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Original Research Article

Evaluation of anxiolytic effect of pantoprazole on Swiss albino mice

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ABSTRACT

Background: Anxiety disorders are one of the most common psychiatric disorders and they affect over 7% of the global population. It substantially compromises daily life, productivity, and social functioning. Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines provide only limited relief and are often burdened by side effects including sedation, sexual dysfunction, and dependence. This has created a crucial need for safer therapeutic alternatives. Among the commonly used proton pump inhibitors- pantoprazole has demonstrated neuroprotective and anti-inflammatory properties in preclinical studies. These outcomes raise the possibility that pantoprazole may also exert anxiolytic effects, which have not yet been explored.
Methods: Thirty female Swiss albino mice were divided into five groups, each consisting of 6 animals. The groups were- control (saline), standard (diazepam 5 mg/kg i.p.), and pantoprazole-treated groups (10, 15, 20 mg/kg orally). Drugs were administered daily for 14 days. Mice were assessed using the Elevated Plus Maze (EPM) and Actophotometer on the 1st and 15th day to determine whether pantoprazole produced anxiolytic effects with acute and chronic dosing.
Results: Pantoprazole treatment at 20 mg/kg dose significantly reduced anxiety-like behavior. Mice that were treated with pantoprazole spent more time in the open arms of the EPM compared to the control group. The 20 mg/kg of pantoprazole group produced an effect ($p<0.001$) which was comparable to diazepam's anxiolysis. Locomotor activity remained unchanged across pantoprazole groups, indicating that its anxiolytic effect was not confounded by sedation.
Conclusions: This experimental study provides the first evidence that pantoprazole at 20 mg/kg dose, exerts significant anxiolytic effects in Swiss albino mice. There were no changes in locomotor activity by the pantoprazole group, signifying no sedative side effects. These results showcase pantoprazole's possible utility as a novel or an adjunctive therapeutic agent for anxiety disorders. Although further studies on mechanisms of action and clinical trials are required, these findings open an avenue for repurposing a well-tolerated drug in the management of anxiety.

Keywords: Pantoprazole, Swiss albino mice, Anti-anxiety agents, Elevated plus maze test, Anxiety disorders

INTRODUCTION

Anxiety disorders are common conditions that impair quality of life including the ability to concentrate, sleep, or function peacefully.[1] They are among the most prevalent psychiatric disorders with a worldwide prevalence of 7.3%.[2] Anxiety disorders consist of several diagnostic entities including generalized anxiety disorder (GAD), selective mutism, specific phobia (SP), social anxiety disorder (SAD) and panic disorder all characterized by excessive fear and anxiety with associated behavioral disturbances as described with their respective diagnostic

criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[3] These disorders have a lifetime prevalence of 33.7% and are associated with increased utilization of healthcare services.[3,4] Due to the reduced work productivity, there is a significant burden imposed on affected individuals, their families and society leading to the collective economic cost of over $40 billion per year.[1]

The key drug classes that are commonly used in the treatment of anxiety disorders are SSRIs, selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and benzodiazepines. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are also effective but less commonly used due to their side effect profiles.[3]

However, these current therapies are considered insufficient to address the significant public health burden of anxiety disorders due to limitations in efficacy as well as tolerability. For instance, recent large meta-analyses failed to substantiate the effectiveness of azapirones, such as buspirone, or benzodiazepines in treating panic disorder. Similarly, treatment of post-traumatic stress disorder (PTSD) and GAD with the above mentioned treatments are only partially effective.[3]

SSRIs are first-line drugs, but they commonly cause headaches, sweating, tremor, dry mouth, anxiety, restlessness, gastrointestinal disturbances, dizziness, and somnolence or insomnia. Drugs that enhance serotonergic transmission can cause sexual dysfunction, which affects 30% of SSRI users. In contrast to other side effects, sexual dysfunction does not build tolerance in patients and may occur weeks or months into treatment. A significant concern is that patients are still at risk for a recurrence or relapse of their disorders if they discontinue medication in the maintenance phase of therapy.[5]

Serotonin- norepinephrine reuptake inhibitors (SNRIs) have a different side effect profile at higher doses than SSRIs, which exhibit the same side effect profile across their whole dose range. This is because side effects at lower dosages are mostly mediated by blockage of the 5-HT transporter, whereas side effects at larger levels are driven by blocking of the NE uptake. The adverse effects at lower doses include nausea, diarrhea, lethargy or somnolence, and sexual side effects. Noradrenergic side effects seen at higher doses are hypertension, tachycardia and clinically significant discontinuation syndromes.[6]

