

The antidepressant effect of tramadol and chlorpheniramine combination in mice model

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Abstract

The current study aimed to evaluate the antidepressant effect of Chlorpheniramine and tramadol, each alone or as a novel combination in a mouse model, using forced swimming (FST) and tail suspension test (TST). The results of the two examinations for both drugs, separately or In combination, demonstrated a significant reduction in the mean duration of cumulative immobility time compared with the control group, as well as an increase in the percentage reduction in the cumulative immobility time in both experiments and for both drugs in a dose-dependent manner when given each medication alone, chlorpheniramine at both dosages exhibited a significantly more significant antidepressant effect in the FST and TST test than tramadol at both doses. The anti-depressant effect of tramadol and chlorpheniramine combination at a double dose of ED₅₀ of each was better than simultaneous administration of two drugs at individual ED₅₀, as a significantly reduced the accumulation time of immobility in forced swimming test and tail suspension test compared to the negative control group and each drug alone. The percentage decrease in the duration of cumulative immobility time of tramadol and chlorpheniramine combination at ED₅₀ of each drug was 87 and 89 %, respectively. While at a double dose of ED₅₀, each was 93% and 94%, respectively, compared to each drug alone and with the negative control group. Thus, the interaction between the two medications was synergistic when used together as antidepressants at a single dose.

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Introduction

Depression and anxiety are prevalent neurological or psychiatric illnesses with significant incidence rates that affect people worldwide. Epidemiological data indicate that about one-third of people will have these issues (1). As a result, treating this illness calls for increased attention-one of the several widely used antidepressants that primarily target monoamine regulation (2). Noradrenaline, 5-hydroxytryptamine, and dopamine levels in the brain are functionally deficient, which causes the primary signs and symptoms of depression (3). Drugs that raised or normalized the CNS concentrations of these neurotransmitters provided evidence for antidepressant efficacy (4). The primary

antidepressant drugs restore neurotransmission by elevating the concentration of serotonin, norepinephrine, or both at the synapses (5). Selective serotonin reuptake inhibitors (SSRIs) are the most effective drugs for treating anxiety and depression. SSRIs function by preventing serotonin from acting as a depressant (6). Despite the development of tricyclic antidepressants, selective, reversible inhibitors of monoamine oxidase, and selective serotonin-norepinephrine reuptake inhibitors, depression is still a significant health issue. However, the quest for new antidepressants continues (7). According to some theories, the first-generation antihistamine chlorpheniramine (CPA) 's serotonergic properties help explain its effects on depression and anxiety (8). Additionally, studies on animals show that CPA has

antidepressive and anxiolytic effects (9,10). In the forced swim test (FST) (7) and the tail suspension test (TST) for mice, chlorpheniramine has been demonstrated to exhibit antidepressant-like effects (11). Tramadol inhibits serotonin (5-HT) and noradrenaline (NA) reuptake while a mild agonist on μ -opioid receptors. Additionally, it exhibits antagonistic characteristics on NMDA receptors, 5-HT₂ receptors, and muscarinic acetylcholine receptors (12). Numerous preclinical studies have looked into the possible antidepressant effects of tramadol due to its structural resemblance to venlafaxine (a reuptake inhibitor antidepressant) and the monoaminergic effects of tramadol, which are typical of most antidepressants (13-15). Tramadol's antidepressant properties have been established in early preclinical research in rodents (16-18). The typical antidepressants used to treat depression require a long time and several doses to establish antidepressant action and are associated with undesirable side effects, including addiction (19). Because of this, it became necessary to develop new drugs or creative drug combinations to reduce the dosage needed and the side effects brought on by administering each therapy separately. A synergistic antidepressant effect was established in mice following chronic treatment of tramadol, venlafaxine, and desipramine (monoamine reuptake inhibitors) (20). Additionally, escitalopram (SSRI) and chlorpheniramine interacted synergistically (8).

Furthermore, we need a novel combination that produces a synergistic antidepressant-like effect in a single dose and fewer side effects. Hence, the current study aimed to examine and evaluate the antidepressant efficacy of a unique combination of tramadol and chlorpheniramine administered in a single dose. As well as to identify the sort of pharmacological interaction between tramadol and chlorpheniramine at the level of antidepressant effect employing forced swimming test and tail suspension test in mice model.

