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Investigating the Histological Changes in Heart, Lung, Liver and Kidney of Male Albino Mice Treated with Ivabradine

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Abstract:

The present study aimed to investigate the histological changes of heart, lung, liver and kidney which caused by different concentrations (10, 20 and 40 mg/kg) of Ivabradine. Results of the study revealed some histological changes represented by aggregation of the lymphocytes around respiratory bronchioles of the lung. In the liver, the drug caused hepatocyte necrosis and infiltration of the lymphocytes. In Kidney, there are no histopathological modifications in the tissue after the animals treated with 10 mg\kg of Ivabradine. When the animals treated with Ivabradine drug at 20mg/kg of bw, dose showed vascular congestion between myocardial fibers of heart. Emphysematous changes of the alveoli and infiltration of lymphocytes around respiratory bronchioles of lung. In the liver there were dilated blood sinusoids. Also, there are vascular congestion and congestion of capillaries in the glomerular of kidney. Male mice treated with Ivabradine drug at 40 mg/kg of bw cause increase spaces between myocardial fibers, cardiac atrophy and myocardial degeneration in the heart. In addition, there are infiltration of lymphocytes around respiratory bronchioles, pulmonary congestion and emphysematous changes of the alveoli in lung. In the liver, the drug cause amyloid deposition and degeneration of hepatocytes. Furthermore, the drug caused vascular congestion in the kidney. Conclusion: From the current study, we conclude that the different concentrations of Ivabradine caused tissue changes in the heart, lung, liver and kidneys. The study should continue using different drugs and concentrations.

Key words: Histological changes, Ivabradine, Kidney, Liver, Lung.

Introduction:

Heart rate is a major marker of angina in the coronary artery disease; it is also an important indicator for cardio-vascular mortality. Lower heart rate, is therefore one of the most important therapeutic approach in treatment of stable angina.
So far, some beta blockers calcium channel antagonists reduce heart rate, but use it may be limited, due to adverse reactions, or contra-indications. Ivabradine is the first specific rate of heart rate reduction factor that completed the clinical development of stability heart attack. Ivabradine is selective in the current state, and reduced heart rate in concentrations does not affect other heart diseases ionic currents (1). Specific heart rate reduction, with Ivabradine reduces the demand for myocardial oxygen; simultaneously improve oxygen supply (2). Ivabradine is one of the most advanced drugs for the treatment of angina; it has an exclusive heart rate reduction activity (3). Ivabradine lowers heart rate, through its action on the sinus node.

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It is licensed to treat angina in patients, who are in the normal sinus rhythm, in combination with beta blockers, or when beta blockers are contra-indicated, or cannot be tolerated. Ivabradine, along with standard treatment including beta blockers, is also licensed for mild to severe stable chronic heart failure, in patients who are in sinus rhythm(4). Despite the overall superiority of beta blockers in management of heart failure, the Ivabradine can reduce heart failure (5) (6).

The present study aimed to investigate the histological changes in the heart, lung, liver and kidney tissues of the male albino mice caused by Ivabradine drug.

Materials and methods

In this study, 40 albino mice with 25 - 30 grams were used. The animals were housing in the Biotechnology Research Center / Al- Nahrain University. They were randomly divided into 4 groups, A, B, C, and D. Groups, group A, was control while B, C, and D, were experimental groups (treated groups). Each group includes 10

mice. The animals were orally treated with the drug in a daily dose of 10ml/kg, 20ml/kg, and 40ml/kg, respectively. These groups were orally administrated for 14 days. Mice of the entire group were sacrificed. Heart, lung, liver, and kidney were collected immediately, in order to avoid diagnosis error and fixed in 10% formalin. Harris hematoxylin and eosin stain were used to stain the sections of all the above organs.

Results:

Results of the present study revealed the following:

- **Heart**

At 10mg/kg bw, dose of Ivabradine, as in a control group (Fig. 1) did not show any histological changes in the heart tissue of male albino mice (Fig. 2). At 20mg/kg bw, dose of Ivabradine showed vascular congestion between myocardial fibers of heart (Fig. 3). At 40mg/kg bw, dose of Ivabradine showed cardiac atrophy and myocardial degeneration in the heart (Fig. 4).

