RESEARCH

Effect Haloperidol and Olanzapine Alone and in Combination with Ofloxacin in the Experimentally Induced Seizures

M. Rajesh[1]

[1]Associate Professor, Department of Pharmacology, Sri Muthukumaran Medical College Hospital & Research Institute, Chennai, Tamil Nadu, India

Abstract: Background: To evaluate the effect of haloperidol & olanzapine, on maximal electroshock (MES) seizure in rats and pentylenetetrazol (PTZ) induced convulsions in mice and to observe their effect in ofloxacin pre-treated animals in these models. **Materials and Methods:** For this study 60 healthy albino rats and 60 albino mice were randomly selected and divided into 10 groups of each. MES seizure was induced in rats of groups 1 to 10 after intraperitoneal (ip) administration of the following drugs. Groups 1 to 5 were administered normal saline 0.5 ml, haloperidol 0.5, 1mg/kg and olanzapine 0.5, 1mg/kg respectively, while groups 6 to 10 were pre-treated with ofloxacin 25mg/kg after which the above mentioned drugs were administered. The latent period, onset & duration of tonic extensor phase & recovery or mortality was noted in each animal. Mice of groups 11 to 20 were exposed to PTZ induced convulsion after i.p administration of above mentioned drugs and combinations, respectively. The onset & duration of clonic convulsion and mortality in mice was noted. The results were analysed statistically using ANOVA test followed by LSD test. **Results:** Olanzapine exhibited greater proconvulsant activity than haloperidol in both the models. These effects were potentiated by ofloxacin. **Conclusion:** Olanzapine lower the seizure threshold more than haloperidol. They should be used with caution in epileptic patients. Their co-administration with quinolones may further aggravate this adverse effect.

INTRODUCTION

Antipsychotic medications are used widely for the treatment of schizophrenia spectrum disorders, mania, resistant cases of depression and several non-psychiatric disorders like anxiety and emesis.[1] Most of these agents possess D2 antagonistic properties which predispose them to their most common adverse effect i.e. extrapyramidal symptoms, which constitute one of the main disadvantages of the first-generation antipsychotic drugs.[2] These effects can be offset by use of newer atypical antipsychotics whose prominent 5HT2 receptor antagonism and reduced D2 blockade allow them to be advantageously used in clinical settings, thereby expanding their use in the last decade.[3]

However, findings suggest that some of the neuroleptic drugs may lower seizure threshold and induce EEG changes typical of seizure disorders.[4] FDA analysis reports suggest that seizures are a serious adverse event that can occur with psychopharmacological treatment, and also that concern regarding seizure threshold can result in the under treatment of psychiatric disorders.[5] Studies have shown that maximum incidence of seizure among the first generation and second generation antipsychotics is observed with chlorpromazine in high dose (>1000mg/d) and clozapine in moderate & high doses (>600mg/d) respectively, inducing epileptiform EEG changes in 1 – 5 % patients.[6]

Studies undertaken in our institution reveal that, presently, haloperidol is the most frequently prescribed conventional antiepileptic agent and olanzapine, a thienobenzodiazepine, is the most frequently prescribed atypical antipsychotic. Unfortunately, rigorously controlled studies comparing the effects of these two commonly used antipsychotics on seizure threshold are relatively infrequent and lack of adequate literature limit the confidence with which firm conclusions can be drawn.

Quinolone antibiotics are another class of frequently used drugs documented to lower seizure threshold,[7-11] and the individual agents vary in their ability to induce seizures.[12] Among the fluoroquinolones, ofloxacin shows higher incidence of seizures clinically as compared to other agents.[13,14]

Hence this study was planned to evaluate the effect of haloperidol and olanzapine in experimentally induced seizures using maximal electroshock (MES) induced seizure model in rats and pentylenetetrazol (PTZ) induced convulsions model in mice. The effect of combination of ofloxacin with haloperidol and olanzapine is also studied in the same seizure models.

