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Research Article

EVALUATION OF ANTIDEPRESSANT ACTIVITY OF TOPIRAMATE IN MICE

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ABSTRACT

Objective: To study the antidepressant activity of topiramate in experimental models
Methods: Topiramate (15mg/kg), amitriptyline (10mg/kg) and combination of both topiramate (7.5mg/kg) and amitriptyline (5mg/kg) were administered to different groups of albino mice daily for fourteen days. The immobility period was recorded on day one and day fourteen in both forced swim test and tail suspension test. The P value less than 0.05 was considered as statistically significant
Results: There was a statistically significant reduction in the immobility period in animals treated with topiramate compared to control group in both experiments on day one and day fourteen ($P<0.05$). There was also statistically significant difference in immobility period in the group treated with both topiramate and amitriptyline compared to group of animals treated with topiramate alone. There was no statistically significant difference in the immobility period between groups of animals treated with topiramate (15mg/kg) and amitriptyline (10mg/kg) alone.
Conclusion: Topiramate at a dose of 15 mg/kg has demonstrated antidepressant activity which was comparable to amitriptyline. There was synergism in antidepressant activity of topiramate and amitriptyline.

Keywords: Depression, Forced swim test, Tail suspension test

INTRODUCTION

The lifetime prevalence of major depression in adults is estimated to be 7 to 12 percent in men and 20 to 25 percent in women [1]. The risk of depression increases in presence of comorbid conditions like obesity, diabetes mellitus, cancer, and myocardial infarction [2,3,4]. Depression is associated with an increased risk of substance abuse particularly in adolescents [5]. The risk of relapse after first, second and third attack of depression is 50, 70 and 90 percent respectively [6]. The repeated attack of relapse contributes to high therapeutic failure [7].

Depression is third important cause for morbidity based disability adjusted life years (DALYs) and is projected to become first by the year 2030. The economic burden of depression is same as that of coronary heart disease. Suicidal rates are two times more in depressed individuals than that in general population [6]. Early diagnosis and treatment of depression improves the quality of life, and maybe useful to prevent early death [5]. Unrecognized cases of depression is common in non-psychiatric out patient departments. In a study conducted by Charu et al, prevalence of unrecognized depression was as high as 24 % [8].

Ketamine, an antagonist of glutamate N-methyl-D-aspartate **(**NMDA) receptors is known to have antidepressant properties [9]. The investigational drug, topiramate is known to regulate the activity of NMDA receptors [10]. Therefore the present study has been under taken to evaluate the antidepressant activity of topiramate in experimental models.

MATERIALS & METHODS

The albino mice with weight 20-25g were used for the study. They were kept in standard laboratory environment with laboratory food and water *ad libitum*. The animals were subjected to tail suspension and forced swim tests on first day and fourteenth day of drug administration. Two experiments were performed using the same groups of animals with washout period of two weeks. The animal ethics committee approval was taken prior to the experiment. The P value less than 0.05 was considered as statistically significant.

The animals were grouped and administered drugs as follows (N=6 each)

Group 1: (Control): Normal saline (1 ml)
Group 2: (Test drug): Topiramate (15mg/kg) orally for 14 days
Group 3: (Standard) Amitriptyline (10mg/kg) for 14 days
Group 4: Topiramate (7.5mg/kg) and Amitriptyline (5mg/kg) for 14 days

The test and standard drugs were administered orally after diluting in 1 ml of normal saline. The recommended dose of topiramate in human was used to calculate the dose for experimental animal [11]. The selection dose of amitriptyline used was based on previous study [12].

Forced Swim Test

Forced swim test (FST) is frequently used to evaluate potential antidepressant activities in experimental models. Immobility is produced during prolonged periods of forced swimming. The potential antidepressants reduce the duration of immobility and increase the escaping behavior such as climbing and swimming.

A transparent Plexiglas cylinder of 20 cm diameter and 50 cm height was used for the study. Water level of 20 cm was maintained in the cylinder throughout the experiment. One day prior to experiment, the animals were subjected individually to forced swim for a period of 15 minutes. On the day of experiment, animals were administered either test drug/standard drug orally one hour prior to forced swim. Animals were placed individually in water filled glass cylinder for a period of 6 minutes. The duration of immobility during last five minutes of forced swim is calculated by subtracting total time (5 minutes) from time spent in escaping behavior. Climbing was defined as upward-directed movements of the forepaws by the side of the swim chamber and swimming is considered as movements throughout the swim chamber [13].

Tail suspension test

Mice tail was wrapped with adhesive tape to cover 4/5 of the tail length and suspended from a metal rod fixed 50 cm above the

surface area. The duration of immobility is noted during 5 minutes period. Animals were considered to be immobile if it does not show any movement of body and remain hanging passively. On the day of tail suspension, animals were administered drugs orally one hour prior [14].

RESULTS

Forced swim test

There was significant reduction in immobility period in the animals treated with amitriptyline, topiramate and combination of both topiramate and amitriptyline compared to control group (P <0.05, Table 1). There was no statistically significant difference in the immobility period among groups of animals treated with amitriptyline and topiramate alone. However, animals treated with both amitriptyline and topiramate showed significant decrease in immobility compared to topiramate alone (P <0.05, Table 1). Similar findings were obtained when experiments were repeated after 14 days of drug administration (P <0.05, Table 1)

Tail suspension test

Mean duration immobility in all the groups of animals was significantly reduced compared to animals in control group. (P <0.05, Table 2). Decrease in the immobility due to topiramate was not found to be statistically significant compared to amitriptyline alone. Mean reduction in immobility in the animals treated with both topiramate and amitriptyline was significantly reduced compared to topiramate alone. (P<0.05, Table 2). The results were similar when animals were subjected to tail suspension test on day 14. (P<0.05, Table 2).

