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Research Article

ANXIOGENIC EFFECT OF AN ATYPICAL ANTIPSYCHOTIC, OLANZAPINE IN PRE-CLINICAL MODELS

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ABSTRACT

Objective: Atypical antipsychotics, such as olanzapine, act on multiple neurotransmitter pathways and produce complex central nervous system effects. Pre-clinical and clinical studies conducted in the past, to study their effects on anxiety, have come up with confusing and contradictory observations. Some studies have even indicated anxiogenic effect of these novel drugs. These observations are significant, because anxiety symptoms are known to be present in about 65% of schizophrenia patients. Any possible anxiogenic effect by one of the extensively used antipsychotic can have adverse impact on these patients. Hence, this study was undertaken with the aim of evaluating olanzapine for its effects on anxiety, in preclinical models.

Methods: Rats of either sex weighing between 150 and 300 g were placed into three groups of six each. For 10 days, oral doses of the test drug (olanzapine 2 mg/kg), the control drug (distilled water), and the standard drug (diazepam 1 mg/kg) were given. The animals were taken for the elevated plus maze (EPM) and light dark arena (LDA) screening tests on the 10th day, 1 h after the compounds were administered.

Results: Olanzapine treatment significantly reduced the amount of time that animals spent in open arms ($p<0.05$) of the EPM, and highly lighted compartments ($p<0.05$) of LDA, as compared to animals receiving control treatment, showing a significant anxiogenic impact.

Conclusions: Olanzapine has exhibited potential to produce anxiogenic effect in preclinical models. Hence, it is suggested to use olanzapine with caution in patients of schizophrenia with anxiety symptoms.

Keywords: Olanzapine, Anxiogenic, Caution, Schizophrenia.

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INTRODUCTION

The burden of sickness in the world is largely made up of mental disorders. They seriously threaten health systems, especially in low- and middle-income nations. One such debilitating mental illness that has a long-term effect on a person's life is schizophrenia. This terrible mental illness has an impact on job, social interaction, and family ties. The expense of healthcare for those with this crippling condition is extremely high all over the world. Significant changes in perception, thought, mood, and behavior are hallmarks of schizophrenia. Positive and negative symptoms are used to define its symptoms. While more recent atypical antipsychotics are successful in reducing both symptoms, classic typical antipsychotics are good at reducing the positive symptoms [1].

Olanzapine, an atypical antipsychotic, which is available as an oral formulation is used in treatment of schizophrenia and bipolar disorder. Olanzapine has a high affinity antagonistic effect on the 5HT2A, 2C, 5HT6, D1-4, and adrenergic 1 receptors and a moderately antagonistic effect on the M1-5 and 5HT3 receptors [2].

Since olanzapine, in particular and atypical antipsychotics in general, acts on multiple neurotransmitter pathways of human central nervous system, central nervous system effects of these novel drugs are not clearly understood till date. This holds especially relevant when it comes to effects of these drugs on anxiety. Numerous pre-clinical and clinical studies conducted to study their effects on anxiety have come up with confusing and contradictory observations and results [3].

While the studies such as the ones conducted by Mead *et al*., Siemiatkowski *et al*. and Frye and Seliga [4] reported anxiolytic effects, other pre-clinical studies such as Cao and Rodgers [5] failed to confirm anxiolytic effects. Some preclinical studies have even suggested anxiogenic effects of atypical antipsychotics such as Karl *et al*. [6]. This is significant considering the fact that 38.3% of schizophrenia spectrum disease patients suffer from comorbid anxiety disorders. Since olanzapine is one of the most commonly prescribed antipsychotic in treatment of schizophrenia, any possible anxiogenic adverse effects can further complicate the management of this debilitating mental disorder.

Hence, this study was undertaken with the aim of evaluating olanzapine for its effects on anxiety, in preclinical models.

METHODS

Animals

Before conducting studies, the Institutional Animal Ethics Committee's (IAEC) approval was taken (YU – IAEC Number 2a/26/08/2013). We used adult, 200–300 g Wistar albino rats of both sexes. They were housed in typical housing conditions.

Drugs and chemicals

Olanzapine (test drug) 2 mg/kg, distilled water, and diazepam (Standard) 1 mg/kg were obtained from our institutional pharmacy.

Methodology

Three groups of six rats each were created from 200 to 300 g rats of either sex.

- Group I: Control (distilled water)
- Group II: Test drug (2 mg/kg) olanzapine
- Group III: Standard therapy (1 mg/kg of diazepam).

Wistar albino rats received the medications orally once every day for 10 days.

Animals were taken for screening tests in the elevated plus maze (EPM) and light dark arena (LDA) on the 10th day, an hour after test drugs had been administered to them.

It is believed that the EPM is an etiologically accurate model of anxiety. Three anxiogenic elements are considered in its evaluation: novelty, height, and open space. It has been observed that the time spent in the open arm and numbers of entries will increase with anxiolytics drugs, while they decrease with anxiogenic agents.

The animal was placed on the main platform and faced one of the closed arms for 5 min of observation. The amount of time spent in open and closed arms throughout the 5-min test period was noted. The amount of time spent with an open arm was used as a measure of anxiolytic activity.

