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Research Article

EVALUATION OF ANTIDEPRESSANT ACTIVITY OF DIPHENHYDRAMINE IN MICE

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ABSTRACT

The study aims to evaluate the antidepressant activity of different doses of diphenhydramine in mice at (0.5, 1, 2 mg /Kg, IP).

Materials and Methods: The mice were divided into 5 groups for each testing methods, each group consist of five animals. Group 1 served as a control and was given normal saline 0.9% (5ml/kg,IP), group 2 received (20 mg /Kg, IP) fluoxetine as a standard control. Group 3, 4, 5 were treated with three different doses of diphenhydramine (0.5, 1, 2 mg /Kg, IP) respectively. The normal behaviors of each group of mice were evaluated after 30 min. of drug administration. The test was used to evaluate the antidepressant activity of diphenhydramine in Open Field, Modified Forced Swimming Test and Tail Suspension Test

Results: It is found that the increase in the locomotor activity in open field cage by increasing the number of square cross to (94.2±28.7) (93.2±25.6) (86.6±22.1) respectively according to the doses of diphenhydramine in comparison with control group (69.4±27.2) at $p \leq 0.05$. In modified forced swimming test, the result also showed that the administration of diphenhydramine at (0.5, 1, 2 mg /Kg, IP) were reduced the immobility time (68.8 ± 21.1) (56.4 ± 17.7) (47.6 ± 21.7) Sec. respectively in comparison with control group. In the present study, It is found that the administration of diphenhydramine at (0.5, 1, 2 mg /Kg,IP) were significantly increased in the swimming time (143.2 ± 16.2) (152.6 ± 18.7) (160.02 ± 15.5) Sec. Sec. in comparison with control group (28.8 ± 3.4) Sec.

Conclusion: Thus, this study suggested that the administration of diphenhydramine is produced a good therapy used in the treatment of depressed patients without side effect .

Keywords: Antidepressant, Tail suspended test, Open failed test, Diphenhydramine, Force swimming test.

INTRODUCTION

Depression is a serious mood disorder that affect of most population nowadays (Yagiela et al., 2011). The main symptoms of depression are due to functional deficiency in the levels of monoaminergic transmitters' noradrenalin, 5- hydroxytriptamine and dopamine in the brain (Harvey et al 2012). Drugs that increase the level of these neurotransmitters in the CNS showed antidepressant activity (Meyers 2000). The major antidepressant therapies aim to increase the synaptic concentration of serotonin or norepinephrine or both and thus normalize the neurotransmission (Jithan and Chinnalalaiah, 2009). Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed drugs for the treatment of depression and several anxiety, the actions of SSRIs at disorder (David et al., 2009). In the past decayed, we found drugs that inhibit reuptake of the neurotransmitter serotonin have antidepressant activity therefore increase the search for viable of antidepressant drugs with fewer side effects (Domino and Edward, 1999).

Diphenhydramine is a first generation H_1 antihistamine. It the oldest H_1 antihistaminergic drug used clinically for the treatment of many conditions such as common cold, anaphylaxis, pruritus and Parkinsonism disease (Raphael et al., 2006). Diphenhydramine is an H_1receptor antagonist receptor; these receptors are found in most part of the body such as smooth muscles, vascular endothelial cells, heart tissues, and the central nervous system (Yagiela et al., 2004). Histamine is considered as central neurotransmitters because it is have many criteria for a neurotransmitter substance (Montoro et al., 2006). Brain histamine is suggested to have physiological role in thermoregulation, body fluid balance, sleep and wakefulness (Barbier and Bradbury 2007) and release of certain hormones (Bealer and Crowley, 1999). Brain histamine appears to play some biological roles in control of mood, locomotor activity, emotion and other behavioral functions (Leza et al, 1991, Browen et al , 2001). Histamine exist in both peripheral and central system therefore the disturbance in central histamine neuronal system may be considered as an one of behavior disorders because If histamine is found in high levels, the patients are depressed, but low histamine levels are causes nervous, anxious and paranoid (Prousky et al 2002). This action of histamine in neuronal system might be responsible on pathophysiology of depression and therefore used drugs that modulation of central histamine neuronal system may be useful in the treatment of depression (Kano et al, 2004).

