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Research Article

Profile of pharmacological effects of combination of buspirone with selected antidepressants: a behavioral study in mice

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ABSTRACT

Background: Antidepressants are commonly prescribed drugs. Co-existing disorders like anxiety require therapy with other drugs. The profiles of pharmacological effects of these drugs on central nervous system are influenced by the administration of these drugs either as single or combination. This study is designed to observe the behavioral effects of antidepressants along with the antianxiety agent buspirone in mice.
Methods: Four antidepressant drugs belonging to different groups are selected for the study. Amitriptyline, citalopram, venlafaxine and mirtazapine are given orally for 2 weeks. Subsequently, buspirone is added to each antidepressant drug for a period of 3 weeks. The behavioral effects in mice are observed at weekly intervals using photoactometer, rotarod, forced swim test and elevated plus maze.
Results: The antidepressant drugs amitriptyline and citalopram showed any change in spontaneous motor activity recorded by photoactometer. In rotarod test venlafaxine showed an increase in values, which showed further increase when buspirone was added. In the forced swim test also, venlafaxine showed a different pattern of effects when compared to other antidepressants. In the elevated plus maze test, the four antidepressants did not show any increase in the time spent in open arm excepting citalopram. Venlafaxine showed an increase in time spent in closed arm.
Conclusions: The test drugs do not show any significant depression of central nervous system at the dose used. Venlafaxine showed a different pattern of activity in the rotarod test and swim test. The variation in response is attributed to their effects on central neurotransmitter.

Keywords: Antidepressants, Buspirone, Motor activity, Swim test, Elevated plus maze test

INTRODUCTION

Depression is common affective disorder with varying clinical features.[1] Characteristic symptoms include loss of interest in activities, disturbances in sleep and thoughts of worthlessness. The pattern of symptoms vary in intensity in individuals and may be associated other conditions like anxiety.[2] There are several groups of drugs available, which can be prescribed to these patients. Selection of suitable drugs either single or in combination produce remarkable improvement in majority of patients.[3] Anxiety is a common phenomenon, which is associated with depressive disorder.[4] Drugs prescribed for such co-existing disorders may interact with antidepressants and may produce some beneficial systemic effects.[5] In this study, profiles of pharmacological effects of four different groups of antidepressants are observed in groups of mice. In addition, effect of a combination with an anxiolytic drug, buspirone is also observed. The observations on the central nervous system activity were based on the behavioral effects of mice on motor activity, swimming test and on elevated plus maze.

METHODS

Groups of mice weighing 20-30 g of either sex were used for this study. Each group consists of 6 mice. One group served as control, and four groups were given antidepressants alone for 2 weeks. After 2 weeks these groups were administered a combination of drugs for 3 consecutive weeks. Drugs were administered along with drinking water.

Animals were housed in polypropylene cages, each cage containing 3 mice only. Male and female mice were kept in separate cages. Mice were acclimatized for 1-week prior to using them for studies. Paddy husk was used as bedding material, which was changed on alternative days. The animals were maintained in a well aerated room with exhaust

and ceiling fans – Animals were maintained 12 hrs light and dark cycle. The room temperature was between 28 and 32°C. Food was provided in the form of pellets. Water was given as planned in the study, Drugs were administered in the drinking water for a fixed time during the day between 10 am and 4 pm. Prior to drug administration animals were not given water for 2 hrs.

The test drugs used were amitriptyline, citalopram, venlafaxine and mirtazapine. One group was given buspirone alone. Mice were given antidepressants for 2 weeks following which they were given a combination of test drugs and buspirone. The details of groups are listed below.

Group I: Control (distilled water)
Group II: Amitriptyline (6.5 mg/kg)
Group III: Citalopram (2.6 mg/kg)
Group IV: Venlafaxine (9.75 mg/kg)
Group V: Mirtazapine (1.95 mg/kg)
Group VI: Buspirone (1.95 mg/kg).

The dose of drugs was calculated from the conversion factor based on doses used in human.[6] Calculated amounts of drugs were powdered, and planned amount of distilled water was added to make the required strength of solution. Each animal was to receive the daily dose 0.5 ml of the drug solution, each cage containing three animals received 1.5 ml of drug solution was added to 8.5 ml of drinking water making up the total volume to 10 ml water. The water was sweetened by adding lactose to mask any probable distaste due to the drugs. In the evening by which time the water containing drug is finished, animals were supplied with fresh drinking water *ad libitum* until next day morning.

Four tests were conducted to determine the activity of the animals. These include activity on photoactometer (Plate 1), rotarod (Plate 2),[7] forced swimming test (Plate 3) and elevated plus maze (Plate 4).[8] The animals were well acclimatized with the instruments before the actual commencement of the experiment. Observations were made at the start of the study and at weekly intervals until the end of 5 weeks. Permission of the Animal Ethics Committee was taken before commencement of study and guidelines for animal studies were followed.

Statistical tests used: Paired t-test one tailed.

RESULTS

The behavioral effects of all the groups of mice were observed during the period of study. Recording of weight at weekly intervals showed no change with the different test drugs. Weight of animals remained between 35 and 40 g.

