Original Research Article

An experimental study to evaluate the potential of Blonanserin to induce catalepsy

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Abstract

Background: Schizophrenia is an important psychiatric illness. Antipsychotic drugs available for the treatment of schizophrenia have different side effects. One of such side effect is motor disturbances. Blonanserin is an atypical antipsychotic agent which is well tolerated at all doses. **Aim:** This study was aimed to evaluate D2 receptor mediated catalepsy of Blonanserin in animal models **Material and methods:** Bar test was used to evaluate Blonanserin (0.8 mg/kg) for its D2 receptor mediated catalepsy. Animal ethics protocols were followed strictly. Total 30 rats (10 rats per group) were used. Haloperidol (0.5 mg/kg) was used as a control drug. Doses were selected from previous references as well as by extrapolating human doses. **Results:** Blonanserin (0.8 mg/kg) when given alone did not produce catalepsy. But when Blonanserin (0.8 mg/kg) was given along with Haloperidol (0.5 mg/kg), catalepsy produced was significantly more than that of Haloperidol (0.5 mg/kg) given alone. **Conclusion:** Blonanserin did not produce catalepsy itself but strengthened the haloperidol induced catalepsy.
Keywords: Antipsychotic, Blonanserin, Catalepsy.

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INTRODUCTION

In today's busy life, a psychiatric disorder may get neglected, and may lead to an illness requiring chronic treatment. Schizophrenia is one of the most important forms of psychiatric illness, because it affects young people, is often chronic and is usually highly disabling. [1] Drugs used in its treatment are typical and atypical antipsychotic agents which have D_2 receptor blocking and/or $5HT_{2A}$ receptor antagonistic property. But many of these drugs have different side effects like motor disturbances, endocrine disturbances, sedation, hypotension and weight gain. These side effects have potential long term health risks for patients and also may lead to poor patient compliance. In such scenario, we require a drug with better profile. Blonanserin is a novel atypical antipsychotic agent approved in Japan and Korea for the treatment of patients with schizophrenia, providing short and long term efficacy against both the positive and negative symptoms of the disorder in several randomized and non-comparative trials[2-7]. It is approved in India in 2012.[8] Blonanserin has a high affinity for receptors of dopamine D_2 and 5-HT_{2A}, higher for D_2 than for 5-HT_{2A}, which is different to other second generation atypical antipsychotic drugs. It also has a low affinity for receptors of adrenaline α_1, histamine H_1, muscarinic M_1 and serotonin 5-HT_{2C} .[9] It has relatively high affinity for 5-HT_6 receptors. It also has indirect 5-HT_{1A} partial agonistic activity.[10] Blonanserin is generally well tolerated at all doses. Nevertheless, extrapyramidal symptoms and hyperprolactinemia were among the most common adverse reactions associated with Blonanserin in non-comparative studies. Further studies are required in order to definitively position Blonanserin with respect to other antipsychotic agents. [11-13] In one study, Ohno Y

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et al., AD-6048, a metabolite of Blonanserin, attenuated haloperidol induced catalepsy which is attributed to its relatively high affinity to D3 receptors.[14] So, the present study was planned to investigate Blonanserin induced D_2 receptor mediated catalepsy. We further studied whether Blonanserin has got any agonistic effect on D_2 receptor in presence of an antagonist like Haloperidol.

MATERIAL AND METHOD

Study was carried out in 3 groups of rats (10 rats / group) of either sex for test of catalepsy at Department of Pharmacology and central animal house, Bharati Vidyapeeth (Deemed to be University), Medical College and Hospital, Sangli. The protocol and synopsis was discussed in IAEC (Institutional Animal Ethical Committee), including number of animals, reuse of animals and end point of test. The study was started after approval of IAEC. (IAEC approval number is – BVDUMC and H/Sangli/CAH/IAEC/2012-13/05.)

ANIMALS-

Male and female (non pregnant) wistar rats weighing 200-250 grams of body weight were used. They were housed under standardized conditions (temperature 25^0 Celsius, relative humidity 60% and 12 hour light and dark cycle). They had access to standard pellet diet and water *ad libitum*. Experiments were conducted between 9:00 to 16:00 hours. All animal procedures were carried out in accordance with the SOPs approved by IAEC as per recommendations of CPCSEA guidelines

DRUGS-

The clinical doses of various drugs were converted to rat equivalent doses using standardized formula.[15] The volume of the drug administered orally and intraperitoneally was <1ml/100 gm of a rat. All the drugs were freshly prepared on the day of the experiment and used on the same day. All the drugs and chemicals were purchased locally.