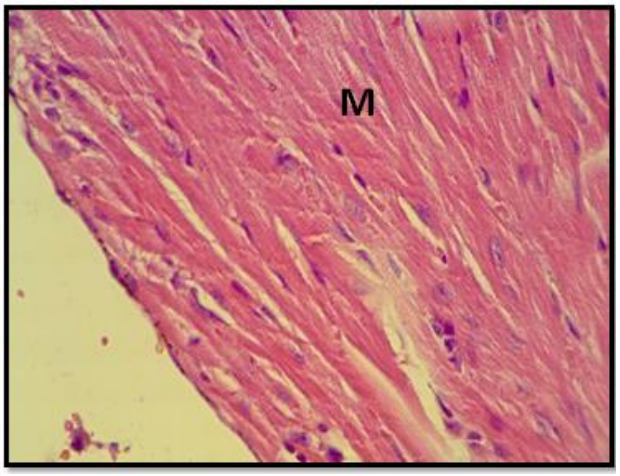

Figure 1. Photomicrograph of heart section of male mice control group: showing normal myocardial fibers (M) (400X) H&E.

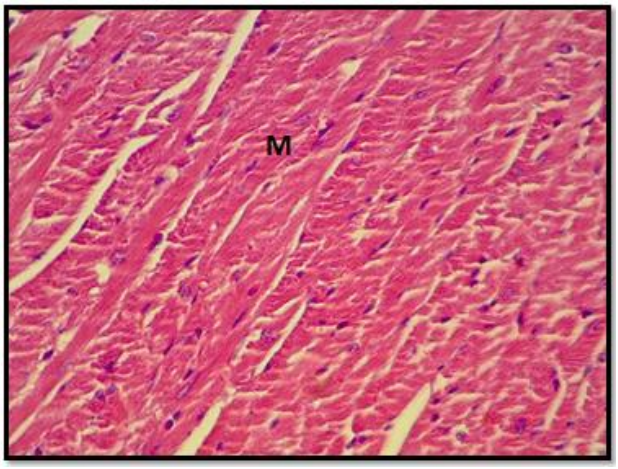

Figure 2. Photomicrograph of heart section in male mice treated with 10 mg/kg Ivabradine, showing normal structure of myocardial fibers (M). X400 H&E.

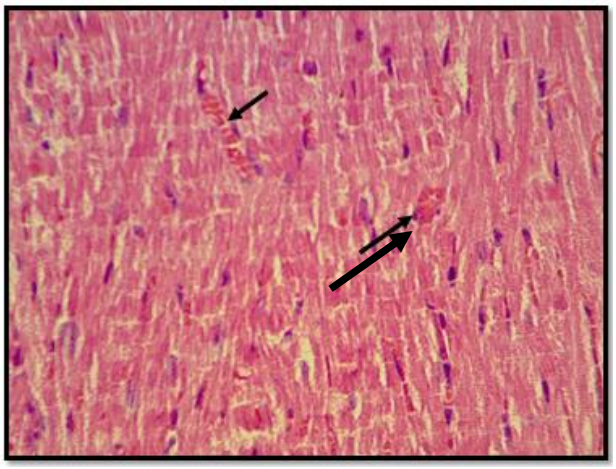

Figure 3. Photomicrograph of heart section in male mice treated with 20 mg/kg Ivabradine showing vascular congestion (arrows) between myocardial fibers (400X) H&E.

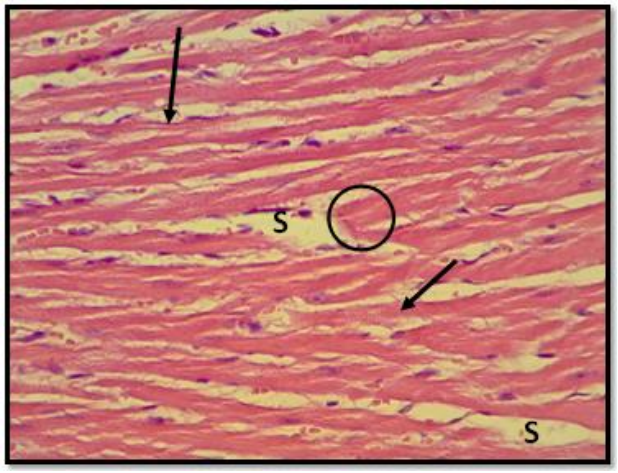

Figure 4. Photomicrograph of heart section in male mice treated with 40 mg/kg Ivabradine showing: increase spaces between myocardial fibers (S) cardiac atrophy (arrows) and myocardial degeneration (circle) (400X) H&E.