Benzodiazepines, although not commonly used in first line therapy, are still frequently prescribed as adjunctive treatment. Acute administration causes sedation, amnesia, and learning difficulties. Long-term benzodiazepine use can lead to cognitive impairment that may not be reversible after discontinuation.[7]

The various side effects of conventional treatment along with their modest efficacy have prompted the development of novel agents that better balance anxiolytic efficacy with minimal side effects. Recent studies have shown that proton pump inhibitors have beneficial effects on the central nervous system. In an experimental epilepsy study-, pantoprazole treatment delayed seizure onset, and protected memory, while reducing 8-hydroxy-2 deoxyguanosine (8-OhdG), caspase-3, and increased brain derived neurotrophic factor (BDNF) in the brain. Pantoprazole also significantly improved oxidative stress and apoptosis, and it was concluded that it could be used as a supportive agent in epilepsy.[8]

Proton pump inhibitors (PPIs) have also been shown to decrease interferon (IFN)-γ-induced neurotoxicity of human astrocytes through inhibition of the signal transducers and activators of transcription 3 (STAT3) signaling pathway. These findings indicate that PPIs possess anti-neurotoxic properties which may represent a potential treatment option for Alzheimer's disease and other neuroinflammatory disorders associated with activated astrocytes.[9]

Since the pathophysiology of anxiety involves oxidative stress and neuroinflammation via different signaling pathways the above-mentioned central effects suggest possible anxiolytic-like effects by pantoprazole. [10,11] These properties have not yet been systematically evaluated in preclinical models.

Therefore, this study aimed to evaluate the anxiolytic effect of pantoprazole on Swiss albino mice. We hypothesized that pantoprazole would exhibit anxiolytic effects in these models.

METHODS

Animals

Female Swiss albino mice (3-4 months old, 25-30 g) were housed in polypropylene cages under controlled conditions (temperature 22-25ºC, humidity 50-55%, 12 h light/12 h dark cycle) with free access to food and water. They were randomly distributed into experimental groups described below. All experiments were conducted between 9:00 and 17:00 h. The procedures in this study were approved by the Institutional Animal Ethics Committee (PIMS/27-IAEC/N-27/2023) and were performed in accordance with the CPCSEA guidelines.

Drugs

Pure drug form of diazepam was obtained from Anglo French Drugs and Industries Ltd. Pantoprazole was formulated by Metrochem API Pvt Ltd, Hyderabad and supplied by Medistark Biotech Pvt Ltd. Both drugs were diluted in distilled water and freshly prepared daily before drug administration.

Diazepam was administered intraperitoneally, while pantoprazole was administered orally

Experimental groups

Thirty animals were divided into five groups (n=6 per group). Group I served as control and received normal saline 10 ml/kg, orally. Group II served as the standard and received diazepam 5mg/kg, intraperitoneally. Group III, IV and V received pantoprazole at doses of 10 mg/kg,15 mg/kg and 20 mg/kg orally.

All the animals in various groups received the assigned treatment daily in the Department of Pharmacology in Pondicherry Institute of Medical Sciences (PIMS) for 14 consecutive days in March 2024. The anxiety behavioral assessments were performed on the 1st day and on the 15th day. Behavioral assessments on day 1 represented the acute effect, while assessments on day 15 represented the chronic effect of treatment. Animals were habituated to the apparatus 24h before the first behavioral testing session. The dose of diazepam was chosen from previous studies done by Churihar and McNamara, and the dose of pantoprazole was chosen from an earlier study by Taskiran et al.[8,12,13]

Assessment of behavioral tests

Elevated plus maze: The elevated plus maze test is one of the most widely used tests for measuring anxiety-like behavior and is based on the natural aversion of mice for open and elevated areas. The apparatus consists of two opposing open arms (50×10 cm) and two opposing closed arms (50×10×30 cm), crossing in the middle perpendicularly to each other, and elevated 70 cm above the floor. Each mouse was placed in the central area and allowed free access to all the arms for five minutes after a 1-minute habituation period. The apparatus was cleaned with 70% ethanol between trials to remove olfactory cues. Time spent in the open arms was recorded.[14,15]

Actophotometer

Locomotor activity (horizontal activity) was assessed using an actophotometer which operates on photoelectric cells connected in circuit with a counter. Each mouse was placed individually in the arena for five minutes after a minute habituation period. When the beam of light falling on the photocell is cut off by the mouse, a count is recorded. Changes in locomotor activity were used to assess potential stimulant or sedative effects of the drugs.[16]

Statistical analysis

Data are expressed as mean±standard deviation (SD). Statistical analysis was performed using GraphPad InStat software version 3.06 (Dotmatics, Boston, Massachusetts, United States of America). Between-group comparisons were made using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A $p<0.05$ was considered statistically significant and $p<0.001$ was extremely statistically significant. Data obtained on Day 1 (acute study) and Day 15 (chronic study) were analyzed separately.

