PHYSIOLOGICAL AND HISTOLOGICAL STUDIES OF THE EFFECT OF SILDENAFIL ON ADENINE-INDUCED NEPHROTOXICITY IN THE SPRAGUE–DAWLEY RAT

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ABSTRACT

This study was conducted to demonstrate the effect of sildenafil on some biochemical parameters of kidney function assessment, body and kidney weight effects were studied, Nine to ten weeks old male Sprague–Dawley rats weighing 250–300 g mean ± SD (287.3±1.23) were housed and used in this study, 1 week after the adaptation period, 48 rats were divided into six groups, each group contains 8 mice (n = 48) with different treatment for 5 consecutive weeks as the following: one group (control group) continues to receive the same diet and did not receive any treatment until the end of experiment. Second group (induced adenine) which treated by powder adenine diet (0.25% w/w in feed), third and fourth group which given normal food and oral sildenafil (1 and 2 mg/kg) per single body weight, respectively. Body weight of mice treated with three adenine have (201.5 ±1.03) is very significant different from the control have (287.3±1.23). The sildenafil taking with the supplement with adenine (Sildenafil) should not cause any obvious symptoms, so, the dose is based on the weight loss caused by adenine. Other part of experimental, the results was found Adenine induces Nephrotoxicity have changes the gross morphology of the kidney and induces renal fibrosis and damage tissue, necrobiotic tubular cells with interstitial hemorrhage, In conclusion: the sildenafil administration suggesting a beneficial effect and its possible to use in the chronic kidney disease.

Keywords: sildenafil, chronic kidney disease, adenine

Introduction

Penile erection is caused by sexual stimulation and caused corpus cavernosum with vascular smooth muscles relaxed in the penis, a second messenger of nitric oxide (NO) was play an important role in relaxing corporal smooth muscles (Francis, & Corbin, (2005)). Sildenafil citrate is a erectile dysfunction pills was used to improve the penis response to sex Stimulating by selective inhibition of phospholipids V-type enzyme and accelerates degradation of cGMP (Boolell et al., 1996).

Chronic kidney disease is a disease in which the kidneys are damaged and cannot filter blood as expected, therefore, excess fluids and waste products remain in the body blood circulation in the body some time causing main problems which include heart disease and stroke, other complications were recorded as, high blood pressure, anemia and bone disease (Ketteler et al., 2018), the diagnosis of this disease is passed on estimated glomerular filtration rate (eGFR) by blood test, as well as measured albumin through urine test (Nidhi et al., 2019).

CKD is associated with a mortality, morbidity, especially deaths due to cardiovascular failure, and progression-end-stage kidney disease (ESRD) causes huge social costs (Vanholder et al., 2005). Chronic kidney disease is also known to cause severe impairment of the gonads function of both sexes (Palmer & Clegg, 2017).

To date, there was no drug development for the treatment of chronic kidney disease, the treatments was used to slow its progression are limited to normalizing insulin, blood pressure and glucose (Obi et al., 2016). Therefore, there is an urgent need to develop new treatments especially from drugs that were previously known for other purposes to slow down the progression and deterioration of kidneys' job.

There have been several studies in which some plant extracts have been used in a treatment chronic renal failure e.g. gum Arabic, Aerva lanata, Ocimum basilicum and punica granatum (Shirwaikar et al., 2004; Ali et al., 2010; Singh et al., 2011 and Zaveri et al., 2011).

The animal model of CKD helps to understand the potential Biochemical, physiological, and histological processes involved in CKD and the development and testing of potential therapeutic agents (Ali et al., 2018).

Sildenafil has been shown to be effective conducting clinical research on patients with erectile dysfunction Organic, mental or mixed disorder reasons. However, the effectiveness of the drug that used through self-assessment need conducting patient questionnaires and it is still tough (Wang et al., 2007).

In this study, our study was demonstrated the effect of sildenafil on some biochemical parameters of liver and kidney function assessment in wistar Kyoto rats,
**Materials and Methods**

Nine to ten weeks old male Sprague–Dawley rats (weighing 300–320 g) mean ± SD (287.3±1.23) were housed in a private room at 20 ± 2 temperature, 60% relative humidity and twelve hour light–dark cycle was calculated as day light at 6:00 PM and dark at 18:00 PM, standard pellet chow diet and tape water was provided according to experimental of (Ali et al., 2018). This experimental study was performed in department of physiology, Al-Qadyssiah University of veterinary medicine college, Iraq.

Ethical guidelines and protocol was approved by the ethics committee in department of veterinary medicine, Veterinary Medicine College.

One week after the adaptation period, 48 mice were divided into six groups, each group contains 8 mice (n = 48) with different treatment for 5 consecutive weeks as the following; one group (control group) continues to receive the same diet and did not receive any treatment until the end of experiment. Second group (induced adenine) which treated by powder adenine diet (0.25% w/w in feed), third and fourth group which given normal food and oral sildenafil (1 and 2 mg/kg) per single body weight, respectively. The five and six group was treated as third and fourth group but were also given adenine like second group figure 1.

