

Effect of fluoxetine and paroxetine on intestinal motility**Ayesha Afzal^{1*}, Mahjabeen Sharif², Ammara Khan³, Bushra Tayyaba Khan², Iffat Ara¹**¹Department of Pharmacology,
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medium, provided the original
work is properly cited.**ABSTRACT****Background:** Serotonin (5-HT) is a biogenic amine that functions as a neurotransmitter of sensorimotor functions in the digestive tract. The role of 5-HT agents in the modulation of lower gastrointestinal function. Selective serotonin reuptake inhibitors (SSRIs) are of potential benefit in functional gastrointestinal diseases although formal evidence is lacking. Apart from central effects, they may have peripheral. The present study was carried out to find out the possible effects of fluoxetine and paroxetine on gastrointestinal smooth muscles of rabbit as they cause severe nausea and vomiting initially.**Methods:** Experimental study design. Power lab (USA) for recording the contractions of ileal smooth muscle of rabbit in response to serotonin, fluoxetine and paroxetine.**Results:** The percent responses with serotonin, fluoxetine and paroxetine were 100, 10.53, and 4.75 percent respectively.**Conclusions:** SSRIs (fluoxetine and paroxetine) were unable to enhance the serotonergic transmission in vitro in turn decreases the qualitative response.**Keywords:** Diarrhea, Fluoxetine, Gastrointestinal tract, Paroxetine, Power lab, Serotonin**INTRODUCTION**

There are many neurotransmitters which are involved in the pathophysiology of nausea and vomiting. The most common are serotonin, dopamine and substance P (Neurokinin 1). Their receptors are present in high concentration in dorsal vagal complex, area postrema and gastrointestinal tract.

Deficiencies or fluctuation in the levels of serotonin, nor-epinephrine and dopamine is now thought to be the basis

for the etiology of depression. Several clinical studies suggested that by targeting the specific serotonin receptors with selective agonist or antagonist not only improves the efficacy but also reduces time required for the therapeutic effect of antidepressants to appear. Aside from depression SSRIs are also prescribed worldwide for anxiety disorder, various types of eating disorders, acute attack of migraine, chemotherapy induced nausea and vomiting, obsessive compulsive disorders, pain due to neuropathy, fibromyalgia's, panic disorder and schizophrenia.¹

The primary pharmacological activity of SSRIs is inhibition of the serotonin transporter (SERT) which is responsible for the reuptake of serotonin (5-HT) from the extracellular space back into the nerve terminals that release it. Inhibition of this transport alters the spatiotemporal dynamics of serotonin signalling such that activity in the serotonergic neuron causes greater and more prolonged increases in extracellular serotonin than would normally occur.²

Due to this nausea and vomiting are common adverse effects of these therapeutic drugs. Such symptoms are more often due to CNS effects than to direct toxic effects on the gastrointestinal tract (GIT). Drugs may cross the blood-brain barrier and activate the chemoreceptor trigger zone in the brainstem, which contains cells that are responsive to cholinergic, dopaminergic and serotonergic stimulation. Binding of serotonin to its receptors stimulate the chemoreceptor trigger zone (CTZ) and vomiting centre (VC) in the medulla. Once activated the vomiting centre modulate the efferent transmission to the respiratory vasomotor and salivary center. Vomiting center also modulate impulses to the abdominal muscles, diaphragm, and esophagus resulting in emesis.³

The present study was carried out to explore the underlying mechanism of excessive nausea and vomiting produced by selective serotonin reuptake inhibitors, we observed the effects of fluoxetine and paroxetine on ileal smooth muscles of rabbits in vitro and also observed that which among these two has better tolerability against nausea and vomiting. So serotonin-mediated intestinal activity was taken as control in our research study.⁴

METHODS

This experimental study was carried out in Multidisciplinary Lab Army Medical College Rawalpindi, from May 2016 to July 2016.

Chemicals

Serotonin Carnitine Sulfate, fluoxetine hydrochloride and paroxetine hydrochloride were purchased from local market. All the solutions and dilutions (10^{-9} to 10^{-6} M) were prepared fresh at the time of experiments.³

Preparation of tissue

Twenty-four healthy rabbits weighing from 2.5-3.0Kg were randomly divided into four groups (n=6). We sacrificed an overnight fasting rabbit, small intestine was taken out, ileum was cut into 2 inches pieces.⁴ The isolated tissue was then transferred to organ bath containing tyrode's solution and aerated continuously with 95% oxygen and 5% carbondioxide.⁵ One end of the ileal strip was attached to the bottom of oxygen tube in tissue bath and the other end was connected to a research grade force Displacement transducer.⁶ After equilibration the isotonic

ileal smooth muscle activity was recorded through the Displacement Transducer on Power lab.⁷

Group 1- Cumulative concentration response curve of Serotonin (n=6)

Using varying concentrations (10^{-9} - 10^{-6} M) we construct the cumulative dose-response curves of acetylcholine. To prevent tissue sensitization new tissue was used each time (n=6). This group served as a control for our study. So, fluoxetine and paroxetine mediated contractions are compared with acetylcholine induced contractions.

