Iraqi Journal of Veterinary Sciences

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Toxicity of fluoxetine hydrochloride on some selected vital organs of pregnant mice *Mus musculus*

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Article information

Article history:
Received April 02, 2021
Accepted September 08, 2021
Available online December 20, 2021

Keywords:
Fluoxetine
Mice
Histopathology
Pregnancy
Lung

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Abstract

The current study intends to look at the impact of the fluoxetine hydrochloride on specific tissues lung and pancreas of mature pregnant mice. The two doses used during the study were 45,75mg/kg b.w. from the 7th to the 17th day of pregnancy. Experimental animals received fluoxetine orally at a dosage of 45mg/kg b.w. The findings indicate variable pathologic changes in the lungs. At the dose of 75 mg/kg b.w. Hyperplasia of pneumocytes occurred. There were no detectible lesions in the pancreas at the dose of 45mg/kg b.w. While at the dose of 75 mg/kg b.w. The severity of tissue lesions was seen. In conclusion, antidepressants may stimulate oxidative injury throughout the body's internal organs, particularly if taken at high doses during pregnancy. Consequently, these lesions significantly impact the health of both fetus and pregnant mice since the most common lesions were observed in the fetus, which causes abortion, which affects the health of pregnant mice.

DOI: 10.33899/ijvs.2021.129864.1695,

Introduction

Recently, the abuse of antidepressants such as fluoxetine has been a significant problem worldwide (1). Those drugs are often used in depression treatment. They may help depressed people to recover from their sickness, especially pregnant women who suffer from depression and emotional changes during pregnancy and after childbirth (2). One of the newest antidepressant drugs is Fluoxetine Hydrochloride (3). The drug's chemical formula is C_{17} H_{18} F_3NO, and the scientific name of the drug is N-methyle-3-phenyle1-1-3 (4-trifluoromethyl) phenoxylpropan-1-amine (4). Fluoxetine metabolism is done in the liver, and the drug is metabolized into norfluoxetine. Norfluoxtine is the drug's active metabolite, directly linked to medical and toxicological effects. The drug's active metabolite is directly related to medical and toxicological impact (5). About 80% of the drug is excreted with urine, and 57% with faeces (6). Moreover, the drug has a maternal effect. The severity of the impact depends on the dose and duration of exposure (7). Medical reports showed that the drug causes pulmonary hypertension syndrome in babies (8). Fluoxetine administration throughout gestation may cause a slow formation of the lungs (9). The drug caused an increase in mortality and altered the structure of phospholipids, hepatic changes when given to rats at a dosage of 10,50 mg/kg b.w. (10). The drug induces oxidative stress, which causes testicular damage, a significant decrease in the weight of reproductive organs, and affects the level of testosterone in the mice (11). Drug administration also causes injuries in the body's vital organs (12). Several studies referred to the drug's effect on carbohydrate metabolism and the function of beta cells (13).

The objective of this research project was to assess the impact of fluoxetine administration on the concentrations of 45,75 mg /kg of b.w. along with the maternal lung and pancreas of pregnant mice *Mus musculus* to evaluate the harmful effect of the drug on them.

Materials and methods

In our investigation, twenty-one pregnant mice, aged three months, weighted 29 ± 3 gm, were used. Animals were taken from the College of Veterinary Medicine's animal house, Mosul University, Mosul, Iraq, and housed in the animals' house of the Biology Department, College of Education for Pure Science. Animals were caged in plastic cages, supported with free access to food and water, fed with a standard diet; the room temperature was 25ºC, the animals were exposed to a regular light-dark cycle (14). The drug used in the study is fluoxetine 20 mg capsules produced by Bristol Laboratories Ltd., Bristol house, Unite 3, Canalside, Northbridge Road, United Kingdom. For the mating process, two females for one male were placed together in the same cage overnight. The next morning females with vaginal plugs were isolated in separate cages and kept together until the 7th day of pregnancy. Animals' housing was done following the standard guidelines for the use and care of experimental animals.

