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Effect of Luminally Released Psychoactive Drugs on Intestinal Motility in Vitro

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Abstract: Gastrointestinal system is predominantly supplied by the serotonin. Serotonin has both central & peripheral actions. The SSRIs increases the release of serotonin in the synapse by inhibiting the transporter, which results in excessive nausea & vomiting initially. We carried out this study to determine the effects of SSRIs on intestinal motility. Power lab (USA) was used for recording the contractions of ileal smooth muscle of rabbit. The percent responses of serotonin, fluoxetine, paroxetine and citalopram were 100, 15.48, 7.45, and 6.75 percent correspondingly indicating that serotonin has a greater impact on intestinal motility as compared to SSRIs. Failure of SSRIs (fluoxetine, paroxetine and citalopram) to augment the serotonergic transmission in vitro causes a decline in its qualitative response. Fluoxetine causes the minimal effect on intestinal activity amongst its fellow drug & therefore can be prescribed safely in patients of depression with abnormal motility.

Keywords: Serotonin, Fluoxetine, Paroxetine, Citalopram, SSRIs, Nausea, Vomiting.

INTRODUCTION

Serotonin is an important neurotransmitter, a local hormone in the gut, over 90% of the serotonin in the body is found in enterochromaffin cells in the gastrointestinal tract. Serotonin is also found in the raphe nuclei of the brainstem, which contain cell bodies of serotonergic neurons that synthesize, store, and release serotonin as a transmitter. Serotonin also appears to be involved in clinical conditions such as depression, anxiety, and migraine. 5-HT receptors in the gastrointestinal tract and in the vomiting center of the medulla participate in the vomiting reflex.

They are particularly important in vomiting caused by chemical triggers such as cancer chemotherapy drugs. 5-HT $_{1P}$ and 5-HT $_{4}$ receptors also play important roles in enteric nervous system function. Serotonin is a powerful stimulant of gastrointestinal smooth muscle, increasing tone and facilitating peristalsis. This action is caused by the direct action of serotonin on 5-HT$_2$ smooth muscle receptors plus a stimulating action on ganglion cells located in the enteric nervous system. 5-HT $_{1A}$ and 5-HT$_7$ receptors may also be involved in this complex action. Activation of 5-HT$_4$ receptors in the enteric nervous system causes increased acetylcholine release and thereby mediates a motility-enhancing or "prokinetic" effect[13].

Compounds such as fluoxetine and other SSRIs, which modulate serotonergic transmission by blocking reuptake of the transmitter, are among the most widely prescribed drugs for the management of depression and similar disorder[1, 6].

The current study was taken to discover the underlying fundamental mechanism of nausea & vomiting produced by selective serotonin reuptake inhibitors; we observed the effects of fluoxetine, paroxetine & citalopram on ideal smooth muscles of rabbits in vitro. So serotonin induced intestinal activity was taken as a control in our experimental study [8].

METHODS

This observational study was done in Multidisciplinary Lab Army Medical College Rawalpindi, from May 2015 to July 2015. Chemicals Serotonin Carnitine Sulfate, fluoxetine hydrochloride, paroxetine hydrochloride and citalopram sulphate was borrowed from local market. All the solutions and dilutions (10^{-9} to 10^{-6}M) was prepared fresh [14].

Preparation of tissue

Twenty four healthy rabbits weighing from 2.5-3.0 Kg were haphazardly divided into four groups (n = 6). Sacrifices an overnight fasting rabbit. We take out small intestine by recognizing the ceacum & cut down two centimeter pieces of rabbits ileum [10]. Pass a thread at both ends & transfer to isolated organ bath containing oxygenated Tyrode's solution [1,8]. One end of the piece of tissue was attached with the hook of the oxygen tube by means of thread while the other end was connected to the frontal writing lever [1]. The lever moves with the contractions of the ileal smooth muscles which are recorded with the transducer on power lab[13].

Cumulative dose response curves for Groups 1-4 (n=6)

Utilizing changing concentrations (10^{-9}-10^{-6}M) we plot the cumulative dose-response curves for group 1 (serotonin), group 2 (fluoxetine), group 3 (paroxetine) & group 4 (citalopram). To maintain tissue viability new tissue was utilized each time (n = 6). Group 1 serotonin group graded response curve served as a control for our study[1].

STATISTICAL ANALYSIS

The outcomes have been communicated as means ± standard deviation. The mean computing methods for amplitudes of contractions and SDs were computed utilizing Post Hoc Tukey's test (One-Way Anova).