The goals of the present investigation were undertaken to evaluate the antidepressant effect of different doses of diphenhydramine in mice as a model of an depressive state induced by (tail suspended test, swimming test, open field test) and the ability to treat depression without adverse effects.

MATERIALS AND METHODS

Animals

Healthy albino mice of either sex weighing 25-30 gm were selected for the study. The animals were housed under laboratory condition, at temperature 22± 2 °C with a natural light \ dark cycle and fed with standard diet. The animals were transferred to the laboratory environment for at least one hour before used. Each animal was used only one and received only one dose of the drugs tested. Animals were obtained from animal care house in Dentistry Collage /Mosul University/ Iraq.

Experimental design

The drugs used in this Experiment were Diphenhydramine (NDI-IRAQ), Fluoxetine. Diphenhydramine and fluoxetine were dissolved in normal saline. All drugs were administered intraperitoneally (IP) in a volume 5ml\kg body weight. The mice were divided into 5 groups for each testing methods, each group consist of five animals. Group 1 served as a control and was given normal saline 0.9% (5ml/kg, IP), group 2 received (20 mg /Kg, IP) fluoxetine as a standard control. Group 3, 4, 5 were treated with three different doses of diphenhydramine (0.5, 1, 2 mg /Kg, IP) respectively. The

normal behaviors of each group of mice were evaluated after 30 min. of drug administration.

Antidepressant activity test

Open-field test

The standard Open Field Test is commonly used to assess locomotor activity and anxiety like behaviors in laboratory animals (rats/mice) (Lowery et al, 2005). Parameters are measured within 5 min. into the open field, a wooden box of dimensions (35×35×25) cm, where the ground consisted of the fund divided to equal to 25 square dimensions (Moser et al., 1988; Molinengo et al., 1989).

After thirty minutes of administration of fluoxetine, diphenhydramine, the animals were subjected to the test activity in the open field cage. The mouse was placed in the central square to measure onset to move from central square and the ambulation (number of squares cross)/ 5 min.

Modified forced swimming test

Antidepressant activities of different doses of diphenhydramine were assessed using modified Porsolt test (Jintanaporn et al, 2007). Mice were placed individually in a transparent glass cylinder (12 cm in diameter, height 25 cm), which was filled with water to a height of 12 cm. 30 minutes after drugs injected the mice were forced to swim in the cylinder for 6 minutes.

The following behaviors were recorded during the last 4 min (Moallem et al., 2007).

Immobility: floating in water without swimming.

Swimming: active movements of extremities and circling in the container.

Climbing: active movements of forelimbs on the container wall.

Tail suspension test

The Tail Suspension Test was performed according to the method described by Steru et al. 1985 .The principle of this test is that suspending mice from tail, suspended upside down of mice produce characteristic behavior immobility which same as to human depression. Thirty minutes after the administration different doses of diphenhydramine and fluoxetine, mice were suspended upside on the edge of the table 50 cm above the floor by transparent adhesive tape placed about 1 cm from the tip of the tail. Cumulative Immobility time was calculated for the last 4 min during 6 min period. When mice were unable to movement fore and hind limb and the head toward in striated line to the floor. A decrease in the immobility period is indicative of antidepressant-like activity (Vogal and Vogel, 2002).

Statistical analysis

The data were expressed as mean ± SD , difference between three experimental groups were statistically analyzed by one way analysis of variance (ANOVA) followed by the least significant difference test and Duncan test . The level of significance was at $p \leq 0.05$.

RESULTS

In the present study, the antidepressant effect of diphenhydramine was evaluated in mice. Thirty minutes after administration of fluoxetine, diphenhydramine were evaluated the antidepressant activity using the three test as indicated for the antidepressant effect of drugs in mice.