The pregnant mice (n=21) were divided into three groups (each group consisted of 7 pregnant mice). Group I (control group): The pregnant mice (n=7) were administered with 0.2ml of distilled water orally from the day 7th until the 17th of pregnancy. Group II: The pregnant mice (n=7) were administered orally with 45mg/kg b.w. of fluoxetine drug from the 7th day until the 17th day of pregnancy. Group III: in this group, the pregnant mice (n=7) were administered 75 mg/kg b.w. of fluoxetine drug from day 7th until day 17th of pregnancy.

Doses preparation

The drug solution was prepared by dissolving each concentration in 5 ml of distilled water (stock solution). The doses rates were between o.13 - 0.15 ml, depending on the weight of pregnant mice. Those doses had been chosen depending on the LD_{50} of the drug, which is 100 mg/kg b.w. (15). The doses (drug solution) were prepared freshly every day during the experiments period.

Histopathological preparation

On the day 17th of pregnancy, all pregnant mice were sacrificed and dissected, maternal lung and pancreas were dissected. Specimens were fixed in formalin 10% for 48 hours; later, they were washed with distilled water for two hours and processed with routine paraffin embedding technique (16). Sections were stained with hematoxylin and eosin (17).

Results

Lung histopathology in adult pregnant mice

Light microscope examination of the control lung section of the pregnant mice *Mus musculus* showed normal appearance of lung histology (Figure 1). Lung sections collected from pregnant mice performed 45 mg/kg b.w. of fluoxetine from the 7th until the 17th day of pregnancy showed satisfactory histopathological lesions represented with serofibrinous oedema in the air space of alveoli and infiltration of inflammatory cells as well as enlarged airspace and mild thickening of alveolar septa (Figure 2) as well as degeneration of the pulmonary lining epithelium cells and congestion (Figure 3). While the examination of the lung sections obtained from pregnant mice given 75 mg/kg b.w. of fluoxetine drug orally for the same period above showed that previous lesions were increased, especially the congestion of blood vessel (Figure 4), as well as hyperplasia of the lung epithelium tissue, was observed (Figure 5).

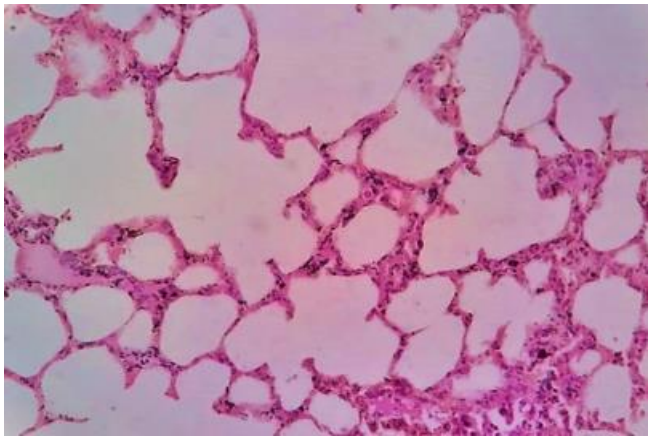

Figure 1: A cross-section photomicrograph of the control pregnant mouse *Mus musculus* lung showing normal lung histology. (10x. H&E).

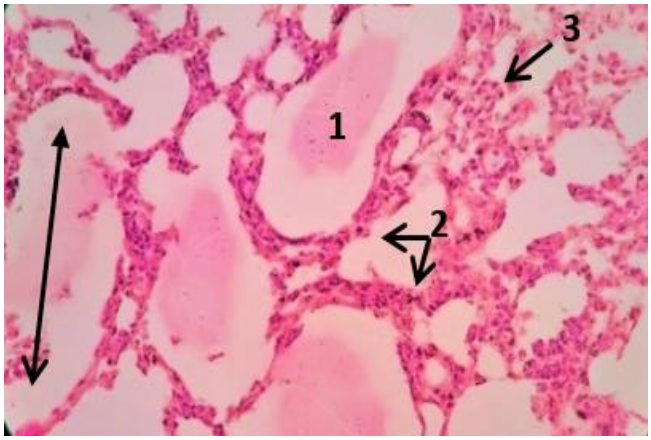

Figure 2: A cross-section photomicrograph of the lung of pregnant mouse *Mus musculus* treated with fluoxetine drug at the dose of 45 mg/kg of b.w. from the 7th day until 17th day of pregnancy showing serofibrinous oedema (1), enlargement of pulmonary air space (black arrow), mild thickening of alveolar septa (2), infiltration of inflammatory cells (3). (400x. H&E).

