ORIGINAL RESEARCH PAPER

Volume-6 | Issue-12 | December-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 93.98

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ONDANSETRON INDUCED QT INTERVAL CHANGES IN INDUCTION WITH ISOFLURANE AND HALOTHANE IN HEALTHY SUBJECTS UNDERGOING GENERAL ANAESTHESIA - A PROSPECTIVE, RANDOMIZED, OBSERVER BLIND, CONTROLLED, PARALLEL GROUP STUDY.

Anaesthesiology

Prof (Dr) Sampa Dutta Gupta	Head . Department of Cardiac Anaesthesiology.N.R.S.Medical college. Kolkata.
Dr.Chhandasi Naskar*	Assistant Professor. Department of Anaesthesiology. NEIGRIHMS. Shillong. *Corresponding Author
Dr.Smita Gogia	Senior Resident (Former) Dept of Anaesthesiology. IPGME&R.Kolkata.
Dr.Aritra Bhattacharya	House staff. Department of Radiology. Central Hospital. South eastern railway. Garden reach. Kolkata.
Dr. Sandipan Banerjee	Senior Resident . Department of Anaesthesiology. Zoka ESI hospital. Kolkata.

ABSTRACT

SUMMARY: Many drugs administered to patients in the perioperative period are known to prolong Qtc like thiopentone, inhaled anaesthetics, ondansetron. Therefore we aimed to study ondansetron induced QT interval changes with isoflurane and halothane in healthy subjects undergoing general anaesthesia.

54 patients were divided randomly into three groups. Group C (control) received ondansetron, Group H (halothane) received ondansetron and halothane, Group I (isoflurane) received ondansetron and isoflurane. QTc and haemodynamic parameters were measured at baseline, immediately after giving ondansetron and five minutes (post induction) after giving ondansetron.

Five minutes after giving ondansetron there was a statistically significant prolongation of the QTc interval (QTc3) in Group C and Group I as compared to baseline (QTc1). QTc3 in group I showed statistically significant prolongation as compared to the group H.

So, concomitant use of isoflurane and ondansetron may prolong the QTc, predisposing to the development of arrhythmias.

KEYWORDS

ondansetron,halothane,isoflurane,QTc interval

INTRODUCTION

The QT interval of the electrocardiogram reflects the period from the start of ventricular depolarization to the onset of ventricular repolarisation. Its prolongation is associated with arrhythmias, such as polymorphic ventricular tachycardia (torsade de pointes) and ventricular fibrillation.[1,2] A number of anesthetic drugs are known to prolong Qtc (corrected QT interval) like thiopentone, inhaled anesthetics.

Previous studies have documented the ability of the volatile anesthetic isoflurane to prolong the QT interval and the QT interval corrected for the level of heart rate and halothane to shorten it. Ondansetron, a 5HT3 receptor antagonist, one of the first line drugs used in general anaesthesia to prevent post operative nausea and vomiting, is known to cause ECG changes including a prolongation of the QTc. The combination of two or more agents prolonging the QT interval is believed to increase the risk of arrhythmia development.[1] Furthermore a marked stress response including hypertension, tachycardia, arrhythmias[3] and an increase in intracranial pressure[4] often follows direct laryngoscopy.[5] Concern about hepatotoxicity has virtually eliminated the use of halothane in adults in the developed countries. However it is still possibly the most commonly used inhalational anaesthetic in all patients in developing countries. Therefore we aimed to study Ondansetron induced QT interval changes in induction with isoflurane and halothane in healthy subjects undergoing general anaesthesia with an objective to find out the changes in QT interval at different time points in each group.

METHODS

This is a prospective, randomized, double blind, controlled, parallel group study. After obtaining approval of the institutional research and ethics committee 54 patients of either sex aged 20 - 50 yrs (ASA physical status I & II), scheduled for elective surgery under general anaesthesia were enrolled in the study. All patients were randomly allocated into three groups [group C (control), group H (halothane), group I (isoflurane)] with eighteen patients in each group through a computer generated random number table.