Locomotor activity

Administration diphenhydramine at (0.5, 1, 2 mg /Kg,IP) were found that increase in the locomotor activity. This indicated by increasing the number of square cross were (94.2±28.7) (93.2±25.6) (86.6±22.1) respectively according to the doses of diphenhydramine in comparison with control group (69.4±27.2) at $p \leq 0.05$ but this increase was not significant difference with standard treated group (Fluoxetine) (111.8±7.21) Whereas there is a significantly difference between control (69.4±27.2) and standard treated group (111.8±7.21) at $p \leq 0.05$ (Figure 1).

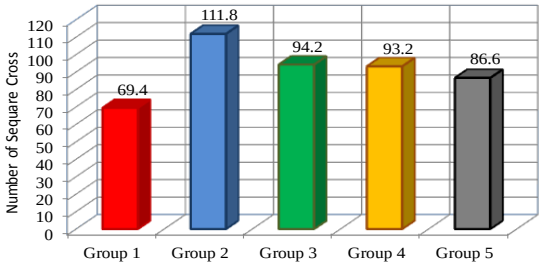

Figure 1: Effect of diphenhydramine (0.5, 1,2 mg\kg, IP) and Fluoxetine (20 mg/Kg ,IP) on Number of Square Cross in Open Field Test:Group1: Normal Saline.Group 2: Fluoxetine. Group 3: Diphenhydramine0.5mg/kg.Group 4: Diphenhydramine 1mg/kg. Group5: Diphenhydramine 2mg/kg

There were no significant difference in the onset time to move from central square between control (3.5±0.4), fluoxetine (2.8±0.6) and (2.9±0.2), (3.1±0.5), (2.8 ±0.5) Sec. respectively according to the doses of diphenhydramine (figure 2).

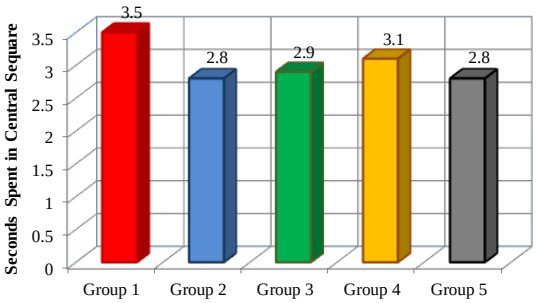

Figure2: Effect of diphenhydramine (0.5, 1,2 mg\kg, IP) and Fluoxetine (20 mg /Kg ,IP)on Time Spend in Central Square in Open Field Test. Group1: Normal Saline.Group 2: Fluoxetine. Group 3: Diphenhydramine 0.5mg/kg. Group 4: Diphenhydramine 1mg/kg. Group5:Diphenhydramine 2mg/kg.

Modified forced swimming test

Administration fluoxetine significantly reduced the immobility time in comparison with control group (183.4 ± 21.7) Sec at $p < 0.05$. the results also showed that the administration of diphenhydramine at (0.5 , 1, 2 mg /Kg ,IP) were reduced the immobility time (68.8 ± 21.1) (56.4 ± 17.7) (47.6 ± 21.7) Sec respectively in comparison with control group, but this decrease in immobility time significantly less than fluoxetine (32.4 ± 7.8)Sec in all doses of diphenhydramine.(Table1)

Table1:Effect of diphenhydramine (0.5, 1,2 mg\kg, IP) and Fluoxetine (20 mg /Kg ,IP) on Immobility time in Force Swimming Test in mice

Treatment	Dose mg kg-1	Cumulative immobility time (Second)	% inhibition
Normal saline	5ml	183.4± 21.7	-
Fluoxetine (standard control)	20	32.4± 7.8*	86.5
Diphenhydramine	0.5	68.8±21.1*a	71.4
Diphenhydramine	1	96.4±17.7*	76.6
Diphenhydramine	2	47.6±21.7*	80.1

- value are mean ± SE for 5 mice /group .
***:Significantly different from the control group at P< 0.05 .**
a: Significantly different from the Fluoxetine group at P< 0.05 .

The percentage of inhibition Immobility time in fluoxetine treated group were (86.5%) and (71.4%) (76.6%) (80.1%) respectively according to the doses of diphenhydramine (0.5, 1, 2 mg /Kg, IP) in comparison with control group (Table 1).

