EFFECT OF (RS)-ONDANSETRON AND ITS ENANTIOMERS ON QTC INTERVAL IN RATS

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Summary

Objectives: Ondansetron (5-HT_3 receptor antagonists) is widely used in the prophylactic treatment of chemotherapy-induced nausea and vomiting and reported to cause prolongations of QTc and JT intervals as one of its major side effect. Antagonistic potential of enantiomers of Ondansetron (R- and S-) against 5-HT_3 receptor were reported to differ significantly in heart. The objective of this study was to study effect of (RS)-ondansetron and its two enantiomers viz R- and S-ondansetron on QTc interval in electrocariocram of rats.

Material and Methods: Wistar rats of either sex were anaesthetised with urethane (1.5 g/kg) and electrocardiogram (ECG) was recorded by four channel physiological data acquisition system (BIOPAC). Rats were administered either with ondansetron and its enantiomers (R- and S-) in the dose of 3 mg/kg, i.v.) and ECG was recorded after the equilibrium period of 30 min. Amiodarone (25 mg/kg, i..v) was used as a standard drug.

Results: (RS)-Ondansetron, (S)-ondansetron, and amiodarone produced significant prolongation of QTc interval. But, (R)-ondansetron did not prolonged QTc interval in rat ECG.

Conclusion: The (R)-ondansetron appears to be safer alternative than (RS)-ondansetron.

Keywords: Ondansetron, (RS)-ondansetron, (R)-ondansetron, (S)-ondansetron, QTc interval, Rat, Electrocardiogram (ECG)

Introduction

Ondansetron (5-HT_3 receptor antagonists) is widely used in the prophylactic treatment of chemotherapy-induced nausea and vomiting. The incidences of QTc and JT intervals prolongation are reported with ondansetron (1, 2) as side effects.

Two isomers R- and S-ondansetron are found in recemic (RS)-ondansetron in equal proportion and these enantiomers may interact in different ways with biological structures and, therefore, may exhibit widely different properties (3). Recently, stereoisomer of 5-HT_3 receptor antagonist S-zacopride was reported to show 10-fold higher effect against von Bezold-Jarisch reflex (The protective reflex of the heart) (4). Many other 5-HT_3 anatgonists and their enantiomers have exhibited differential effects on 5-HT_3 receptors (5-7). Similarly, (R)- and (S)- enantiomers of ondansetron were reported to show significantly different effects against 5-HT_3 receptors in case of isolated tissue experiments (8). However, effects of ondansetron and it's enantiomers on QTc interval of ECG are not yet reported. Therefore, effects of (RS)-ondansetron and their enantiomers (R- and S-) on QTc prolongation were investigated.

Material and Methods

Drugs and chemicals

Samples of ondansetron and its enantiomers were supplied by Emcure Pharmaceuticals Ltd., Pune. Amiodarone (Cordarone, Sanofi Synthelabo) and urethane (Hi Media, India) were purchased. The test drugs were dissolved in beta-cyclodextrin and used in the doses of 0.75, 1.5 and 3.0 mg/kg (ondansetron enantiomers) and 25 mg/kg, i.v. (amiodarone).

Experimental animals

Wistar albino rats of either sex, (200–300g)were purchased from National Toxicological Centre, Pune and housed in polypropylene cages at a ambient housing conditions (Temperature of 25 $\pm$ 1°C and relative humidity of 45 to 55% in clean environment under 12:12 light:dark cycle, with free access to food pellets and filtered water *ad libitum*. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of Poona College of Pharmacy constituted under Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Effect of ondansetron and its enantiomers on rat ECG (9)

The rats were anaesthetized with urethane (1.5 g/kg, i.p) and stainless steel needles (21 gauge x ½") were inserted subcutaneously in flexor aspects of right fore limb, right hind limb and left hind limb. Needles were clipped to the electrode lead set (SS2L). Negative terminal of electrode lead set was connected to right fore limb, positive to left hind limb and neutral to right hind limb.

Electrode lead set was connected to four channel physiological data acquisition system (MP 30, Biopac Systems Inc., Santa Barbara, CA, USA) and ECG (lead II) signals were recorded in a waveform. Vehicle (0.5 ml/kg, i.v.) was administered and heart rate was allowed to stabilize. An equilibration period of 45 min. was allowed before administration of drugs. The drugs were injected intravenously. ECG was recorded before immediately before (0 min) and at 2, 5, 15, 30, 45, 60, 120 and 180 minutes after drug administration and stored digitally. Changes in QT and RR interval and heart rate were calculated with the Biopac system. The QT interval corrected for heart rate (QTc) was calculated using the Bazett's formula (10): QTc = [QT interval / (RR interval)$^{1/2}$]

Statistical analysis

The data were expressed as mean ± SEM of 6 observations for each dose in separate animals for ondansetron and its enantiomers. For control, observations were recorded for each dose in separate animals. Comparisons between groups were made using two-way ANOVA followed by Bonferroni's post hoc test.

