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The Effects of Ziprasidone on Motor Functions in Experimental Parkinson Model in Mice

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Abstract: The management of Parkinson's Disease Psychosis (PDP) is a challenge requiring to diminish antiparkinson treatment or to use classical antipsychotics which worsen motor symptoms. Second generation antipsychotics are current interest to treat PDP. This study aims to examine the effects of ziprasidone, an atypical antipsychotic agent, on locomotor activity and motor functions in mice with experimental Parkinson's disease. 2.5, 5 and 10 mg kg⁻¹ doses of ziprasidone were used. Oxotremorine was injected i.p. for inducing experimental Parkinson's disease. Mice were observed to score Parkinson's disease tremors; then assessed with activity meter, rotarod and grip test. The results were statistically analysed with Mann-Whitney U test. There was no significant difference between groups according to Parkinson's disease tremor scores and grip test scores. The time of standing on rotarod device was significantly higher in control group than ziprasidone 5 and 10 mg kg⁻¹ groups. Stereotypical movements, total activity and distance were higher in ziprasidone 2.5 and 10 mg kg⁻¹ groups than control while resting values were less than of control group. We found that ziprasidone did not deteriorate motor functions at lower dose in mice with experimentally induced Parkinson's disease and showed a biphasic effect on stereotypical movements, total activity, distance and resting values. We concluded that ziprasidone 2.5 mg kg⁻¹ introduces a relatively suitable dosing than ziprasidone 5 and 10 mg kg⁻¹ doses because it didn't worsen motor functions when considering the worsening effects of ziprasidone 5 and 10 mg kg⁻¹ doses on rotarod test. We suggest that ziprasidone may be a safe agent at low dose in PDP.

Key words: Parkinson's disease psychosis, ziprasidone, atypical antipsychotics, motor function

INTRODUCTION

As the life span of human being increases in the industrialized world, growing numbers of diagnosis in neurodegenerative diseases are seen (Amid *et al.*, 2010). Parkinson's Disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and is seen in nearly 1% of the elderly population (Weintraub and Hurtig, 2007). Motor and non-motor symptoms are features of PD (Ansari *et al.*, 2010). In the course of the disease, behavioral and psychological or neuropsychiatric symptoms are frequently seen and complicate the management of PD (Kummer and Teixeira, 2009). Neuropsychiatric symptoms are considered to be the most significant factors affecting the life quality of patients with PD (Gomez-Esteban *et al.*, 2011) and includes depression, anxiety, apathy and sleep disturbances (Tahir and Manap, 2012). Neurodegenerative process, psychological mechanisms and effects associated with pharmacological and non-pharmacological treatments are involved in the pathophysiology of these symptoms (Kummer and

Teixeira, 2009) as well as environmental and genetic factors (Sameri *et al.*, 2011).

Antiparkinsonian treatment-related neuropsychiatric complications like psychosis and hallucinations are common in the late stages of the disease (Schrag, 2004) and probably, they are the most important complications considering their morbidity, negative effects on life quality and complexity of treatment (Rabey, 2009). Psychotic symptoms are thought to be the most frequent psychiatric complication associated with antiparkinsonian treatment (Kummer and Teixeira, 2009).

The accurate prevalence of Parkinson's disease psychosis (PDP) is not easily predicted (Ravina *et al.*, 2007) however, it is estimated about 15 and 20% (Kummer and Teixeira, 2009). PDP may be seen in 6% of uncomplicated patients when first receiving dopaminergic therapy (Poewe and Seppi, 2001).

The use of antipsychotics in psychiatry allowed many patients to maintain their lives in community (Owiredu *et al.*, 2009). However, typical antipsychotics have unfavorable effects on extra pyramidal motor symptoms in PD therefore, they are not convenient

agents to treat hallucinations or psychosis (Schindehutte and Trenkwalder, 2007). It is suggested that typical neuroleptics show their antipsychotic effect by decreasing dopaminergic activity in the mesolimbic system whereas extrapyramidal side effects of these drugs are due to reduction of dopaminergic activity in the caudate-putamen (Meltzer, 1991). The term "atypical" is referred to anti-psychotic drugs with low extrapyramidal side-effects. Hence, atypical antipsychotics are preferential drugs for the treatment of PDP (Schindehutte and Trenkwalder, 2007).