RESULTS

Acute study (Day 1)

On the first day of the experimental study (Figure 1), significant differences were observed between groups in the time spent in the open arms of the elevated plus maze (one way ANOVA, $p<0.001$). The animals treated with diazepam showed a significantly higher open-arm time than control ($p<0.001$). Dose dependent increase in open arm time was observed in the groups treated with pantoprazole. The groups treated with 15 mg/kg and 20 mg/kg showed a moderate increase in time spent in open arms. Post hoc analysis showed that diazepam (5 mg/kg, IP) and pantoprazole 20 mg/kg (PO) compared to the control group produced a significant increase in open arm time ($p<0.001$). It was noted that anxiolytic effect remained lower than that of diazepam. However, there was no significant change in the pantoprazole group of 10 mg/kg and 15mg/kg compared to that of control. The animals treated with pantoprazole did not show any significant change in the locomotor activity at any given dose (Table 1). There was no statistically significant difference in locomotor activity between the groups either.

Chronic study (Day 15)

At the end of 14 days of treatment (Figure 2), there was a significant overall treatment effect on open arm time ($p<0.001$). The animals treated with diazepam exhibited prolonged time in the open arms compared to the control ($p<0.001$). Even though, 10 mg/kg and 15 mg/kg group demonstrated a moderate increase in open arm time when compared to control, 20 mg/kg exhibited a more robust increase. This group was statistically different from control ($p<0.05$). On Day 15, locomotor activity of the standard group was significantly different compared to control group (Table 2). Pantoprazole groups at all tested doses showed locomotor activity comparable to control.

Table 1: Effect of diazepam and pantoprazole on locomotor activity in mice (Day 1).

Groups	Treatment (route, dose)	Locomotor activity (count/5 minutes), mean±SD
I	Normal saline 10 ml/kg, orally	218.33±20.007
II	Diazepam 5 mg/kg, intraperitoneally	206.67±20.304
III	Pantoprazole 10 mg/kg orally	217.00±67.764
IV	Pantoprazole 15 mg/kg orally	217.67±15.214
V	Pantoprazole 20 mg/kg orally	226.83±25.063

