min after-before) (95%CI) =-1.98 (-5.81:1.85), p= 0.30 Mean difference (45 min after-15 min after) (95%CI) =2.07 (-1.08:5.21), p= 0.19		

Fifty of studied patients received IM ondansetron. EGCs were obtained. QRS duration, PR and QTcB intervals was measured before and 30, and 60 after a 0.15mg/kg IM dose of ondansetron given for children with vomiting. The mean baseline QTc before ondansetron injection was 416.48±24.18 milliseconds. The mean difference (30 min after-before) (95%CI) was 3.21 (0.21 to6.22) milliseconds (p= 0.04). The mean difference (60 min after-before) (95%CI) was 6.60 (3.56 to9.62) milliseconds (p =0.0001), the mean difference (60 min after-30 min after) (95%CI) was 3.38 (1.04 to5.73) milliseconds (p =0.006). There was significant increase in QTc interval after 30 minutes and 60 minutes and there was a change between peak effect of 30 minutes and 60 minutes post peak that was clinically significant.

The mean baseline PR was 127.31±15.83 milliseconds. Mean difference (30 min after-before) (95%CI) =-25.40 (-30.98:-19.83), p<0.0001. Mean difference (60 min after-before) (95%CI) =-5.44 (-

10.72:131.71), p= 0.04, Mean difference (60 min after-60 min after) (95%CI) =19.96 (13.31:26.61), p<0.0001. There was significant decrease in PR interval after 30 minutes and 60 minutes and a change between 30 minutes and 60 minutes post peak that was clinically significant.

The mean baseline QRS duration was 78.44±11.85 milliseconds. Mean difference (30 min after-before) (95%CI) =-9.5 (-12.84: -6.16), p= <0.0001. Mean difference (60 min after-before) (95%CI) =-2.87 (-6.81:1.09), p= 0.15, Mean difference (60 min after-30 min after) (95%CI) =6.63 (3.41:9.86), p<0.0001. There was a statistically significant decrease between QRS duration before and after 30 minutes of ondansetron injection and between 30 minutes and 60 minutes post peak but there was no significant change between QRS duration before and after 60 minutes post peak (Table 3).

Table (3): ECG changes in patients received ondansetron by IM injection (n=50)

Before injection	At 30 minutes after injection	At 60 minutes after injection
QTc interval		
416.48±24.18	419.69±24.35	423.08±25.09
Mean difference (30 min after-before) (95%CI) =3.21 (0.21:6.22), p = 0.04 Mean difference (60 min after-before) (95%CI) =6.60 (3.56:9.62), p = 0.0001 Mean difference (60 min after-60 min after) (95%CI) =3.38 (1.04:5.73), p = 0.006		
PR interval		
127.31±15.83	101.90±15.92	121.87±17.61
Mean difference (30 min after-before) (95%CI) =-25.40 (-30.98:-19.83), p <0.0001 Mean difference (60 min after-before) (95%CI) =-5.44 (-10.72:131.71), p = 0.04 Mean difference (60 min after-30 min after) (95%CI) =19.96 (13.31:26.61), p <0.0001		
QRS duration		
78.44±11.85	68.94±9.10	75.58±10.36
Mean difference (30 min after-before) (95%CI) =-9.5 (-12.84: -6.16), p = <0.0001 Mean difference (60 min after-before) (95%CI) =-2.87 (-6.81:1.09), p= 0.15 Mean difference (60 min after-30 min after) (95%CI) =6.63 (3.41:9.86), p<0.0001		

DISCUSSION

Vomiting is symptom of many pediatric diseases. Vomiting can originate from the gastrointestinal (GI) tract itself or it can be a symptom of systemic disorders. Pediatricians should avoid serious associated complications, including electrolyte abnormalities, dehydration, and serious causes as functional or mechanical intestinal obstruction [(5)].

Treatment of dehydration and electrolyte disturbances is the most important step in managing a child with vomiting. Stopping oral fluids/feeds and using a nasogastric tube to decompress the stomach in children with bilious vomiting. Antiemetic ondansetron is a selective serotonin (5-hydroxytryptamine; 5-HT) 5-

HT3 receptor antagonist that can be used in both adults and children. Ondansetron (parenteral 0.15 mg/kg; maximum 4 mg) is used to treat children who have chronic vomiting caused by a variety of causes [(6)].