In the present study we found that the administration of diphenhydramine at (0.5, 1, 2 mg /Kg, IP) were significantly increased in the swimming time (143.2 ± 16.2) (152.6 ± 18.7) (160.02 ± 15.5) Sec. in comparison with control group (28.8 ± 3.4) Sec (Table 2), but this decrease in swimming time by diphenhydramine is less than fluoxetine treated group (170.8 ± 17.7) Sec (Table 2). In the present study we found that no significantly difference in climbing time between groups treated with fluoxetine (36.8 ± 10) Sec. control (28.2 ± 11.1) and diphenhydramine at (0.5, 1, 2 mg /Kg ,IP) (28.0 ± 6.4) (31.2 ± 8.7) (32.2 ± 12.8) Sec respectively (Table 2).

Table2 :Effect of diphenhydramine (0.5, 1,2 mg\kg, IP) and Fluoxetine (20 mg /Kg, IP) on Swimming Time and Climbing Time in Force Swimming Test.

Treatment	Dose mg kg-1	Swimming Time (Second)	Climbing Time (Sec)
Normal saline (control)	5ml	28.8 ± 3.4	28.2 ± 11.1
Fluoxetine(standard control)	20	170.8 ± 2.7*	36.8 ± 10.0
Diphenhydramine	0.5	143.2 ± 16.2*	28.0 ± 6.4
Diphenhydramine	1	152.6 ± 18.7*	31.2 ± 8.7
Diphenhydramine	2	160.02 ± 15.5*	32.2 ± 12.8

- value are mean ± SE for 5 mice /group .
***:Significantly different from the control group at P< 0.05 .**

Tail suspension test

Administration diphenhydramine in different doses (0.5, 1, 2 mg /Kg, IP) were reduced the total immobility time in tail suspended test in mice (72.4±9.5) (63±3.7) (57.2±9.9) respectively according to the doses of diphenhydramine (Table 3). Mean duration of cumulative immobility time was significantly decreased in fluoxetine (48.6±5) in comparison with control treated group (97.4±6.2). Also we found that the administration diphenhydramine at (0.5, 1, 2 mg /Kg ,IP) were produced same effects of fluoxetine by decreasing the duration of immobility time in comparison with control treated group (Table 3).

Table3: Effect of diphenhydramine (0.5, 1,2 mg\kg, IP) and Fluoxetine (20 mg /Kg, IP) on Cumulative Immobility time in Tail Suspended Test in mice

Treatment	Dose mg kg-1	Cumulative Immobility time (Second)	% inhibition
Normal saline	5ml	97.4±6.2*	-
Fluoxetine(standard control)	20	48.6±5*	79.75
Diphenhydramine	0.5	72.4±9.5*a	70
Diphenhydramine	1	63±3.7*	73.7
Diphenhydramine	2	57.2±9.9*	76.2

value are mean ± SE for 5 mice /group .
***:Significantly different from the control group at P< 0.05 .**
a: Significantly different from the Fluoxetine group at P< 0.05 .

The percentage of inhibition Immobility time were (70%) (73.7%) (76.2%) respectively according to the doses of diphenhydramine(0.5 , 1, 2 mg /Kg ,IP) in comparison with control and fluoxetine group (79.75%) (Table 3).

DISCUSSION

In the present study, antidepressant effects of different doses of diphenhydramine have been studied. The drug showed that it has antidepressant activity. The increase in locomotor activity indicates a stimulant effect of diphenhydramine. These results are in agreement with previous study suggested that H1 receptor antagonist effect on locomotor behavior in mice (Leza et al., 1991). From the results obtained by the depressant models tests used in this study, it can be showed that the effect of the diphenhydramine on the reduction of immobility time were more strongly in the forced-swimming model and the tail-suspension test than open field test. All three doses of diphenhydramine reduced immobility time and increased swimming time in modified forced swimming test. This effect of diphenhydramine may be return to the action on inhibition of serotonin and noradrenalin which play important role in in motor activity. (Volkow et al., 1998). These results are in agreement with other study suggested that H_1 antagonist is showed to increase levels of noradrenalin and serotonin in the brain (Domino and Edward, 1999). Accumulated extracellular serotonin binds to receptors on the transporter, therefore changes occur in the transporter and serotonin, Na^+, and Cl^- are moved into the cell. After this step binding of intracellular K^+ that cause in return of the transporter to its original conformation and the release of serotonin inside the cell (Katzung et al., 2012)