1. Blonanserin (Elicia 4 – Zydus Neurosciences): suspended in oil
2. Haloperidol (Serenace – RPG Life Sciences Ltd): dissolved in distilled water

TEST FOR CATALEPSY-

Bar test[16] was used to study the catalepsy in rat as described below.

Table 1: Drug treatment schedule to study catalepsy (bar test)

Group No	No of Rats	Treatment
I	10	Blonanserin (0.8 mg/kg)
II	10	Haloperidol (0.5 mg/kg)
III	10	Haloperidol (0.5 mg/kg)+ Blonanserin (0.8 mg/kg)
Total		30 rats

Bar test

For observation and measurement of catalepsy the animals were placed in individual perspex cages (30×20×20cm), 30 min before drug treatment to allow adaptation to the new environment. Test drug Blonanserin was administered per orally (p.o.) while Haloperidol was administered intraperitoneally according to body weight. Group I and Group II received Blonanserin and Haloperidol respectively, 30 min prior to behavioral observations. In group III, Blonanserin and Haloperidol both were administered in each rat 30 min before behavioral observations. Animals were tested for catalepsy by placing both front limbs of the animal over an 8 cm high horizontal bar and measuring the time that the animal maintained this posture. The animals were considered cataleptic if they maintained this imposed posture for more than 10 sec. Animals were tested for catalepsy at 30 min, 60 min, 90 min, 120 min, 150 min and 180 min after treatment with Blonanserin (0.8 mg/kg) i.e. group I, Haloperidol (0.5mg/kg) i.e. group II and Haloperidol (0.5mg/kg) plus Blonanserin (0.8 mg/kg) i.e. group III. During the test due care was taken to avoid any injury to animal. At the end of the study no animal showed any grave injury or disability. After washout period of 2 weeks the healthy animals were mixed with common pool.

STATISTICAL ANALYSIS

Data was expressed as mean ± standard error of mean (S.E.M.). Statistical analysis was carried out using one way ANOVA (Analysis of variance) for significance between groups. The level of significance between individual groups was detected using unpaired "t" test. For all tests effects with a probability of $p < 0.05$ considered to be significant.

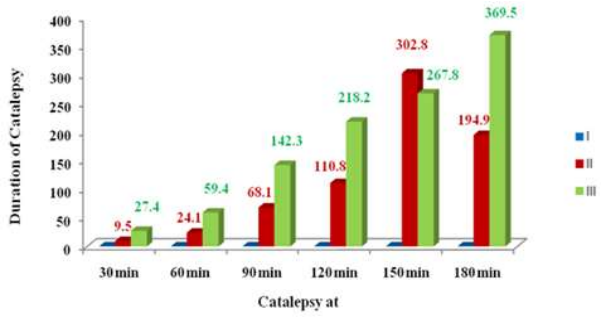
RESULT

Table 2: Effect of various treatments on onset and duration of catalepsy

Group	Drug	Dose	N	Mean Duration of Catalepsy(sec) at the end of					
				30 min	60 min	90 min	120 min	150 min	180 min
I	Blonanserin	0.8 mg/kg	10	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
II	Haloperidol	0.5 mg/kg	10	9.5 ± 0.269	24.1 ± 1.714	68.1 ± 2.316	110.8 ± 4.294	302.8 ± 10.075	194.9 ± 3.573
III	Haloperidol + Blonanserin	0.5 mg/kg + 0.8 mg/kg	10	27.4 ± 1.293*	59.4 ± 1.784*	142.3 ± 8.046*	218.2 ± 8.426*	267.8 ± 14.987	369.5 ± 7.647*

Data is expressed as Mean ± S.E.M; $p < 0.05$ is significant; *= $p < 0.05$ when compared with Haloperidol

