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Histopathological Effect of Dexamethasone Drug on Some Organs of Female Albino Rats

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Abstract

The study has been conducted in Animal House/Faculty of Sciences/University of Kufa, fifteen female Albino Rats are used. Dexamethasone is widely used as glucocorticoids for anti inflammation and allergic diseases. The present study has been intended to show the histolopathologiacl effect of dexamethasone on liver and kidneys of female Albino Rats. The females Rats are randomly divided into three main groups, comprising five rats for each group. The control group is given intra peritoneal injection of physiological normal saline and the second and third group are given intra peritoneal injection of dexamethasone doses twenty, forty mg/kg/day respectively for twenty days from the first day to the end of experimental allocated for each female. The rats are sacrificed to study liver and kidneys morphologically and histologically. Dexamethasone doses twenty, forty mg/kg/day caused significant increase (p<0.05) in relative weights of liver and kidney female rats compare to control

Keywords: Rats, Dexamethasone, Kidneys, Liver

1. Introduction

Glucocorticoids are a class of corticosteroids, which are a class of steroid hormones. Glucocorticoids are part of the feedback mechanism in the immune system which reduces certain aspects of immune function, such as inflammation (Ingawale and Mandlik, 2020). Dexamethasone (DEX) is a type of corticosteroid medication and produces the effects of antiinflammation, antiangiogenesis, control of estrogen activity (Jiang et al., 2020). Glucocorticoids used in medicine to treat diseases caused by an overactive immune system, such as allergies, asthma, autoimmune diseases, and sepsis (Zyma and Pawliczak, 2020). They also interfere with some of the abnormal mechanisms in cancer cells, so they are used in high doses to treat cancer, this includes inhibitory effects on lymphocyte proliferation, as in the treatment of lymphomas and leukemias, and the mitigation of side effects of anticancer drugs (Fan, et al., 2019). Dexamethasone side effects get emergency medical help if you have signs of an allergic reaction to dexamethasone hives, difficulty breathing; swelling of your face, lips, tongue, or throat (Perza and Nomura, 2019). The liver is the largest important organ and the site for essential biochemical reactions and detoxifying toxic substances in the human body. Long-term, high-dose dexamethasone administration can cause severe alterations in liver function. dexamethasone-induced hepatotoxicity by attenuating antioxidant defense system (Abou-Seif et al., 2019)^[1]. The kidney is a frequent target for organ-specific toxicity as a result of its primary function in controlling body fluids, for example, via resorption of amino acids, peptides, nutrients, ions, xenobiotics and water from the primary urine as well as excretion of metabolic waste products, dexamethasone has protective effects for cells and tissues of the kidney by inhibiting oxygen consumption and hypoxia or by improving mitochondrial dysfunction via TNF- α in the renal cells. (Kiyonaga and Kanmura, 2020). Dexamethasone induced hypertension in rat mode, hypertension is the fundamental cause of cardiovascular and cerebrovascular disorders (Savitha et al., 2019). Acute lung injury (ALI) is characterized by neutrophilic infiltration,

group. The histological study on kidneys of female rats treated with twenty dose mg/kg/day of dexamethasone have shown deformation of glomerulus, proximal convoluted tubule degeneration and hemorrhage. While the kidneys from the forty-dose mg/kg/day dose of dexamethasone have shown severely affected, they are appeared enlargement of glomerulus, proximal convoluted tubules degeneration and hemorrhage. The histological study on sections from liver related to female rats treated with twenty dose mg/kg/day of dexamethasone has shows hepatocytes degeneration and hemorrhage. While the liver from the forty-dose mg/kg/day dose of dexamethasone has shown severely affected, they are appeared hepatocyte degeneration and enlargement of nuclei.

In conclusion; dexamethasone caused increased in size of kidneys and some histopathological effects while in liver caused hepatotoxicity.

uncontrolled oxidative stress and inflammatory processes, dexamethasone (DEX), a synthetic glucocorticoid, has been routinely used as an adjuvant therapy in treating inflammatory diseases (Du *et al.*, 2020).

2. Material and Methods

2.1 Animal Model

This study achieved on pregnant white rat *Rattus norvegicus* females (15) and males (5) for mating. All rat weights ranging from 200-250 g. They should be in good health. The rats are placed in plastic cages with metal covers, 48 cm wide, 15 cm wide and 7 cm wide. The sawdust, which should be replaced three times a week, is considered in its care to clean the hatching of the special diet and plastic bottles can be used to make a watering tough with a cork equipped with metal pipes. The animals are placed under suitable laboratory conditions in terms of temperature 18-26 C° and light/dark cycle 10/14 and ventilation rate time/hour 10-15 and also the relative humidity 30-70 (Tan & Tan, 2017)^[16].