It is advised to use atypical antipsychotics when parkinsonism is worsened by withdrawal of antiparkinson drugs due to occurrence of psychotic symptoms (Fernandez *et al.*, 2003). Atypical antipsychotic drugs are preferred because they have easy usage with reasonable side effects and these drugs mainly differ in their tendency of motor function deterioration (Fernandez *et al.*, 2003). Amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine are classified as 'atypical' antipsychotic drugs (Subramanian *et al.*, 2010).

Schizophrenia which is a major mental disorder is seen with a lifetime risk of 1% and presents a variety of symptoms (Uma Devi and Chinnaswamy, 2008). Ziprasidone has been found to treat positive, negative and affective symptoms of schizophrenia and schizoaffective disorder effectively together with few adverse-effects (Keck *et al.*, 1998). However, there is inadequate evidence to conclude on its use in PDP because almost all data about ziprasidone in PDP achieved from small case series (Eng and Welty, 2010).

This study aims to examine the effects of ziprasidone on motor functions in an experimental animal model of Parkinson's disease to provide a contribution to data about use of ziprasidone in PDP.

MATERIALS AND METHODS

Animals: Female Swiss albino mice were used for the study. All mice were kept on a 12 h light/dark cycle under standard laboratory conditions and allowed free access to food and water *ad libitum* in their cages. All experiments were carried out between 9 A.M. and 2 P.M. This study was carried out with the permission of the Local Ethics Committee for Animal Experimentation of Eskisehir Osmangazi University (Decision No. 128/2009).

Drugs: Oxotremorine was supplied from sigma and ziprasidone was supplied from Pfizer. Both of them were dissolved in saline.

Experimental design: Animals were divided into 4 groups each containing 8 mice: control group and ziprasidone

2.5, 5 and 10 mg kg⁻¹ administered groups. Mice in control group were injected saline. Experimental Parkinson's disease was induced by oxotremorine injection to score tremors and then animals were assessed with activity meter monitoring, rotarod device and grip test setup.

Data analysis: The results of all tests were statistically analysed with Mann-Whitney U test. Results were given as median (25 and 75% percentile) and mean±SEM. Statistical analyses were performed using SPSS version 15.0 statistical pack software 15.0 (SPSS Inc., Chicago, IL, USA).

Oxotremorine induced experimental Parkinson's disease: Forty five minutes after i.p. injection of ziprasidone or vehicle; 200 µg kg⁻¹ oxotremorine was injected i.p. for inducing experimental Parkinson's disease. Five minutes later mice were observed for 15 min to score Parkinson's disease tremors as below (Sahin *et al.*, 1990): 0: none; 1: slight (or slow tremor of head); 2: moderate (or fast tremor of head, trunk or limbs) and 3: severe (or intensely fast tremor).

Locomotor activity: Locomotor activities of mice were then assessed with activity meter (MAY AMS 02 Animal Activity Monitoring System, COMMAT, Ankara/TURKEY) after scoring of Parkinson's disease tremors. Stereotypical movements, total activity, rest values and distance (in centimeters) were recorded automatically for 5 min.

Rotarod: Rotarod-an apparatus with a rotating cylinder-(MAY 972-A ROTA ROD, COMMAT, Ankara/TURKEY) was used to assess motor coordination (Pandy *et al.*, 2009) and if there was any motor deficit. The time of each mouse remained on the rotating rod was recorded as seconds immediately after locomotor activity assessment.

Grip test: The method of Moran *et al.* (1995) was used to perform grip test after rotarod scoring. A string of 50 cm length was stretched between two vertical sticks. Mice were placed on the string by forepaws and scored with the scale as: 0: falls off, 1: hangs onto string by two forepaws, 2: as for 1 but attempts to climb onto string, 3: hangs onto string by two forepaws plus one or both hindpaws, 4: hangs onto string by all four paws plus tail wrapped around string, 5: escape. This method evaluates grip strength and co-ordination.

RESULTS

Oxotremorine induced experimental Parkinson's disease: There was no significant difference between groups according to Parkinson's disease tremor scores as shown in Table 1.