The most common cause of acute vomiting in children is gastritis and gastroenteritis (AGE). Vomiting is a common symptom of acute gastroenteritis in babies and children, and it is the most prevalent reason for oral rehydration treatment failure. When given with acute gastroenteritis, ondansetron can help increase the effectiveness of oral rehydration treatment in children who have persistent vomiting [(7)].

Ondansetron (oral mucosal absorption preparation) lowers emesis, allowing for more efficient oral rehydration. It is also a well-established emergency treatment for AGE in high-resource settings, decreasing the need for intravenous fluids and hospitalization. A single sublingual dosage of an oral dissolvable tablet of ondansetron (4 mg for children 4-11 years old [usually 0.2 mg/kg]) may be administered since recurrent vomiting can decrease ORS. Most children, however, do not require antiemetic treatment; cautious ORS is typically enough [(8)].

Niño-Serna *et al.* [9], documented that Ondansetron is the only intervention that revealed an effect on the cessation of vomiting, on preventing hospitalizations, and in reducing the need for intravenous rehydration. Ondansetron was also considered a safe intervention. **Safaeian *et al.* [10],** found that the risk of arrhythmias with the use of ondansetron in otherwise healthy candidate is very low. However, the drug may induce significant changes in ECG parameters.

This study investigated the effect of anti-emetic doses of ondansetron on ECG recordings in children with vomiting in the emergency department. This study included 110 patients presented with vomiting. vomiting was due to gastroenteritis in 37 patients (33.64%), 30 patients (27.30%) had pneumonia, 12 patients (10.90%) had metabolic causes of vomiting, 8 patients (7.27%) had CNS infection ,7 patients (6.36%) had acute tonsillitis ,6 patients (5.45%) had OM, 6 patients (5.45%) had UTI and 4 patients (3.64%) had obstructive uropathy. In **Sturm *et al.* [3]** study who conducted a retrospective study on 32,971 children administered ondansetron in the PED; to determine the indications for which ondansetron is used in the PED. 12,620 (38%) were non-GE patients. Children with diagnosis other than gastroenteritis were older (8.3 vs 4.3 years, $P < 0.001$) compared with children with gastroenteritis. The most common primary diagnoses for non-GE discharged patients were fever (15%), abdominal pain/tenderness (13%), head injury/concussion (7%), pharyngitis (6%), viral infection (6%), migraine variants (5%), and otitis media (5%). The most common diagnoses of patients admitted were appendicitis (11%), asthma (6%), pneumonia (4%), and diabetes (4%) [3].

In a similar study done by **Hoffman *et al.*[11]** to determine the effect of intravenous ondansetron on QTc interval in pediatric patients with gastroenteritis. 134 children with gastroenteritis received ondansetron. Their age ranged between one month age and 14 years, the study included 46% male patients with an mean age of 47.8 months with a range of 4.8 months to 168 months (14 years) and 54 % female patients with an mean age of 50,2 month. In **Krammes *et al.*[12]** study of the Effect of Intravenous Ondansetron on the QT Interval of Patients' Electrocardiograms One hundred patients were included. 55% of studied children were female with a mean age of 8.3 years. Their age ranged between 6 months to 18 years administered IV ondansetron for vomiting, or the inability to take fluids in the emergency department. **Safaeian *et al.*[10]** studied the effects of ondansetron versus dexamethasone on electrocardiographic markers of ventricular repolarization in children undergoing cochlear implant. The study was conducted on 63 children for elective cochlear implantation. Two patients were excluded as their baseline ECG showed long QT syndrome.

In this study CBC done for children with vomiting showed mean leucocytic count of 13.62 cells per cmm and standard deviation of 6.99 as vomiting in most of cases was due to infections, mean HB level was 10.16 (g/dL) with standard deviation of 2.43, mean HCT level was 30.41% with standard deviation of 7.74, mean MCV was 76.37 femtoliters with standard deviation of 12.88, mean Platelet count was 371.3 per cmm with standard deviation of 164.54. Iron deficiency anemia (IDA) is the most common nutritional deficiency primarily in developing countries [13].

