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Assessment of anxiolytic effect of nerolidol in mice

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» Abstract

Aim and Objectives: The present study was to assess the anxiolytic effect of nerolidol in mice.
Materials and Methods: The anxiolytic activity was examined using the elevated plus maze (EPM) and open field test (OFT), and motor coordination by rotarod test. Thirty Swiss albino mice were divided into five groups of six mice each. Group 1 received vehicle control (normal saline); Group 2 received diazepam (1 mg/kg); Groups 3, 4, and 5 received nerolidol 12.5, 25, and 50 mg/kg, respectively.
Results: Nerolidol (12.5, 25, and 50 mg/kg) significantly ($P < 0.05$) increased the time spent and a number of entries in open arm as compared to vehicle control in EPM test. In OFT, the nerolidol showed a significant ($P < 0.05$) increase in number of rearings and time spent in center and periphery, suggesting exploratory behavior of animals. Furthermore, nerolidol did not alter the fall down latency in rotarod test.
Conclusion: Our findings indicated that nerolidol exerts an anxiolytic effect without altering the motor coordination.

Keywords: Anxiety, diazepam, elevated plus maze, nerolidol, open field test

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Anxiety is the common psychiatric disorder that affects approximately one-eighth of the world population.[1] Currently, various psychotropic drugs are available to grapple with this psychiatric disorder. Among the available psychotropic drugs, benzodiazepines are commonly prescribed to the patients. However, the regular use of the benzodiazepines leads to various side effects.[2] Thus, there is a need to explore newer and safer pharmacological agents to treat anxiety. To resolve this issue, various alternative therapies such as aromatherapy have been used to manage the anxiety and other psychiatric disorder.

Nerolidol is a sesquiterpene alcohol frequently found as a major component of essential oil obtained from various species of well-known aromatic plants such as *Aframomum pruinosum* (<90%), *Myrceugenia cucullata* (<90%), *Siparuna guianensis* (90%), *Melaleuca quinquenervia* (87%), *Piper clausseniamum* (83%), *Eucalyptus nova-anglica* (<80%), *Salvia runcinata* (72%), and many more. It is widely used as a fragrance ingredient in the various pharmaceutical formulations.[3]

Studies focusing on nerolidol have shown various pharmacological properties such as antiulcer,[4] antioxidant,[3] antifungal,[5] anti-inflammatory,[6] and anticonvulsant.[7] However, the literature revealed that nerolidol has been least explored with respect to central nervous system. Therefore, this prompted us to investigate the anxiolytic effect of nerolidol in different experimental models.

Animals

Male Swiss laka mice, weighing 20–30 g obtained from Central Research Institute, Kasauli, were employed in the present study, in different groups ($n = 6$). The animals were housed in standard cages and were maintained at room temperature with natural day and night cycles. The animals were allowed free access to food (standard laboratory rodents chow) and water during the study period. All experiments were carried out between 07:00 and 16:00 h. All procedures were conducted according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. The experimental protocol was approved by the Institutional Animal Ethical Committee established by the University (CPCSEA Protocol No: 107/99/CPCSEA/2014-13).

Drugs and Treatments

Nerolidol (Sigma-Aldrich) was diluted with tween eighty to prepare nerolidol emulsions (12.5%, 25%, and 50%) before the experiments. Diazepam (Jackson Laboratories Pvt. Ltd., India) was dissolved in normal saline and used as positive control (1 mg/kg). It was administered intraperitoneally (i.p.) at a volume of 0.1 ml/10 g of body weight.

Elevated Plus Maze

This is a behavioral paradigm that takes advantage of the conflict behavior of rodents between exploration of a novel area and aversion to open and elevated spaces.[8] The maze consists of four arms with opposite facing two open (16 cm × 5 cm) and two enclosed arms (16 cm × 5 cm × 12 cm) connected by a central platform. The whole maze is raised 25 cm above the floor. Mice were tested on the plus maze in a room with low direct lighting and low noise levels. On the day of testing, the mouse was placed at the center of the maze with head facing an open arm and allowed to explore for 5 min. The number of entries and time spent in each arm was recorded. The entry into arm was considered when all four paws of the animal were placed on the arm. The maze was wiped clean with 70% ethanol solution and dried after testing each mouse. Increase in time spent and frequency of open arms entries relative to control mice were considered as indicators of anxiolytic behavior.

Open Field Test

Open field test (OFT) was used to evaluate locomotor and thigmotactic behavior of mice.[9] The open field consisted of 72 cm × 72 cm plexiglass square with 36 cm walls. For analysis, the chamber was divided into sixteen 18 cm × 18 cm squares. A central square was withdrawn in middle of the open field with red line for counting the crossings in case of high locomotor activity. Each mouse was placed in the center of the open field area and allowed to explore it for 5 min. During the 5 min test session, the variables of locomotor activity (number of black line crossings and central square entries), basic movements, fine movements (such as head-twitching and grooming), and time spent in periphery and central zones were recorded. Open field area was cleaned with 70% ethanol solution and let dry after testing each mouse.