Table 1: The effects of ziprasidone on Parkinson's disease tremor scores

Groups	Median	(25-75 percentile)
Control	3	2-3
Zip 2.5 mg kg ⁻¹	3	2.5-3
Zip 5 mg kg ⁻¹	3	2.5-3
Zip 10 mg kg ⁻¹	2	2-3

The occurrence of tremors were scored during a 15 min. period. The results were analysed statistically by using Mann-Whitney U test and were given as median and 25-75% percentile (H = 1, 831; P = 0, 608), Zip: ziprasidone

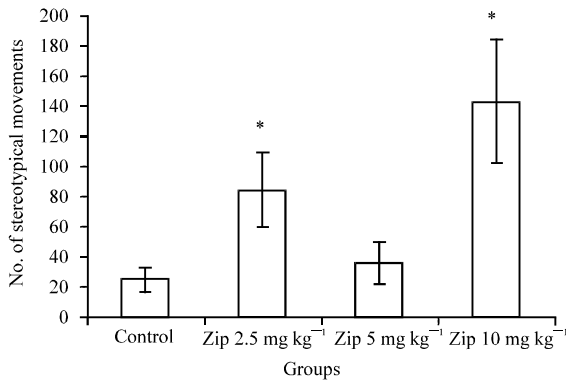


Fig. 1: The effects of ziprasidone on the number of stereotypical movements. Stereotypical movements were recorded automatically on activity meter for 5 min. The results were analysed statistically by using Mann-Whitney U test and were given as Mean±SEM, Zip: ziprasidone. *: p<0.05 (compared to control)

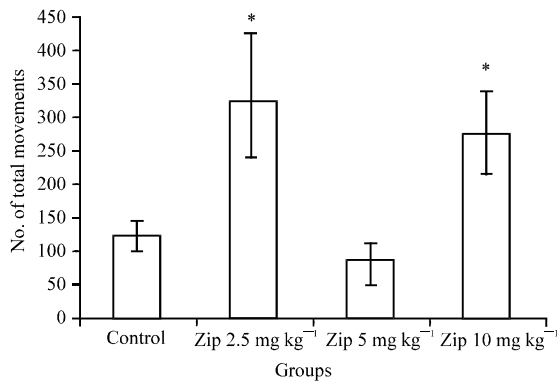


Fig. 2: The effects of ziprasidone on the number of total movements. Total movements were recorded automatically on activity meter for 5 min. The results were analysed statistically by using Mann-Whitney U test and were given as Mean±SEM, Zip: ziprasidone. *: p<0.05 (compared to control)

Locomotor activity: Stereotypical movements, total activity and distance were higher while resting values were less in ziprasidone 2.5 and 10 mg kg⁻¹ groups

Table 2: The effects of ziprasidone on grip test scores

Groups	Median	(25-75 percentile)
Control	1	1-1
Zip 2,5 mg kg ⁻¹	1	1-1
Zip 5 mg kg ⁻¹	1	1-1
Zip 10 mg kg ⁻¹	1	1-1

The results were analysed statistically by using Mann-Whitney U test and were given as median and 25-75% percentile (H = 1, 292; P = 0, 731), Zip: ziprasidone

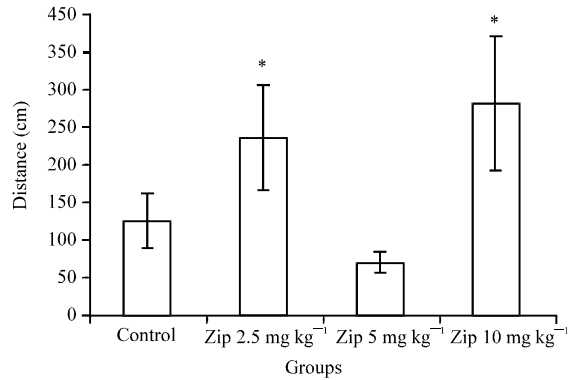


Fig. 3: The effects of ziprasidone on distance values. Distance (in cm) were recorded automatically on activity meter for 5 min. The results were analysed statistically by using Mann-Whitney U test and were given as Mean±SEM, Zip: ziprasidone. *: p<0.05 (compared to control)

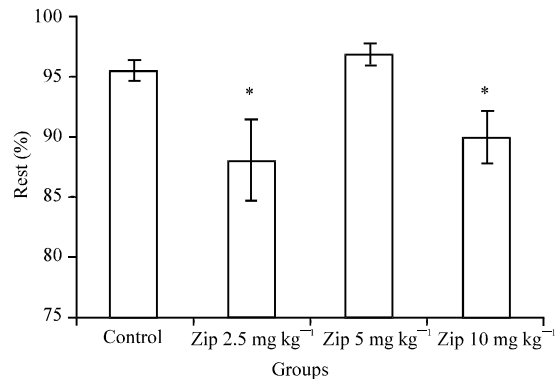


Fig. 4: The effects of ziprasidone on rest values. Rest values (as%) were recorded automatically on activity meter for 5 min. The results were analysed statistically by using Mann-Whitney U test and were given as Mean±SEM, Zip: ziprasidone *: p<0.05 (compared to control)

than of control and ziprasidone 5 mg kg⁻¹ group as shown in Fig. 1-4 suggesting that 5 mg kg⁻¹ is the suitable dose.

