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REVIEW ARTICLE

A Reviw on Lamotrigine: On Psychosis Disease

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Abstract:

Psychosis (from the Ancient Greek "psyche", for mind/soul, and ―-osis", for abnormal condition) means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". Psychosis has been traditionally linked to the neurotransmitter dopamine. In particular, the dopamine hypothesis of psychosis has been influential and states that psychosis results from an over activity of dopamine function in the brain, particularly in the mesolimbic pathway. The two major sources of evidence given to support this theory are that dopamine receptor D2 blocking drugs (i.e., antipsychotics) tend to reduce the intensity of psychotic symptoms. Lamotrigine, is anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. For epilepsy, it is used to treat focal seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Lamotrigine is a member of the sodium channel blocking class of antiepileptic drugs. Early studies of lamotrigine's mechanism of action examined its effects on the release of endogenous amino acids from rat cerebral cortex slices in vitro. These studies suggested that lamotrigine acts presynaptically on voltage-gated sodium channels to decrease glutamate release.

Keyword: Psycosis, Lamotrigine, Amphetamine.

INTRODUCTION:

Psychosis (from the Ancient Greek "psyche", for mind/soul, and ―-osis", for abnormal condition) means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". People suffering from psychosis are described as psychotic. Psychosis is term a given to the more severe forms of psychiatric disorder, during which hallucinations and delusions and impaired insight may occur. Prolonged or high dose use of psycho-stimulants may alter of functions like the manic phase of bipolar disorder.

Psychosis has been traditionally linked to the neurotransmitter dopamine. In particular, the dopamine hypothesis of psychosis has been influential and states that psychosis results from an over activity of dopamine function in the brain, particularly in the mesolimbic pathway. The two major sources of evidence given to support this theory are that dopamine receptor D2 blocking drugs (i.e., antipsychotics) tend to reduce the intensity of psychotic symptoms .

Lamotrigine, is anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. It is also used as an adjunct in treating depression, though this is considered off-label usage. For epilepsy, it is used to treat focal seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome.

Lamotrigine is a member of the sodium channel blocking class of antiepileptic drugs. Early studies of lamotrigine's mechanism of action examined its effects on the release of endogenous amino acids from rat cerebral cortex slices in vitro. As is the case for antiepileptic drugs that act on voltage-dependent sodium channels, lamotrigine inhibited the release of glutamate and aspartate evoked by the sodium-channel activator veratrine and was less effective in the inhibition of acetylcholine or GABA release. At high concentrations, it had no effect on spontaneous or potassium evoked amino acid release. These studies suggested that lamotrigine acts presynaptically on voltage-gated sodium channels to decrease glutamate release.

MATERIALS AND METHODS :

Pharmacological studies:

Two following models were used this study:

1. Inhibition of amphetamine-induced stereotype activity in rats
2. Inhibition of apomorphine-induced stereotype activity in rats.

Procedure of Inhibition of amphetamine-induced stereotype activity in rats

- Amphetamine is an indirect sympathomimetic agent. It induces a characteristic stereotypic behavior (lip smacking, grooming, catalepsy & gnawing) in rats, which can be successfully prevented by classical neuroleptic agent. Inhibition of amphetamine-induced stereotype activity in rats Amphetamine also induces a characteristic stereotype behavior in rats. The test is predictive for antipsychotic drugs with D2 receptor antagonism.
- Three groups of adult wistar rats, weighing between 180 to 220 g were treated with control, test or standard drug and then placed in cage. They were injected with d-amphetamine (5 mg/kg) after 30 min.
- The onset of stereotype behavior, its duration and intensity was evaluated at 30 min interval for 3 hours. Rats were protected if the behavior was reduced or abolished.
- If the drug has antipsychotic activity, the above mentioned stereotype behavior is abolished.

TABLE: 1 PROTOCOL FOR INHIBITION OF AMPHETAMINE INDUCED STEREOTYPE IN RATS

S.NO.	Group	No.of animal	Treatment	Route of administration
1	Control	06	Vehicle (normal saline)	i.p.
2	Standard	06	Haloperidol (5 mg/-kg)	i.p.
3	Test	06	Lamotrigine (20 mg/-kg)	i.p.

Evaluation Parameters

$$\% \text{ Effectiveness of Drug} = \frac{\text{Control-Test} \times 100}{\text{Control Standard}}$$

Procedure Inhibition of Apomorphine-induced stereotype in rats

- Apomorphine stimulates dopamine autoreceptor and induces stereotype behaviour in rodents like pole climbing, licking, sniffing, gnawing and yawning.
- Apomorphine induced climbing behavior can be inhibited by antpsychotic drug and is predictive for the development of extrapyramidal side effect and dyskinesia.

- The rats were placed in Cook‘s pole climbing apparatus. After an adaptation period of 30 min ,the rats has treated with either control,test drug or standard drug.
- 1 hour later apomorphin (0.75 mg/kg sc) was administered Immediately afterward, the behavior was assessed for climbing namely all the paws on the floor,forefeet and all the paws held on the wall,which is rated on scale of 0- 2,respectively.