Results of the control group did not show any significant variation during the period of study. The values were comparable to pre-drug values. The results of single drug or combination were compared to pre-drug values (day 0) in each group. Values recorded for a single drug during 2 weeks were observed. The results of the combination used in each group in the final 2 weeks were observed. Results are presented accordingly.

Spontaneous motor activity was measured using photoactometer. Results are presented in Table 1. The antidepressant drugs did not show any significant change from pre-drug values. Combination of buspirone with amitriptyline and citalopram showed lower readings when compared to single drug administration ($p<0.05$). These effects were marked at week 5 at the end of 3 weeks of drug combination. Buspirone alone showed lower values at week 4 and 5 when compared to pre-drug values.

Results of the rotarod test are presented in Figure 1. Busprione when given alone showed an increase in recorded time. Combination of busprione with amitriptyline and

Table 1: Comparison of mean and SD of motor activity using photoactometer.

Drug	Mean	SD
Amitriptyline		
Day 0	319.66	70.01
Week 1	305.16	172.29
Week 2	304	123.25
Week 4	209	75.74
Week 5	183.16	68.91
Citalopram		
Day 0	258	104.80
Week 1	284.82	111.73
Week 2	346.66	113.47
Week 4	181.83	60.65
Week 5	150.33	47.18
Venlafaxine		
Day 0	282.83	110.67
Week 1	326.16	116.08
Week 2	347	126.55
Week 4	253.66	136.10
Week 5	258.83	159.33
Mirtazapine		
Day 0	257.5	142.65
Week 1	267.5	177.58
Week 2	318.66	178.06
Week 4	235	92.81
Week 5	206.5	82.32
Buspirone		
Day 0	287.5	94.20
Week 1	256.66	77.28
Week 2	325.83	97.35
Week 4	175.66	107.78
Week 5	198.83	118.31

SD: Standard deviation

citalopram showed a significant increase in duration of motor co-ordination. Venlafaxine showed an increase in duration during the 2nd week, combination with busprione showed further significant increase in duration during week 4 and 5 ($p<0.001$ at week 5).

Results of forced swim test are presented in Figure 2. Venlafaxine showed some increase in recordings during the 1st week of drug administration. Combination of buspirone and venlafaxine also showed a significant increase in recordings in week 5. The effects of other drugs did not show any significant change from the pre-drug values. Elevated plus maze was used to record the time spend in open arm and closed arm. Time spent in each arm after drug administration is presented in Tables 2a and 2b. After administration of citalopram with buspirone, there is a significant increase in the open arm recordings at week 4 compared to pre-drug

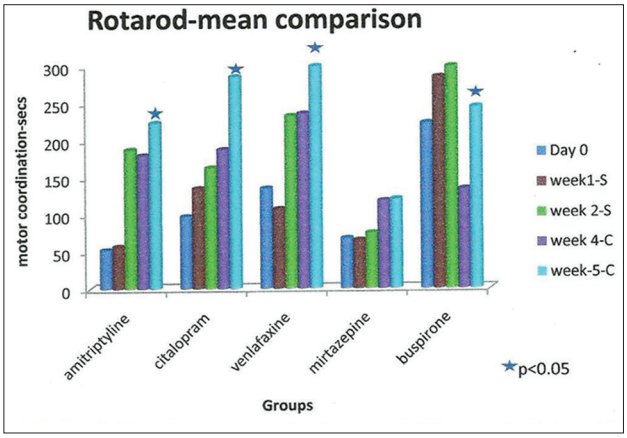

Figure 1: Comparison of the mean values of motor coordination using Rotarod. Mean readings on day 0, week 1, week 2, week 4 and week 5 are depicted.

Table 2a: Comparison of the mean and SD of time spent in closed arm using Elevated Plus Maze.

Drug	Mean	SD
Amitriptyline		
Day 0	206.5	19.53
Week 1	238	43.96
Week 2	218.67	54.09
Week 4	233.67	38.88
Week 5	229	59.46
Citalopram		
Day 0	212.83	24.09
Week 1	223.16	54.39
Week 2	170	54.83
Week 4	236.33	48.49
Week 5	224.5	44.22
Venlafaxine		
Day 0	175	39.21
Week 1	148	43.54
Week 2	177.67	40.53
Week 4	206	60.44
Week 5	254	39.76
Mirtazapine		
Day 0	232.33	46.04
Week 1	194.83	53.08
Week 2	236.33	59.83
Week 4	218.83	56.63
Week 5	251.67	29.03
Buspirone		
Day 0	239.67	39.95
Week 1	192.67	80.45
Week 2	194.67	53.27
Week 4	239.67	25.47
Week 5	246	48.88

SD: Standard deviation

Table 2b: Comparison of the mean and SD of time spent in open arm using Elevated Plus Maze.