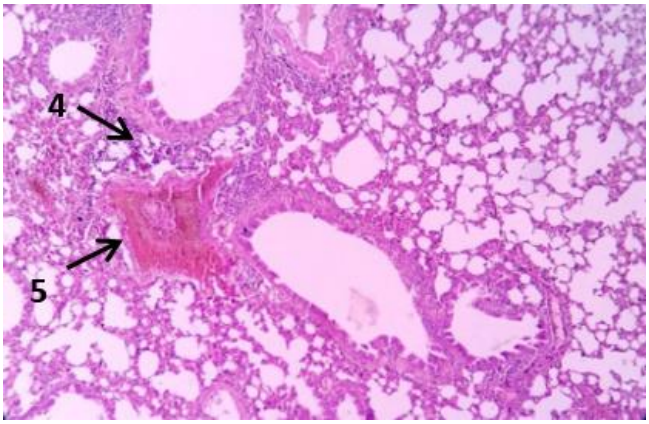

Figure 3: A cross-section photomicrograph of the lung of the pregnant mouse *Mus musculus* treated with fluoxetine drug at the dose of 45 mg/kg of b.w. from the 7th day until the 17th day of pregnancy showing degeneration of lung epithelium cells (4) and congestion (5). (10x. H&E).

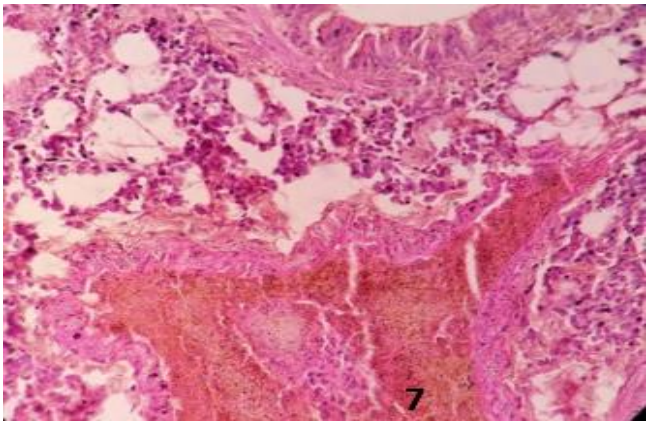

Figure 4: A cross-section photomicrograph of the lung of the pregnant mouse *Mus musculus* treated with fluoxetine drug at the dose of 75 mg/kg of b.w. from day 7 to day 17 during pregnancy shows an increase in the congestion of blood vessels (7). (10x. H&E).

Histopathological observations of the pancreas of pregnant mice

Light microscope examination of the control pancreas of pregnant mice *Mus musculus* showed normal lobules and normal pancreatic cells (Figure 6). Pancreas sections were obtained from pregnant mice given 45mg/kg b.w. of fluoxetine drug orally from the 7^{th} until the 17^{th} day of pregnancy. The histological changes and the dose increase were increased, so sections of the pancreas obtained from the pregnant mice given 75mg/kg b.w. of fluoxetine drug orally for the same period above revealed vacuolation of the pancreatic cells (Figure 7). Hypertrophy of some of them, congestion of the blood vessel, and the increase of eosinophilia of some pancreatic cells cytoplasm (Figure 8).