Al Laham *et al.*[14] conducted a study to investigate possible changes in blood parameters that are associated with gastroenteritis infection among kindergarten children. They found that the prevalence of enteric pathogens among cases (88.5% [85/96]) was significantly higher than in asymptomatic controls (11.1% [6/54]). Blood tests revealed that 21.8% of cases and 14.8% of controls had iron deficiency anemia, which were not significantly different. Meanwhile, a significant difference was found between the TIBC and hemoglobin in cases compared to controls and concluded that the study indicates that gastroenteritis infection could be considered as a common health problem in kindergarten children in Gaza, and it is possibly associated with changes in hemoglobin concentration and TIBC.

In this study, IV ondansetron administration resulted in a significant increase in QTc interval after 15 minutes and 45 minutes $p= 0.03$ and $p= 0.0003$ respectively, significant decrease in PR interval after 15 minutes $p= 0.02$ and there was a significant decrease in QRS duration at 15 minutes after injection of ondansetron $p= 0.02$.

In this study, IM ondansetron administration resulted in a significant increase in QTc interval after 30 minutes and 60 minutes and there was a change between peak effect of 30 minutes and 60 minutes after Ondansetron injection that was clinically significant $p= 0.04$, $p= 0.0001$ and $p= 0.006$ respectively. There was also significant decrease in PR interval after 30 minutes and 60 minutes and a change between 30 minutes and 60 minutes post peak that was clinically significant. $p<0.0001$, $p= 0.04$ and $p<0.0001$respectively and there was a statistically significant decrease between QRS duration before and after 30 minutes of ondansetron injection and between 30 minutes and 60 minutes post peak), $p<0.0001$.

ECG changes occurred in this after Ondansetron administration are in contrast to **Krammes *et al.* [11]** study which concluded that ondansetron did not affect the QTc of pediatric patients receiving the medication for nausea, vomiting, or inability to take fluids in the emergency department. They concluded that no changes in the QTc were clinically significant and also in contrast to **Hoffman *et al.* [12]** study who concluded that**:** In children, 0.15mg/kg of intravenous ondansetron did not cause prolongation of QTcB or QTcF measured 15min after administration, nor at later times.

This study results are in concordance with **Safaeian *et al.*[10]** study who documented that Ondansetron resulted in no significant changes in RR, JTc and QTc intervals; while prolonged Tp-e interval. Multivariable logistic regression analysis showed that use of ondansetron was an independent predictor of QTc prolongation after adjustment for age, gender and baseline QTc (OR = 17.94, CI 95% 1.97-168.70, p = 0.011). The incidence of postoperative vomiting in ondansetron group was significantly lower than dexamethasone group. (3.2% vs. 26.7%, p = 0.011). they concluded that the risk of arrhythmias with the use of ondansetron in otherwise healthy candidates of cochlear implant is very low. They concluded that the drug may induce significant changes in ECG parameters. The clinical significance of these changes in patients with cardiac conduction abnormalities should be investigated in further studies [10].

This study results are also in concordance with **Pinarli *et al.* [15]** study who evaluated the ECG changes after administration of 5-HT3 receptor antagonists and chemotherapeutic agents in children with cancer. They found a significant shortening of the PR interval and QRS complex durations in the granisetron group at 90th min and at 24th hr, respectively. Also, granisetron infusion caused a significant prolongation of the QTca interval at 90 min. They concluded that although they observed minor ECG changes after 5-HT3 receptor antagonists and chemotherapy, neither dangerous rhythm disturbances nor serious ECG changes were seen.

Also, NICE clinical guideline advised that ondansetron prolongs the QT interval in a dose-dependent manner and it should be avoided in people with congenital long QT syndrome and used with caution in people who have or may develop prolongation of QTc, such as those with electrolyte abnormalities, congestive heart failure, bradyarrhythmia or people taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. Hypokalemia and hypomagnesaemia should be corrected prior to ondansetron administration [1].

CONCLUSION

It could be concluded that significant ECG changes occurred in children receiving a single dose of parenteral Ondansetron 0.15 mg/ kg. None of the patients had an ondansetron related cardiac adverse events.

RECOMMENDATIONS

Multiple doses of Ondansetron should be avoided in children with vomiting as most of them have electrolyte disturbances that causes further QT prolongation and increases risk of ventricular arrhythmia.

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