Patient exclusion criteria were : history of gastro intestinal disease, hormonal therapy, evidence of uncontrolled (clinically important) neurological, renal, hepatic, cardiovascular, metabolic or endocrine dysfunction, vomiting during the 24 hours period before surgery or have received anti emetics during 24 hours study period, pregnancy, obesity, history of taking Williams class 1 or 3 anti-arrhythmics, if they had a history of heart disease or circulatory insufficiency, or if they were receiving psychotropic or other drugs known to prolong the QT interval.

Anaesthetic management was standardized for all patients. Following overnight fasting, all the patients were premedicated with oral lorazepam 0.04mg/kg, 2 hours prior to induction of anaesthesia. On arrival in the operating room baseline parameters (heart rate, 5-lead ECG, NIBP, $ETCO_2$, SpO2) were recorded and long lead II ECG was taken to calculate baseline Qt interval (QT-1). Inj. Ondansetron was administered in a dose of 0.08mg/kg to every patient over a period of 5 minutes following i.v. access. After preoxygenation, patients were induced with etomidate 0.2mg/kg , fentanyl 1-2 µg/kg and atracurium 0.5 mg/kg. After giving atracurium all the patients were ventilated with a mixture of N_2O 66% and O_2 33% targeting $ETCO_2$ between 35 and 40. Equianaesthetic concentrations of halothane 0.45% and isoflurane 0.75% (1MAC) were given along with N_2O 66% and O_2 33% in group H and I respectively, maintaining BIS between 45 and 60. Second recording of long lead II ECG was taken to calculate Qt interval changes immediately following ondansetron administration (QT-2). Four minute following proper ventilation with N_2O:O_2(group C), N_2O:O_2:isoflurane(group I) and N_2O:O_2:halothane(group H), third long lead II ECG was recorded and noted (QT-3) in each group. This was the end point of the study.

All patients were monitored during the study period for heart rate, 5-lead ECG, NIBP, $ETCO_2$, SpO_2, FiO_2 , end tidal anaesthetic concentration, airway pressures and temperature.

After tracheal intubation, the patients' lungs were ventilated mechanically. At the end of surgery, residual neuromuscular blockade was reversed with 50 µg/Kg neostigmine along with 10 µg/Kg glycopyrrolate after fulfilling the criteria of extubation.

Mean QT was calculated from QT intervals of three consecutive cycles in lead II. Qtc was calculated by the Bazett,s formula $QTc = QT / \sqrt{RR}$.

QT interval was accepted as "prolonged," when QTc values exceeded 440 ms.

Statistical analysis

The minimum group size of 18 was calculated in order to achieve a study power of 90% with type I error rate (alpha) of 0.05. For the purposes of the calculation, we used values of the QTc interval (range, mean, standard deviation) from the study of Benhorin and colleagues.[6] The data were presented as mean (SD). Intra group comparison was done by 'Repeated measures ANOVA' followed by post hoc Dunnet's test with QTc1 as control group. Intergroup comparison was done by 'One Way ANOVA' followed by post hoc Dunnet's test with group C as control group. P value of < 0.05 was considered statistically significant.

RESULTS

Data from 54 patients were collected and analysed. Patients were randomly allocated into three groups each having 18 subjects. The patients were similar in all the three groups in relation to age, body mass, weight and the duration of anaesthesia (Table 1).

Table 1 Characteristics of the patients. Mean (SD or range)

	Group C	Group H	Group I
Number of patients	18	18	18
Age (yrs)	41.11(22-50)	40.45(22-48)	43.28(24-50)
Weight (kg)	57.06 (5.89)	60.28 (6.67)	59.61 (5.64)
BMI(kg/m2)	23.69(1.81)	24.02(1.95)	25.42(2.68)
Ondansetron dose (mg)	4.56 (0.47)	4.81 (0.53)	4.76 (0.45)
Duration of anaesthesia (min)	63.17(12.57)	64.17(13.85)	62.22(14.9)

Table 1 shows that demographics were comparable in all groups
A comparison of the corrected QT values recorded in all the groups is presented in Table 2.

