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Effect of paroxetine on intestinal motility in the presence of ondansetron

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Abstract: Chemotherapy, radiotherapy, surgery and depression are the conditions that run in parallel fashions. All these conditions cause the release of an increased amount of serotonin in the body. Serotonin acts on these 5HT3 receptors and causes nausea and vomiting. Ondansetron acts by blocking serotonin from acting on the receptors and thus is useful in decreasing episodes of nausea and vomiting but when used concomitantly with SSRIs (selective serotonin reuptake inhibitors) as cancer patient also suffered from depression. This combination tends to decrease the efficacy of ondansetron. The present study was carried out to observe the modulatory role of ondansetron on ileal smooth muscle motility in vitro. Experiments were performed in four groups (n=6) and ileal smooth muscle activity was recorded on the power lab (USA). The effects of increasing concentrations of serotonin, ondansetron and paroxetine alone were observed. In the fourth group effects of paroxetine in the presence of fixed concentration (1ml) of ondansetron (10^{-6}M) was observed. The maximum response obtained by serotonin served as a control for our study (100%). Paroxetine response on intestinal motility was completely blocked in the presence of ondansetron. Our findings hence, reinforce the hypothesis that paroxetine decreases the antiemetic activity of serotonin antagonist ondansetron, by super sensitization of serotonergic receptors resulting in an increased incidence of nausea and vomiting in cancer patient despite adequate antiemetic prophylaxis.

Keywords: Serotonin, ondansetron, paroxetine, intestinal motility, SSRI's, 5 HT_3

INTRODUCTION

Chemotherapy, radiotherapy, surgery and depression are the conditions that run in parallel fashions. All these conditions cause the release of an increased amount of serotonin in the body. Serotonin acts on these $5HT_3$ receptors and causes nausea and vomiting. Ondansetron acts by blocking serotonin from acting on the receptors and thus is useful in decreasing episodes of nausea and vomiting (Afzal *et al.,* 2016).

Ondansetron has been shown to delay or increase gastric emptying, increase gastric mucosal blood flow and basal acid and sodium secretion, prevent or reduce stress- or alcohol (ethanol)-induced gastric mucosal damage, inhibit fluid loss and inflammation in small bowel obstruction, and reduce abdominal responses to rectal distension and viscerosensitive changes during experimental colitis (Camelleri 2008). In healthy volunteers, ondansetron did not significantly affect gastric emptying, distension or compliance. However, colonic transit times were significantly longer with ondansetron than with placebo, and ondansetron inhibited tonic colonic postprandial responses (Tuladhular *et al.,* 2007).

The monoamine hypothesis of endogenous depression suggests that depression is caused by a functional deficit of NE (norepinephrine) and/or 5-HT (5-hydroxytryptamine (or of dopamine) at certain sites in the brain; while mania results from a functional excess of these neurotransmitters (Chetty *et al.,* 2006). This theory is based on the ability of the NE and 5-HT uptake inhibiting or monoamine oxidase- A inhibiting drugs to facilitate NE/5-HT neurotransmission and to act as effective antidepressant drugs (Tanko *et al.,* 2012). The Ondansetron mechanism of action is due to blockade of $5HT_3$ receptors in the Central nervous system leading to enhance the release of monoamines 5HT, NE (Tsukaamoto K *et al.,* 2008). Recently clinically effective antidepressants with rapid onset of action and fewer side effects are developed (Thompson *et al.,* 2009). Here selective serotonin reuptake inhibitors like fluoxetine, paroxetine & escitalopram are used in combination with ondansetron. SSRIs are having gastrointestinal side effects which can be inhibited by ondansetron and also show additive antidepressant effect (Trigg *et al.,* 2007). In the present study an attempt was made to find out that ondansetron decreases the intestinal activity of paroxetine when given in combination (Ondansetron + Paroxetine) thus abolishing its anti-emetic effects.

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MATERIALS AND METHODS

Animals and housing conditions

Twentyfour healthy local rabbits (*Oryctolagus cuniculus*) both male and female (non-gravid)) of 1-2 Kg weight were used for the current study and were purchased from the local market. The animals were kept in animal house Army Medical College, Rawalpindi at room temperature and were fed with a standard di*et al*ong with tap water ad libitum (Jabeen *et al.,* 2011: Aapro *et al.,* 2008).