Materials and methods

Ethical consideration

The research was conducted according to the international ethical standards for the Care and Use of Laboratory Animals (21). the scientific committee of the College of Veterinary Medicine, Department of Physiology, biochemistry, and Pharmacology, University of Mosul approved the study.

Study animals and design

The Animal House Facility of Applied Science at the College of Veterinary Medicine at the University of Mosul in Iraq provided 64 male Swiss albino mice employed in the current study. The mice were 6-8 weeks old and 28 ± 2 g in weight. Mice were kept in separate cages with constant air ventilation at $22 \pm 2^\circ\text{C}$ and 50-60% humidity (22). Before the trial, the animals were given a week to become used to their

home circumstances and free access to food and water. Between 9:00 AM and 3:00 PM, all tests were run. Before injection, all dosages of each medication were freshly dissolved in normal saline. The treatment regimen included a single dosage of each drug at a volume of injection 5 ml/kg of body weight for each group of eight animals.

Evaluating the antidepressant effect of tramadol and chlorpheniramine, each alone or together

The mice were divided into eight groups (n=6 per group). First groups where negative control group animals were given physiological saline (Marksanspharma, India) at a 5ml/kg body weight dose by intraperitoneal injection. Second group, animals in the positive control group, fluoxetine (Produced by GerotLannach, Austria) was given to the animals orally via a gavage needle at 20 mg/kg body weight, the positive control group was guaranteed since fluoxetine at three distinct dosages of 20 mg/kg body weight 24, 5, and 1 hour before the antidepressant test (23), it was designed to identify the acute antidepressant impact of tramadol, chlorpheniramine, and fluoxetine. Third group received tramadol 100 mg/2ml (Duopharma, Malaysia) IP at the previously estimated median analgesic effective dose (ED₅₀) of 12 mg/kg. Fourth group received ED₅₀ of the analgesic dose of chlorpheniramine (Pioneer Pharmaceutical, Iraq) intraperitoneally, estimated in our previous experiment at 18.4 mg/kg b.w. The ED₅₀ of each drug was estimated by the up-and-down method. These doses succeeded in producing an analgesic effect on the hot plate. Here in our present study, we re-exam their development as antidepressants as the first study to use chlorpheniramine and tramadol to treat depression at a single dose treatment. The animals in this group were given both medicines simultaneously, with tramadol and chlorpheniramine injected intraperitoneally at 12 and 18.4 mg/kg b.w. The animals in this group were injected with tramadol intraperitoneally in a twofold dosage of the median analgesic effective 24 mg/kg dose. In this group, animals were intraperitoneally injected with chlorpheniramine, a double dose of the analgesic median effective dosage of 36.8 mg/kg b.w. The animals in this group were simultaneously injected with tramadol at 24 mg/kg, i.p., and chlorpheniramine at 36.8 mg /kg, i.p, respectively. The antidepressant effect impact was evaluated by submitting all the animals in each group individually to special testing to identify the antidepressant effects included.

Tail suspension test (TST)

In this experiment, the mouse was placed in a box with the dimensions 55*15*11.5 cm, its head hanging downward, and a suspension rod with the dimensions 1*1*60 cm inserted to turn the mouse tail separately from the upper portion of the mouse. Using sticky tape, the mouse is suspended from the tail in the middle, leaving 2 cm of the tail's tip free so that the animal may move freely inside the

box without coming into contact with the walls. The animal's head is 20-25 cm from the box's floor. Typically, a 17 cm long sticky tape is utilized. The tail is attached to the box with 2 cm, leaving 15 cm for the mouse to hang within. After inspecting each mouse, the box is cleaned with cotton soaked in a sterile liquid. The experiment is conducted in a closed space with no outside stimuli, and the observer stays away from the animal during the test to prevent any potential impact on its behavior (24). The results of this test are recorded immediately after hanging the mouse and for six continuous minutes. The immobility time is recorded during the last four minutes only, neglecting the first two minutes of observation because most of the mice are very active in the first two minutes and, therefore, can hide the potential therapeutic effect of the drug. Thus, we neglect it and adopt the last four minutes (24).

