

Paroxetine: An update of response on intestinal motility

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Abstract

Objectives: To find out the possible effects of paroxetine on gastrointestinal smooth muscles in vitro as they can cause severe nausea and vomiting at the start of therapy which later settles down.

Method: Power lab (USA) was used for recording the contractions of ileal smooth muscle of rabbits in response to acetylcholine, serotonin and paroxetine.

Results: The percent responses with acetylcholine, serotonin and paroxetine were 100, 158.7 and 6.45 percent respectively indicating that acetylcholine and serotonin causes an increase in contractility of isolated ileal smooth muscle in comparison to paroxetine which has a depressant effect on motility.

Conclusion: Inability of paroxetine to enhance the serotonergic transmission in vitro causes a decrease in its qualitative response.

Keywords: Serotonin, Paroxetine, Acetylcholine, Gastrointestinal tract, Diarrhea, Power lab. (JPMA 66: 240; 2016)

Introduction

Developments of antidepressants in the last five decades were based on monoaminergic hypothesis, which postulates that depression is because of deficiencies or fluctuation in the levels of serotonin, nor-epinephrine and dopamine. Several preclinical studies have 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.¹ To explore the underlying mechanism of excessive nausea and vomiting produced by selective serotonin reuptake inhibitors, we observed the effects of paroxetine on ileal smooth muscles of rabbits in vitro. About 95% of serotonin is released in the gastrointestinal tract in response to release of acetylcholine.^{2,3} So acetylcholine and serotonin-mediated intestinal activity was taken as the control.⁴

Method

This experimental study was carried out in Multidisciplinary Lab Army Medical College Rawalpindi, from March 2013 to July 2013 after obtaining approval from the institutional ethical committee.

Chemicals Acetylcholine Chloride, Serotonin Carnitine Sulfate 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.⁵

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Preparation of Tissue

Eighteen healthy rabbits weighing between 2.5-3.0 Kg were randomly divided into three groups (n=6). One overnight fasting rabbit was sacrificed and the small intestine was removed. The ileum was cut into 2 inches pieces⁶ and transferred to an organ bath of 50ml capacity containing tyrode's solution (in mM: NaCl, 136.8mM; KCl, 2.7mM; MgCl₂, 0.5mM; CaCl₂, 1.3mM; NaH₂PO₄, 0.14mM; NaHCO₃, 12.0mM, Dextrose, 5.5mM) and aerated continuously with 95% oxygen and 5% carbon dioxide.⁵ One end of the ileal strip was attached to the bottom of the oxygen tube in tissue bath and the other end was connected to a research grade force Displacement transducer.² 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 acetylcholine (n=6)

Using varying concentrations (10^{-9} - 10^{-6} M) the cumulative dose-response curves of acetylcholine was constructed. To prevent tissue sensitization new tissue was used each time (n=6). This group served as a control for the study, and serotonin and paroxetine mediated contractions were compared with acetylcholine induced contractions.²

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

Serotonin mediated isotonic contractions were recorded using concentrations 10^{-9} to 10^{-6} M in the same manner as used for acetylcholine.²

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

By using varying concentrations of paroxetine (10^{-9} - 10^{-6}

M) the ileal smooth muscle activity was recorded in a similar manner as for group 1 and 2.

Statistical Analysis

The results were expressed as means \pm standard deviation. The arithmetic means of amplitudes of contractions and SDs were calculated using Kruskal-Wallis test (One-Way Anova).

Results

Paroxetine exerts a depressive effect on contraction of ileal smooth muscles and a significant decrease of paroxetine-induced contractions was observed at 10^{-7} M and 10^{-6} M concentrations (Figure). To evaluate the decrease in magnitude of paroxetine-induced ileal contractility the response was compared with that of

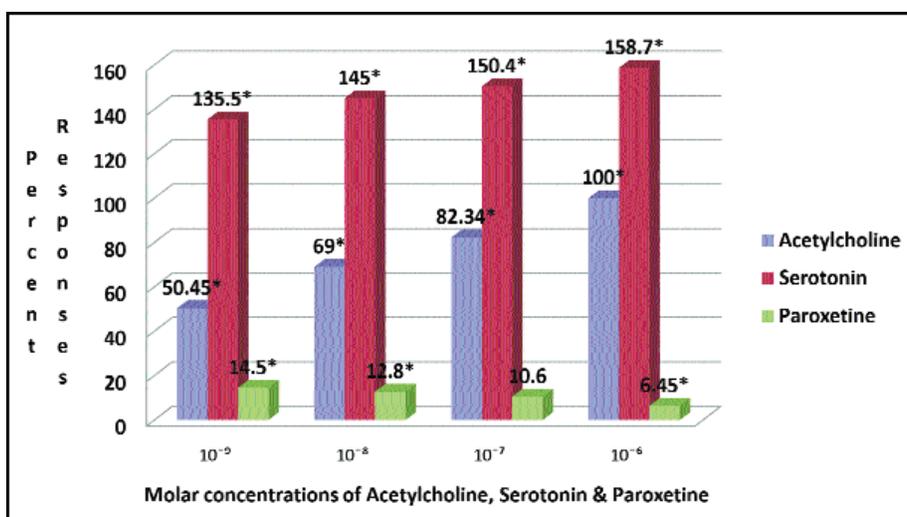


Figure: Cumulative dose response curve of Acetylcholine, Serotonin & Paroxetine.

*P- value significant (< 0.001)
P- value non-significant (> 0.001)

acetylcholine and serotonin on isolated ileal smooth muscle. Maximum constrictor response of serotonin was 58.7% more than the maximal acetylcholine response.

Paroxetine caused a significant decrease in ileal smooth muscle contractions compared to the control group (100% to 6.45%) and amplitude of contractions was found statistically significant.

Discussion

The current study was carried out to observe the effects of paroxetine on ileal smooth muscle of rabbit in vitro and to find out the possible reason that may be responsible for causing severe nausea and vomiting at the start of therapy. Acetylcholine and serotonin gradually increases the ileal smooth muscle contractility, whereas paroxetine

in contrast to acetylcholine and serotonin decreases the smooth muscle contractility. Acetylcholine mediated ileal contractions was taken as a standard for comparison in our experimental study.⁸

By acting via muscarinic receptors (M_3) acetylcholine causes an inositol triphosphate (IP_3) mediated release of intracellular calcium,⁹ the release of diacylglycerol (which activates protein kinase C), causing contraction of smooth muscles.¹⁰

Serotonin produced 158.7 percent of acetylcholine mediated response on ileal smooth muscles of rabbit.¹¹ Serotonin by acting directly through 5-HT₄ (G- protein coupled receptors) located on both cholinergic interneurons and motor neurons² on enterocytes and indirectly via 5-HT₃ receptors on mucosal nerves and vagal afferents effects the intestinal motility.¹² The 5-HT₄ receptors stimulation by serotonin leads to an increase in the acetylcholine release which in turn increases the intestinal activity.¹³

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.¹⁴ 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,¹⁵ hence causing decrease in

amplitude of contractions.¹⁶

Conclusion

Paroxetine decreases the intestinal motility due to unmasking of its anticholinergic activity. In addition it also causes down regulation of serotonin transporter in the gastrointestinal tract in vitro.

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