![Fig. 1: Schematic diagram for experimental design](image)

Table 4-4 : Effect of adenine on body and kidney weight in male rat. (Mean ± SE)  (n=6)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Body weight Mean±SE</th>
<th>Kidney weight Mean±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>N=8</td>
<td>N=8</td>
</tr>
<tr>
<td>Control</td>
<td>287.3±1.23</td>
<td>1.13±0.05</td>
</tr>
<tr>
<td>Adenine</td>
<td>201.5±1.03</td>
<td>1.96±0.11</td>
</tr>
</tbody>
</table>

Capital letters denote differences between groups, (P<0.05).

**Results and Discussion**

Adenine is a chemotherapy agent that associated with nephrotoxicity or acute kidney injury, Several drugs have been studied for the possible improvement of the nephrotoxicity of adenine induced renal failure, including sildenafil and gemfibrozil (Lee et al., 2009 and Kabel et al., 2013). In this work, we examined the effect and influence of sildenafil on the prevention of adenine nephrotoxicity or the therapeutic effect of sildenafil on adenine which induce nephrotoxicity.

Adenine is added at the end of the end period of experimental design (35 days). It caused a significant decrease in the body weight of the treated male rat (Table 1). Weight loss after adenine induction treatment may be attributed to damage to the renal tubules, and subsequent loss of renal tubular cells to absorb water, leading to dehydration and weight loss (Nemmar et al., 2016). The figure 2 showed weight loss of male rat after administration of adenine.
Body weight of mice treated with three adenine have (201.5 ±1.03) is very significant different from the control have (287.3±1.23). The sildenafil taking with the supplement with adenine (Sildenafil) should not cause any obvious symptoms, so, the dose is based on the weight loss caused by adenine.

Our research has proven the therapeutic properties of sildenafil, which can be used instead to treat kidney disease. Investigations in our results have also examined whether the herbal extracts can improve impaired kidney and cardiovascular function common in diabetes (Mohamed & Faddah, 2007). The results showed that although some extracts, such as Hypoxis hemerocallideae cord, had effects on lowering blood sugar, they could have harmful effects on kidney function (Ogunibeju et al., 2016).

The activity and expression of Phosphodiesterase 5 can be found in various tissues the most of tissue are kidneys (Osterloh, 2004) Sildenafil is known to significantly reduce oxidative stress in the brains of mice and kidneys with acute kidney injury and diabetic nephropathy caused by cisplatin injury or ischemia.

In the table 2, our result found significantly different (P< 0.05) between control and adenine induced nephrotoxicity in wistar rats as 31.5± 2.12 Mg/dl and 88.36± 2.01 Mg/dl in the urea, respectively, on the other hand, 0.44± 0.02 Mg/dl and 2.37± 0.315 Mg/dl in the creatinine serum levels figure 3, this results was agreed with (Rahman et al., 2018) who was found Adenine induced nephrotoxicity was obscurely elevated creatinine level which impaired kidney function, and didn’t induce anemia, whereas, fifty microgram per kilogram of adenine daily for twenty eight days were showed severe kidney disease (serum creatinine levels 1.9 ± 0.10 mg/dL).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Groups</th>
<th>Urea Mg/dl mean ± SE</th>
<th>Creatinine Mg/dl mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n=6</td>
<td>n=6</td>
</tr>
<tr>
<td>Control</td>
<td>B</td>
<td>31.5 ± 2.12</td>
<td>0.44 ± 0.02</td>
</tr>
<tr>
<td>Adenine</td>
<td>A</td>
<td>88.36 ± 2.01</td>
<td>2.37 ± 0.315</td>
</tr>
<tr>
<td>Statistical analysis (LSD)</td>
<td>22.8</td>
<td>0.86</td>
<td></td>
</tr>
</tbody>
</table>

The Capital letters in the tables showed differences between the groups, (P≤0.05).

The result was not consisted with (Rahman et al., 2018) who was found an adenine at twenty five milligram per kilogram wasn’t affect the body weight during the routes of administration as compared with vehicle control group.

In rats, Urea and creatinine level were changed during after adenine administration , In contrast, sildenafil at 1 and 2 milligram per kilogram body weight caused a significant reduction in Urea and creatinine level as (39.15±1.87) and (40.87±2.13) compared with Nephrotoxicity-treated rats (129.23 ± 10.06)

Other part of experimental, the results was found Adenine induces Nephrotoxicity have changes the gross anatomy of both kidney and induces renal fibrosis and damage tissue, necrotibiotubular cells with Interstitial hemorrhage figure 3, enlarged and hypercellular with endothelial and mesangial proliferation with infiltration by few neutrophils. capillary wall thickening, focal splitting of capillary wall noted figure 4.
Fig. 3: Showed a Necrosis with interstitial hemorrhage of the renal tubules of wistar rats. (Hematoxylin–eosin stain, magnification x20)

Fig. 4: Enlarged and hypercellular with endothelial and mesangial proliferation.

After sildenafil administration group 5 and 6 our results found no capillary wall thickening is seen, and no tubular atrophy. Blood vessels appear and no significant tubuointerstitial changes figure 5

Fig. 5: Renal tissue with sildenafil administration

In conclusion: These results have concluded that oral doses with adenine at is suitable to induce nephrotoxicity in rats, otherwise sildenafil administration suggesting a beneficial effect and its possible to use in the chronic kidney disease.

References