Group 2- Cumulative concentration-response curve of fluoxetine (n=6)

Fluoxetine mediated isotonic contractions were recorded using concentrations 10^{-9} to 10^{-6} M in the same manner as used for serotonin.⁸

Group 3- Cumulative concentration-response curve of paroxetine (n=6)

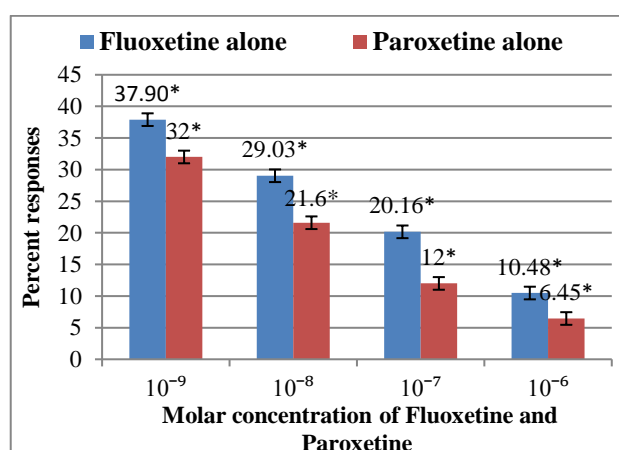
By using varying concentrations of paroxetine (10^{-9} - 10^{-6} M) we record the ileal smooth muscle activity in similar manner as for group 1 and 2.

Statistical analysis

The results have been expressed as means±standard deviation. The arithmetic means of amplitudes of contractions and SDs were calculated using Post Hoc Tukey's test (Two-Way Anova).

RESULTS

SSRIs exert a depressive effect on contraction of ileal smooth muscles right from the beginning.



Data is represented as mean ± standard error of means (SEM)

*= Significant (p < 0.05)

=Non-Significant (p > 0.05)

Figure 1: Comparison of group 2 (fluoxetine) and group 3 (paroxetine) on isolated ileal smooth muscle of rabbit (n=6).

However, a significant decrease of paroxetine induced contractions was observed at 10^{-7} M and 10^{-6} M concentrations (Figure 1, Table 1). To evaluate the decrease in magnitude of SSRIs-induced ileal contractility we compare its response with the response of serotonin on isolated ileal smooth muscle.

Fluoxetine causes a decrease in constrictor response upto 10.53%, paroxetine causes a significant decrease in ileal smooth muscle contractions from 100% (control group) to 6.45%. Thus, its obvious that paroxetine has a more depressive effect on intestinal motility as compared to fluoxetine. So, fluoxetine will be a preferred antidepressant than fluoxetine as it will cause less marked nausea and vomiting.

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

Concentration (M) of fluoxetine	Amplitude of contractions (Mean±SEM) mm control group n=6	Amplitude of contractions (Mean±SEM) mm fluoxetine n=6	Percent (%) response fluoxetine	Amplitude of contractions (Mean±SEM) mm paroxetine n=6	Percent (%) response paroxetine
10^{-9}	13.2±1	9.4±0.453	37.90	8±3.55	32
10^{-8}	16.8±1.6	7.2±2.09	29.03	5.4±1.60	21.6
10^{-7}	20±1.5	5±2.095	20.16	3±1.03	12
10^{-6}	24.8±1.22	2.6±1.16	10.48	1.6±0.98	6.45

DISCUSSION

The current research study was carried out to observe the effects of Selective serotonin reuptake inhibitors (Fluoxetine and Paroxetine) on ileal smooth muscle of rabbit in vitro and to find out the possible reason that may underlies in causing severe nausea and vomiting at the start of therapy. Serotonin gradually increases the ileal smooth muscle contractility, whereas SSRIs in contrast to serotonin decreases the smooth muscle contractility.⁹

Serotonin by acting directly through 5-HT₄ (G- protein coupled receptors) located on both cholinergic interneurons and motor neurons¹⁰ on enterocytes and indirectly via 5-HT₃ receptors on mucosal nerves and vagal afferents effects the intestinal motility.¹⁰ The 5-HT₄ receptors stimulation by serotonin leads to an increase in the acetylcholine release which in turn increases the intestinal activity, leading to increase in amplitude of contractions and also an increase in intestinal motility.¹¹ Thus, serotonin mediated contractions was taken as a control in our study (100%).

5-HT₄ is responsible for relaxation of gastrointestinal tract, fluoxetine antagonizes 5-HT₄ the mediated responses causing decrease in contractile response of ileal smooth muscles upto 10.48%.¹² Paroxetine causes a dose dependant decrease in the contractile activity of isolated ileal smooth muscle, in turn causing an increase in the gut transient time because of its influence on vagal and adrenergic inputs.¹³ In addition serotonergic receptors (5-HT_{1A} and 5-HT₃) they are also known to influence vagal afferents pathway and alter the reflex accommodation pathways, hence causing decrease in amplitude of contractions upto 6.45%.¹⁴⁻¹⁶

Thus, it can be deduced from our observation as well as by the studies carried out by other researchers that paroxetine has a more depressive effect on intestinal motility (6.45%) as compared to fluoxetine (10.48%).¹¹⁻¹⁶ So, fluoxetine will be causing less nausea and vomiting at start of therapy than paroxetine. Fluoxetine also have the advantage of long half life (48hrs) requiring single daily dose.¹⁷

CONCLUSION

From this study, Thus, the decrease in response by SSRI's was most likely a consequence of accumulation of endogenous serotonin in vitro at the receptor site leading to desensitization.

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