Grip test: There was no significant difference between groups according to grip test motor function assessment scores as shown in Table 2.

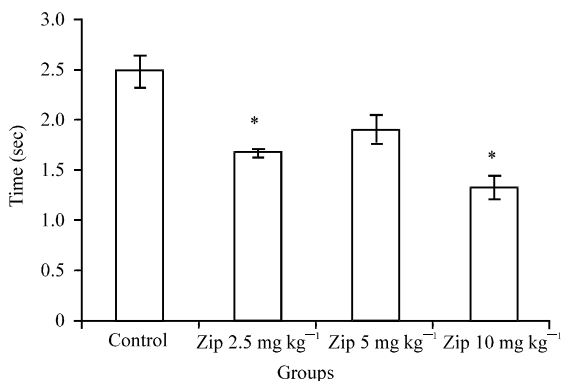


Fig. 5: The effect of ziprasidone on standing time on rotarod. Values are given in seconds. The results were analysed statistically by using Mann-Whitney U test and were given as Mean \pm SEM, Zip: ziprasidone, *: $p < 0.05$ (compared to control)

Rotarod test: The time of standing on rotarod device was significantly lower in 2.5 and 10 mg kg⁻¹ ziprasidone groups than of control group as shown in Fig. 5 suggesting that 5 mg kg⁻¹ is the suitable dose.

DISCUSSION

In this study, we have observed that ziprasidone, an atypical antipsychotic agent, didn't make any change on the scores of Parkinson's disease tremors when compared to control group. There was no significant difference between groups according to scores of Parkinson's disease tremors. Atypical antipsychotic drugs have complex receptor binding profile affecting dopaminergic systems in different ways from typical antipsychotics. The effects of typical antipsychotics arise from their dopamine (D₂) receptor antagonism properties while atypical antipsychotics both act as weak D₂ receptors antagonists and contribute presynaptic dopamine release providing less parkinsonian adverse effects (Shelton and Papakostas, 2008).

In PD, primary pathology is the degeneration of dopaminergic neurons and dysfunction of basal ganglia (Gad Elhak *et al.*, 2010) which causes motor symptoms (Ardestani, 2010). The reason of the dopaminergic degeneration may be due to genetic and environmental factors (Sarkaki *et al.*, 2009). It is expected that ziprasidone should reduce locomotor activity due to its antidopaminergic properties. Conversely, In locomotor activity assessment, we found that stereotypical and total movements and distance were higher while resting values

were less in doses of 2.5 and 10 mg kg⁻¹ ziprasidone than control and 5 mg kg⁻¹ group indicating a biphasic effect. This finding is suggested to be due to atypical characteristic of ziprasidone. Atypical antipsychotics affect not only dopaminergic systems but also other neurotransmitter systems which makes them superior to typical antipsychotics in terms of treating many schizophrenia symptoms and inducing less extrapyramidal side effects (Masri *et al.*, 2008).

In this study, it was also observed that ziprasidone didn't deteriorate grip test motor function assessment scores evaluating grip strength and co-ordination. There was no significant difference between groups according to grip test motor function assessment scores. Impairment was observed with doses of 2.5 and 10 mg kg⁻¹ ziprasidone on rotarod test assessing motor deficit. The time of standing on rotarod device was significantly lower in doses of 2.5 and 10 mg kg⁻¹ ziprasidone than control and 5 mg kg⁻¹ group. Standing time in 5 mg kg⁻¹ group was similar to control which was also composed of mice with experimentally induced Parkinson's disease. However, the other doses worsened standing time on rotarod.

The treatment of PD is difficult due to side effects of antiparkinsonian drugs which are needed to be overcome with antidopaminergic medication. However, deterioration of motor functions are associated with antidopaminergic treatment (Lertxundi *et al.*, 2008), hence second-generation antipsychotics gradually take place in the treatment of PDP (Duggal and Singh, 2008). Typical and atypical antipsychotic drugs differ basically on receptor binding properties. Typical antipsychotics block D₂ receptors stronger than atypical antipsychotics which leads to a motor worsening tendency. Therefore, atypical antipsychotics have priority to be preferred because of their favorable side effects profile (Rabey, 2009). Atypical antipsychotic drugs exhibit distinctive clinical features in PD (Schindehutte and Trenkwalder, 2007).