2.2 Drug Used

In this study, dexamethasone is used in the form of ampoule 80mg /2ml, from AL-Foraf Drug Store, MEDLAK PHARMA ITALI company which is used for intravenous or intramuscular in human, injection of experiment animals by Intraperitoneal (IP) using disposable syringe. The dose given to the animal is prepared as follows:

The required dose of dexamethasone intraperitoneally in rat weight 100 g (standard) dose 80 mg/kg calculated as follows:

Step 1: Dosage calculation

Dose required for 100 g rat = Animal weight / 1000 g x Standard dose (mg)

Step 2: Required volume calculation for intra peritoneal injection

Depending on above calculation, 8 mg of dexamethasone requires for each 100 g of rat and this dosage (8 mg) can be withdrawn directly from the stock of dexamethasone which is present as 80 mg/2 ml (40 mg/ml) ampoule.

Thus, 40 mg = 2 ml

100 g rat requires 8 mg which is equivalent to = 2 ml / 40 mg x 8 mg = 0.2 ml.

From the ampoule of dexamethasone, required dosages can be administered to animals of varying body weights as illustrated in table below:

Standard dose	Stock solution	Animals body weight (g)	Calculated dose in mg	Equivalent dose in ml
	80	100 g	8 mg	0.20 ml
dexamethasone, 80 mg/kg for Rats	mg/2ml	150 g	12 mg	0.30 ml
	=40 mg/ml	250 g	20 mg	0.5 ml

Single dose= 20 mg/kg/day (equivalent 0.5 ml of dexamethasone). Double dose= 40 mg/kg/day (equivalent 1 ml of dexamethasone). The average weight of animals = 250 g equivalent 0.25 kg (Erhirhie *et al.*, 2014)^[7].

2.3 Experimental Groups

First: Control group: Included five female rats injected by normal saline (Nacl 0.9%) intraperitoneally for seven days, the group sacrifice it in the end of experiment, for knowledge of retinol effect on implantation.

Second: First treated group: Included five female rats injected intraperitoneally by dose 20mg /kg/day of dexamethasone for twenty days, the group sacrifice it in the end of experiment.

Third: Second treated group: Included five female rats injected intraperitoneally by dose 40mg /kg/day of dexamethasone for twenty days, the group sacrifice it in the end of experiment.

2.4 Animals Sacrifice and Collection of Kidneys and Liver

The experimental animals of all groups were sacrifice after general anesthesia by combination of Ketamine: Xylazine (90mg/ kg: 10mg/ kg intraperitoneal), used ketamine 0.5 ml & xylazine 0.1 ml to each 250 g of body weight for anesthesia when sacrifice the female rat from the control & treated croups, after the anesthesia the females rats put in anatomical dish and made linear incision by scissors in abdominal region for extraction the kidneys and liver that contains for collected, by anatomical tools. Saved in containers contains 10% formalin (AITameemi, 2014)^[2].

2.5 Histological Preparations

Done samples saved after remove them from animals in containers contains 10% formalin (38%100ml formalin in 900ml tap water) and then done series of operations depending on the method described in (Suvarna *et al.*, 2018).

2.6 Staining and Mounting

Used the following special stains to colorize slides of different types of tissue:

2.6.1 Harris Hematoxylin Stain

A general base color used to color the nucleus in dark blue color.

2.6.2 Eosin Stain

A general acidic color used to color the cytoplasm in dark red color. (Suvarna *et al.*, 2018).

3. Results & Discussion

3.1 Macroscopic Observations

3.1.1 Macroscopic Features of Kidneys and Liver of Female Rats

The liver of female rats of control groups and treated groups with dexamethasone 20 and 40 mg/kg/day consider the largest organ that looks normal with four lobes: median, right lateral, left lateral and caudate. The kidneys of female rats of control groups are normal of convex shape and the main regions are renal cortex, renal pyramid and renal hilus moreover the color is normal pink to red while in treated groups with dexamethasone 20 and 40 mg/kg/day looks similar shape and regions but pale in color and largest size (Fig 1). This is caused by edema in organ tissue which effect on functional role of liver (detoxification) and lead to dysfunction (hepatotoxicity) such as histological effects of dexamethasone especially which providing by light microscope. The results have produced significant increase (p<0.05) in relative weight of kidney for all periods of intra peritoneal injection of concentration 20 and 40 mg/kg/day of dexamethasone as compared to control groups, this occurs due to edema in organ tissue which influences on functional

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role of kidney (filtration) and lead to dysfunction (nephrotoxicity) such as histological effects of dexamethasone especially which providing by light microscope. The study observed pale color of kidneys and large size that treated with dose 20 and 40mg/kg/day of dexamethasone as compared to control groups only because the basic excretory organ of our body is kidney, these results accepted with (Hall, 2016)^[8].