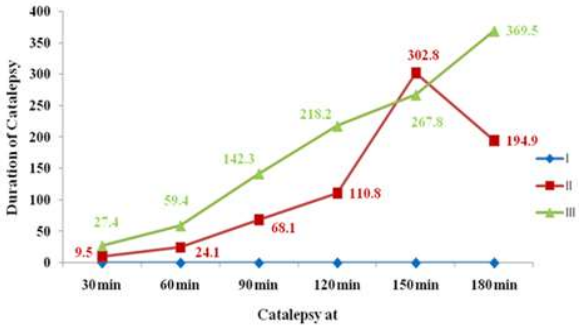
With reference to table no 2,
Blonanserin(0.8 mg/kg) did not produce catalepsy at any time interval. Onset of catalepsy for Haloperidol (0.5 mg/kg) treated group was at the end of 60 minutes which remained upto 180 min and maximum catalepsy duration was seen at the end of 150 minutes. Onset of catalepsy for Haloperidol (0.5 mg/kg) + Blonanserin (0.8 mg/kg) treated group was at the end of 30 minutes which gradually increased upto 180 minutes and maximum catalepsy duration was seen at the end of 180 minutes. There was statistically significant difference in mean catalepsy duration in Haloperidol (0.5 mg/kg) + Blonanserin (0.8 mg/kg) treated group when compared with Haloperidol (0.5 mg/kg) treated group at the end of 30, 60, 90, 120 and 180 minutes which indicates that Haloperidol (0.5 mg/kg) + Blonanserin (0.8 mg/kg) when given simultaneously cause more catalepsy than when Haloperidol (0.5 mg/kg) given alone. There was statistically no significant difference in mean catalepsy duration in Haloperidol (0.5 mg/kg) + Blonanserin (0.8 mg/kg) treated group when compared with Haloperidol (0.5 mg/kg) treated group at the end of 150 minutes.



Graph 1: Duration of catalepsy in bar test

Group I – Blonanserin (0.8 mg/kg)
Group II – Haloperidol (0.5 mg/kg)
Group III - Haloperidol (0.5 mg/kg) + Blonanserin (0.8 mg/kg)

Graph 2 :- Duration of catalepsy in bar test



Graph 2: Catalepsy

Group I – Blonanserin (0.8 mg/kg)
Group II – Haloperidol (0.5 mg/kg)
Group III - Haloperidol (0.5 mg/kg) + Blonanserin (0.8 mg/kg)

DISCUSSION

Schizophrenia affects about 1% of the population. The main clinical features of the disease are as follows-

- Positive symptoms - delusions, hallucinations, thought disorder, abnormal disorganized behavior and catatonia.
- Negative symptoms - withdrawal from social contacts, flattening of emotional responses, anhedonia, reluctance to perform everyday tasks, deficits in cognitive function together with anxiety, guilt, depression and self-punishment, leading to suicide attempts in up to 50% of cases.

There are different hypotheses of schizophrenia depending on different neurotransmitters involved viz. serotonin, dopamine and glutamate hypothesis. The dopamine (DA) overactivity hypothesis has led to the development of the various drugs like first generation (chlorpromazine, haloperidol) and second generation (clozapine, risperidone) antipsychotic agents. Important side effects common to many of these drugs are: motor disturbances, endocrine disturbances (increased prolactin release). Sedation, hypotension and weight gain are also common. Obstructive jaundice sometimes occurs with