- **Lung**

At 10mg/kg bw, dose of Ivabradine when comparing with controls (Fig. 5) showed aggregation of the lymphocytes around respiratory bronchioles of the lung (Fig. 6). At 20mg/kg bw, dose of Ivabradine represented by emphysematous changes of the alveoli and infiltration of lymphocytes around respiratory bronchioles of lung (Fig. 7). At 40mg/kg bw, dose of Ivabradine showed infiltration of lymphocytes around respiratory bronchioles, pulmonary congestion and emphysematous changes of the alveoli in lung (Fig. 8).

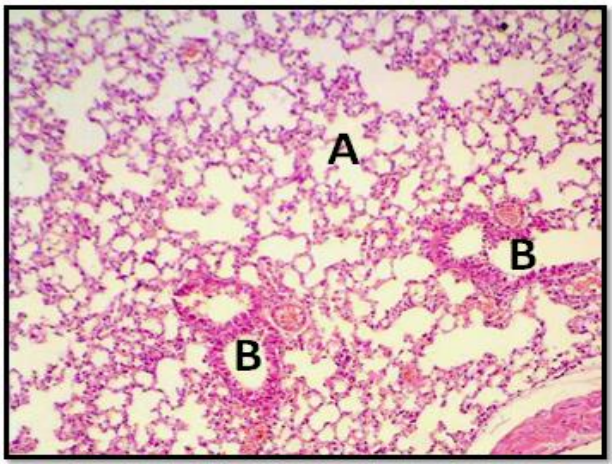

Figure 5. Photomicrograph of lung of the male albino mice in control group show: normal respiratory bronchioles (B) and alveoli (A). (100X) H&E.

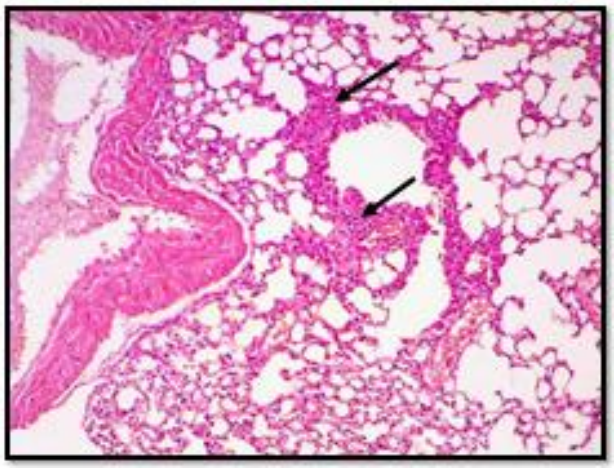

Figure 6. Photomicrograph of lung section of male mice treated with 10 mg/kg of Ivabradine: show aggregation of inflammatory cells around respiratory bronchioles (arrows). (100X) H&E.

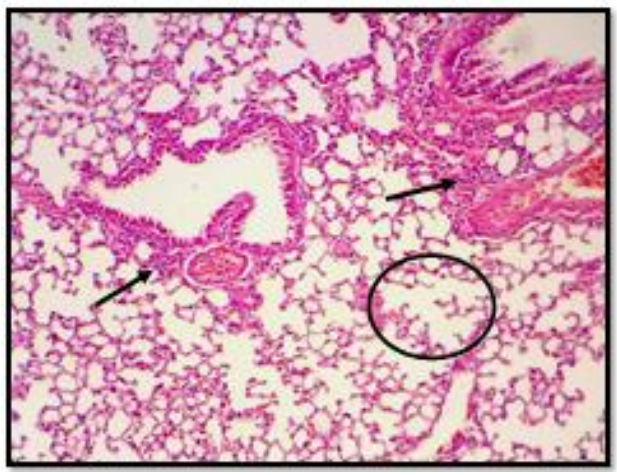

Figure 7. Photomicrograph of lung section of male mice treated with 20mg/kg of Ivabradine: show emphysematous changes of the alveoli (circle) and infiltration of lymphocytes around respiratory bronchioles (arrows) (100X) H&E.