Forced swimming test (FST)

A clear water tank or cylinder with a 15 cm diameter and 30 cm height is used for each mouse. The water is poured into the tank to a height of 15 cm. The tank's size must be sufficient to keep the mouse from swimming and contacting the bottom with its feet or tail. Additionally, the water level in the tank needs to be high enough to keep the mouse from attempting to escape outside. The test is performed by holding the mouse by the tail and carefully placing it into the water to prevent the animal's head from entering. Once the animal enters the water inside the aquarium, the time it takes to remain slick (not swimming by moving the legs quickly and not turning around) is calculated within 6 minutes of the experiment's start, and the monitoring results are approved for the last 4 minutes only, with the first two minutes of observation being ignored to avoid hypothermia, the animal is taken out after the test and thoroughly dried with tissue paper before being returned to the cage. The test should be performed in a separate and calm environment, and the examiner should be separated from the animal during observation to avoid any influence on its behavior (25).

Statistical analysis

The data findings were subjected to an analysis of variance test, followed by a least significant difference test (26,27). The significance threshold of the different tests for the trials was less than or equal to 0.05.

Results

The oral administration of fluoxetine (a common antidepressant drug) to mice at a dose of 20 mg/kg body weight resulted in a significant decrease in the mean duration of cumulative immobility time in the tail suspension test. It forced swimming test for four consecutive minutes 45 ± 3.66 and 82 ± 1.92 , respectively, in comparison to the negative control group 132.80 ± 4.38 and 149.20 ± 2.90 second. Table 1

and 2 shows that the percentage of lowering in the mean amount of cumulative immobility time in the FST and TST test was 45 and 66%, respectively.

The intraperitoneal administration of tramadol at 12 and 24 mg/kg body weight produced a significant decrease in the mean duration of cumulative immobility time in the TST and FST in a dose-dependent manner 71.50 ± 2.87 and 73.25 ± 20 second respectively for a dose of 12mg/kg body weight. while at 24 mg/kg 60.25 ± 2.68 and 63.25 ± 2.56 second, respectively. comparison with the negative control group 132.8 ± 4.38 and 149.2 ± 2.9 second, respectively table 1 and 2. The percentage of decrease in the mean duration of cumulative immobility time was 51 and 46%, respectively, for a dose of 12 mg/kg and 57 and 54%, respectively, for a dose of 24 mg/kg body weight in comparison with the negative control group table 1 and 2, figures 1 and 2.

The two doses of chlorpheniramine produced the same effect on the animals, represented as a significant and dose-dependent reduction in the mean duration of cumulative immobility time in both the forced swimming and tail suspension test 33.25 ± 1.60 and 30 ± 2.34 second, respectively, for 18.4 mg/kg dose and 19.50 ± 1.50 and 16.75 ± 0.47 second, respectively for 36.8 mg/kg dose in comparison with the negative control group 149.20 ± 2.90 and 132.80 ± 4.38 second, respectively. The percentage of decrease in the mean duration of cumulative immobility time for the FST and TST was 77 and 77%, respectively, for a dose of 18,4 mg/kg body weight and 86 and 87% for an amount at 36,8 mg/kg body weight in compared with the negative control group (Figures 1 and 2). The two doses of chlorpheniramine were superior to tramadol, with both doses in the antidepressant effect in the FST and TST (Tables 1 and 2). compared with the negative control group. Whereas, when the two medications are injected together as a combination at the median analgesic effective dose, tramadol and chlorpheniramine significantly reduced the mean duration of cumulative immobility time in the FST and TST 16.25 ± 0.85 and 16.25 ± 1.54 seconds, respectively, and 8.75 ± 1.03 and 8.75 ± 1.31 second, respectively at a double dose of the median analgesic effective dose for each of them compared with the negative control group 149.20 ± 2.90 and 132.80 ± 4.38 second, respectively for both FST and TST (Tables 1 and 2). The percentage of decrease in the mean duration of cumulative immobility time was 89 and 87%, respectively, at the analgesic effective dose for each of them and 94 and 93, respectively, at the doubled amount of each compared with the negative control group Figures 1 and 2. The antidepressant effect of the combination of tramadol and chlorpheniramine at the double dose of the median effective amount of each was better than the administration of the two drugs together with the analgesic median effective dose because of its superiority and significantly in reducing the mean duration of cumulative immobility time in the FST and TST (Tables 1 and 2).