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Corresponding Author:
M. Rajesh
E-mail; drrajeshkm@gmail.com
ORCID: 0009-0009-9787-9472
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MATERIAL and METHODS

Experimental animals: Healthy albino rats weighing 150 to 250 gms and healthy albino mice weighing 20 to 30 gms, of either sex, were procured from the Central Animal House of S.C.B Medical College, Cuttack, for the study using MES test and PTZ test respectively. They were preliminarily screened and animals which responded positively to the respective stimuli were included into the study. The animals were housed in groups of 6 in separate polypropylene cages and maintained at a temperature of 28±1ºC and relative humidity 45 – 55%, in a 12:12 light: dark cycle. They were fed with standard diet and given water ad libitum, food was withdrawn 6hrs before and during experimentation, which was performed during 1200 -1400hr. The study protocol was approved by the Institutional animal ethics committee.

Experimental groups: A. MES induced seizure: The albino rats were randomly divided into 10 equal groups. Group 1 served as control and was given normal saline 0.5ml intraperitoneally (ip). The rats of groups 2 and 3 were administered haloperidol in low and high dose i.e. 0.5 and 1mg/kg ip respectively. Groups 4 and 5 received olanzapine in low and high dose i.e.0.5 and 1 mg/kg ip respectively. Rats of groups 6 to 10 were pretreated with ofloxacin 25mg/kg (which was proved to produce proconvulsant activity in both models) and normal saline and antipsychotic medications were administered to groups 6 to 10, as in groups 1 to 5, respectively.

B. PTZ induced seizure: 60 albino mice were randomly divided into 10 equal groups and normal saline and antipsychotic drugs were administered in the similar fashion as in rats. The mice of groups 6 to 10 were pretreated with ofloxacin 25mg/kg and the same drugs were administered to groups 6 to 10 respectively. All experiments were undertaken in accordance to ethical guidelines of animal experimentation.

Drugs and chemicals: Pentylenetetrazol (Sigma, USA), haloperidol (Serenace, Sun Pharma, Sikkim, India), Olanzapine (Oleanz, Sun Pharma, Sikkim, India) and ofloxacin (Oflomac, McLeads Pharmaceuticals Ltd, Mumbai, India) were used for the study. All the drugs were administered ip, dissolved in distilled water for injection wherever necessary, 30 min prior to induction of seizure.

MES induced seizure test: A maximum electroshock of 120mA for 0.2sec was administered through ear electrode from an electroconvulsiometer (Techno) 15 to rats of groups 1 to 10, 30mins after ip administration of test and control drugs and combinations. The latent period, onset & duration of tonic extensor phase & recovery / mortality was noted in each animal.

PTZ induced convulsions test: Mice of groups 11 to 20 were exposed to PTZ (60mg/kg subcutaneously) induced convulsion15 after i.p administration of above mentioned drugs, respectively. The animals were observed for 30 mins after PTZ for onset & duration of clonic convulsions. Recovery or morality in each mouse was noted.

Statistical analysis: The results were expressed as mean ± SEM. Mortality was expressed as percentage. The data were analyzed using SPSS 17.0 (Statistical Package for Social Sciences) software, using One-Way ANOVA followed by LSD post hoc test. A P-value of ≤ 0.05 was considered significant.

RESULTS

MES induced seizures: In the animals treated with both doses of haloperidol, there was no significant change in the duration of tonic extensor phase, in comparison to the control group treated with normal saline ($P \geq 0.05$). But in the animals treated with both low and high doses of olanzapine, there occurred significant prolongation of duration of extensor phase, with the higher dose also showing significant decrease in latent period and decrease in onset time to hind limb extension ($p<0.05$). There occurred 17% and 33% mortality with low and high dose of olanzapine, respectively, in comparison to none with haloperidol. The proconvulsant effect observed with olanzapine was dose-dependent. In rats treated with ofloxacin 25mg/kg + normal saline (i.e. in ofloxacin control group - gr 6) significant prolongation of tonic extensor phase was observed, with 33% mortality. With administration of haloperidol and olanzapine to the ofloxacin treated animals, in both doses, there occurred greater prolongation of the tonic extensor phase, in comparison to the ofloxacin control animals ($P<0.001$). There also occurred significant decrease in the latent period ($P<0.05$) and greater incidence of mortality with the high dose of haloperidol and low and high dose of olanzapine (50%, 50% and 67% respectively) [Table 1].