Rotarod Test

In this test, the animals were preselected in a training session 24 h before the test based on their ability to remain on the bar (at 12 rpm) for 2 min. Groups of preselected animals were treated with vehicle, nerolidol (12.5, 25, and 50 mg/kg; i.p.), or diazepam (1 mg/kg; i.p.). Thirty minutes after the treatment, the animals were placed with all four paws onto the bar, and the fall down latency was evaluated.[10]

Effect of Nerolidol on Behavior of Mice in Elevated Plus Maze

In the elevated plus maze (EPM), diazepam-treated animals showed ($P< 0.001$) a significant increase in a number of entries and time spent in the open arm as compared to vehicle control animals. Similarly, nerolidol-treated animals (12.5, 25, and 50 mg/kg) exhibited significant increase ($P< 0.05$) in the number of entries and time spent in the open arm as compared to vehicle control animals. However, nerolidol-treated animals showed a significant reduction ($P< 0.05$) in the time spent in enclosed arm as compared to vehicle control animals [Table 1].

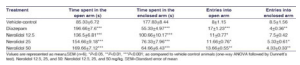

Table 1: Effect of nerolidol on behavior of mice in elevated plus maze

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Effect of Nerolidol on Behavior of Mice in Open Field Test

Diazepam- and nerolidol-treated animals (12.5, 25, and 50 mg/kg) showed a significant increase in the number of rearings and time spent in center and periphery as compared to vehicle control animals suggesting exploratory behavior as compared to vehicle control animals [Table 2].

Treatment	Number of rearing	Time spent in the center (s)	Time spent in the periphery (s)
Vehicle-control	10±0.78	26.5±4.5	253.66±16.48
Diazepam	17.8±1.19***	83.5±3.14***	84±6.51***
Nerolidol 12.5	13.5±2.01**	50±3.65***	126.5±12.68***
Nerolidol 25	15±1.83***	64±3.18***	111.66±8.97***
Nerolidol 50	21.3±3.26***	74±3.21***	95.33±5.94***

Values are represented as mean±SEM (n=6); *P<0.05, **P<0.01, ***P<0.001; as compared to vehicle control animals (one-way ANOVA followed by Dunnett's test). Nerolidol 12.5, 25 and 50: Nerolidol 12.5, 25 and 50 mg/kg. SEM=Standard error of mean

Table 2: Effect of nerolidol on behavior of mice in open field test

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Effect of Nerolidol on Rotarod Test

Neither diazepam (1 mg/kg) nor nerolidol (12.5, 25, and 50 mg/kg) at anxiolytic dose, significantly altered the fall down latency in the rotarod test as compared to vehicle control animals [Table 3].

Treatment	Fall down latency (s)
Vehicle-control	298.33±0.84
Diazepam	293±1.59
Nerolidol 12.5	297.66±0.91
Nerolidol 25	295.33±1.64
Nerolidol 50	292.66±2.34

Values are represented mean±SEM (n=6). Nerolidol 12.5, 25, and 50: Nerolidol 12.5, 25, and 50 mg/kg. SEM=Standard error of mean

Table 3: Effect of nerolidol on the rotarod test

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» discussion

Essential oils are concentrated volatile oils mainly found in aromatic plants and characterized by their fragrance. They have been widely used in the aromatherapy due to their medicinal properties. Moreover, various essential oils have been reported to possess anxiolytic effects through animal model of anxiety.[11],[12] In the present study, nerolidol an essential oil significantly decreased the levels of anxiety. The methodology used to evaluate anxiolytic effect is discussed below.

Among models used to evaluate anxiolytic effect, the EPM is considered to be most widely validated test because it uses natural stimuli such as brightly lit open space, the fear of a new, and fear of balancing on a relatively narrow raised platform. In the EPM, an anxiolytic drug specifically increases the number of entries and the time spent in the open arms.[13],[14] Similarly, in the current study, nerolidol-treated animals significantly increased the number of entries and the time spent in the open arms indicating its anxiolytic effect. Diazepam is a known anxiolytic drug used in the current study also increased the number of entries and the

time spent in the open arms as expected.

In the OFT, anxiolytic treatment decreases the anxiety-induced inhibition of exploration.[2],[15] Nerolidol 50 mg/kg dose showed almost similar exploratory behavior as that of standard anxiolytic drug used in the current study.

A deficit in motor coordination would like to affect the performance in the behavioral tests. Therefore, we evaluated the motor effects of nerolidol in the rotarod test, a conventional animal model used to evaluate the motor coordination.[10] Our results showed that anxiolytic dose of nerolidol (12.5, 25, and 50 mg/kg) as well as diazepam (1 mg/kg) had no significant effect on motor coordination.

The nerolidol has been reported as a positive modulator of gamma aminobutyric acid receptor.[16],[17] Moreover, anxiolytic profile and effect on motor coordination at anxiolytic dose of nerolidol is similar to that of diazepam, suggesting GABAergic modulation as a possible mechanism for its anxiolytic effect. However, further experiments are required to ascertain this.

» Conclusion

Nerolidol showed the anxiolytic effect without altering the motor coordination in mice. Further pharmacological investigations are warranted to elucidate the exact mechanism of action.

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Conflicts of Interest

There are no conflicts of interest.

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Tables

[Table 1], [Table 2], [Table 3]

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