Table 1: Mean duration of cumulative immobility time in tail suspension test

Treatment groups	% inhibition mean duration of cumulative immobility time (s) for TST	
Negative control	132.80±4.38	0%
Positive control (Fluoxetine, orally, 20 mg/kg)	45±3.66*	66%
Tramadol (12 mg/kg)	71.50±2.87 a	46%
Chlorpheniramine (18.4 mg/kg)	30±2.34 ab	77%
Chlorpheniramine and tramadol (18.4+12 mg/kg)	16.25±1.54 ac*	87%
Tramadol (24 mg/kg)	60.25±2.68 ad*	54%
Chlorpheniramine (36.8 mg/kg)	16.75±0.47 abe*	87%
Chlorpheniramine and tramadol (36.8+24 mg/kg)	8.75±1.31 acf*	93%

Fluoxetine was administered orally in three doses of 20 mg/kg 1, 5, and 24 hours before subjecting the animals to the tests. Values represent the mean±SE of 8 mice per group. The value is significantly different compared to the negative control group*. a: The value is significantly different compared to the positive control group. b: The value differed significantly compared to the tramadol group alone. c: The value is significantly different compared to the chlorpheniramine group alone and the tramadol group alone. d: The value differed significantly compared with the tramadol group 12 mg/kg. e: The value is significantly different compared to the chlorpheniramine group 18.4 mg/kg. f: The value is significantly different compared to the group of tramadol with chlorpheniramine at 12+ 8.4 mg/kg. All values in the table are at a probability level of less than or equal to 0.05.

Table 2: mean duration of cumulative immobility time in the forced swimming test (FST)

Treatment groups	% inhibition mean duration of cumulative immobility time (s) for FST	
Negative control	149.2±2.90	0%
Positive control (Fluoxetine, orally, 20 mg/kg)	82±1.92 *	45%
Tramadol (12 mg/kg)	73.25±2 a*	51%
Chlorpheniramine (18.4 mg/kg)	33.25±1.60 ab*	77%
Chlorpheniramine and tramadol (18.4+12 mg/kg)	16.25±0.85 ac*	89%
Tramadol (24 mg/kg)	63.25±2.56 ad*	57%
Chlorpheniramine (36.8 mg/kg)	19.50±1.50 abe*	86%
Chlorpheniramine and tramadol (36.8+24 mg/kg)	8.75±1.03 acf*	94%

Fluoxetine was administered orally in three doses of 20 mg/kg 1, 5, and 24 hours before subjecting the animals to the tests. Values represent the mean±SE of 8 mice per group. The value is significantly different compared to the negative control group*. a: The value is significantly different compared to the positive control group. b: The value differed significantly compared to the tramadol group alone. c: The value is significantly different compared to the chlorpheniramine group alone and the tramadol group alone. d: The value differed significantly compared with the tramadol group 12 mg/kg. e: The value is significantly different compared to the chlorpheniramine group 18.4 mg/kg. f: The value is significantly different compared to the group of tramadol with chlorpheniramine at 12+ 8.4 mg/kg. All values in the table are at a probability level of less than or equal to 0.05.

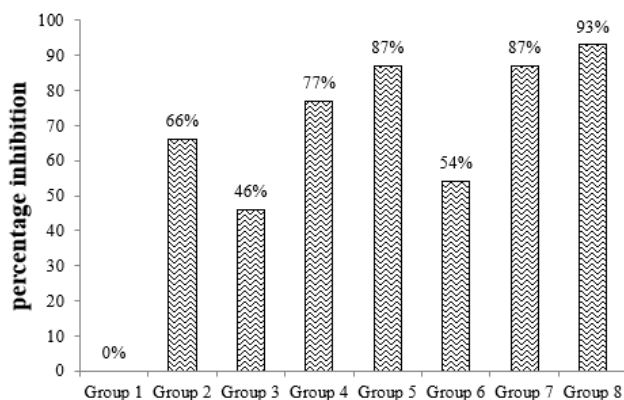


Figure 1: The percentage of decrease in the mean duration of cumulative immobility time of the TST in mice.

