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Research Article

To investigate the role of Memantine as anxiolytic in elevated plus maze test and as antidepressant in tail suspension test in Swiss albino mice

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ABSTRACT

Background: The magnitude of improvement seen with present conventional medicines for anxiety and depression remain disappointing thereby providing a scope for the study of newer drugs. In the literature, there is evidence demonstrating the modulation of N-methyl-D-aspartate (NMDA)receptors in anxiety and depression. The present study is undertaken to evaluate the antianxiety effect of memantine in elevated plus maze (EPZ) test and its antidepressant effect in tail suspension test (TST)in Swiss albino mice.

Methods: Animals were divided into six groups (n=6). First group mice were given normal saline (10 ml/kg), second group were administered lorazepam (0.5 mg/kg), third group with memantine (3 mg/kg) and fourth group with memantine plus lorazepam, fifth group was administered amitriptyline (10 mg/kg)and sixth group received memantine plus amitriptyline. All drugs were administered by intraperitoneal route daily for 7 consecutive days. Results were analyzed by one-way ANOVA followed by *post-hoc* Tukey's test.

Results: Memantine treated mice showed significant increase (p<0.001)in time spent and number of entries in open arm and significant decrease in time spent and number of entries in closed arm in EPZ when compared to control group. Duration of immobility was significantly (p<0.001)reduced in animals treated with memantine when compared to the control group in TST.

Conclusions: NMDA antagonist, memantine has showed significant antianxiety effect in EPZ test and antidepressant effect in TST.

Keywords: Memantine, N-methyl-D-aspartate-antagonist, Elevated plus maze test, Antianxiety, Tail suspension test, Antidepressant

INTRODUCTION

The incidence of anxiety disorders in the world is very high and is associated with a lot of morbidities. Prevalence of anxiety in women is 30.5% and in males is 19.2% during their lifetime.[1] Benzodiazepines are the standard anti-anxiety drugs, but they are associated with side effects of sedation and addiction. Buspirone, is a non-sedative anxiolytic agent which causes gastric discomfort, tachycardia, palpitation, as side effects in its long-term usage.[2]

Similarly, depression is one of the major mental disorders. It is common in women, who have a lifetime prevalence of 21.3% when it is compared to 12.7% in men.[3] Most antidepressant medications increase the levels of serotonin and norepinephrine neurotransmitters in the synaptic cleft. Approximately, two-thirds of the patients with depression respond better to the currently available treatments but still the desired magnitude of improvement is not achieved.[4]

Around 5-10% of patients on selective serotonin reuptake inhibitors discontinue therapy because of side effects related to the gastrointestinal tract and central nervous system as well as weight gain.[5] Therefore, research for newer antidepressants with greater effectiveness has to be explored.

It has been well-accepted that glutamate deregulation also contributes significantly to anxiety-like disorders.[6] Among them, N-methyl-D-aspartate (NMDA)receptor is particularly known to play a key role in anxiety disorders.[7,8] Similarly, over the past decade, interest has turned to a potential role of the glutaminergic system in depression, particularly giving importance to mainly NMDA receptor.[7] This is a departure from our previous thinking, which had focused on serotonin and norepinephrine. It was reported from an earlier study that the statin dose independently improves depression and anxiety via modulating NMDA receptors.[9]

Memantine is a non-competitive NMDA antagonist, which is used in Alzheimer's disease. Previous studies undertaken by us had established the antidepressant[10] and antianxiety effect of memantine in other experimental models.

In our previous study, we demonstrated antidepressant effect of memantine in other behavioral assessment parameters of depression in animal models like forced swim test and locomotor activity in photoactometer. Memantine-treated mice when compared to the control group revealed significant reduction in the duration of immobility in forced swim test on day "7" when compared to day "0". Although the immobility time in Forced swim test, is also reduced by central nervous system stimulants, but they tend to increase the locomotor activity in the animals. In our previous study it was also found that memantine administered for "7" days, did not show any significant change in locomotor activity of mice, as compared to the control group. Which helps to confirm the antidepressant like activity, which is not a false positive finding.

Rationale for using lorazepam in our study as standard antianxiety drug- is to observe for any interaction of memantine (NMDA antagonist)as a test drug with lorazepam as positive control (which also allosterically modulates NMDA receptors), allowing little similarity with standard and test drug action in accordance with NMDA receptor. Lorazepam by interacting with GABA enhances chloride ion conductance and increases the frequency of channel opening events. In addition to this, it was demonstrated from an earlier study that there is interplay of NMDA receptors conditioning and $GABA_A$ receptors subunits desensitization. In hippocampal neurons, conditioning with 20 μM NMDA for 20 sec caused 50% suppression of GABA responses and lorazepam potentiation reliably increased with $GABA_A$ receptors when NMDA-induced suppression in plasticity of fast synaptic transmission.[11] Although either potentiation or suppression can occur, under many conditions Ca^{2+} influx through NMDA-type glutamate receptors suppresses subsequent responsiveness of $GABA_A$ receptors.[12] Lorazepam is having poor lipid solubility and high degree of protein binding (85-90%), means its volume of distribution is mainly the vascular compartment, causing relatively prolonged peak effects. The plasma levels of lorazepam are proportional to the dose given. There is no evidence of accumulation of lorazepam on administration up to 6 months. The half-life of lorazepam is 10-20 hrs.