Results

Administration of (RS)-ondansetron (3 mg/kg, i.v.) and (S)-ondansetron significantly ($P < 0.001$) prolonged QTc interval in all time points (Figure 1). On the other hand, (R)-ondansetron and standard drug, amiodarone did not cause such prolongation (Figure 1) as compared to vehicle treated group.

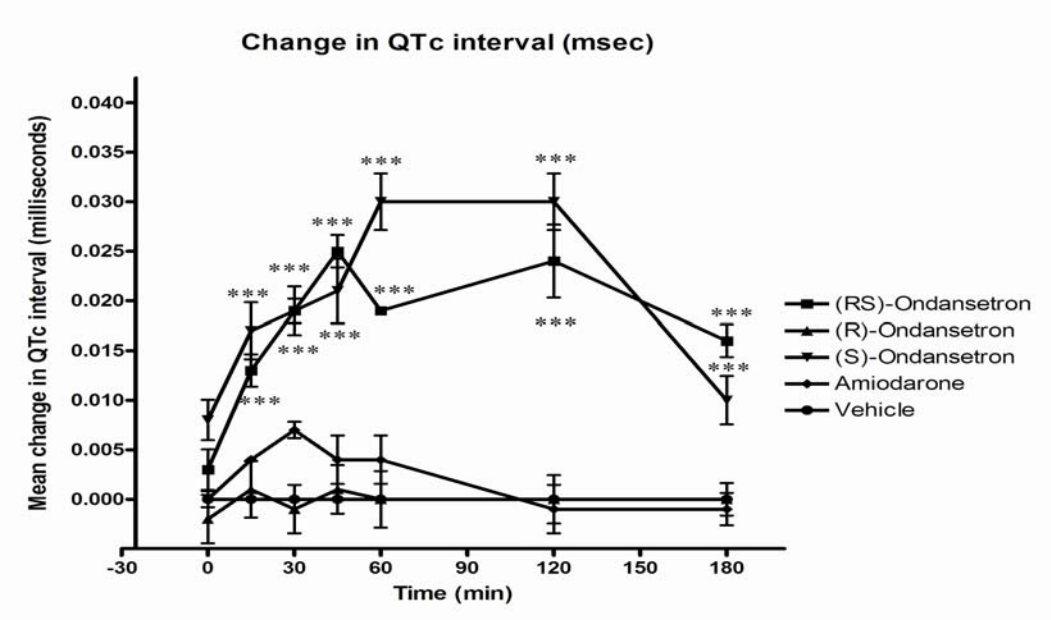

Figure 1: Effect of ondansetron and its enantiomers on mean change in QTc interval (milliseconds) form baseline (at 0 min). Data represents mean change ± SEM of six rats per group. *** $P < 0.001$ as compared with vehicle treated group values at respective time. All other values are non-significant

Discussion

Drug-induced QTc-prolongation, resulting from inhibition of HERG potassium channels may lead to serious ventricular arrhythmias and sudden death (11). Ondansetron has been reported to prolong PR, QRS, QT, QTc and JT intervals in adult patients (12), healthy volunteers (2, 13) and children (14, 15). Although, clinically, the potential for adverse events due to QT prolongation with ondansetron is considered to be low, it still poses considerable threat to the safety of the patients.

Aantagonistic potential of many 5-HT_3 receptor were reported to differ significantly in case of heart (5-7) in case of many drugs and also with ondansetron (8). Therefore, enantiomers of 5-HT_3 antagonist are expected to show differential effects on adverse effect profiles such as QTc prolongation as well.

The results of our study indicated that R-ondanstron is safer on heart. Intravenous administration of 5-HT induces the Bezold-Jarisch reflex and causes small reversible changes in electrocardiogram (ECG) parameters (16). S-ondansetron might have higher inhibitory effect on Bezold-Jarisch reflex and thereby might have caused QTc prolongation. Bezold-Jarisch reflex as (S)-zacopride, an enatiomer of 5-HT_3 antagonist (4).

In the present investigation, amiodarone did not cause any change in QTc interval. Amiodarone is one of the most efficient and safe antiarrhythmic drugs in the treatment of atrial fibrillation (AF) and our results are in line with the clinical effects of amiodarone that pro-arrhythmic effects of amiodarone therapy are rare except patients in pts with structural heart disease and AF that are concomitantly treated with beta-blockers and digitalis (17).

It is apparent that the clinical use of (R)-ondansetron which is a potent antiemetic could be a viable option to reduce the cardiovascular risks associated with ondansetron use.

Acknowledgements

The author would like to thank Dr. S.S. Kadam, Principle, Poona College of Pharmacy and Pro-vice-chancellor, Bharati Vidyapeeth Deemed University, and and Dr. K.R. Mahadik, Vice-Principal, Poona College of Pharmacy, Pune, India for providing facilities. The authors also thank Emcure Pharmaceuticals Ltd. Pune for providing samples of ondansetron and its enantiomers.

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