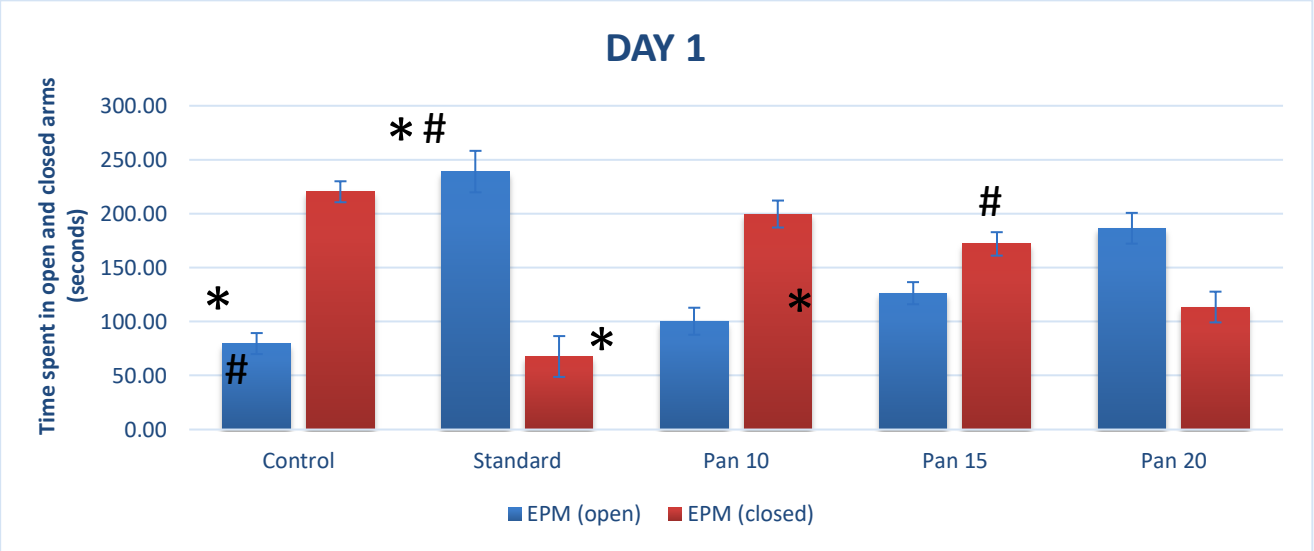

Figure 1: Effect of diazepam and pantoprazole on time spent in open arms of elevated plus maze in mice (Day 1).
The error bars represent the standard error of the means. *p<0.001 when compared with the standard group, #p<0.001 when compared with the control group; one way ANOVA followed by Tukey's post hoc test.

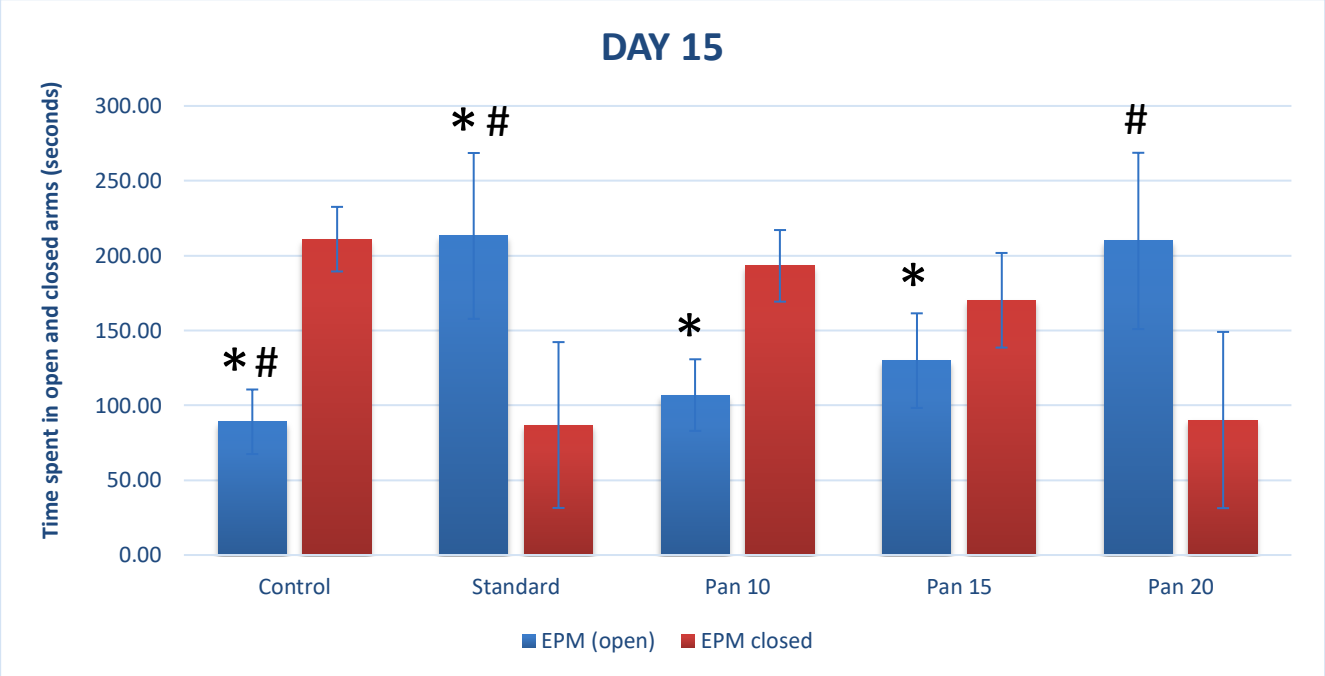

Figure 2: Effect of chronic administration of diazepam and pantoprazole on time spent in open arms of the elevated plus maze in mice (Day 15).
The error bars represent the standard error of the means. *p<0.05 when compared with the standard group, and #p<0.001 when compared with the control group; one way ANOVA followed by Tukey's post hoc test.

Table 2: Effect of diazepam and pantoprazole on locomotor activity in mice (Day 15).

