



SCIENTIFIC EVENTS GATE

The International Innovations Journal of Applied Science

Journal homepage: <https://ijias.eventsgate.org/ijias>

The effect of pentoxifylline on kidney tissue and some biochemical parameters in female albino rats

Reem Saud Abdel^{1*}, Assistant Professor Mona Salah Rashid²^{1,2} Department of Life Sciences, College of Science, Tikrit University, Iraq.

ARTICLE INFO

Article history:

Received 18 Nov. 2023

Revised 2 Feb. 2024,

Accepted 20 Feb. 2024,

Available online 15 Mar. 2024

Keywords:

Kidney

Pentoxifylline

Urea

Creatinine

Histology

ABSTRACT

This study aims to determine the effect of pentoxifylline on the histological and biochemical structure of the kidneys in female white rats. Two groups of rats were given pentoxifylline, 52.9 mg/kg and 105 mg/kg, respectively, in addition to a control group that was given Normal Saline solution, and each of these groups was divided into and used white rats, and were given orally for 20 consecutive days. The results showed some structural effects on kidney tissue, as 52.9 mg/kg in the cortex appeared in the second group, shedding of the lining of the urinary tubules with the presence of Cast, necrosis of renal cell and the spread of inflammatory cells. The study also showed the presence of fibroblasts in the pulp with shedding of the urinary lining with necrosis of the urinary cells. The third group (105 mg/kg) was shedding of the lining of the urinary tubules, necrosis of the urinary tubule cells with the presence of fibroblast cells, with the creatinine and urea levels remaining within the levels.

1. Introduction

Pentoxifylline is a xanthine derivative (1-5-oxohexyl-3-7-dimethylxanthine) with structural similarities to caffeine and theophylline, Pentoxifylline is created by combining hexanone with theobromine, a cocoa bean alkaloid. Pentoxifylline is a non-selective PDEI (phosphodiesterase inhibitor). It promotes protein kinase A (PKA) while inhibiting leukotriene and tumor necrosis factor (TNF) Furthermore, pentoxifylline is thought to be an adenosine 2 receptor (A2R) antagonist Pentoxifylline inhibits innate immune activation and inflammatory cytokine release (Al-Kuraishy et al, 2019).

Pentoxifylline has been in clinical use since 1972, and the Food and Drug Administration (FDA) approved it I 1984 (Frampton JE . 1995)Pentoxifylline is used to treat peripheral vascular disease, claudication induced by arterial disease, and chronic leg ulcers.

Wikipedia (2014) Pentoxifylline lowers blood viscosity by decreasing fibrinogen levels, improves red blood cell flexibility, and inhibits platelet aggregation (Chandan N . et al 2018) Reduces free radical production and prevents neutrophil activation and adhesion Furthermore, by inhibiting connective tissue growth factor (TGF), pentoxifylline reduces fibrotic alterations (Rasyid A. et al 2018) Pentoxifylline may be useful in the treatment of sarcoidosis by suppressing tumor necrosis factor-induced granuloma development it is also useful in the treatment of alcoholic hepatitis and diabetic neuropathy (Delanian S et al 2005)Several studies have also suggested that pentoxifylline may be useful in the treatment of erectile dysfunction (Whitfield K . et al 2006) hearing and Peyronie's disease(Law YX . et al. 2022).

2. Methodology

2.1 Preparation of animals

For this investigation, thirty mature female albino rats (Sprague-Dawley) were employed. They were purchased from the Tikrit University College of Veterinary Medicine's animal house. They weighed 167 grams on average and were in good health. The rats were

* Corresponding author

E-mail address: reem.s.abd70@gmail.comThis work is licensed under a [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/)

4.0 International License.



housed in the animal house and distributed at random. Five animals were assigned to each group at random, and they were housed in cages with sawdust floors. The cages were cleaned and sterilized, and the sawdust was replenished regularly. The animals were treated to consistent laboratory conditions in terms of ventilation, temperature (23–27 degrees Celsius), and feeding.

It was also considered to keep them away from noise and not to place them in congested groups inside the cage for a week prior to the experiment to assure their safety from infections and to provide them enough time to adapt.