PTZ induced seizures: In this test, the mice treated with lower dose of haloperidol did not show any significant change in the duration of clonic convulsions ($P>0.05$), but the higher dose of the drug produced increase in the duration of clonus ($P<0.05$). No mortality was observed in the mice with this drug. In the mice treated with both the low and high doses of olanzapine, there occurred significant decrease in the onset time and prolongation in the duration of clonic convulsions ($P<0.05$), and mortality observed was 17% and 33% respectively. Ofloxacin treatment produced significant prolongation of clonus and mortality of 33%. Administration of both doses of both antipsychotics produced significant decline in the onset time for clonus and increase in the duration of clonic convulsions in

Table 1: Effect of Drugs on MES Induced Seizure in Albino Rats

Sl No	Drug-Dose in mg/Kg	Latent Period (Sec)	Hind Limb Extension		Mortality (%)
			Onset (Sec)	Duration (Sec)	
1	NS - 0.5ml	9.00 ± 0.37	13.17 ± 0.48	15.00 ± 1.58	0
2	Halo - 0.5	8.50 ± 0.43	13.33 ± 0.40	16.33 ± 2.02	0
3	Halo - 1	8.83 ± 0.31	13.00 ± 0.52	17.00 ± 2.72	0
4	Olan - 0.5	8.83 ± 0.48	12.33± 1.31	18.95 ± 1.22*	16.67
5	Olan - 1	7.83± 0.31 *	11.0 ± 0.31*	21.97 ± 2.49**	33.33
6	Oflox -25+ S-0.5ml	8.50 ± 0.43	13.50 ± 0.43	20.00 ± 1.52*	33.33
7	Oflox -25 + Halo -0.5	8.83± 0.31	13.50± 0.58	22.50 ± 2.43 ** b	33.33
8	Oflox -25 + Halo - 1	7.67 ± 0.42 *a	12.17± 0.31*	24.30 ± 1.43** b	50
9	Oflox -25 + Olan- 0.5	6.67 ± 0.33 **b	11.33 ± 0.49**a	26.17 ± 1.48**b	50
10	Oflox -25 + Olan - 1	5.17 ± 0.31**b	10.00 ± 0.37 **b	28.17 ± 2.48 ** b	66.67

NS-Normal saline, HALO-Haloperidol, OLAN-Olanzapine, OFLOX-Ofloxacin
One Way ANOVA with LSD Post hoc test, n = 6 , df – 11
* P < 0.05 * * P < 0.001 (in comparison to NS control group – Gr 1))
a P < 0.05 b P < 0.001 (in comparison to Ofloxacin control group – Gr 6)

Table 2: Effect of Drugs on PTZ Induced Seizure in Albino Mice

Sl No	Drug-Dose in mg/Kg	Onset of Clonus (Sec)	Duration of Clonic Convulsion (Sec)	Mortality (%)
1	NS - 0.5ml	168.00 ± 4.53	247.67 ± 4.43	0
2	Halo - 0.5	159.00 ± 6.52	252.33 ± 4.60	0
3	Halo - 1	149.67 ± 5.67	274.33 ± 3.49 *	0
4	Olan - 0.5	141.00 ± 4.97 *	279.33 ± 5.02 *	16.67
5	Olan - 1	133.33 ± 7.28 *	298.67 ± 4.92 **	33.33
6	Oflox -25+ S-0.5ml	160.00 ± 5.86*	284.50 ± 5.41 *	33.33
7	Oflox -25+ Halo -0.5	152.00 ± 4.24 * **a**	295.33 ± 7.88 * **a**	33.33
8	Oflox -25+ Halo - 1	149.83 ± 5.87 * **b**	300.17 ± 6.64** **b**	50
9	Oflox -25+ Olan- 0.5	118.33 ± 3.84 ** **b**	341.17 ± 5.87 ** **b**	66.67
10	Oflox -25+ Olan - 1	109.33 ± 4.88 ** **b**	398 ± 7.98 ** **b**	66.67

