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Histological Study of the Effects of Propranolol on the Kidney and Liver of Rabbit(*Oryctolagus cuniculus*)

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Summery

Twelve healthy adult rabbits were included (20 to 40 mg of propranolol per rabbit daily with drinking water). The 2nd group received only water without propranolol as a control. The liver and kidneys were collected and prepared for histopathological study. After 40 days of treatment, most of animals suffer from weakness ,rough coat, loss of appetite, and lacrimation, enlargement of the liver and gall bladder ,petechial hemorrhage on the liver surface. Vacuolation of the hepatic tissue and hemorrhagic spots scattered among and within hepatic tissue. Small-droplet of fat is found in virtually all hepatocytes. This change is most often associated with long-term use of high doses of propranolol. slight enlargement of the kidney , with petechial hemorrhage edematous fluids in the parenchyma between the tubule, the kidney show loss of bowman space and thickening of the wall of proximal and distal convoluted tubules

Key words: propranolol, kidney, liver, rabbit.

Introduction

Propranolol (Inderal®)is one of the betarecepter-blocker used to treat abnormal heart rhythms (arrhythmias). It is also used for short periods of time to treat hypertension caused by thyrotoxicosis and pheochromocytoma. Its use for the treatment of arrhythmias in cats, dogs, ferrets, and horses is "off-label" or "additional indication". In veterinary medicine, many drugs are commonly prescribed for off-label use.

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In such cases, veterinary instructions and precautions should be followed carefully as they may differ significantly from those listed on the label (1). Propranolol used in virtually all cases where the aim is to decrease convention and decrease the heart rate. This activity will review the indications, dosages, contraindications, mechanisms, and controlling of propranolol treatment by the interprofessional health care group (2). Propranolol is a competitive β-adrenoceptor antagonist without agonist activity and is the prototype for comparison with other β-antagonists (3). Sir James Black, a British scientist, has the first attempt to use of propranolol angina pectoris treatment. Subsequently, propranolol began to gain recognition and became a widely used drug in the treatment of different cardiac diseases(4).

propranolol has been established to recover mortality and morbidity in hypertensive patients with heart failure, angina pectoris, and preexisting myocardial infarction. Also an ideal drug for hyperthyroidism-induced thyrotoxicosis (5).Propranolol has also uses in the treatment of noncardiovascular diseases. It is used as a means of migraine prophylaxis, dealing of restless leg syndrome, essential tremors, and wide using of infantile hemangioma treatment (6).

another uses of propranolol include performance anxiety, a subgroup of social phobia that happened with tachycardia, sweating, and blushing secondary to increased sympathetic nervous system beginning (7).

The other important use of propranolol in the medical field the critical importance to culture of the discovery of this drug. Like most drugs, beta-

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blockers are mainly metabolized in the liver. About one quarter of consumed drugs reach the systemic circulation by first-pass metabolism in the hepatic circulation (8).

The main member of propranolol is 4-hydroxypropranolol, which is molded through hydroxylation spending the CYP2D6 enzyme(9).

In addition, as with most ingested drugs, propranolol is primarily eliminated by the renal system, with a half-life of approximately 3-6 hours in patients with healthy renal systems (8).

It might be administered orally or intravenously. With intravenous administration, ECGs should be constantly monitored during slow infusion. This way of administration is primarily used in hospitalized patients(9).

The effect of Propranolol to preventing strokes weaker than that of calcium-channel blockers and renin-angiotensin system inhibitors (10).

Absorption of more than 1 g of propranolol in a 24-hour period can be lethal, causing severe bradycardia, bradyarrhythmias, hypotension, and bronchospasm.

If a beta-blocker overdose is suspected, the patient must give glucagon immediately. Glucagon has been shown to be very effective in retreating beta-blocker overdose, increasing heart rate, and increasing myocardial contractility (11).

The rabbit is a laboratory animal model that has been used in many scientific studies, including evaluation of new drugs, production of vaccines, and testing of new surgical techniques (12). The liver of the domestic rabbit is a

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soft, lobulated organ located in the upper abdomen caudally to the diaphragm, extending between the rib arches from the right seventh rib to the left ninth rib and abutting the left and right abdominal walls (13,14). It is composed of multiple lobes, each lobule consisting of an irregular plate of hepatocytes with an intervening sinusoid that drains into a central vein. The cells are polyhedral, with eosinophilic cytoplasm and prominent nuclei (15,16).