2.2 Preparing the medicine

Pentoxifylline tablets were purchased from local pharmacies. The tablets were crushed without any further purification, and doses were determined according to the formula

$$\text{Rat dose} = \text{human dose mg/kg} \div 0.162$$

$$\text{Rat dose} = (400/60) \div 0.162$$

$$\text{Rat dose} = 52.9 \text{ mg/kg}$$

It is dissolved in normal saline solution and given to animals orally in the specified doses.

The rats were divided into three groups: a 5-rat control group, a 52.9 mg/kg treatment dosage group, and a 105 mg/kg overdose group. The

3. Results and discussion

The effect of the drug on kidney tissue:

3.1 Control group:

- cortex

Histological examination of the studied sections showed the normal shape of the renal glomeruli, and the regularity of convoluted proximal and distal urinary tubules, which are lined with simple cuboidal tissue cells. (Image 1).

gavage dosage was used to provide the medication to animals orally.

2.3 Tissue preparation :

was carried out in accordance with the procedure given (Ibrahim A. et al 2019) In brief, all sections were fixed with 10% formalin and dehydrated twice with 50, 70, 90, 96%, and 100% ethanol for 30 minutes each. Following that, the pieces were xylol-cleared, infiltrated, and embedded in paraffin wax. The tissues were subsequently sectioned and stained with hematoxylin and eosin using a rotary microtome (Microtec Rotary Microtome Cut4060, Germany). Finally, the slides were made by DPX, examined with an optical microscope (OBL-137C832 400x -100x digital microscope kit with 3W LED (transmitted light), 5MP plate camera, WLAN, USB 2.0, HDMI, SD, CMOS 1/2 size, 2.5 inches including CMOUNT ADAPTER), and processed with Photoshop (Adobe Photoshop CC 2021, USA).

Measurement of urea and creatinine

- Urea: Estimate the concentration of urea in the serum using only a ready-made analysis kit (Patton and Crouch, 1077).

-Creatinine: The concentration of creatinine in the serum was estimated using a ready-made analysis kit according to Tiez, 1987.

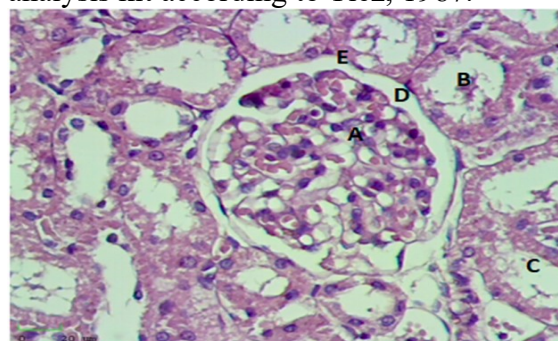


Image (1) of the kidney of a female rat (control group) shows: A- The renal glomerulus is spherical in shape. B- Proximal convoluted tubule. C- Distal convoluted tubule H&E 400X.

- Medulla

It shows the normal appearance of the pulp, which contains renal tubules lined with cuboidal epithelial cells and containing the renal filtrate.

Lymphocytes are also shown Image (2).

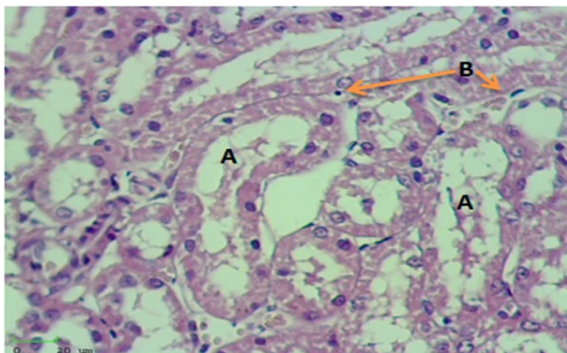


Image (2) The kidney of a female rat (control group) showing: A- Renal tubules lined with cuboidal epithelial cells and containing the renal filtrate. B- Lymphocyte. H&E400X

Therapeutic dose for adult rats (cortex)

Histological sections of kidney medulla tissue showed the presence of sloughing of the lining of the urinary tubules with necrosis of the urinary tubule cells and the proliferation of fibroblast cells Image (3).