Table 2 Comparison of QTc at different time points

	QTc1	Qtc2	QTc3
Group C (n=18)	0.332 (0.026)	0.341 (0.024)	0.388* (0.034)
Group H (n=18)	0.35 (0.020)	0.357 (0.023)	0.352 (0.025)
Group I (n=18)	0.339 (0.027)	0.345 (0.023)	0.410* (0.027)
Intergroup# comparison	n.s.	n.s.	P<0.01

Table 2 shows changes in QTc interval in groups C,H and I. Data are mean (SD). Within the group, compared with baseline using repeated measures annova;

#one way annova followed by post hoc Dunnet's test. *P<0.05

There was no significant intra group or intergroup difference in the corrected QT values in any of the groups immediately after giving ondansetron (QTC2). After induction of anaesthesia and five minutes after giving ondansetron there was a statistically significant prolongation of the QTc interval (QTc3) in Group C (P value < 0.05) and Group I (P value < 0.05) as compared to baseline QTc (QTc1) in these groups. The post induction QTc interval (QTc3) in group I (0.41) showed statistically significant prolongation as compared to the group H (0.35) (P value < 0.01).

Table 3 Number of patients with QTc >0.44 s

	QTc1	Qtc2	QTc3
Group C (n=18)	0	0	0
Group H (n=18)	0	0	0
Group I (n=18)	0	0	4

QTc > 0.44 s was seen in four patients only in group I post induction

Table 3 summarizes the number of patients in whom the QTc value exceeded the reference value of 0.44 s during the course of study. This phenomenon was observed almost exclusively in group I. No arrhythmia was seen in any of these patients.

There was no significant difference in mean heart rates between the groups prior to induction, the mean (SD) 65.67 (6.68) in group C, 68.56 (6.15) in group H and 67.83 (6.35) in group I.

Post induction there was a statistically significant decrease (P<0.05) in mean heart rate of group H (65.56; SD 7.01) as compared to group C (71.56;SD6.45) and group I(75; SD 8.54).The mean blood pressures were also comparable between the groups prior to anaesthesia induction, group C(95.61;SD 5.65), group H (89.17; SD 9.85) and group I (89.33; SD 14.7). Post induction there was a statistically significant decrease (P<0.01) in mean blood pressures of group H (72.61; SD13.76) and group I (75.22; SD 12.5) as compared to group C (93.94; SD 4.59)

DISCUSSION

A number of medications given to patients under anaesthesia prolong QT interval. A combination of such drugs may increase the risk of arrhythmia development[1]. $5HT_3$ antagonist ondansetron is known to cause QTc prolongation[7,8] The present study also showed the same results with a significant increase in QTc in group C (0.388; p value < 0.05). Although the result was statistically significant but none of the patients in this group had QTc values > 0.44sec. Inhalational anaesthetics especially isoflurane[9,10] is also known to prolong QTc while halothane[9,10] shortens it. The main finding of our study is that patients receiving ondansetron for prevention of post operative nausea and vomiting are more prone to prolongation of the QTc interval during administration of isoflurane than halothane anaesthesia. The mean QTc in the isoflurane group was 0.41(a statistically significant prolongation from baseline QTc of 0.33) compared to 0.35 in the halothane group. Furthermore four patients in the isoflurane group developed QTc prolongation of > 0.44s, although no arrhythmias were noted. It may be possible that combined use of isoflurane and ondansetron has an additive effect on QTc prolongation. Also, higher concentrations of isoflurane than those used in our study may prolong the QTc much more and further increase the risk of arrhythmias especially when used simultaneously with ondansetron. The mean QTc of 0.35 in the halothane group indicates that it might be safer to use with ondansetron because of the opposite effects of these two on the QTc. Although halothane is not used anymore in the developed countries but its use is still very widespread in developing nations not only in children but also in adults.

CONCLUSION

We hereby conclude that concomitant use of isoflurane and ondansetron may prolong the QTc significantly, predisposing to the development of arrhythmias.

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