The aim of this study is to detect the desired and un desired effects of prolonged use of propranolol drug as a histopathological effects on the liver and kidney of domestic rabbits.

Methodology

Animals and Housing Condition

Twelve healthy mature rabbit of an average body weight (BW) of 1000 grams were obtained from the Diyala city local markets, animals were kept in the animal house, College of veterinary medicine, University of Diyala; under the laboratory conditions, with controlled room temperature 20-25^{o}c, good ventilation, fed rodent diet and tap water.

Experimental Design

Animals randomly subdivided into two groups of exposure (n = 6 rabbit for every group) and treated with (20 to 40 mg of propranolol per rabbit daily with only drinking water). The 2nd group received only water without propranolol as a control. Clinical notes made after dosing and examine the body after the end of the experiment.(17)

4.1.The Results

Most of the animals in the 1st group don't show any changes either in behavior or in the body weight after 20 days of treatment. After 40 days of treatment, Most of the animals suffer from weakness, lacrimation and loss of appetite (Fig.1).

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Fig.1: show animal treated after 40 days suffer from lacrimation.

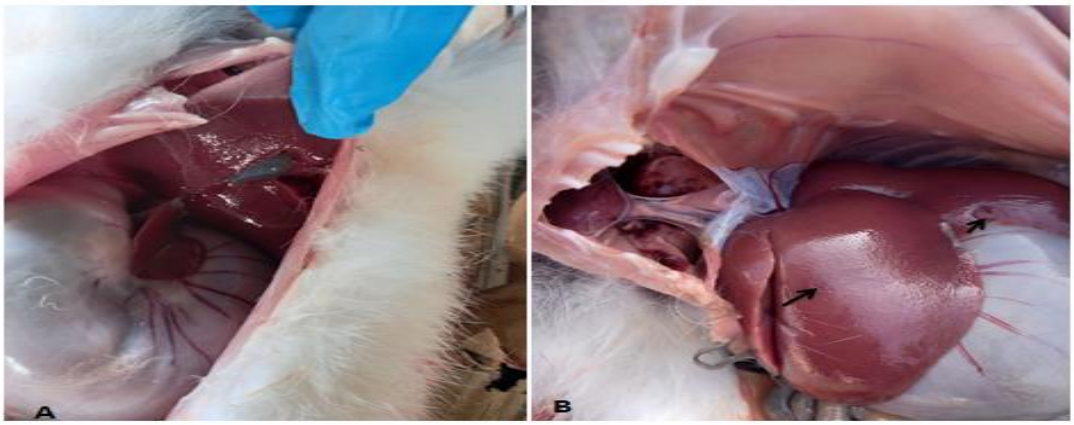

Fig.2:show the liver suffering from petechial hemorrhage (A control) ,(B treated)

The histopathological study of liver include petechial hemorrhage scattered among and within hepatic tissue(Fig.2). Vacuolation of the hepatic tissue. The small-droplet of fat is found in virtually all hepatocytes. This change is most often associated with mild toxicity of long term use of propranolol. Apoptosis happens (Fig. 3). Increase capsule thickness and the sinusoid diameter and hepatocyte diameter . (Tab.1)

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Table (1):Histometric parameters of rabbit liver

parameters	Control group	Treated group
Capsule thickness(um)	9.6±**0.03 SE**	10±**0.03 SE**
Hepatocyte diameter(um)	93±**0.06 SE**	91±**0.06 SE**
Nucleus diameter(um)	36±**0.03 SE**	35±**0.03 SE**
Sinusoids diameter(um)	41±**0.03 SE**	40±**0.03 SE**
Central vein diameter(um)	124±**0.08 SE**	123±**0.08 SE**