The monoamine theory suggested that depression is occurring due to deficiency of serotonin and\or noradrenaline. In depressed patients showed a reduction of monoamine turnover with decrease levels of monoamine in cerebrospinal fluid, plasma and urine (Katzung et al., 2009). For this reason, the main pharmacological action of antidepressant drug is the inhibition of synaptic reuptake of monoamine catabolism, thus increasing the levels of synaptic neurotransmitter (Feighner, 1999).

In the 1960s, diphenhydramine was found to inhibit reuptake of the neurotransmitter serotonin (Domino and Edward, 1999). The central serotonergic system may play an important role in the locomotor activity (Risch and Nemeroff, 1992). This action is mediated by postsynaptic 5-HT_1A receptor, which caused an increased in serotonin levels (Zelman and Garver 1990). In the modified forced swimming test, we observed that all doses of diphenhydramine were significantly reduced the immobility period and increase in the swimming time without effect on climbing time, this result indicated that that the diphenhydramine act as antidepressant due to action on serotonin reuptake inhibitors because antidepressant drugs that increase the swimming time is consider as serotonin reuptake inhibitors of serotonin while increase in the climbing time is occur due to norepinephrine reuptake inhibitors (Detke and Lucki 1996). These results are in agreement with other study suggested that the single injection of diphenhydramine reduce time of immobility (Leza et al., 1991).

Other mechanism explanation about the antidepressant activity of diphenhydramine may be return to the action on H1 receptor as antagonist Because histamine neurotransmitter when binding with H1 receptor as agonist, Facilitate release of GABA neurotransmitter which in turn inhibits serotonin release (Payne and Neuman , 1997). Therefore blocking of H1 receptor by diphenhydramine abolish this effect of histamine i:e increase the release of serotonin as well as diphenhydramine inhibit the reuptake of serotonin and norepinephrine that cause increase the concentration of serotonin in nerve ending and increase activity.

Another mechanism about the action of diphenhydramine as antidepressant may be due to histamine has been showed to inhibit noradrenaline release from nerve ending (Barbier and Bradbury, 2007). These actions indicated that histamine decrease the release of these neurotransmitter which causes depression. Therefore the action of diphenhydramine (H1 antagonist) prevents this action of histamine. Because dysfunctions of serotonergic and noradrenergic neurotransmitters are represented the major causes of mood and other neuropsychiatric disorder (Leonard, 1997, Souza et al., 2004). Block reuptake of serotonin causing increase serotonin in the synapse thus concentrated of serotonin in the cleft is alleviated neuronal activity (Brunton and Parker, 2008) and when used H1 antagonist is shown cause decrease in the brain histamine levels (Yagiela et al, 2011). Therefore the effect of diphenhydramine in present study might be inhibiting the effect of histamine on brain monoaminergic system by H1 receptor blocker or decrease histamine release. The result of all these effects of diphenhydramine may be lead to an increase in monoamine level in brain. This action same as the action of tricyclic antidepressant which inhibit histamine neurotransmitter, which responsible for depression. There are inverse relationships between histamine and (serotonin and epinephrine) because patient with increased level of histamine have low serotonin and noradrenalin level which manifested as

depression (Cowen, 1990). Therefore increase the concentrations of serotonin and epinephrine in the synapse and prolonging their duration of action at postsynaptic level is the aim for used selective 5-HT or NE reuptake inhibitors in the treatment of major depressive disorder (Guiard et al., 2009).

CONCLUSION

In the present study, we showed that administration of diphenhydramine in mice reverse the behavior dysfunction induced by tail suspended test, swimming test and open field test. Thus, our study suggested that the administration of diphenhydramine is considered a good therapy used in the treatment of depressed patients without side effect that produce when used some antidepressant drugs as well as the rapid onset of diphenhydramine action compare with others antidepressants drugs.

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