RESULTS

SSRIs impose a depressive impact on withdrawal of ileal smooth muscles from the earliest starting point. However a massive diminishing of paroxetine and citalopram-mediated response was seen at 10^{-7} M and 10^{-6} M dilutionss (Fig. 1). To measure the decline in amplitude of SSRI mediated ileal contractility we contrast its reaction and serotonin on ileal smooth muscle in vitro.

Fluoxetine causes a decline in constrictor reaction upto 15.48%, paroxetine causes a noteworthy reduction in ileal smooth muscle contractions from 100% (control) to 7.45% while citlopram causes a extreme abatement in contractility by 6.75%, yet their methods for compressions of sufficiency was found statistically significant.

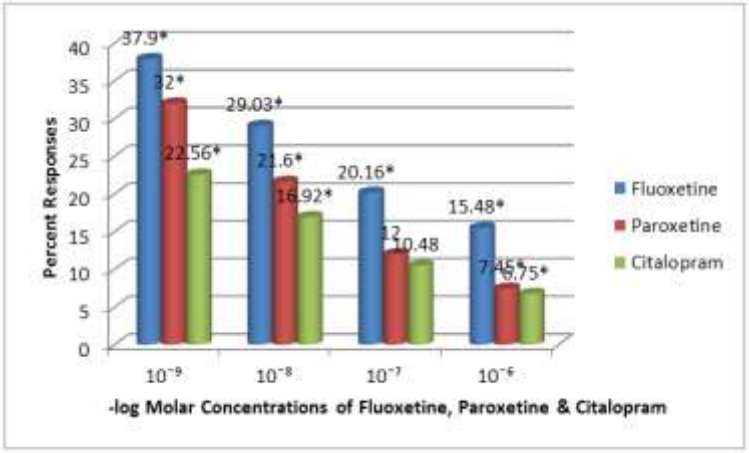

Fig-1: **Comparison of semi log concentration response curve of Group 2 (Fluoxetine), group 3 (Paroxetine) and group 4 (Citalopram) on isolated ileal smooth muscles of rabbit (n=6). Data is represented as mean ± standard deviation (SD)**

*P- value significant (< 0.001)

P- value non-significant (> 0.001)

DISCUSSION

This study was done to observe the effects of SSRIs on ileal smooth muscle of rabbit in vitro and to discover the plausible reason for extreme nausea and vomiting at start of therapy[7,3].

Majority of 5-HT in the body is released from enterochromoffin cells (EC) in the intestinal mucosa. Enterochromaffin cells utilize the protein tryptophan hydroxylase 1(TpH1) to release serotonin. The serotonin-specific reuptake transporter (SERT), which is similarly in charge of 5-HT uptake in the cerebrum, is present in each single epithelial cell of the intestinal mucosa. The serotonin transporter is different from the neurotransmitter: sodium symporter (NSS) family, TC 2.A, which incorporates the monoamine transporters DAT (dopamine) and NAT (norepinephrine), and differs from 5-HT by means of a sodium and chloride intake mechanism[6]. SERT inhibit the reuptake of 5-HT into the epithelial cells from the intestinal mucosa, SERT fills in as a source of 5-HT accessibility and activities in the digestive organs[1, 6]. Thus, increasing the motility & enhancing the adverse effects of SSRIs (Nausea & Vomiting).

5-HT_4 is involved in relaxation of gastrointestinal tract, fluoxetine block the actions of 5-HT_4, causing imapairments of its effects on ileal smooth

muscles[8]. Paroxetine causes a dose dependent decrease in the contractility of ileal smooth muscle[8] causing an increase in the gut transient time[20], due to its effect on vagal and adrenergic inputs[1,5]. Serotonergic receptors (5-HT_{1A} and 5-HT_3) are additionally known to affect vagal afferents pathway and modify the reflex inhibitory pathways[6], subsequently causing diminished contractile response[4]. Citalopram acts via inhibitory effect on nor-epinephrine reuptake[1,6], also block α1 receptors and furthermore has some antihistaminic activity as well[11].

CONCLUSION

Thus, the decrease in response by SSRI's was most likely a consequence of accumulation of endogenous serotonin at the receptor site leading to desensitization of serotonergic receptors in the enterochromoffin cells of gastrointestinal tract[11].

Conflict of interest

Author show no conflict of interest.

Abbreviations: SSRIs; 5-HT; 5-HT_4-Receptors;

DECLERATION

Part of the study has been published in articles-

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