Rationale for using amitriptyline in our study as standard antidepressant drug - is to observe for any interaction of memantine (NMDA antagonist)as a test drug, with amitriptyline as positive control (which also allosterically modulates NMDA receptors), allowing little similarity with standard and test drug action in accordance with NMDA receptor. Amitriptyline acts primarily as a serotonin-norepinephrine reuptake inhibitor, with strong actions on the serotonin transporter and moderate effects on the norepinephrine transporter.[13] It has also been shown to be a relatively weak NMDA receptor negative allosteric modulator at the same binding site as phencyclidine.[14] Recently, amitriptyline has been demonstrated to act as an agonist of the TrkA and TrkB receptors. It promotes the heterodimerization of these proteins and has potent neurotrophic activity both *in-vivo* and *in-vitro* in mouse models.[14,15] These are the same receptors which activate brain-derived nerve growth factor (BDNF), an endogenous neurotrophic with powerful antidepressant effects. In a recent study, it has been indicated that amitriptyline increases reuptake of glutamate through its transporters, resulting in prevention of NMDA-induced excitotoxicity.[16,17] Amitriptyline is highly bound to plasma and tissue proteins, therefore, have large volumes of distribution (~20 L/kg)and its t½ is 16-24 hrs.

The present study was undertaken in order to further strengthen the evidence of memantine as an antianxiety in elevated plus maze (EPZ)test and as an antidepressant drug in tail suspension test (TST)in Swiss albino mice.

METHODS

Aims and objectives

To study the antianxiety effect of memantine in EPZ test and to study the antidepressant effect of memantine in TST.

Swiss albino mice of either sex weighing between 25 and 30 g were obtained from the central animal house of MVJ Medical College and Research Hospital. The animals were housed in cages and kept under controlled environmental condition (temperature 22±2°C, humidity 50-55%, natural light/day cycle). All the experiments were performed in the daytime between 09:30 and 15:30 hrs. Care of animals was done according to CPCSEA guidelines. Permission was taken from the Institutional Animal Ethics Committee to carry out the experiment.

Drugs and chemicals

Memantine (Sun Pharma Drugs Pvt. Ltd. India) and Amitriptyline, Lorazepam (Intas Pharmaceuticals Ltd. India) diluted in normal saline were used.

Experimental design

The animals were divided into six groups (n=6). Group I - was administered normal saline (10 ml/kg, intraperitoneal [i.p.])serve as control. Group II - received lorazepam (0.5 mg/kg, i.p.). Group III - was given the memantine (3 mg/kg, i.p.).Group IV - was administered memantine (3 mg/kg, i.p.)+ lorazepam (0.5 mg/kg, i.p.). Group V - was treated with amitriptyline (10 mg/kg, i.p.) and Group VI - received memantine (3 mg/kg, i.p.)+

amitriptyline (10 mg/kg, i.p.). Memantine, lorazepam, amitriptyline, normal saline were administered by i.p. route daily for 7 days of the experimental period to assess their effects on "0" and day "07". The mice were administered drugs and assessment was conducted 30 minutes after drug administration.

Assessment of behavioral tests

EPZ (Elevated Plus Maze)[18]

The elevated plus-maze comprised of two open (30 cm ×5 cm × 0.25 cm)and two enclosed (30 cm×5 cm×15 cm) arms that radiated from a central platform (5 cm×5 cm)to form a plus sign. The maze is kept elevated 40 cm above the floor in a dimly-lit room. The test was done by placing an animal on the central platform of the maze facing an open arm. A mouse was considered to have entered an arm, when all four paws were on the arm. As a positive standard, mice were administered lorazepam i.p. During the 5 mins test, preference of the animal for the first entry, the number of entries into the open or closed arm and the time spent in each arm of the maze were noted.

TST (Tail Suspension Test)

The method is similar to that described by Steru et al.[19] Mouse was suspended upside down on a metal rod at a height of 55 cm from the ground with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Initially, the mouse tried to escape by making vigorous movements but when unable to escape became immobile. The animal was considered immobile when it did not show any movement of the body and hanged passively. The immobility displayed by rodents when subjected to this kind of unavoidable stress and behavioral despair reflects mental depression in humans. The total duration of immobility is noted during 6 mins period.

