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RESEARCH ARTICLE

EVALUATION OF SIDE EFFECT OF NETHISTERONE TABLET ON ANXIETY.

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ABSTRACT

Drug is a chemical material used to prevent, cure, and diagnose a disease. *Nethisterone* is adrug that consumed to prevent pregnancy, but it can produce androgenic side effects such as hirsutism, acne and voice changes of slight vehemence in some women at average and high dosages. Since no study has been done onside effect of *Nethisterone* tablet on anxiety, therefore, the aim of the study was determination of side effect of the tableton anxiety in female mice. As a screen test to discover side effect of the drug on anxiety, Light/dark Transition test was employed. The light/dark transition defecation test was done in a 21x42x25cm cage partitioned by 2 same sized chambers with a door. One chamber was illuminated brightly and the other was dark. In the test, the time spent and defecation in during test in both chambers are good indexes of anxiety-like behavior. The results indicates that mice in group 2 (In the group, mice received *Nethisterone*) to group 1 (Control group=in the group, mice received saline) tend to stay in the light chamber and defecation in both chamber. Thus, the present research demonstrates the effect of *Nethisterone* in increasing anxiety. It is recommended that women do not use this drug in averages and high doses.

INTRODUCTION

Disease is any condition that influence part or all of body, and lead to disorder of structure, dysfunction, pain, mental health problems, anxiety, or death[1].Mental disease is a wide, public label for a category of diseases that may include behavioral dysregulation, efficacious or emotional inconsistency, cognitive dysfunction or disorders[2]. Specific diseases known as mental diseases include attention deficit hyperactivity disorder, major depression, generalized anxiety impairments, and schizophrenia[3, 4]. Mental illness can be of biological or psychological origin. It can mar the affected person's ability to work, exercise, study, communicate and can endamage interpersonal relationships[5]. Anxiety is an emotion characterized by a plague some state of inner agitation, often attended by nervous behavior[6-8]. There are a number of anxiety disorders including specific phobia, social anxiety impairment, generalized anxiety disorder, separation anxiety impairment, agoraphobia, panic disorder, and selective mutism[9]. Since these disorders varies by what results in the symptoms, so their prevention, control and treatments differs. People often have more than one anxiety disorder[10].

Drugs are efforts to treat or ameliorate a disease but some drugs usually have substantial side effects. A side effect is typically considered as an unfavorable effect which happens in addition to the eligible remedial effect of a drug. Side effect of drugs usually affected function of different part of body such as brain, heart, kidney, liver and etc. Many of these drugs with effects on the brain, causing severe anxiety[11-13]. Contraceptive drug such as *Nethisterone* prevent unwanted pregnancies. *Nethisterone* or *Linestrol* reducing level of androgenic steroids, by inhibiting secretion of LH and FSH and prevent pregnancies. In high dose, this drug cause many side effects

such as mental and behavioral disorders[14].Based on knowledge of authors, in comparison to many other pharmaceutical-industrial drug, there is a very little data about side effect of *Nethisterone* tablet on anxiety. Hence, the aim of the recent study was evaluation of side effect of the *Nethisterone* tablet on anxiety in female mice.

MATERIAL AND METHODS

Animal

Twelve female mice with Balb/C bread weighing 35–40 g were used. The animals were housed under standard environmental conditions (23±1°C, with 55±5% humidity and a 12 h light/dark cycle) and maintained with free access to water and ad libitum standard pelleted food.

Study design

Mice divided in two group (group 1 (control group): In the group, mice received saline. group 2 (treatment group): In the group, mice received *Nethisterone* tablet (35 µg/kg, p.o.)). The apparatus used for the light/dark transition test subtended of a cage (21x42x25 cm) divided into two sections of alike size by a partition with door. One chamber is brightly illuminated, whereas the other chamber is dark. In 15, 20, 25, and 30 days after treatment, mice are allowed to waggle freely between the two chambers with door open for 600 seconds. Three seconds after placing the mouse in the dark chamber, the door between the chambers opens and the mouse can move freely between the two chambers. The time spent and number of stools in the each chamber were measured. After each trial, all chambers are cleaned with ethanol to inhibit a bias based on olfactory cues[15].