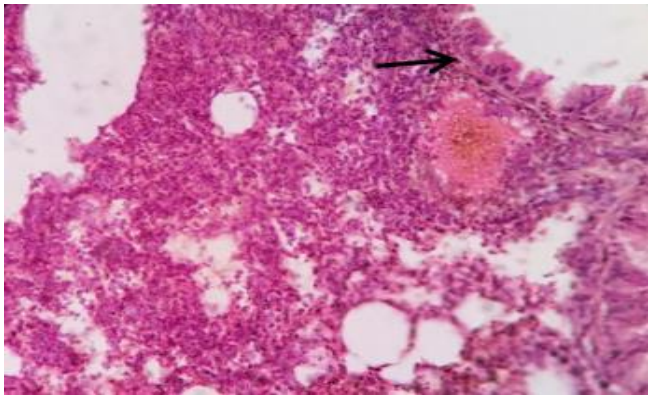

Figure 5. A cross-section photomicrograph of the lung of the pregnant mouse *Mus musculus* treated with fluoxetine drug at the dose of 75 mg/kg of b.w from day 7 to day 17 during pregnancy, showing hyperplasia of tracheal epithelium cells (black arrows). (10x. H&E).

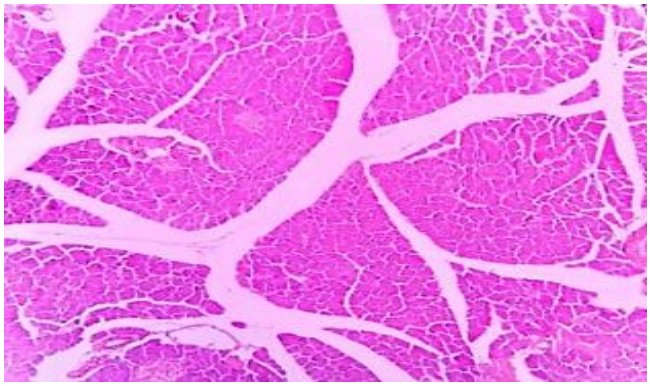

Figure 6: Cross-section photomicrograph of the pregnant mouse *Mus musculus*'s control pancreas shows normal pancreatic lobules and normal pancreatic cells. (10x. H&E).

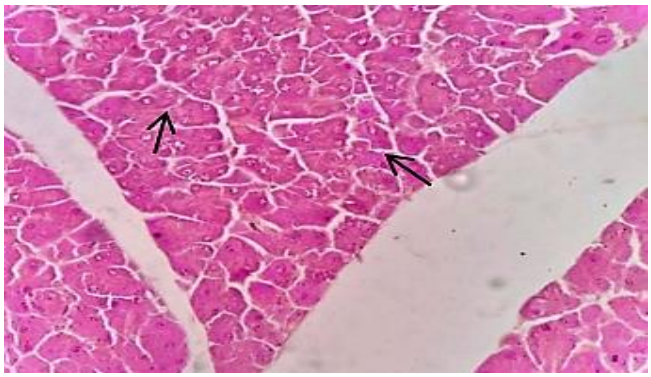

Figure 7: Cross-section photomicrograph of the pancreas of pregnant mice *Mus musculus* treated with fluoxetine drug at the dose of 75 mg/kg of b.w. from day 7 to day 17 during pregnancy showing vacuolation of pancreatic cells (black arrows). (10x. H&E).

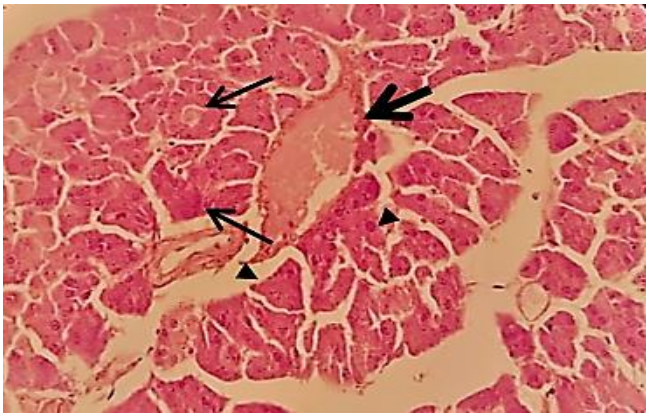

Figure 8: Cross-section photomicrograph of the pancreas of pregnant mouse *Mus musculus* that treated with fluoxetine drug at the dose of 75 mg/kg of b.w. from day 7 to day 17 during pregnancy showing hypertrophy of some pancreatic cells (thin black arrow), eosinophils of some pancreatic cells cytoplasm (black arrows heads), congestion of the blood vessel (thick black arrow). (400x. H&E).