TABLE 2: PROTOCOL FOR INHIBITION OF APOMORPHINE INDUCED STEREOTYPE IN RAT

S.NO.	Group	No.of animal	Treatment	Route of administration
1	Control	06	Vehicle (normal saline)	i.p.
2	Standard	06	Haloperidol (5 mg/-kg)	i.p.
3	Test	06	Lamotrigine (20 mg/-kg)	i.p.

Evaluation Parameters

% Effectiveness of Drug = $\frac{\text{Control-test} \times 100}{\text{Control Sample}}$

Statistical analysis-

The mean of wound area measurement between the groups were statistically analyzed by one way analysis of variance (ANOVA) at different time intervals, followed by tukey‘s test (compare all pair of column). Data were analyzed through graph pad software, P value 0.05 was considered statistically significant.

Results:

TABLE 3: AMPHETAMINE INDUCED STEREOTYPE ACTIVITY IN RATS

Parameter %Effectiveness of drug	**Group I(Control)**	**Group I(standard)**	**Group III(test)**
Day 1	3.3±0.48	1.8±0.48 (45%)	1.3±0.25 *(60.60%)
Day 2	3±0.41	1.5±0.41 (50%)	1.00±0.41**(66%)
Day 3	3.5±0.29	1.0±0.41 ** (57.14%)	0.75±.48**(78.57%)
Day 4	3.0±0.41	1.0±0.41 *(66.66%)	0.50±0.29**(83.33)
Day 5	3.0±0.58	1.0±0.41** (66.66%)	0.25±0.25**(91.66%)
Day 6	3.8±0.25	1.3±0.48** (65.78%)	1.00±0.41**(73.68%)
Day 7	4.0±0.0	1.5±0.50** (62.50%)	0.50±0.29***(87.5%)
Day 8	3.3±0.25	1.5±0.65** (54.54%)	1.00±0.41**(69.69%)
Day 9	3.3±0.48	1.0±0.41**(69.69.60%)	0.50±0.29*(84.84%)
Day 10	3.3±0.48	1.3±0.48*(60.60. %)	1.0±0.0(69.69%)
Day 11	3.8±0.25	0.75±0.48**(80.26%)	0.50±0.29***(86.84%)
Day 12	3.8±0.25	1.3±0.48 (65.78%)	1.0±0.41**(86.84%)
Day 13	3.3±0.48	1.5±0.29 (54.54%)	1.0±0.71** (69.84%)
Day 14	3.8±0.25	0.75±0.48** (80.26%)	0.50±0.29*(86.84%)
Day 15	3.0±0.41	1.0±.071 (66.66%)	0.75±0.48** (75%)
Day 16	3.3±0.25	1.5±0.50*(54.54%)	0.50±0.29** (84.25%)
Day 17	4.0±0.0	2.0±0.41 (50%)	0.75±0.48** (81.25%)
Day 18	3.8±0.25	1.8±0.48 (52.63%)	0.75±0.48*(80.26%)
Day 19	3.3±0.48	1.5±0.65 (54.54%)	1.0±0.41*(69.69%)
Day 20	2.5±0.65	1.5±0.65 (40.0%)	1.5±0.65(40%)
Day 21	3.0±0.41	2.3±0.48 (23.33%)	1.3±0.48 (56.56%)

P values: * 0.05;** 0.001; *** 0.0001 showed significant as compared with control Inter group comparison were made using ANOVA.

TABLE 3: AMPHETAMINE INDUCED STEREOTYPE ACTIVITY IN RATS

Parameter %Effectiveness of drug	Group I (Control)	Group I (standard)	Group III (test)
Day 1	1.5±0.29	0.50±0.29(66.66%)	0.25±0.25(83.33%)
Day 2	1.8±0.25	1.0±0.41(44.44%)	0.50±0.29*(72.22%)
Day 3	2.0±0.0	0.75±0.48**(62.5%)	0.25±0.25***(87.5%)
Day 4	1.8±0.25	0.50±0.29*(58.83%)	0.25±0.25**(86.11%)
Day 5	1.5±0.29	0.25±0.25*(83.33%)	0.25±0.25*(83.33%)
Day 6	2.0±0.0	0.75±0.48(62%)	0.50±0.29*(75%)
Day 7	1.8±0.25	0.50±0.50(72.22%)	0.25±0.25(86.11)
Day 8	1.5±0.29	0.50±0.29(66.66%)	0.25±0.25*(83.33%)
Day 9	1.8±0.25	1.0±0.50(44.44%)	0.75±0.25*(58.33%)
Day 10	1.8±0.25	0.25±0.25**(86%)	0.50±0.29*(86%)
Day 10	1.8±0.25	0.25±0.25**(86%)	0.50±0.29*(86%)
Day 12	1.8±0.29	0.75±0.48(58.33%)	0.25±0.25*(86.11%)
Day 13	1.3±0.48	0.25±0.25(80%)	0.25±0.25*(80.76%)
Day 14	2.0±0.0	1.0±0.58(50%)	0.50±0.50(75%)
Day 15	1.8±0.25	0.25±0.25(86.11%)	0.25±0.25(86%)
Day 16	2.0±0.0	0.75±0.48**(62.5%)	0.25±0.25**(87.5%)
Day 17	1.3±0.25	0.50±0.50*(80.76%)	0.25±0.25**(61.53%)
Day 18	1.8±0.25	0.75±0.48(58.33%)	0.25±0.25(86%)
Day 19	1.5±0.29	0.25±0.25(83.33%)	0.25±0.25*(83.33%)
Day 20	1.3±0.25	0.50±0.50*(61.53%)	0.25±0.25*(80.76%)
Day 21	1.8±0.25	0.50±0.50(61.53%)	0.25±0.25*(80.76%)