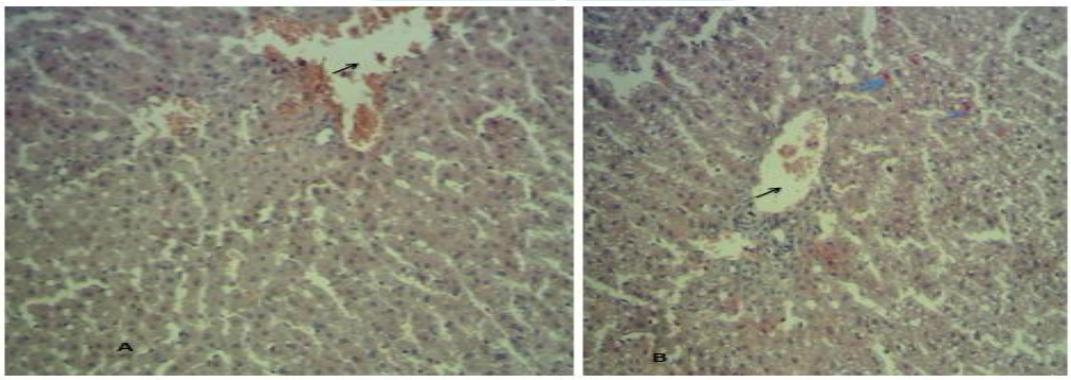

Fig.3:A. Photomicrograph from non-treated rabbit liver. B. treated animal liver showing central vein (black arrows) ,hemorrhage(blue arrows)(H&E 10X).

In the current study there is slight enlargement of the kidney (fig.4).

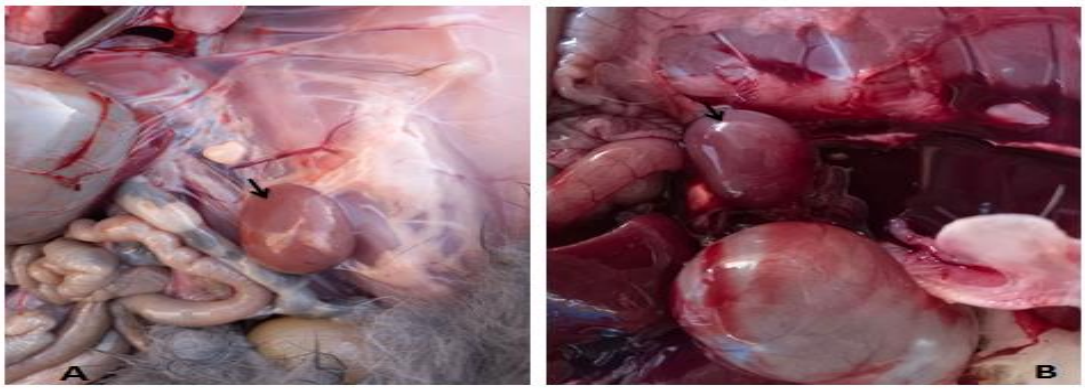

Fig.4: kidney of rabbit show petechial hemorrhage (A control) ,(B treated).

Animals after 60-90 days after administration of propranolol. the morph pathological finding include: slight enlargement of the kidney.

Histopathological picture show the edematous fluids in the parenchyma among the tubules, the kidney show thickening of the lumen of proximal

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and distal convoluted tubules (fig.5). Bowman capsule and cell diameter in non-treated animals are slightly larger than that of treated animals(fig.6).Slight increase in the diameter of the kidney cells and bowman capsule (tab.2).