Statistical analysis

Descriptive statistics including the mean, standard error, median, minimum and maximum were calculated for all variables. The one-way ANOVA followed by Tukey post hoc test were used for comparison of different parameters. The data were analyzed by SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA) and $P<0.05$ was accepted as statistically significant.

RESULTS

The time spent in light and dark chamber shown in following tables. Also, number of stools in the each chamber and total stools in both chambers in 15, 20, 25, and 30 days indicated underneath.

Table 1 The time spent and number of stools in the each chamber and total stools in both chambers in 15 day.

Day	Group	Time spent		Number of stools		
		In light chamber	In dark chamber	In light chamber	In dark chamber	Total
15	1	242.83±8.01^{b}	358.83±5.30^{a}	0.16±0.40^{b}	0.16±0.40^{b}	0.33±0.51^{b}
	2	461.25±7.93^{a}	138.75±1.70^{b}	0.75±0.50^{a}	1.25±1.25^{a}	2.66±1.15^{a}

Table 2 The time spent and number of stools in the each chamber and total stools in both chambers in 20 day.

Day	Group	Time spent		Number of stools		
		In light chamber	In dark chamber	In light chamber	In dark chamber	Total
20	1	245.50±6.37^{b}	354.50±6.37^{a}	0.00±0.00^{b}	0.00±0.00^{b}	0.00±0.00^{b}
	2	444.00±7.83^{a}	156.00±7.83^{b}	0.25±0.50^{b}	0.75±0.50^{ab}	3.75±0.95^{a}

Table 3 The time spent and number of stools in the each chamber and total stools in both chambers in 25 day.

Day	Group	Time spent		Number of stools		
		In light chamber	In dark chamber	In light chamber	In dark chamber	Total
25	1	168.00±8.36^{b}	432.00±8.36^{a}	0.16±0.40^{b}	0.33±0.81^{b}	0.50±0.83^{b}
	2	432.50±10.27^{a}	167.50±10.27^{b}	1.75±1.25^{a}	2.00±0.81^{a}	2.25±2.06^{a}

Table 4 The time spent and number of stools in the each chamber and total stools in both chambers in 30 day.

Day	Group	Time spent		Number of stools		
		In light chamber	In dark chamber	In light chamber	In dark chamber	Total
30	1	234.83±9.06^{b}	365.16±9.06^{a}	0.16±0.40^{b}	0.33±0.51^{b}	0.50±0.83^{b}
	2	424.00±8.04^{a}	176.00±8.04^{b}	0.75±0.95^{ab}	1.50±2.38^{a}	1.33±0.57^{ab}

DISCUSSION AND CONCLUSION

Drug side effects can be noisome, but they must be measured against the benefits of the remedy and the risks of not receiving the treatment. While unanticipated side effects can happen, most side effects can be auspicate because certain drugs are more likely than others to affect specific types of body tissues, such as nervous system[11-13].Contraceptives are used to prevent unwanted pregnancy. *Nethisterone*, also known as *norethindrone*or *Linestrol***,** is a drug that is used in combination with estrogen or alone in hormone replacement therapy, hormonal contraceptives, and in the treatment of gynecological impairments. It is a synthetic progestogen of the 19-nortestosterone group and has similar effects to those of natural progesterone. *Nethisterone* commonly are used as contraceptive drug. *Nethisterone*, reducing level of androgenic steroids, by inhibiting secretion of LH and FSH. In addition to *Nethisterone*, the drug are consumed in preventing ovarian or endometrial cancers, decreasing ovarian cysts, menstrual blood volume, premenstrual stress, number of painful menstruation, and regulating the menstrual cycle[14]. *Nethisterone* has many side effects, and overdose of the drug causes breast cancer, venous thromboembolism, hypertension, bile diseases and gallbladder stones, nausea, vomiting, mild headache or severe migraine headaches, weight gain, and irregular bleeding during menstruation[16, 17].