The LDA exploration test is based on the fact that rats naturally avoid areas that are well-lit. Anxiolytics increase time spent in lighted spaces and lessen natural aversion to light, whereas anxiogenic drugs are known to have the reverse effect.

After being placed inside the light container, the animal was watched for 5 min. The amount of time spent in the light and dark compartments during the observation period was noted. An indicator of anxiolytic/anxiogenic activity was the length of time spent in a lit compartment.

RESULTS

EPM model

Olanzapine-treated animals had spent considerably less time in open arms than their control-treated counterparts ($p<0.05$). Diazepam treated animals spent significantly higher time in open arm than control treated ones ($p<0.001$). Observations suggest significant anxiogenic effect of olanzapine, as the animals spent more time in the closed arm of EPM indicating higher level of anxiety.

LDA Model

Olanzapine-treated animals had considerably less time in the light compartment than control-treated animals ($p<0.05$). Animals treated with diazepam spent much more time in the light compartment than those treated with controls ($p<0.001$).

Observations suggest significant anxiogenic effect of olanzapine, as the animals spent more time in the dark chamber of LDA indicating higher level of anxiety.

Results (Tables 1 and 2) show that olanzapine significantly increases anxiety when tested using EPM and LDA.

Table 1: Effect of drugs on the time spent in open arm and closed arm of elevated plus maze

Drugs/Groups	Time spent in open arm (sec)	Time spent in closed arm (sec)
Group I Distilled Water	42.50±14.557	257.50±14.557
Group II Olanzapine (2.0 mg/kg)	16.67±9.725[A]	283.83±9.725[A]
Group III Diazepam (1.0 mg/kg)	90.50±15.694[B]	209.50±15.694[B]

There are six animals total, and the observations are expressed as Mean±SD. One-way ANOVA followed by the Tukey Kramer multiple comparison test with a n=6 sample size. A: When comparing Group II to Group I, $p<0.05$ was deemed significant. B: When comparing Group III to Group I and Group II, $p<0.001$ is considered significant.

Table 2: Effect of drugs on time spent in light and dark compartment of light dark arena

Drugs/Groups	Time spent in light compartment (sec)	Time spent in dark compartment (sec)
Group I Distilled Water	40.67±17.682	259.33±17.682
Group II Olanzapine (2.0 mg/kg)	10.33±7.230[A]	289.67±7.230[A]
Group III Diazepam (1.0 mg/kg)	95.83±20.517[B]	204.17±20.517[B]

There are six animals in total, and the observations are expressed as Mean±SD. One-way ANOVA followed by the Tukey Kramer multiple comparison test with a n=6 sample size. A: When comparing Group II to Group I, $p<0.05$ was deemed significant. B: When comparing Group III to Group I and Group II, $p<0.001$ is considered significant

DISCUSSION

In this study, an atypical antipsychotic, olanzapine, was screened for its effects on anxiety using two different animal models; the EPM and LDA. Animals treated with olanzapine 2 mg/kg per orally for 10 days, spent significantly less time in open arms ($p<0.05$) of the EPM and in brightly lit compartment ($p<0.05$) of and LDA than control-treated animals indicating significant anxiogenic effect.

The exact pharmacological basis of this anxiogenic effect of olanzapine is unclear. This anxiogenic effect may be related to serotonin ($5HT_{2a/2c}$ receptor) antagonism**.** Ketanserin, a selective serotonin ($5HT_{2a/2c}$) antagonist, has been reported to produce anxiogenic effect in earlier preclinical studies. Olanzapine, being potent antagonist at these receptors, possibly causes anxiogenic effect by serotonin antagonism [7,8].

The anxiogenic effect may also be due to modulation of GABA receptors. Clozapine and olanzapine are reported to markedly decrease the density of $GABA_A$ receptors in CNS in rats in earlier studies [9]. This also could also be the basis of the anxiogenic effect. Further, extensive research is required to establish the exact pharmacological basis of the anxiogenic effect of olanzapine.

Even though the pharmacological basis of this anxiogenic effect is unclear; these observations are clinically significant, because anxiety symptoms are known to be present in about 65% of schizophrenia patients. According to a meta-analysis of 52 studies involving a total of 4032 patients with schizophrenia spectrum disorders, 38.3% of them also had an anxiety disorder [10]. Anxiogenic effect by one of the extensively used antipsychotic can have adverse impact on these patients and can further complicate the management of this crippling disease [11].

Hence, it is suggested to screen the patients of schizophrenia for existing anxiety symptoms and use olanzapine with caution in patients of schizophrenia with comorbid anxiety.

CONCLUSIONS

Olanzapine has exhibited potential to produce anxiogenic effect in preclinical models. Hence, it is suggested to use olanzapine with caution in patients of schizophrenia with anxiety symptoms, in clinical setting. The significance of thorough pharmacovigilance is, further, shown by this study.

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ETHICAL APPROVAL

The study was approved by Yenepoya University Institutional Animal Ethics Committee.

COMPETING INTERESTS

None declared.

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