P values: * 0.05;** 0.001; *** 0.0001 showed significant as compared with control Inter group comparison were made using ANOVA.

RESULT

Based on our experimentation which includes the facts that the result of standard drug is equivalent to the test drug with regarded abetment of psychosis in albino rats. The onset of psychosis is evident by the following symptoms lip smacking,grooming,catalepsy gnawing) .In First model amphetamine induced stereotype activity in rats the mean score of the 21 days of control animal was 3.38 the haloperidol treated group (standard group) the mean score was 1.37and the Lamotrigine treated group (test group) the mean score was 0.80.The score indicate the level of stereotype activity which indicate the onset of psychosis. The % effectiveness indicates the antipsychotic activity of drug. The higher % effectiveness of the test drug on the 4th ,5th,9th ,12th,16th,18th days respectively was found to be 83.33% , 91.66% 84.84%, 86.84%, 84.25%, 80.26% and % effectiveness of the test drug on the 4th ,5th,9th ,12th,16th,18th days respectively was found to be 66.66%, 66.66%, 69.69%,65.78%, 54.54%, 52.63%,.this % indicates the effectiveness of the drug candidates elevation of psychosis which evident by Lessing of psychomotor agitation or stereotype . In our second model Apomorphine induced stereotype activity in rats the mean score of the 21 days of control animal was 1.69 the haloperidol treated group (standard group) the mean score was 0.52 and the Lamotrigine treated group (test group) the mean score was 0.32.The score indicate the level of stereotype activity which indicate the onset of psychosis. The % effectiveness indicates the antipsychotic activity of drug. The higher % effectiveness of the test drug on the 2nd ,8th,11th ,12th,14th,16th ,18th ,20th days respectively was found to be 72.22% , 83.33%, 83..11% , 86.11% ,75% 87.5%, 86% , and 80.76%. effectiveness of the test drug on the 2nd ,8th,11th ,12th,14th,16th ,18th ,20th days respectively was found to be 44.44% , 58.83% , 66.66% ,58.33% , 50 % , 62.5%, 58.33% and 61.53%.This % indicates the effectiveness of the drug candidates elevation of psychosis which evident by Lessing of psychomotor agitation or stereotype . Based on our result we can say that our Lamotrigine was comparable on even better than the standard drug which is haloperidol. As work on this thesis is one experimental model the analysis and performance of our test drug can be better measured. If we used more experimental models we can arrived on basic conclusion that Lamotrigine is ecology effective and even better then Haloperidol in the treatment of psychosis. **DISCUSSION**

Based our experimental models which were first was Inhibition on Amphetamine induced stereotype activity in rats and second was Inhibition on Apomorphine induced stereotype activity in rats. Apomorphine and amphetamine are inducing agent which are induced the psychosis or stereotype activity. Apomorphine is a non-selective dopamine agonist which activates both D1-

like and D2-like receptors, with some preference for the latter subtypes. It is historically a morphine decomposition product by boiling with concentrated acid, hence the *-morphine* suffix. Apomorphine does not actually contain morphine or its skeleton, or bind to opioid receptors. The *apo-* prefix relates to it being an aporphine derivative. Apomorphine has been tried for a variety of uses including psychiatric and the amphetamine is the drug which increases activity related to the neurotransmitters dopamine and norepinephrine in the brain which is responsible for stereotype activity.

In the treatment of psychosis use many type anti-psychotic drug are used. Haloperidol is a anti-psychotic drug which is used in our experiments as a standard drug and lamotrigine was is used as a test drug.Lamotrigine is anti-epileptic drug and also used in bipolar disorder it is inhibit the dopamine secretion in mesocortical area in brain.

The lamotrigine abolish the stereotype repose to apomorphine and amphetamine incuced psychosis.

CONCLUSION

Based on our experimental models which were first was Inhibition of amphetamine-induced stereotype in rats and second was Inhibition of apomorphine-induced stereotype in rats.We can conclude that lamotrigine is ecology effective or better than haloperidol in elevating psychosis. In experimental animals this research paves way for the result to be verified in human subject.

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