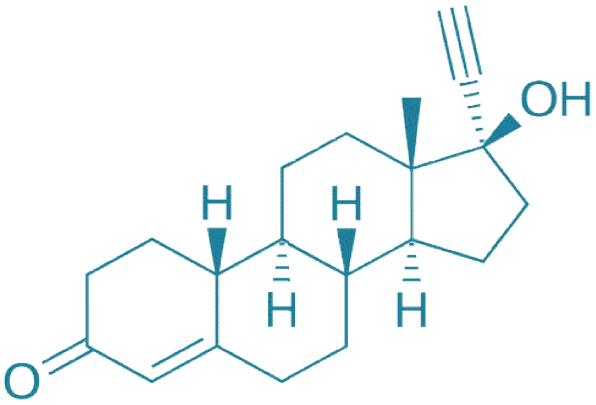

Figure 1 Structural diagram of *Nethisterone*. Created using ACD/ChemSketch 8.0 and Inkscape.

The light/dark transition test is one of the most widely used tests to evaluate anxiety-like behavior in mice. The time spent in the light chamber and number of stools in both chamber are good indexes of anxiety-like behavior[15].

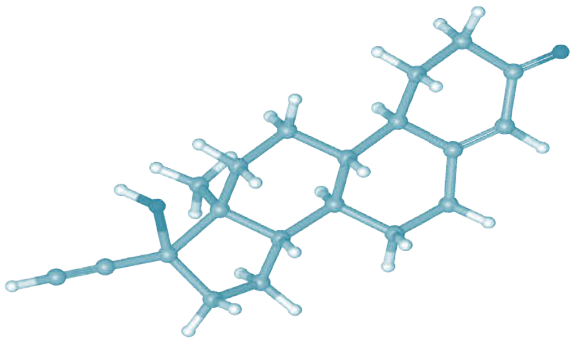

Figure 2 Ball-and-stick model of *Nethisterone*furoate molecule. The structure is taken from ChemSpider. ID 5994.

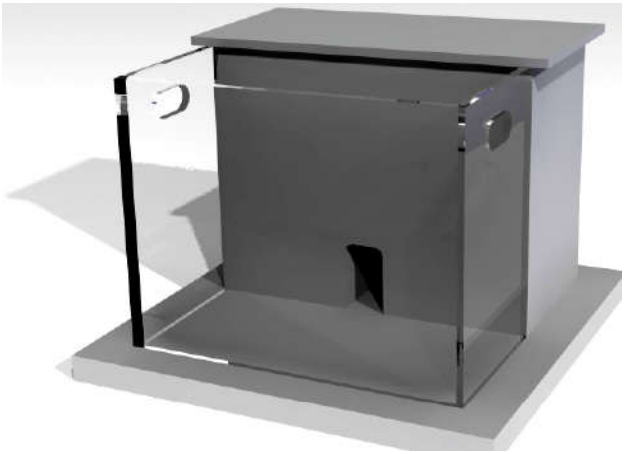

Figure 3 Light/dark Transition box.

Findings from the current study revealed that in 15, 20, 25, 30 days, are seen time spent in the light chamber and total stools in both of chamber reduced in Group 1 to Group 2 and time spent in the dark chamber increased in Group 1 to Group 2. Altogether, this results indicates that mice in group 2 tend to stay in the light chamber and defecation in both chamber, and for as much as the time spent in the light chamber and number of stools in both chamber are good characteristics of anxiety-like behavior, so the tablet caused anxiety in female mice. In previous study, indicated that female mice given Contraceptive HD tablet (35 µg/kg, p.o.) tended to stay in the light chamber longer and defecated more in both chambers compared with saline control group, so this drug increased anxiety[13].

This study suggests that women for avoiding unwanted pregnancies, shouldn't use a long time from *Nethisterone* tablet (Because of anxiety). Additional clinical trials would be needed to justify and further evaluate side effect of *Nethisterone* tablet on anxiety.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

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