Statistical analysis

Results are presented as mean±SEM. One-way ANOVA is used for comparison between the groups, followed by *post-hoc* Tukey's test. For all the tests, $p \leq 0.05$ was considered statistically significant.

RESULTS

In group treated with lorazepam as a standard, animals gave first preference to open arm, there was significant increase $(p<0.001)$ in number of entries and time spent in open arm and significant decrease $(p<0.001)$ in number of entries and time spent in closed arm $(p<0.001)$ on day "0" and on day "07" as compared to control group as shown in Tables 1 and 2.

The mice which received memantine when compared to control group, animals gave first preference to open arm, though there was slight increase in the number of entries and time spent in open arm and slight decrease in the number of entries and time spent in closed arm as compared to control on day "0" which was not statistically significant. Whereas, on day "07" there was significant increase $(p<0.001)$ in number of entries and time spent in open arm and significant decrease $(p<0.001)$ in number of entries and time spent in closed arm as shown in Tables 1 and 2.

When lorazepam-treated group was compared with memantine received group, animals showed significant increase $(p<0.001)$ in number of entries and time spent in open arm and significant decrease $(p<0.001)$ in number of entries and time spent in closed arm on day "0". But on day "07", there was significant increase $(p<0.01)$ in number of entries in open arm and significant decrease $(p<0.01)$ in number of entries and time spent in closed arm but no statistical significant difference was observed in the time spent by the mice in open arm as shown in Tables 1 and 2.

On day "0" and day "07", (memantine + lorazepam)treated group, animals showed significant increase $(p<0.001)$ in number of entries, time spent in open arm and significant decrease $(p<0.001)$ in number of entries, time spent in closed arm when compared to memantine alone treated group as shown in Tables 1 and 2.

When evaluating for the antidepressant effect in TST, the group treated with Amitriptyline as a standard, animals showed significant decrease $(p<0.001)$ in immobility period on day "0" and day "07" as compared to control group as shown in Tables 3 and 4. When memantine treated group was compared to the control group, animals showed a slight decrease in the period of immobility on day "0" which was not statistically significant. Whereas, on the day "07", a

Table 1: Effect of a single dose observation in EPZ test on day 0.

Groups, (dose)	Number of entries in O.A	Time spent in O.A (sec)	Number of entries in C.A	Time spent in C.A (sec)
1. Normal saline (10 ml/kg, i.p.)	2.3±0.36	23.8±1.59	16.43±1.18	265.4±3.48
2. Lorazepam (0.5 mg/kg, i.p.)	13.4±0.77*	201.6±5.83*	4.7±0.55*	96.8±2.24*
3. Memantine (3 mg/kg, i.p.)	3.1±1.04††	31.3±2.59††	14.5±0.61††	253.2±2.94††
4. Memantine+lorazepam	15.8±1.15‡‡	245.6±2.53‡‡	3.5±0.31‡‡	52.5±2.16‡‡

O.A: Open arm, C.A: Closed arm, n=6, values expressed as mean±SEM. *p<0.001 versus normal saline, †p<0.01, ††p<0.001 versus lorazepam, ‡p<0.01, ‡‡p<0.001 versus memantine. SEM: Standard error mean, EPZ: Elevated plus maze

Table 2: Effect of the multiple dose observation in EPZ test on day 7.

Groups, (dose)	Number of entries in O.A	Time spent in O.A (sec)	Number of entries in C.A	Time spent in C.A (sec)
1. Normal saline (10 ml/kg, i.p.)	3.2±0.34	21.9±0.89	13.8±1.49	269.7±14.43
2. Lorazepam (0.5 mg/kg, i.p.)	15.3±1.29*	210.4±6.94*	3.2±0.41*	82.7±1.85*
3. Memantine (3 mg/kg, i.p.)	10.8±1.18*,†	194.9±4.08*	7.7±0.65*,†	123.1±1.91*,†
4. Memantine+lorazepam	17.5±0.82‡‡	260.8±5.01‡‡	2.8±0.43‡‡	37.2±1.18‡‡

O.A: Open arm, C.A: Closed arm, n=6, values expressed as mean±SEM. *p<0.001 versus normal saline, †p<0.01, ††p<0.001 versus lorazepam, ‡p<0.01, ‡‡p<0.001 versus memantine. SEM: Standard error mean, EPZ: Elevated plus maze

Table 3: Effect of a single dose observation in TST on day 0.

Groups, (dose)	Duration of immobility (sec)
1. Control (10 ml/kg, i.p.)	175.8±2.63
3. Memantine (3 mg/kg, i.p.)	167.5±3.56†
5. Amitriptyline (10 mg/kg, i.p.)	107.2±2.87*
6. Memantine+Amitriptyline	86.3±1.54‡‡

n=6, values expressed as mean±SEM. *p<0.001 versus normal saline-control, †p<0.01 versus Amitriptyline, ‡p<0.01, ‡‡p<0.001 versus memantine. SEM: Standard error mean, TST: Tail suspension test

Table 4: Effect of the multiple dose observation in TST on day 7.