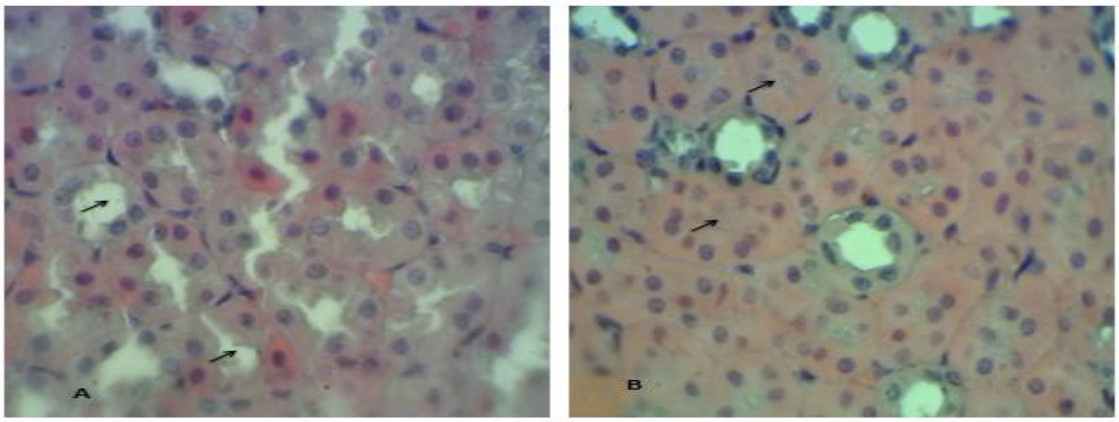

Fig.5: Histopathology of rabbit kidney that shows proximal convoluted tubule(black arrow), (A control, B treated animal kidney show bowman space(black arrows). (H & E.10x).

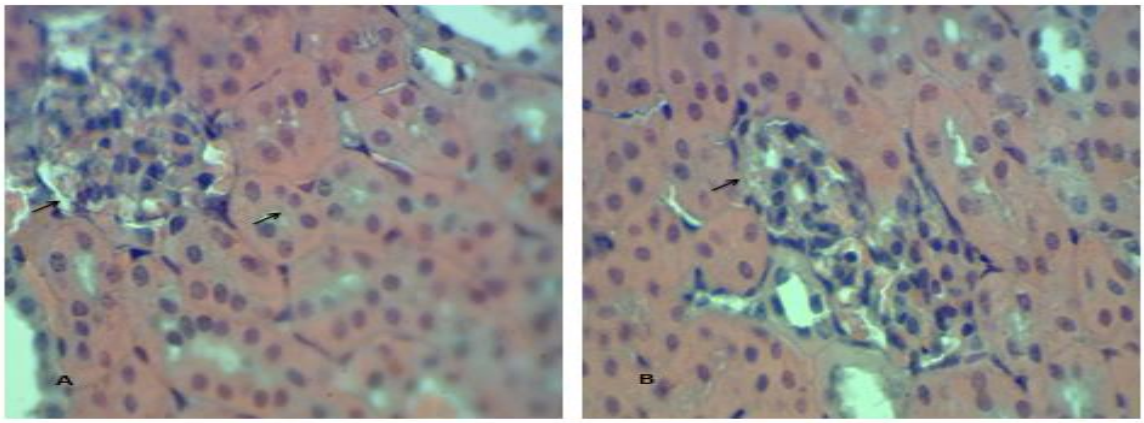

Fig.6: Histopathology of rabbit kidney(A, control ,B treated kidney that shows ,bowman space of bowman capsule(black arrows). (H & E.10x).

Tab(2):Histometric parameters of rabbit kidney.

parameters	Control group	Treated group
Bowman capsule diameter(um)	295±**0.06 SE**	300±**0.0 SE**
Cell diameter(um)	90±**0.03 SE**	92±**0.03 SE**

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Discussion

The histopathological study of liver include vacuolation of the hepatic tissue as well as hemorrhagic spots scattered among and within hepatic tissue. (18) found that there were varying degrees of congestion or hemorrhage in the liver, kidneys, urinary bladder, of sheep. examination of tissue sections exposed degeneration and focal necrosis of hepatocytes and necrosis of tubular epithelium in kidneys, fatty degeneration and infiltration of mononuclear inflammatory cells in liver.

The small-droplet of fat is found in virtually all hepatocytes This change is most often associated with mild toxicity of long term use of propranolol. Apoptosis happened. Increase capsule thickness and the sinusoid diameter and hepatocyte diameter .

In the current study there is slight enlargement of the kidney. Histopathological picture show the edematous fluids in the parenchyma between the tubules, the kidney show thickening of the wall of proximal and distal convoluted tubules. Bowman capsule and cell diameter in non-treated animals are slightly larger than that of treated animals. (19) noted that the kidney was significantly aggravated in rats treated with propranolol, blood flow to the kidneys, liver and intestines significantly decreased, and injuries were aggravated. (20) noted that in contrast, these conditions were greatly improved in the rats treated by Curcumin.

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