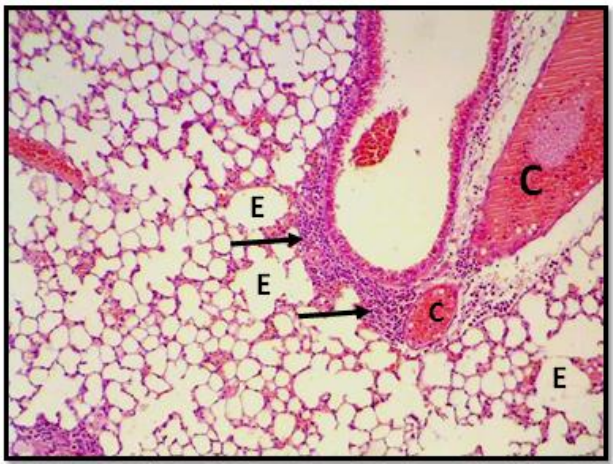

Figure 8. Photomicrograph of lung section in male mice treated with 40 mg/kg Ivabradine administration for 14 days showing infiltration of lymphocytes around respiratory bronchioles (arrows) pulmonary congestion (C) and emphysematous changes of the alveoli (E). (100X) H&E.

- **Liver**

At 10mg/kg bw dose of Ivabradine when comparing with controls (Fig. 9) showed necrosis of hepatocytes and infiltration of inflammatory cells (Fig. 10). At 20mg/kg bw, dose of Ivabradine showed the dilated blood sinusoids in the liver tissue (Fig. 11). At 40mg/kg bw, dose of Ivabradine showed amyloid deposition and degeneration of hepatocytes (Fig.12).

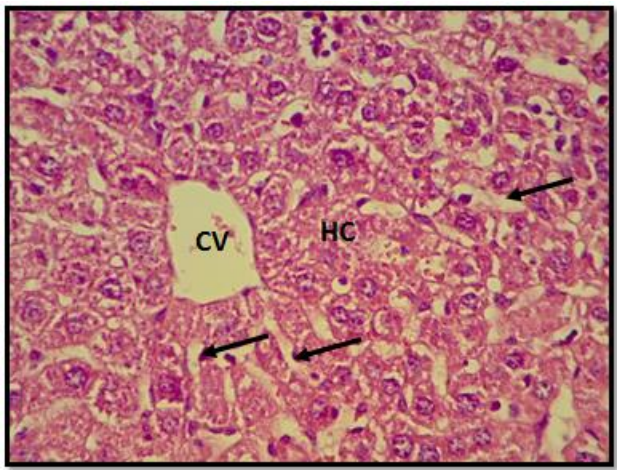

Figure 9. Photomicrograph of liver section of the male mice control group: showing central vein (CV) and surrounding hepatocytes (H), sinusoids (arrows) (400X) H&E.

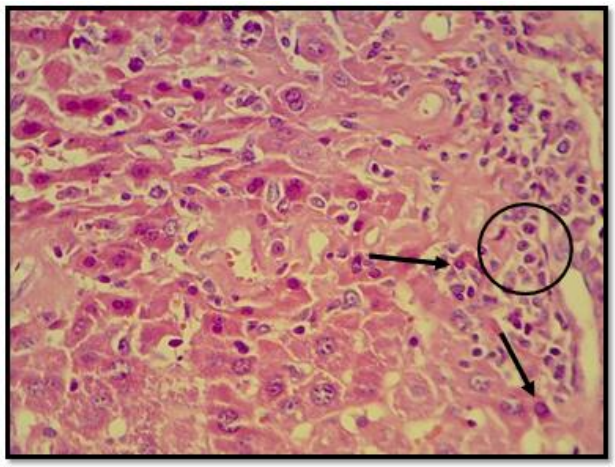

Figure 10. Photomicrograph of liver section of the male mice with 10 mg/kg Ivabradine administration for 14 days showing necrosis (arrows) and inflammatory cellular infiltration (circle) (400X) H&E.