Groups, (dose)	Duration of immobility (sec)
1. Control (10 ml/kg, i.p.)	179.6±2.39
3. Memantine (3 mg/kg, i.p.)	93.3±1.54*
5. Amitriptyline (10 mg/kg, i.p.)	84.5±1.71*
6. Memantine+Amitriptyline	78.1±3.96‡

n=6, values expressed as mean±SEM. *p<0.001 versus normal saline-control, †p<0.01 versus Amitriptyline, ‡p<0.01, ‡‡p<0.001 versus memantine. SEM: Standard error mean, TST: Tail suspension test

significant decrease (p<0.001)in immobility period was noticed as shown in Tables 3 and 4.

In group treated with amitriptyline, animals showed significant decrease (p<0.01)in immobility period on day "0". But on day "07", there was no statistically significant difference in the immobility period when compared to memantine treated group as shown in Tables 3 and 4. When (memantine + amitriptyline)-treated group was compared with the group which received memantine alone a statistically significant decrease in immobility period was seen on day "0" (p<0.001) as well as on day "07", (p<0.01)as shown in Tables 3 and 4.

DISCUSSION

The etiology of most anxiety disorders is not fully understood, but various studies have shown the involvement of GABAergic and serotonergic neurotransmission in its etiology.[20,21] The EPZ is commonly used to assess anxiety related behavior. In the EPZ, avoidance of the open arms, increase in time spent in the closed arms, and a decrease in rearing indicates anxiety.[22] Study by Poleszak et al.[23] shows that NMDA receptor activation antagonizes the NMDA antagonist-induced antianxiety effect in the elevated plus-maze test in mice. Over the past decade, interest has turned to a potential role of the glutaminergic system in depression particularly with focus on NMDA receptor.[4] This encouraged us to study the effect of NMDA antagonist, memantine in experimental models of anxiety and depression.

In our study, memantine produced significant anxiolytic effect when compared to the normal saline, as well as the standard lorazepam-treated group. A synergistic interaction between memantine and lorazepam was also observed in their antianxiety effect. Similar antianxiety effects were demonstrated from previous studies depicting antianxiety effect of other competitive NMDA receptor antagonists.[22,23]

When the antidepressant activity of memantine was studied in TST, it showed a significant decrease in the duration of immobility when compared to amitriptyline treated group. Mice treated with memantine when compared to the normal saline-treated group, memantine significantly reduced the immobility in TST, on the day "7" when compared to day "0". A synergistic interaction between memantine and amitriptyline was observed in the antidepressant effect. The above finding of antidepressant activity of memantine was similar to a previous study by Karve et al.[24] Similarly, other previous studies by Patel et al.[25] and Poleszak et al.[26] have demonstrated antianxiety and antidepressant effects as well.

There is improved clinical tolerability of memantine in comparison to other NMDA antagonists which have shown antianxiety effects like phencyclidine.[27-30] The preclinical and clinical data provide strong evidences that diverse antagonists and partial agonists, acting at different sites of NMDA receptor complex exhibit anxiolytic-like activity. Quite often, they have been compared to benzodiazepines or barbiturates.[8,31,32]

The hypothesis by Olney et al.[33] suggest that over-activation of NMDA receptors leads to damage of GABA neurons and secondary damage produced by disinhibited neurons (e.g. glutamate, Ach, neuropeptide Y [NPY]). A new

study in mice by Zarate et al. shows that blocking the NMDA receptor increases the activity of another receptor, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)and this boost in AMPA activity is crucial for rapid antidepressant actions. It has been reported that activation of AMPA glutamate receptors increases BDNF expression and stimulates neurogenesis and neuronal sprouting, in the hippocampus.[34] The infusion of NMDA into either the raphe nuclei or frontal cortex has revealed to alter local 5-HT release and also serotonergic transmission.[35]

The previous study by Wieronska et al.[36] indicates that in the amygdala, the NMDA receptors mediated glutaminergic transmission may regulate NPY neurons. There is also evidence showing topiramate (NMDA receptor modulator) altering the NPY activity in flinders sensitive line "depressed" rats.[37] Activity of memantine on NPY activity, which might contribute to the antidepressant and antianxiety activity, cannot be ruled out providing a new way for its further exploration.

CONCLUSION

Memantine has demonstrated antianxiety effect which was comparable to lorazepam. Memantine could be producing its antianxiety activity by blocking NMDA receptor. There was the synergism in antianxiety activity of memantine and lorazepam. Memantine has also found to exert antidepressant activity which was comparable to Amitriptyline by blocking NMDA receptor. However, it's modulating effect on NPY which might contribute to antianxiety, and antidepressant activity has to be further explored.

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