Chemical for study

Serotonin Carnitine Sulfate (Sigma Chemical Co. USA), Ondansetron Hydrochloride (Werrick Pharmaceuticals, Pak) and paroxetine (Werrick Pharmaceuticals, Pak) were purchased. All the solutions and dilutions were prepared fresh in distilled water at the time of experiments. The molar solutions used for all the drugs including serotonin, ondansetron and paroxetine in strength ranging from 10^{-9} to 10^{-6} M were made (Noor *et al.,* 2011).

Preparation of tissue

We sacrificed an overnight fasting rabbit. The small intestine was taken out by recognizing the caecum and cut down into two, inch pieces (Bajetta *et al* 2009). The intestinal tissue was thoroughly washed with normal saline and fecal content was removed, fatty tissues dissected. The isolated tissue was then transferred to an isolated organ bath of 50-milliliter capacity containing tyrode's solution aerated continuously with 100% oxygen and 5% carbon dioxide (Barrakh *et al.,* 2011). The cumulative dose-response curve was made by using a power lab (USA). One end of the ileal strip was attached to the bottom of the oxygen tube and the other end was connected to a research-grade Force Displacement transducer DT-475 (USA) using a thread. iWorx/214 (USA) was connected to the computer. The tissue was allowed a period of equilibration of 15 minutes and the physiological solution was changed 2 times allowing the tissue to stabilize. The isotonic ileal smooth muscle activity was recorded through the Displacement Transducer (Basch *et al.,* 2011).

Construction of cumulative dose-response curve

Dose-response curve Serotonin Group1 (n=6)

Dose-response curve for serotonin was constructed on the isolated ileal smooth muscle of rabbits by adding the different concentration of 10^{-9}, 10^{-8}, $10^{-7}$and 10^{-6}M of serotonin (Group 1) (Afzal *et al.,* 2016).

Dose-response curve Ondansetron Group2 (n=6)

The cumulative dose-response curve of ondansetron alone (Group 2) was obtained using the concentration of 10^{-9}, 10^{-8}, $10^{-7}$and 10^{-6}M (Afzal *et al.,* 2016).

Dose-response curve Paroxetine Group3 (n=6)

The cumulative dose-response curve of paroxetine (Group 3) using the concentration of 10^{-9}, 10^{-8}, $10^{-7}$and 10^{-6}M was also constructed (Afzal *et al.,* 2016).

Dose-response curve of paroxetine pretreated with ondansetron group 4(n=6)

Paroxetine effects were studied on the isolated ileal smooth muscle of rabbits in the presence of a fixed concentration of ondansetron 10^{-6}M (1ml) using the concentration of 10^{-9}, 10^{-8}, $10^{-7}$and 10^{-6}M.

Ethical approval

The study was carried out after approval from the institutional ethical review committee of Army Medical College Rawalpindi, Pakistan.

STATISTICAL ANALYSIS

The results are expressed as Means±Standard Error of Means (SEM). The arithmetic means and SEMs were calculated using one-way analysis of variance (ANOVA) using SPSS version 20. The difference between

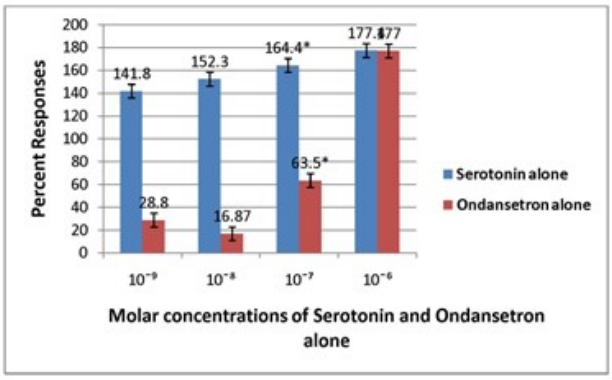
Table 1: Response of isolated ileal smooth muscles of rabbit to paroxetine

		Ondansetron+Paroxetine		
		Concentration M		
Sr No	10^{-9}	10^{-8}	10^{-7}	10^{-6}
1	5(mm)	3(mm)	3(mm)	2(mm)
2	6	2	1	1
3	5	3	1	1
4	6	3	2	1
5	4	2	1	1
6	4	1	1	1
Mean	5	2.2	1.2	1
MIN	4	1	1	1
MAX	6	3	3	2
SD	0.894427	0.816496581	0.83666	0.40824829
SEM	0.298	0.272	0.278	0.136
P Value	0.01	0.01	0.03	0.04

observations was considered significant if the *p*-value is less than 0.05. Percent deviation was also calculated and compared.