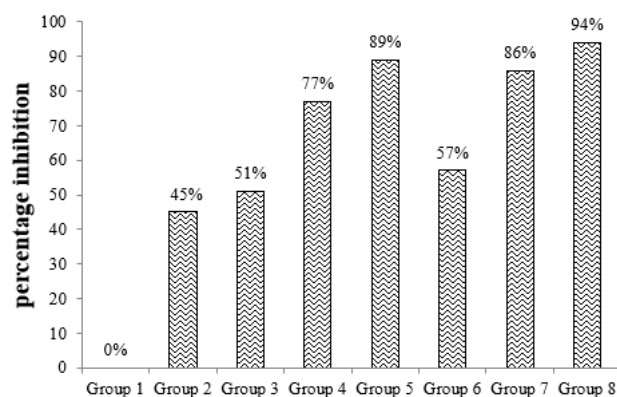


Figure 2: The percentage of decrease in the mean duration of cumulative immobility time of the FST in mice.

Discussion

Our present experiment was designed to detect the novel antidepressant effect of a combination of chlorpheniramine and tramadol in a mouse model as the first study that discovered this effect. The study included examining the antidepressant effect of tramadol and chlorpheniramine alone or together at a single dose of each using the TST and the FST, which are used to evaluate the efficacy of antidepressant drugs and their effects on various neurological behaviors in mice (28). This is expressed by the mouse in a state of despair (behavioral despair), as the animal loses hope of escaping from the stressful environment (29). The results of the two examinations for both drugs, either alone or together, showed a significant decrease in the cumulative immobility period compared with the control group, as well as a higher percentage of the decrease in the cumulative immobility period in both experiments and for both drugs, depending on the dose, by recording a significant decrease in the cumulative immobility period for the double dose for each drug alone or as a combination in compared with an individual dose of each alone. The percentage decrease in the cumulative immobility period of tramadol and chlorpheniramine for the TST and FST was 93% and 94%, respectively. Therefore, the interaction between the two drugs was synergistic when they were used together as antidepressants. The reason for the effectiveness of tramadol as an antidepressant is related to its chemical structure, which is very similar to antidepressants such as mirtazapine, duloxetine, and venlafaxine, which depend on their effect on inhibiting the reuptake of norepinephrine and serotonin SNRI (15). In addition, it is similar to the action of tramadol (30,31). The essential role of noradrenaline and serotonin in treating depression is also known (32). This was confirmed by using tramadol in low doses as an antidepressant (33). Another study indicated that tramadol tends to inhibit the NMDA receptors to produce antidepressants in the compulsory swimming test of mice (34). Our study's results agree with previous studies where tramadol had an antidepressant effect in the TST of mice (35). and in the mice FST (36). the effect was dose-dependent in both studies. Another study suggested that the noradrenergic mechanism (alpha2 adrenoceptors) rather than the serotonergic system was responsible for the antidepressant-like effect of chronic tramadol and desipramine therapy in mice (19). Whereas chlorpheniramine increases the concentration of monoamine (noradrenaline and dopamine) in the synapses between neurons of the central nervous system by inhibiting the reuptake of monoamine within the neurons (37-39). According to separate research, chlorpheniramine is a novel antidepressant that has an antidepressant-like effect in the mouse TST via routes other than imipramine and fluoxetine. These mechanisms include the activation of dopamine D1 and 1-adrenoceptors (40). Our study is consistent with a previous study that confirmed that diphenhydramine (an H1-

