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

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INTRODUCTION

Depression is common affective disorder with varying clinical features. 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. 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. Anxiety is a common phenomenon, which is associated with depressive disorder. Drugs prescribed for such co-existing disorders may interact with antidepressants and may produce some beneficial systemic effects. 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.
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. 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), forced swimming test (Plate 3) and elevated plus maze (Plate 4). 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. Buspirone when given alone showed an increase in recorded time. Combination of buspirone with amitriptyline and

| 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 buspirone 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

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|

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
neurotransmitters. Inhibitors (SSRI). There are variations in their effect on motor activity. Noradrenaline reuptake inhibitor shows different effects on different mechanism. Venlafaxine a prototype 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 anxiolytic action SSRIs are known to be useful as anxiolytic 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 H1 blocker too. 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.

**ACKNOWLEDGMENTS**

Authors are immensely obliged to Dr. Santha Suresh, Ph.D., for contributing her valuable assistance in statistical analysis of the study.

**Funding:** No funding sources

**Conflict of interest:** None declared

**Ethical approval:** The study was approved by the Institutional Animal Ethics Committee

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**doi:** 10.5455/2319-2003.ijbcp20150212

**Cite this article as:** Midhun M, Ravi I, Roy R, Chinnathampi T, Kuruvilla A. Profile of pharmacological effects of combination of buspirone with selected antidepressants: a behavioral study in mice. Int J Basic Clin Pharmacol 2015;4:65-9.