Groups	Treatment (route, dose)	Locomotor activity (counts/5 minutes), Mean±SD
I	Normal saline 10 ml/kg, orally	241.67±36.148
II	Diazepam 5 mg/kg, intraperitoneally	295.17±27.029
III	Pantoprazole 10 mg/kg orally	231.17±33.588
IV	Pantoprazole 15 mg/kg orally	216.17±11.839
V	Pantoprazole 20 mg/kg orally	232.83±31.308

DISCUSSION

The anxiolytic effect of pantoprazole was assessed using the Elevated Plus Maze (EPM) which is a validated animal model of anxiety and Actophotometer for locomotor activity. The findings were that pantoprazole, particularly at a dose of 20 mg/kg, displays prominent anxiolytic activity. In the EPM, time spent in the open arms increased significantly for the P20 group compared to lower doses, indicating a reduction in open-space-induced anxiety. These results are consistent with the anxiolytic effects of diazepam reported in similar animal studies, such as those by Peng et al where diazepam increased the amount of time spent in the open arms in the EPM.[17]

Horizontal locomotor activity was measured using an actophotometer to evaluate sedative activity. Pantoprazole did not alter locomotor activity when compared to the control group. This outcome indicates that there was no sedative effect of pantoprazole at the administered doses and indicates that the anti-anxiety effect was not confounded by sedation. Even though pantoprazole produced profound anti-anxiety effects at the dose of 20 mg/kg, diazepam (5 mg/kg) remained more potent. The difference in efficacy may be attributed to diazepam's well-established role in modulating GABAergic neurotransmission, directly enhancing inhibitory signaling in the central nervous system.[18]

Proton pump inhibitors which are mainly used in the treatment of acid-related gastrointestinal disorders may also influence neurobehavioral processes through various mechanisms according to recent evidence. The gut brain axis is one possible mechanism, which is a bidirectional link between the gastrointestinal tract and the central nervous system. Changes in gastric physiology and gut microbiota composition may have an effect on the neurotransmitters involved in emotional regulation (i.e serotonergic and GABAergic pathways).[19] The next plausible theory is that pantoprazole can regulate important cellular signaling pathways that suppresses nuclear factor kappa B (NF-κB) signaling and reduces the expression of inflammatory mediators such as cyclooxygenase-2(COX-2) and inducible nitric oxide synthase (iNOS). It is also shown to affect mitochondrial function and oxidative stress pathways. Since neuroinflammation and NF-κB activation are a known cause of anxiety, the inhibitory effect of pantoprazole on this pathway may partly explain the anti-anxiety-like effects observed in the present study.[20]

The dose-dependent effects observed in this study are consistent with pharmacological principles reported for other anxiolytic agents, including traditional benzodiazepines.[21] Specifically, the P20 group exhibited the most pronounced anxiolytic effects within the EPM, while lower doses showed modest improvement but did not achieve statistical significance when compared with the standard drug. This dose-response relationship suggests that pantoprazole's anxiolytic activity may involve receptor-mediated mechanisms requiring adequate concentrations to achieve optimal effects. While its efficacy is slightly lower than that of diazepam, the lack of sedative effects observed in the Actophotometer test suggest a favorable therapeutic profile. This is particularly relevant given the adverse effects of currently used drugs, as cited previously.

Limitations

Despite these findings, certain limitations of the study must be acknowledged. The sample size was relatively small and anxiety like behavior was assessed only using the elevated plus maze which is widely validated but reliance on a single behavioral paradigm may not capture the nature of anxiety. Additional models would strengthen the behavioral validation. Although diazepam is known to be sedative, no significant reduction in locomotor activity was observed on chronic dosing (day 15). This may be due to dose selection or timing of the assessment. Therefore, the absence of sedation in the diazepam group should be interpreted with caution.

The present study did not investigate the mechanisms responsible and further studies including but not limited to pantoprazole's interactions with CNS receptors, altering processes linked to apoptosis, inflammation, and oxidative stress, or effects on inflammatory mediators are warranted to explain the anxiolytic effects. [22] Considering the well-established safety profile and common clinical use of proton pump inhibitors, further clinical trials may help determine whether pantoprazole could have potential value in the management of anxiety-related disorders.

CONCLUSION

In summary, 20 mg/kg of pantoprazole showed the most effective anti-anxiety like effect in Swiss albino mice among the treatment groups. These results are comparable with the standard group of diazepam (5 mg/kg i.p). Though the standard group was more efficacious, there were no significant sedative properties at the tested doses of the pantoprazole groups. These results indicate the potential of pantoprazole as an alternative or add on therapy for anxiety disorders. Further studies should focus on the mechanisms of action of these findings.

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