phenothiazines. Other side effects (dry mouth, blurred vision, hypotension, etc.) are due to block of other receptors, particularly muscarinic receptors and α-adrenoceptors. Antipsychotic drugs produce two main kinds of motor disturbance in humans: acute dystonias and tardive dyskinesias, collectively termed extrapyramidal side effects. These all result directly or indirectly from D_2 receptor blockade in the nigrostriatal pathway. Extrapyramidal side effects constitute one of the main disadvantages of first-generation antipsychotic drugs. The term atypical was originally applied to some of the newer compounds that show much less tendency to produce extrapyramidal side effects. Acute dystonias are involuntary movements (restlessness, muscle spasms, protruding tongue, fixed upward gaze, torticollis), often accompanied by symptoms of Parkinson's disease. They occur commonly in the first few weeks, often declining with time, and are reversible on stopping drug treatment. Tardive dyskinesia develops after months or years (hence 'tardive') in 20-40% of patients treated with first-generation antipsychotic drugs, and are one of the main problems of antipsychotic therapy. Its seriousness lies in the fact that it is a disabling and often irreversible condition, which often gets worse when antipsychotic therapy is stopped and is resistant to treatment. The syndrome consists of involuntary movements, often of the face and tongue, but also of the trunk and limbs, which can be severely disabling. It resembles that seen after prolonged treatment of Parkinson's disease with levodopa. The incidence depends greatly on drug, dose and age (being commonest in patients over 50). There are several theories about the mechanism of tardive dyskinesia. One is that it is associated with a gradual increase in the number of D_2 receptors in the striatum, which is less marked during treatment with the atypical than with the first generation of antipsychotic drugs. Another possibility is that chronic block of inhibitory dopamine receptors enhances catecholamine and/or glutamate release in the striatum, leading to excitotoxic neurodegeneration. Drugs that rapidly dissociate from D_2 receptors (e.g. clozapine, olanzapine, sertindole) induce less severe extrapyramidal side effects. A possible explanation for this is that with a rapidly dissociating compound, a brief surge of dopamine can effectively overcome the block by competition, whereas with a slowly dissociating compound, the level of block takes a long time to respond to the presence of endogenous dopamine, and is in practice non-competitive. Adverse motor effects may be avoided if fractional receptor occupation falls during physiological surges of dopamine. An extension of this idea is that perhaps a little D_2 receptor activation may be beneficial. This could be produced, for example, by drugs that are D_2 partial agonists (e.g. aripiprazole) in contrast to simple antagonists. It is thought that partial agonists reduce D_2 hyperactivation in the mesolimbic pathway, thus alleviating positive symptoms of schizophrenia, but provide enough D_2 receptor stimulation in the mesocortical pathway to prevent negative symptoms, and in the nigrostriatal pathway to prevent the development of extrapyramidal side effects.[1] Neuroleptic-induced catalepsy has long been used as an animal model for screening drugs for Parkinsonism. Catalepsy is defined as the failure to correct an externally imposed abnormal posture. Haloperidol induced cataleptic state in rodents has been used as a model to test the extrapyramidal side effects of antipsychotic agents. The pathophysiological basis of catalepsy still remains obscure. Theories implicating central cholinergic dysfunction, gamma-amino butyric acid (GABA) deficiency, oxidative stress, and 5-hydroxy tryptamine (5-HT) dysfunction have been proposed. Neuroleptic induced catalepsy has been linked to blockade of post synaptic striatal dopamine D_1 and D_2 receptors. Haloperidol is a well-known neuroleptic, primarily acting as a D_2 receptor antagonist in the mesolimbic-mesocortical pathway. Due to its non-selective action, it also produces blockade of post-synaptic D_2 receptors in the nigrostriatal pathway leading to the development of extrapyramidal side effects in humans and catalepsy in animals. Despite this evidence, several other neurotransmitters such as acetylcholine, serotonin, angiotensin, adenosine or opioids have also been implicated. In addition to the implications of various neurotransmitters in catalepsy, reactive oxygen species have also been proposed to play a role in haloperidol induced toxicity. Evidence indicates that drugs which potentiate or attenuate neuroleptic induced catalepsy in rodents might aggravate or reduce extrapyramidal signs respectively in human beings.[17] The positron emission tomography (PET) imaging has made it possible to correlate in vivo dopamine (DA) D_2 receptor occupancy of antipsychotic drugs with the observed clinical outcome in patients with schizophrenia. Using this technique, it has been suggested that both antipsychotic response and extrapyramidal side effects (EPS) may be related to D_2 receptor occupancy – albeit with different thresholds. With typical antipsychotics, a D_2 receptor occupancy in the range of 70% was associated with clinical response while EPS emerged at a D_2 receptor occupancy >80%. This relationship has been confirmed by subsequent clinical studies. In a double-blind PET study with haloperidol, it is found that clinical response was manifested at 65–70% D_2 receptor occupancy, but only patients with a D_2 receptor occupancy > 78% showed signs of EPS.[18]