receptor antagonist) has a dose-dependent antidepressant action in mice using the tail suspension test and forced swimming test (41). Another study pointed out that depression is caused by a decrease in the concentration of serotonin and norepinephrine (the monoamine amine) in the central nervous system (42). therefore, the true mechanism of the classic antidepressants is the inhibition of the reuptake of monoamine, thus increasing its levels within the synapses (43). Another research suggested mechanism that explains the antidepressant action of H1 receptor antagonists is that when histamine binds to H1 receptors, it will accelerate the release of the neurotransmitter GABA, which in turn inhibits serotonin secretion (44), so inhibitors of these receptors cancel this effect and increase the secretion of serotonin. In addition, histamine itself inhibits the secretion of noradrenaline from the nerve endings (45), so it is possible to use antihistamines such as diphenhydramine (41) and chlorpheniramine in our current study as antidepressants because they increase the level of serotonin and norepinephrine in the synapses and prolong their survival and its effect on post-synaptic. Previous studies indicated that depression induced by nitric oxide depends on the production of the second messenger, cGMP, inside the cell and that inhibition of the enzyme guanylate cyclase that helps break down cGMP causes antidepressant behavior in rodents (46). chlorpheniramine inhibits the cellular pathway of nitric oxide NO/cGMP when it exerts an antidepressant effect in the FST of mice (47). In addition, this effect depends on the chlorpheniramine dose, which is consistent with our current study's results. The above explanation of the different mechanisms of action of tramadol and chlorpheniramine in causing the anti-depressant effect and increasing this effect when given together may explain the synergistic interaction between them on the level of antidepressant effect, which was discovered recently in our research (48-51).

Conclusion

Our unique study employed quantified tests (FST and TST) to assess the antidepressant impact of combining chlorpheniramine and tramadol. We concluded that chlorpheniramine is more effective as an antidepressant than tramadol. In a dose-dependent manner, the combination of chlorpheniramine and tramadol exhibited a synergistic antidepressant effect in a mouse model. An increase in adverse effects did not accompany the antidepressant effect of the two medications as a combination. The new variety might be highly beneficial in veterinary treatment, especially in dogs and cats.

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Conflict of interests

The authors declare no conflict of interest

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التأثير المضاد للكآبة لتركيبية الترامادول والكلورفينيرامين في نموذج الفئران

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الخلاصة

كان الهدف من الدراسة الحالية هو دراسة وتقييم التأثير المضاد للاكتئاب للكلورفينيرامين والترامادول كل على حدة أو بشكل مزيج باستخدام اختبار السباحة الإجماعي واختبار الذيل المعلق. وأظهرت نتائج الفحصان لكلا العقارين، كل لوحده أو معاً، انخفاضاً معنوياً في معدل مدة السكون التراكمية مقارنةً مع مجموعة السيطرة السالبة، فضلاً عن ارتفاع النسبة المئوية للانخفاض في مدة السكون التراكمية في كلتا التجربتين ولكلا العقارين وبشكل معتمد على الجرعة عند إعطاء كل عقار بمفرده، أظهر الكلورفينيرامين في كلتا الجرعتين تأثيراً مضاداً للاكتئاب أكبر وبشكل معنوي في اختبار السباحة الإجماعي واختبار الذيل المعلق بالمقارنة مع الترامادول في كلا الجرعتين. وكان التأثير المضاد للكآبة لمزيج الترامادول مع الكلورفينيرامين بالجرعة المضاعفة للجرعة الفاعلة الوسطية لكل منهما أفضل من إعطاء العقارين معاً بالجرعة الفاعلة الوسطية المسكنة لتفوقه وبشكل معنوي في التقليل من مدة سكون الحيوان داخل اختبار السباحة الإجماعي واختبار الذيل المعلق مقارنة مع إعطاء كل عقار لوحده أو مع مجموعة السيطرة السالبة. وكانت النسبة المئوية للانخفاض في معدل مدة السكون التراكمية ٨٩ و ٨٧% على التوالي للجرعة الفاعلة الوسطية لكل منهما في حين كان ٩٤ و ٩٣% على التوالي للجرعة المضاعفة للجرعة الفاعلة الوسطية لكل منهما مقارنة مع مجموعة السيطرة السالبة. وبالتالي فإن التداخل بين العقارين تداخلاً تآزرياً عند استخدامهما معاً كمضادات للكآبة وبجرعة منفردة.