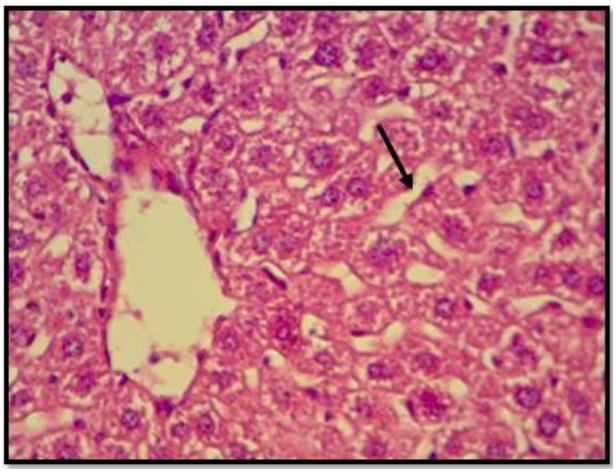

Figure 11. Photomicrograph of liver section of the male mice with 20 mg/kg Ivabradine administration for 14 days: showing dilated blood sinusoids (arrow) (1000X) H&E.

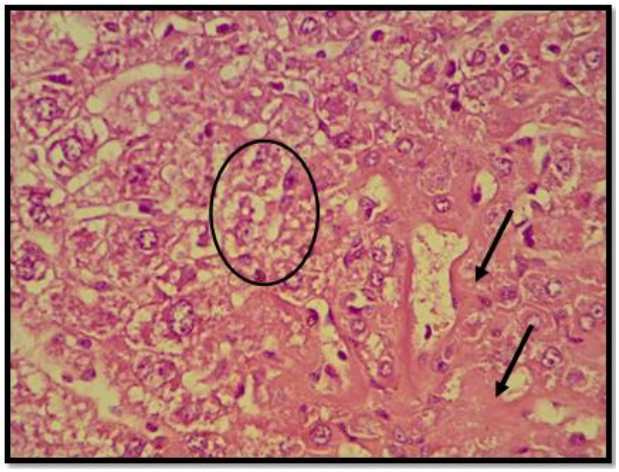

Figure 12. Photomicrograph of liver section of the male mice with 40 mg/kg Ivabradine administration for 14 days: showing amyloid deposition (arrows) and degeneration of hepatocytes (circle) (400X) H&E.

- **Kidney**

At 10mg/kg bw, dose of Ivabradine when comparing to controls (Fig. 13) did not show any histological changes in the kidney tissue (Fig. 14). When the animals treated with Ivabradine drug of 20mg/kg bw , dose showed vascular congestion and congestion of capillaries in the glomeruli of kidney (Fig. 15). Male mice treated orally with Ivabradine drug of 40 mg/kg of bw caused blood vessels congestion (Fig. 16).

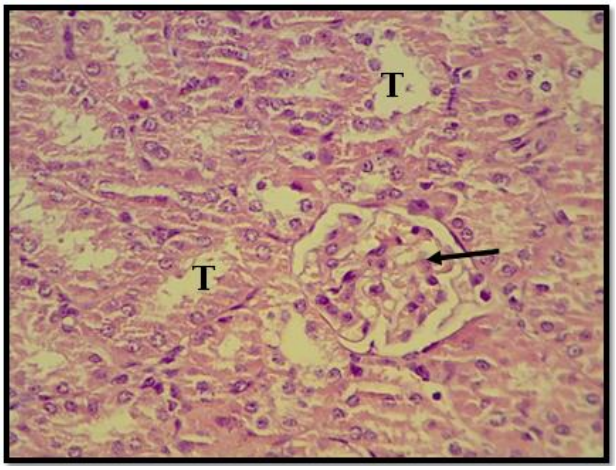

Figure 13. Photomicrograph of kidney section of the male mice control group: showing normal glomerulus (arrow) and proximal and distal convoluted tubules (T) (400X) H&E.

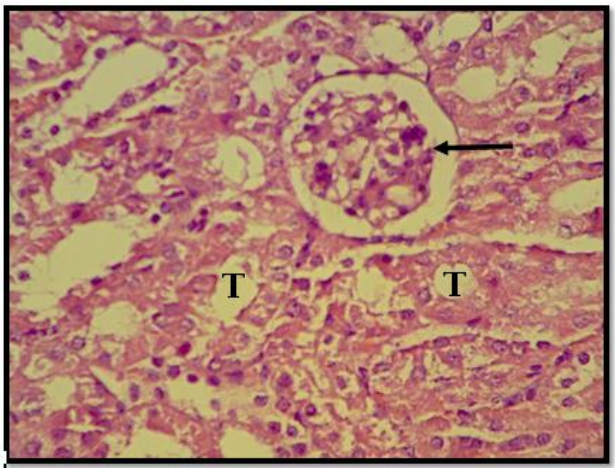

Figure14. Photomicrograph of kidney section of the male mice with 10 mg/kg Ivabradine administration for 14 days showing look like normal structure appearance of renal tubules (T) and the normal glomerulus (arrow). X400 H&E.