Table 1: Effect of topiramate on immobility period in forced swimming test

Group	Mean + SEM (Day 01)	Mean + SEM (Day 14)
Control	135.66±15.31	137.83±16.4
Amitriptyline	53.16±18.24*	38.33±13.94*
Topiramate	74.83±8.46*	74.33±12.54*
Amitriptyline +Topiramate	20.33±1.43*	9.16±4.43 *,#

***P<0.05 compared to control, # P<0.05 compared to topiramate alone**

Table 2: Effect of topiramate on immobility period in tail suspension test

Group	Mean + SEM (Day 01)	Mean + SEM (Day 141)
Control	155.33±8.07	157.83±9.17
Amitriptyline	94±10.27*	90.83±4.65*
Topiramate	118.66±8.92*	119.83±5.59*
Amitriptyline +Topiramate	73.33±8.92*	61.83±13.05*,#

***P<0.05 compared to control, # P<0.05 compared to topiramate alone**

DISCUSSION

Antidepressant activity of selective monoamine reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors is by potentiating monoaminergic neurotransmission [15]. The recent sequence treatment alternatives to relieve depression (STARD) study revealed that only 30% of patients had complete remission after first course of antidepressants during therapy [16].

Selection of best possible antidepressant for an individual should be based on its proven efficacy as well as saftey and tolearbility of the drug. Among 160 patients who took antidepressants, 26.87% reported adverse drug reactions, with at least one possible causality [17]. Around 5–10% of patients on SSRIs discontinue therapy because of adverse effects (AEs) related to gastrointestinal tract and central nervous system [18]. Adherence to prescribed medication is important for achieving complete remission [19]. Patients who experienced AEs with initial antidepressant treatment were likely to report similar adverse events after switching to an alternative antidepressant, even when subsequent treatment is from a different class of antidepressants [20].

In spite of the fact that several meta-analyses found no association between increased suicidal risks with use of antidepressants, yet few studies reported that people on antidepressant have the tendency to commit suicide after 10–14 days of commencement of antidepressant [21]. The suicidal rates were found to be higher in younger people on antidepressants [22].

FST and TST were widely used to screen the chemicals for their antidepressant activity. All the major class of antidepressants including TCAs, SSRIs, MAO inhibitors and atypical antidepressents were evaluated in past using these models [23,24,25]. The immobility observed during FST and TST corresponds to human depression [26].

In the present study, topiramte showed signicant reduction in the mean duration of immobility compared to control in both experiments. There also exists statistically significant difference in the mean duration of immobility in the groups treated with both topiramate (7.5mg/kg) and amitriptyline (5mg/kg) compared to group treated with topirmate alone. This demonstrated synergistic interaction between topiramate and amitryptyline in their antidepressent activity at lower doses. There was no statistically significant difference in mean reduction in the immobility between the groups treated with treated with topiramate and amitryptyline.

The investigational drug topiramate is currently approved for epilepsy. Its anticonvulsant effects is medicated through inhibition of neuronal voltage-dependent sodium channels and L-type calcium-channel activation, enhancement of $GABA_A$ receptor transmission and reduction of glutamatergic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionate), and kainate receptor neurotransmission [27].

Recent studies highlighted the role of glutaminergic pathway in brain ischemia, neurodegenartive disorders and schizophrenia. Glutamate, an excitatory neurotransmitter, co-regulattes many functions including learning, memory and behavior. [28]

Glutamate receptors broadly divided into NMDA receptors and non-NMDA receptors. The non-NMDA receptors include AMPA and Kainate receptors. It is evident that neurotransmission via NMDA receptors is deregulated in depression [29]. Topiramate is known to limit the activation of AMPA-Kainate subtypes of glutamate receptor. NMDA receptors and non-NMDA receptors may be co-localized at postsyanptic membranes. Activation of NMDA requires the full simulateneous depolazation of postsyanpatic membrane through AMPA or kainite receptors [10]. Antagonist of NMDA receptor like ketamine found to have antidepressent activity in may preclinical studies and some clinical trials [9]. Topiramate may be producing its antidepressent action by limiting the activation of NMDA receptors through its intreaction with non-NMDA receptors.

Recent studies also highlighted the role of hypothalamus pituitary adrenal (HPA) axis over activity in both depression and anxiety disorder. The amygdala and the hippocampus control the activity of the HPA axis in a counter-balancing way, and through various neuropeptides such as corticotropin-releasing factor, substance P, galanin, vasopressin and neuropeptide Y (NPY) [30]. There is evidence that topiramate modulate the NPY activity in Flinders Sensitive Line 'Depressed' Rats [31]. Activity of topiramate on NPY activity, which might contribute to the antidepressant activity, cannot be ruled out.

CONCLUSION

Topiramate at a dose of 15 mg/kg has demonstrated antidepressant activity which was comparable to amitriptyline. Topiramate could be producing its antidepressant activity by modulating glutaminergic activity. However, its modulating effect on NPY which might contribute to antidepressant activity cannot be ruled out. There was synergism in antidepressant activity of topiramate and amitriptyline.

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