5-HT_{2A} receptor activation increases the haloperidol induced dopamine release, whereas 5-HT_{2C} receptor activation decreases the haloperidol induced dopamine release. This occurs during the compensatory 'feed-back' increase of the nigrostriatal dopaminergic neuronal activity due to haloperidol induced blockade of the pre- and postsynaptic striatal D_2 dopamine receptors. Consequently 5-HT_{2A} receptor activation, by increasing the release of dopamine from the nigrostriatal dopaminergic neurons, will counteract the haloperidol induced blockade of the postsynaptic striatal D_2 and D_1 dopamine receptors to a greater extent with resultant antagonism of haloperidol catalepsy. However, 5-HT_{2C} receptor activation, by decreasing the release of dopamine from the nigrostriatal dopaminergic neurons, will enhance haloperidol induced blockade of the postsynaptic striatal D_2 and D_1 dopamine receptors with resultant potentiation of haloperidol induced catalepsy.[19] Blonanserin is an atypical antipsychotic drug indicated for use in patients with schizophrenia and approved in Japan and Korea and recently in India. This agent has a high affinity for receptors of dopamine D_2 and serotonin 5-HT_{2A}, higher for D_2 than for 5-HT_{2A}, which is different than other second generation atypical antipsychotic drugs. Blonanserin also has a low affinity for receptors of muscarine M_1, histamine H_1, adrenaline α_1 and serotonin 5-HT_{2C}. [9, 20, 21] Blonanserin has also affinity for 5-HT_{1A} receptors where it shows indirect 5-HT_{1A} partial agonistic activity.[10] Systemic administration of Blonanserin increases extracellular levels of nor-epinephrine and dopamine, but not levels of 5-HT, glutamate, or gamma-aminobutyric acid in the prefrontal cortex. It also enhances neuronal activity in the locus coeruleus and ventral tegmental area without affecting activity in the dorsal raphe nucleus or the mediodorsal thalamic nucleus. The antagonistic properties of Blonanserin towards D_2 and 5-HT_{2A} receptors contributes to the increase in extracellular levels of dopamine and norepinephrine.[22] It also shows low inhibitory activity of neuronal re-uptake of dopamine, serotonin and norepinephrine.[2] A positron emission tomography (PET) study of healthy volunteers showed that Blonanserin occupies approximately 80% of striatal D_2-like receptors with normal clinical doses.[13] With regard to EPS, the tolerability profile of Blonanserin was generally better than that of Haloperidol and generally similar to that of risperidone in 8-week trials.[20,21] In one study, Y. Ohno *et al.*, Blonanserin did not show the catalepsy at 0.3 mg/kg and 1 mg/kg tested. Slight increase in catalepsy time was found with 3 or 10 mg/kg Blonanserin, but these changes were not statistically significant.[14] In same study, AD-6048, a metabolite of Blonanserin, attenuated haloperidol induced catalepsy which is attributed to its relatively high affinity to D_3 receptors since selective D_3 antagonists attenuate antipsychotics- induced EPS and D_3 preferential antipsychotics show reduced EPS liability. It means interaction of AD-6048 with D_3 receptors plays a role in reducing the EPS of Blonanserin. It strongly suggests that AD-6048 contributes at least partly to the atypical nature of Blonanserin with low EPS liability.[14] In another study in rats, Ishibashi T *et al.,* a dose related cataleptic effect was seen with Blonanserin at higher doses with peak effect at 20 mg/kg p.o.[7] In our study, Blonanserin (0.8 mg/kg) did not show cataleptic effect when given alone may be because of its metabolite AD-6048 or because of low D_2 receptor blocking. But when Blonanserin given along with Haloperidol, catalepsy produced was significantly more than that of Haloperidol given alone.

This can be explained by-

1. There may be potentiation of haloperidol induced catalepsy by blocking >80% D_2 receptors.
2. There may be action on feedback mechanism of haloperidol induced dopamine release by Blonanserin. This will modulate Haloperidol induced blockade of postsynaptic D_2 receptors and may cause potentiation of Haloperidol induced catalepsy depending upon receptor occupancy as well as dose of drugs used.

CONCLUSION

Blonanserin is a newly developed atypical antipsychotic drug. It is used in treatment of schizophrenia. Many drugs used for schizophrenia have extrapyramidal syndrome as a major side effect. In our study, Blonanserin did not produce catalepsy itself but strengthened the haloperidol induced catalepsy.

LIMITATION

The limitation of our study is that, it is an animal study and hence results must be confirmed with human studies.

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