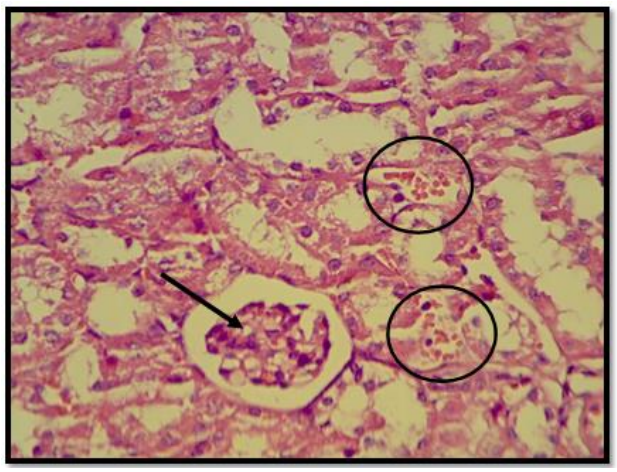

Figure 15. Photomicrograph of kidney section of the male mice with 20 mg/kg Ivabradine administration for 14 days showing vascular congestion (circles) and congestion of capillaries in the glomerulus (arrow). X400 H&E.

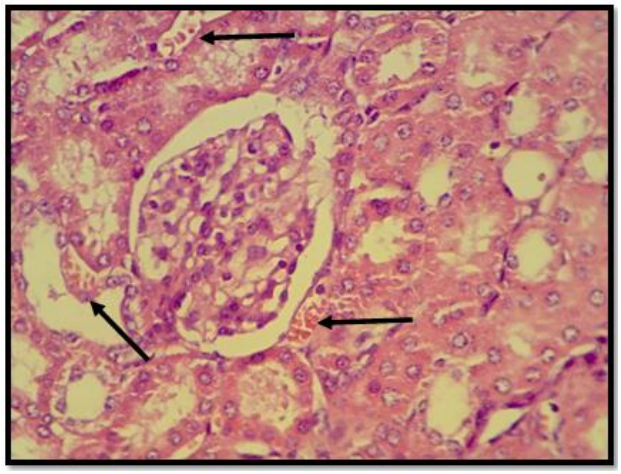

Figure 16. Photomicrograph of kidney section of the male mice with 40 mg/kg Ivabradine administration for 14 days showing vascular congestion (arrows). X400 H&E.

Discussion:

In this study, the effect of Ivabradine on heart, lung, liver and kidney was dependent on dose. There were an increase effects with the increasing of the concentration and prolonged dose administration.

The heart is appeared with normal structure as in a control group after the animals treated with 10 mg/kg of bw from the Ivabradine that is mean there is no effect with low dose. When the animals treated with 20 mg/kg of bw, Ivabradine showed vascular congestions between myocardial fibers the result agreed with (7) who treated the animals with Sunitinib and Paracetamol, and (8) (9) when the animals treated with Doxorubicin. After the treatment of male mice with Ivabradine (40 mg\kg), showed increase spaces between myocardial fibers of heart tissue was observed this result with (10) who treated rat with Diclofenac sodium, in addition to, cardiac atrophy and degeneration in the heart tissue was described this result with (11) when the rats treated by Indomethacin and (12) when the mice treated by Tulathromycin and (13) when the mice treated with Methotrexate and Rituximab.

On the other hand, the lung showed aggregation of the inflammatory cells around respiratory bronchioles after the animals were treated with 10 mg/kg of bw from the Ivabradine as mentioned (14) when used bleomycin. The animals treated with 20 mg/kg of bw of the Ivabradine showed emphysematous changes in the alveoli of lung (15). Infiltration of lymphocytes around respiratory bronchioles of lung as suggested by (14) after used bleomycin and (16) after the mice treated with Cefotaxime. Male mice treated with Ivabradine (40 mg\kg) showed infiltration of lymphocytes around respiratory bronchioles as referred by (14) after treated by bleomycin, pulmonary congestion and emphysematous changes of the alveoli in lung as regarded by (17) when the mice treated by Prostamides and (18) after treated by Gemcitabine.