Fig 1: A-Photograph of maternal kidney of control group show normal color surfaces, the main regions are renal cortex (→), renal pyramid (→), Renal hius (→), B- represented treated dose 40 mg/kg/day of dexamethasone show pale color and largest size with similar regions

3.1.2 Histological Study of Kidney in Female Rats

The kidney of control group is normally enclosed with a renal capsule contained glomerulus, the capsule parital layer continues with the cuboidal epithelium of large enlongated cells that are called proximal convoluted tubules and also presence flat and small cell called distal convoluted tubule (Fig 2). The kidney of female rats treated with 20mg/kg/day dose of dexamethasone, have shown deformation of glomerulus, proximal convoluted tubule degeneration and hemorrhage (Fig 3). While the kidneys from the 40mg/kg/day dose of dexamethasone have shown severely affected, they are appeared enlargement of glomerulus, proximal convoluted tubules degeneration and hemorrhage (Fig 4). Dexamethasone reduced small bowel and kidney oxidative stress and histological alterations (Ozturk et al., 2006) ^[12]. Administration of the synthetic glucocorticoid resulted in a marked suppression of the maternal plasma estrone and estradiol-17 β concentrations in all animals and histological changes in the kidney (Chai et al., 2020)^[4]. Dexamethasone had no direct effect on potassium secretion by single microperfused tubules, but it caused a sharp increase urinary flow and sodium excretion, and secondarily enhanced urinary potassium excretion bv 50%. administration of dexamethasone led to fewer nephrons than controls (Baum, 2018)^[3] Offspring of rats administered dexamethasone 15-16 days had a 30% reduction in glomerular number compared with control, rats receiving dexamethasone 15-16 days had systolic blood pressures, the glomerular filtration rate reduced number of nephrons and hypertension (Ortiz et al., 2001) [11]. Dexamethasone appear to selectively ameliorate glomerular compared to tubular damage, based on histological findings. All three experimental treatments delayed but did not stop the progression of lethal renal injury as measured by kidney function tests and survival time (Rao et al., 2019)^[13].





Fig 2: Cross section of kidney of female rat control group show normal glomerulus (, proximal convoluted tubule (, distal tubule (), H&E, 100X



Fig 3: Cross section of kidney of female rat treated by dose 20 mg/kg/day of dexamethasone show deformation of glomerulus (→), proximal convoluted tubule degeneration(→), distal tubule (→), hemorrhage (→), H&E, 100X



Fig 4: Cross section of kidney of female rat treated by dose 40 mg/kg/day of dexamethasone show enlargement of glomerulus (→), proximal convoluted tubule degeneration (→), distal tubule, (→), hemorrhage(→), H&E, 100X

3.1.3 Histological Study of Female Rate Liver

Liver cells or hepatocytes are epithelial cells that are grouped in interconnected plates, polyhydral hepatic lobules consider structural and functional units of liver, each lobule has three to six portal areas at its periphery and central vein in its center, liver sinusoids presence between the hepatocytes (Fig 5). Sections from liver related to rats treated with dose 20mg/kg/day of dexamethasone has shows hepatocytes degeneration and hemorrhage (Fig 6). While the liver from the 40mg/kg/day dose of dexamethasone has shown severely affected, they are appeared hepatocyte degeneration and enlargement of nuclei (Fig 7). Dexamethasone possible to suppose that glucocorticoids or adrenal insufficiency due to glucocorticoids withdrawal inhibit the enzymatic activity of glycogen synthase and/or induce glycogen autophagy in bovine liver (Divari *et al.*, 2020) ^[6]. Ni *et al.*, (2020) ^[10] show developed dexamethasone loaded in free radicales such as reactive oxygen species (ROS). Dexamethasone treatment resulted in a significant elevation in liver function markers activities, lipid profile, and hematological alterations; also, a remarkable increase in hepatic lipid peroxidation marker whereas decreased antioxidant activities in rats and induced lipid peroxidation, antioxidant enzyme activities, liver function markers and lipid profile, and hematological alterations (Hasona and Morsi, 2019) ^[9]. Dexamethasoneinduced histopathological changes in rat liver tissue that effect in rats against oxidative stress, hyperlipidemia and hematological alterations (Abou-Seif *et al.*, 2019)^[1].



Fig 5: Cross section of liver of female rat control group show central vein (>>>, sinusoid (>>>), hepatocyte (>>>), H&E, 400X



Fig 6: Cross section of liver of female rat treated by dose 20 mg/kg/day of dexamethasone show, central vein (, sinusoid (, hepatocytes degeneration (, hemorrhage), H&E, 400X



Fig 7: Cross section of liver of female rat treated by dose 40mg/kg/day of dexamethasone show, central vein (→), sinusoid (→), hepatocytes degeneration (→), enlargement of nuclei (→), H&E, 400X

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