Drug	Mean	SD
Amitriptyline		
Day 0	23.16	19.62
Week 1	29	25.28
Week 2	29.66	19.47
Week 4	29.83	19.29
Week 5	25.83	18.10
Citalopram		
Day 0	18.83	16.54
Week 1	20.16	16.02
Week 2	46.5	17.13
Week 4	27.67	23.63
Week 5	25.67	18.01
Venlafaxine		
Day 0	74.5	61.39
Week 1	129.17	64.65
Week 2	42.17	30.40
Week 4	36.17	32.90
Week 5	5.83	4.2
Mirtazapine		
Day 0	12.17	8.28
Week 1	60.83	51.77
Week 2	25.5	23.48
Week 4	29.66	16.58
Week 5	11.16	10.62
Buspirone		
Day 0	23.16	13.07
Week 1	52	28.23
Week 2	49.33	19.18
Week 4	20.33	16.49
Week 5	10.33	2.87

SD: Standard deviation

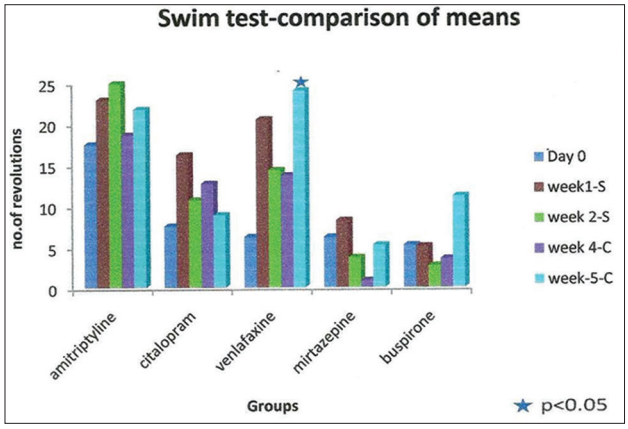

Figure 2: Comparison of the mean values of revolutions (anti anxious behavior) using swim test apparatus. Mean readings on day 0, week 1, week 2, week 4 and week 5 are depicted.

values. There was no change with other antidepressants alone or in combination with buspirone in this test. Mirtazapine group showed an increase in time spent in the closed arm, but this was not significant. Venlafaxine along with Buspirone showed a significant increase in the time spent in the closed arm at week 5 (p=0.01).

DISCUSSION

The four anti-depressant drugs used in this study belong to different groups. These drugs did not show any significant depressant activity on central nervous system as evidenced by the result on spontaneous motor activity. Buspirone when given alone showed lower readings at weeks 4 and 5. Buspirone when added to amitriptyline and citalopram showed decrease in activity. These results indicate that buspirone has mild depressant effect on central nervous system, the pharmacological effects develop slowly as is clear from the results observed during week 4 and 5. Addition of buspirone to amitriptyline and citalopram shows additive action. Buspirone has partial agonist action at 5HT1a presynaptic receptors resulting in a reduction of firing of 5HT neurons.[9] The observed result of decreased activity could be attributed to this action. In the rotarod test the buspirone caused an increase in recorded values at week 5. Amitriptyline and citalopram showed increase in the values while venlafaxine showed significant increase during 2nd week. Combination of busprione with vanlafaxine showed further increase in values indicating synergism. Photoactometer measures spontaneous motor activity while rotarod test gives an index of motor coordination. The variation in the results of these two tests suggests that drugs may influence pharmacological effects with a different mechanism. Venlafaxine a prototype serotonin noradrenaline reuptake inhibitor shows different effects on motor activity.[10] Amitriptyline belongs to tricyclic group, and citalopram is a selective serotonin reuptake inhibitors (SSRI). There are variations in their effect on neurotransmitters.

In the forced swim test venlafaxine showed an increase in readings during 1st week. Combination with buspirone showed increase in recording in week 5. In this test also venlafaxine demonstrates a different pattern of results.

Elevated plus maze is a test to determine the reduction in fear (anxiety) of the mice. At the doses used, citalopram in combination with busprione is the only agent, which showed an increase in the open arm. Citalopram, a selective serotonin reuptake inhibitor is considered as a useful therapeutic agent for anxiety. The other three antidepressants are not showing beneficial effects in this test. Probably higher doses may demonstrate some actions. Buspirone combined with venlafaxine showed an increase in time spent in a closed arm. It is interesting to note this difference in the pattern of effect of venlafaxine.

When combination is used there are varying pattern of systemic effects. In rotarod test and forced swim test venlafaxine shows additive beneficial effects of the increase in activity when combined with Buspirone. These results suggest that this combination is likely to be beneficial in a patient with depression and anxiety. Our results also confirm that citalopram has additional antianxiety action SSRIs are known to be useful as antianxiety agents. Antidepressants are known to act by inhibiting the uptake of amines in the central synapses. Tricyclics like amitriptyline inhibit reuptake of NA predominantly, citalopram inhibit 5HT, venlafaxine inhibit 5HT, NA, mirtazapine is an atypical antidepressant, which blocks α2 auto receptor (on NA neurons) and hetero- (on 5HT neurons) receptors enhancing both NA and 5HT release. It is a H_1 blocker too.[11] Results of this study indicate that variations in pharmacological effects are possible with different compounds and combinations. It is also interesting to note that the effect of the combination is significant in last week. This result suggests that metabolites of Buspirone may possibly be producing some effects. It is important to consider this factor when therapeutic benefit is delayed.

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