Discussion

In our study, the Macroscopical examination of the lung of pregnant mice administrated orally with 45,75 mg/kg b.w. of fluoxetine showed serofibrinous oedema in the alveolar air space, degeneration of the alveolar lining epithelium, infiltration of inflammatory cells, congestion, and hyperplasia. The lesions were increased as well, as the dose increased. Those lesions were similar to those reported by (9,12,18). This study's findings correspond with those of (19) as all of them confirmed that taking fluoxetine during pregnancy causes hyperplasia of alveolar septa. The results of this study may be directly attributable to that inflammatory response induced by fluoxetine. This induction may be linked to fluoxetine impairing the phospholipids metabolism, which involves pathological lesions such as inflammatory cells infiltration and degeneration (20). on the other hand, it may be due to the use of fluoxetine during pregnancy, which may alter some metabolic pathways and increase in the levels of oxidative stress, which in turn cause formation of destructive free radicals, those molecules disturb and destroy the functions and structure of the lung cells (21).

The findings from the current study had shown histopathological lesions in pregnant mice's pancreas that were treated with fluoxetine at 45, 75 mg/kg b.w. for the preceding period, so the most noticeable lesions at the 75 mg/kg dose were blood vessel congestion, vacuolation of pancreatic cytoplasm and hypertrophy of some pancreatic cells. Study findings did not correspond with the findings of (22). At the same time, the present study results were similar to the finding of (23). The results were somewhat similar to the finding of (24). The finding of the current study may be due to the, that using fluoxetine for depression treatment during pregnancy may involve inducing cytotoxic mechanism in the body cells, which in turn increase the production of free radical oxygen species that destroy cellular mitochondria, proteins, lipids, and nucleic acids (25).

Conclusion

In conclusion, antidepressants may stimulate oxidative injury throughout the body's internal organs, particularly if taken at high doses during pregnancy. Consequently, they should always be used caution to avoid adversely.

Acknowledgements

The authors would thank the University of Mosul to support the current study.

Conflict of interest

No conflict of interest.

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سمية الفلوكستين هايدروكلوريد على بعض الأعضاء الحيوية المختارة في الفئران الحوامل *Mus musculus*

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الخلاصة

أخذت الدراسة الحالية على عاتقها التحري عن تأثير عقار فلوكستين هايدروكلورايد على كل من الرئة والبنكرياس في الفئران البالغة الحوامل. استخدمت في الدراسة الحالية جرعتين هما: ٤٥، ٧٥ ملغم/كغم من وزن الجسم. وجرعت الفئران الحوامل فمويا بالعقار من اليوم ٧ إلى يوم ١٧ من الحمل. أظهرت النتائج تغيرات نسجية مرضية مختلفة في الرئة عند الجرعة ٤٥ ملغم/كغم من وزن. ازدادت حدة الآفات النسجية المرضية عند الجرعة ٧٥ ملغم/كغم من وزن الجسم، فضلا عن ظهور فرط التنسج في الخلايا الرئوية. لم تظهر أفات نسجية مرضية واضحة عند الجرعة ٤٥ ملغم/كغم من وزن الجسم في البنكرياس، في حين عند الجرعة ٧٥ ملغم/كغم من وزن الجسم لوحظ احتقان الوعاء الدموي وتفجي سايتوبلازم الخلايا البنكرياسية وتضخم بعضها فضلا عن زيادة الضرر النسجي عند الجرعة ٧٥ ملغم/كغم. نستنتج من ذلك أن استخدام مضادات الاكتئاب قد يسبب زيادة الضغط التأكسدي النسجي في الأعضاء الداخلية للجسم خاصة إذا تم استخدامه خلال فترة الحمل بجرع عالية، وبالنتيجة فان هذه الآفات لها تأثير كبير على صحة كل من الأجنة وأمهات الفئران الحوامل وبما أن اغلب الآفات المرضية التي تم تسجيها كانت في الأجنة والتي تسبب الإجهاض وبالتالي تؤثر على صحة أمهات الفئران الحوامل.

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