The liver of male mice after treated with Ivabradine (10mg\kg) showed necrosis of liver tissue which agreed with the results reported by (19) when the mice treated with Valproic acid, and caused infiltration of inflammatory cells has been as regarded by (20) after the animals treated by Piroxicam and (21) when the mice treated with Aspirin. The animals treated with 20 mg/kg of bw, Ivabradine showed dilated blood sinusoid as founded by (7) after the mice treated with sunitinib and (22) after treated by Azathioprine and (23) after the mice treated with Parkizol. Male mice after co administration of Ivabradine (40mg\kg) showed amyloid deposition and degeneration of hepatocytes as described by (24) after treated by Chlorpromazine and (25) after the rats treated with Doxorubicin.

The kidney of Male mice after treated by Ivabradine (10mg\kg) did not show any histological changes in the renal tissue as referred (17) when the mice treated by Prostamides. The animals treated with 20 mg/kg of bw from the Ivabradine showed congested vasculature and congestion of capillaries in the glomerulus of kidney as referred (20) after the animals treated by Piroxicam. Male mice after co administration of Ivabradine (40 mg\kg) caused vascular congestion in renal tissue as referred by (7) when the mice treated by Paracetamol and (26) when the mice treated with Retin.

Conclusion:

The present study recorded changes in the organs tissue with the co administration of Ivabradine. Ivabradine administration resulted

tissue changes in heart, lung, liver and kidney. In the heart represented by vascular congestion between myocardial fibers, increase spaces between myocardial fibers, cardiac atrophy and myocardial degeneration. However, in lung, the results showed aggregation of inflammatory cells around respiratory bronchioles, emphysematous changes of the alveoli and pulmonary congestion. While, in the liver, the drug caused necrosis in the hepatocyte, inflammatory cellular infiltration, dilated blood sinusoids, amyloid deposition and degeneration of hepatocytes. In the kidney, results were vascular congestion and congestion of capillaries in the glomerular. The results were that the study should continue using different drugs and concentrations.

Conflicts of Interest: None.

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دراسة التغيرات النسجية في القلب والرئة والكبد والكلى في ذكور الفئران البيضاء التي تم معاملتها مع الإيفابرادين

هديل كامل خليل

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الخلاصة:

التغيرات النسجية للقلب والرئة والكبد والكلى التي تسببها تراكيز مختلفة (10، 20، 40 ملغم\كغم) من عقار الايفابرادين. أظهرت نتائج الدراسة بعض التغيرات النسجية تمثلت بترشيح الخلايا الالتهابية حول القصيبات التنفسية في الرئة. وفي الكبد ، تسبب العقار في نخر خلايا الكبد وترشح الخلايا الالتهابية. اما في الكلى ، فلم تظهر تغييرات نسجية بعد تجريع الفئران بتركيز 10 ملغ\كغم من الايفابرادين. وعندما جرعت الحيوانات مع عقار الايفابرادين بتركيز 20ملغم / كغ من وزن الجسم ظهر احتقان الأوعية الدموية بين ألياف العضلة القلبية. تغييرات انتفاخية في الحويصلات الهوائية وترشح الخلايا الليمفاوية حول القصيبات التنفسية في الرئة. وفي الكبد حصل توسع في الجيبانيات الدموية. أيضا ، وحصل احتقان الأوعية والشعيرات الدموية في كبيبات الكلى. جرعت الفئران فمويا مع عقار الايفابرادين عند 40 ملغم / كغم من وزن الجسم سبب زيادة المساحات بين ألياف العضلة القلبية وضمور القلب وتنكس في العضلة. وبالإضافة إلى ذلك ، هناك ترشح الخلايا الليمفاوية حول القصيبات التنفسية ، واحتقان رئوي وتغيرات انتفاخية في الحويصلات الرئوية. في الكبد ، يسبب الدواء ترسب بروتينات الاميلويد وتنكس الخلايا الكبدية. وعلاوة على ذلك ، تسبب هذا الدواء في احتقان الأوعية الدموية في الكلى. الاستنتاج: من الدراسة الحالية يمكننا القول : ان للتراكيز المختلفة من عقار الايفابرادين يؤدي الي تغييرات نسجية في القلب، الرئة، الكبد والكليتين.

الكلمات المفتاحية: التغيرات النسجية، الايفابرادين، الكلى، الكبد، الرئة.