It was reported that available data encourage low-dose clozapine for the treatment of psychosis in PD (Zahodne and Fernandez, 2008) and it was proven to be effective without worsening motor function in PD patients (Lertxundi *et al.*, 2008) but using clozapine necessitates blood count monitoring (Friedman *et al.*, 2006). It was pointed out that clinicians are undecided to use risperidone due to its typical antipsychotic behaviour and many reports about its motor worsening effect PDP (Zahodne and Fernandez, 2008). Olanzapine is reported to cause insufferable motor worsening and to be ineffective in PDP (Zahodne and Fernandez, 2008). Quetiapine is indicated to be not as effective as clozapine for the

treatment of PDP with mild motor worsening (Zahodne and Fernandez, 2008). In a review study, ziprasidone was concluded to be an effective antipsychotic for PDP, with rare or no extrapyramidal side effects (Duran-Ferreras *et al.*, 2008); an extrapyramidal adverse effects profile not as good as quetiapine or clozapine (Zahodne and Fernandez, 2008). It was suggested that aripiprazole might make contribution for the treatment of PD psychosis in some of the patients but with a high risk of adverse effects (Zahodne and Fernandez, 2008).

In our study, we used an experimental animal model to assess the effects of ziprasidone on motor functions in PD. In this study we had to discuss our results with clinical studies of ziprasidone in PDP. Because nearly all data was achieved from case reports and human studies. It was indicated that ziprasidone was suggested to be a proportionally reliable treatment for PDP in a case report (Zahodne and Fernandez, 2008). In an open-label study, it was reported that a meaningful advance in psychiatric symptoms of patients with Parkinson's disease and psychosis was observed with ziprasidone treatment without any motor function deterioration (Gomez-Esteban *et al.*, 2005). Intramuscular ziprasidone was found to be effective in the treatment of acute psychosis of patients with Parkinson's disease with no deterioration of motor function (Oechsner and Korchounov, 2005). However, in a trial of case series it was concluded that ziprasidone may be effective as an additional atypical antipsychotic for the treatment of PDP but can also lead to motor function deterioration (Schindehutte and Trenkwalder, 2007). In these studies, ziprasidone was found to be effective in PDP at relatively lower dose of 80 mg (Duggal and Singh, 2008) mean dose 24-32 mg day⁻¹ (Gomez-Esteban *et al.*, 2005); 10-20 mg for acute agitation of motor symptoms were observed except severe off-periods and pathological laughing (Schindehutte and Trenkwalder, 2007). These results are consistent with our results that point out 5 mg kg⁻¹ ziprasidone, moderate dose used in our study, is the appropriate dose with no deterioration of motor symptoms. In another clinical study, it was found that ziprasidone didn't aggravate motor symptoms at relatively moderate dose of 120 mg kg⁻¹ (Shiah *et al.*, 2006). We found that ziprasidone at 2.5 and 10 mg kg⁻¹, relatively low and high doses used in our study, elicited a motor deficit on rotarod test.

To our knowledge this is the first study assessing ziprasidone in PDP in experimental animal models. Studies of atypical antipsychotics in the treatment of PDP have been conducted in patients. We suggest that moderate

dose (5 mg kg⁻¹) ziprasidone is more suitable than the other doses used in our study when considering its effects on locomotor activity, Parkinson's disease tremor scores, standing time on rotarod and grip test results. In addition, ziprasidone didn't deteriorate Parkinson tremor and grip test scores at all doses. Also, in locomotor activity test, a biphasic effect was observed. In this test ziprasidone 2.5 and 10 mg kg⁻¹ doses enhanced stereotypical and total movements and distance and decreased resting which suggest that dopamine activity increased with 2.5 and 10 mg kg⁻¹ doses. However, we didn't use a comprehensive schizophrenia method to evaluate dopaminergic activity in mesocortical pathway. We only assessed mice with experimental Parkinson's disease which is (Oechsner and Korchounov, 2005) with no aggravations of motor symptoms and in a trial of four case series ziprasidone was used at doses ranging between 40 and 80 mg kg⁻¹ and no deterioration associated with nigrostriatal dopaminergic activity.

In conclusion, ziprasidone at moderate dose may be confident in PDP due to its motor function preservation effect. However, we only examined the effects of ziprasidone on motor functions in PD but its antipsychotic effect wasn't studied comprehensively. So, we can not comment on if ziprasidone didn't deteriorate motor functions with effective doses. This may be the issue of further studies.

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