RESULTS

Serotonin and Ondansetron increases the contractility of intestinal smooth muscle. (Graph A). Both exert a maximal increase in the contractile force of the ileal smooth muscle. However, paroxetine causes a depressive effect on intestinal motility. When the dose-response curve was constructed in a tissue pretreated with ondansetron fixed concentration a further decrease in response was observed (Graph B). This depressive response is responsible for the amelioration of ondansetron effects as a chemotherapeutic agent when used concomitantly with SSRIs. However, the results between paroxetine alone & paroxetine pretreated with ondansetron groups (group 3 & group 4) are statistically significant (table 1).



Graph A: Bar diagram showing the comparison of group 1 (serotonin) and group 2 (ondansetron) on isolated ileal smooth muscles of rabbit (n=6).
Data are represented as mean ± standard error of means (SEM); *= standard error of means (SEM);*=significant ($p<0.05$);=Non-significant ($p>0.05$)

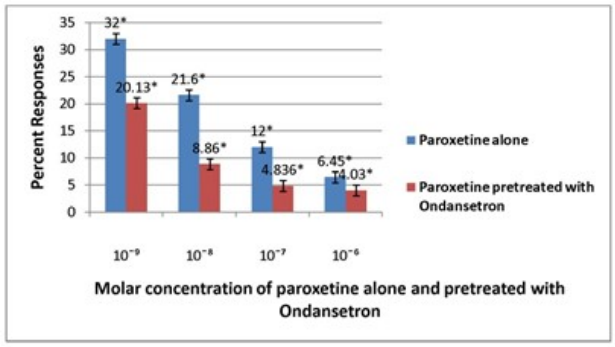
DISCUSSION

The current study was designed to evaluate the contractile effects of commonly used selective serotonin reuptake inhibitors (paroxetine) on gastrointestinal smooth muscles of rabbit *in vitro* and to observe the modulatory role of ondansetron on these agents on the contractility of the smooth muscles of the rabbit.

Serotonin increases the frequency of migrating motor complexes (MMC) which, in turn increases the effect of endogenously released serotonin. The ondansetron, block the Phase III motor activity moreover, motilin which normally precedes the MMC also exhibits inhibition of fluctuation in plasma levels (Hawkin's 2009), raising the possibility that 5-HT3 receptors are also involved in motilin secretion (Tsukaamoto 2007). Serotonin influences the gastrointestinal motility by acting directly through 5-HT_4 receptors on enterocytes and indirectly via 5-HT_3 receptors on mucosal nerves and vagal afferents (Indira Mujezinduic *et al*., 2011).

Ondansetron slows the intestinal transit time which was its basis to be used in ischemic bowel disease. They concluded that SSRIs in the presence of antagonists mimic the direct receptor interactions, they functionally block the 5-HT_3 receptors (Mir *et al* 2012). Our study was further supported by the work of Heather and his co-workers. They also observed the decrease in amplitude of contractions of ileal smooth muscles by paroxetine.

According to their study it was postulated that paroxetine causes an increase in the gut transient time because it influences vagal and adrenergic inputs. In, addition serotonergic receptors (5-HT_{1A} and 5-HT_3) are known to influence vagal afferents pathway and alter the reflex accommodation pathways, hence causing a decrease in amplitude of contractions (Devita 2012).



Graph B: Bar diagram showing the comparison of group 3 (paroxetine) and group 4 (paroxetine + ondansetron) on isolated ileal smooth muscles of rabbit (n=6).
Data are represented as mean ± standard error of means (SEM); *= significant ($p<0.05$); =Non-significant ($p>0.05$)

Gerard Honig and his fellows proposed that a decrease in the contractile response of paroxetine is because on prolong administration of reuptake blockers (paroxetine) intracellular serotonin is buffered by suppression of serotonin degradation which in-turn is further enhanced in the presence of serotonin antagonist ondansetron.

CONCLUSION

Our findings hence, reinforce the hypothesis that paroxetine decreases the antiemetic activity of the 5-HT_3 serotonin antagonist ondansetron, by inhibiting the intestinal activity resulting in an increased incidence of nausea and vomiting in cancer patients despite adequate antiemetic prophylaxis (Rogers and Blackburn 2010: Spiller 2002).

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