NS-Normal saline, HALO-Haloperidol, OLAN-Olanzapine, OFLOX-Ofloxacin
One- Way ANOVA with LSD Post hoc test, n = 6 , df – 11
* P < 0.05 * * P < 0.001 (in comparison to NS control group – Gr 1)
a P < 0.05 b P < 0.001 (in comparison to Ofloxacin control group – Gr 6)

DISCUSSION

Both the conventional and the atypical antipsychotic medications can lower the seizure threshold, increasing the chances of seizure induction.[4] Many factors appear to increase the chances of an antipsychotic medication inducing seizure activity in patients, like age, significant comorbid medical conditions, possible seizure risk factors including the patient's family history of neurological and psychiatric disorders, history of seizure activity, concurrent use of other drugs that lower seizure threshold, rapid dose titration, slow drug metabolism, metabolic factors and drug-drug interactions.[16] Hence this study was designed to observe the direct effect of drugs and combinations on experimentally induced seizures in animals.

In our study, haloperidol in both the doses did not lower the seizure threshold in MES model and only the high dose proved to produce proconvulsant activity in PTZ model, while olanzapine in both the doses exhibited significant proconvulsant activity in both the models.

These findings are in corroboration with studies that reveal that among the conventional antipsychotic medications, chlorpromazine appears to be associated with the greatest risk of seizure provocation, while haloperidol, the most frequently used conventional antipsychotic is associated with a lower risk of seizure induction.[17] Among the atypical drugs, Clozapine is most frequently associated with seizures17. Case reports also document that patients exhibited generalized tonic clonic seizure or myoclonic jerks, when switched over from Haloperidol to Olanzapine, which subsided on return to Haloperidol.[18,19] A study by Centorrino F et al has observed the risk of EEG abnormalities with olanzapine to be 38.5%, which was higher than expected from its reported seizure risk (as low as 0.88%)and 7.3% with haloperidol 20.

The mechanism underlying the proconvulsant activity of these drugs is unknown, though olanzapine also exhibits weak affinity for GABAA, BZD receptor site. Both haloperidol and olanzapine were observed to decrease the density of GABAA receptors in cortical and limbic areas of the brain 21. Compared to haloperidol (0.01 and 0.1 mg kg−1 day−1) and chlorpromazine (0.1 and 1 mg kg−1 day−1), clozapine and olanzapine (0.1 and 1 mg kg−1 day−1) markedly decreased the density of GABAA receptors in these two brain regions22. These data suggest that modulation of GABAergic transmission could be an important action of some antipsychotic drugs, and account for action on seizure threshold.

With the National Institute of Clinical Excellence (2002) recommending the use of atypical antipsychotic drugs as first-line treatment for newly diagnosed schizophrenic patients, because of lower incidence of motor adverse effects produced by them2, concern regarding lowering of seizure threshold by olanzapine, which is most commonly used, needs to be kept in mind.

Our finding corroborate with the results of Shalini et al that ofloxacin shows proconvulsant activity, in the PTZ and MES induced seizure models23. Significant potentiation of proconvulsant activity of ofloxacin is observed with concomitant use of both antipsychotics used in our study. The fluoroquinolones lower seizure threshold by displacing GABA from its receptors and interfering with GABAergic neurotransmission 24. Ofloxacin has higher CNS penetration but lower affinity to GABA as compared to other fluoroquinolones.[10]

Conclusion

Thus, in conclusion haloperidol may be preferred to olanzapine in patients of generalized seizures. Proconvulsant effect is dose-dependent with both drugs, so careful dose titration is required if these drugs are to be used in epileptic patients. Quinolones like Ofloxacin should be avoided in patients on Olanzapine or Haloperidol.

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