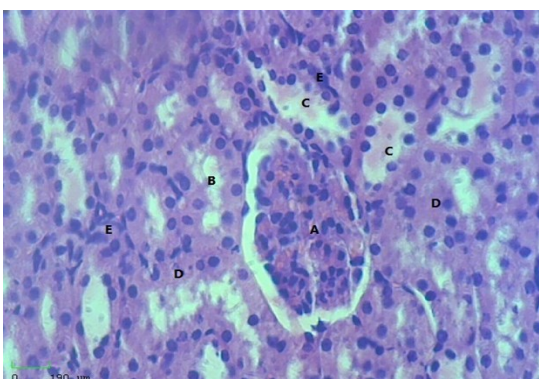


Image (3). Glomerular disintegration (A), sloughing of the lining of the urinary tubules (B), urinary casts (C), hepatic cell necrosis (D) Inflammatory cells (E) H&E 400X,

3.2 Therapeutic dose medulla

Histological sections of kidney medulla tissue showed the presence of sloughing of the lining of the urinary tubules with necrosis of the urinary tubule cells and the proliferation of fibroblast cells.

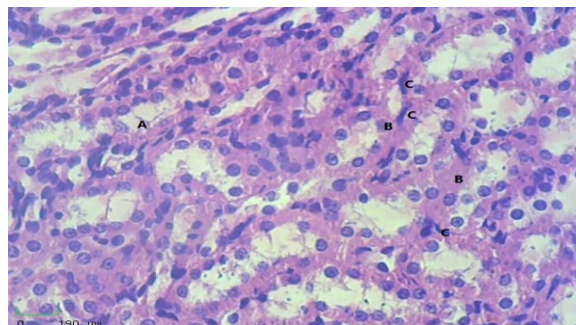


Image (4). Shedding of urinary tubule cells (A), necrosis of urinary tubule cells (B), and proliferation of fibroblast cells (C). H&E 400X.

3.3 Overdose for rats (cortex):

Histological sections of kidney cortex tissue showed hyperplasia in the glomerulus with narrowing of Bowman's space and the disappearance of the lumen in the urinary tubules, hemorrhage, and the spread of inflammatory cells (Image 4).

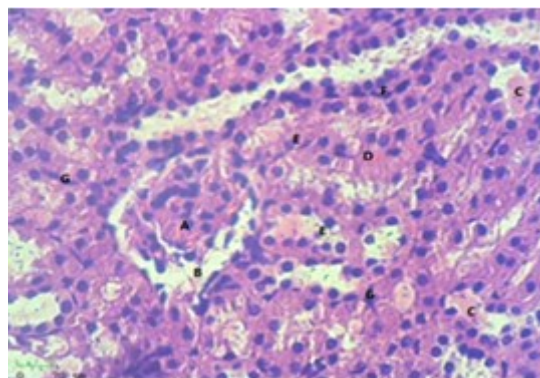


Image (5) Shedding of urinary tubule cells (A), necrosis of urinary tubule cells (B), and proliferation of fibroblast cells (C).bleeding(D) H&E 400X.

3.4 Overdose for rats (Medulla):

Histological sections of the kidney medulla in this group showed the disappearance of the lumen of the urinary tubules, in addition to the presence of cell nuclei at the tip of the cell and empty cytoplasm. The presence of fibroblasts and hemorrhage was also observed (Image 4).

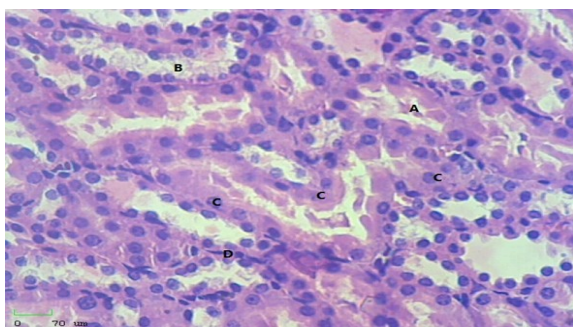


Image (6) shows: glomerular hyperplasia (A), narrowing of Bowman's aperture (B), disappearance of the lumen of the urinary tubules (C), sloughing of the lining in the urinary tubules (D), hemorrhage (E), inflammatory cells (G) H&E 400X .

The study's findings revealed the development of rupture in certain renal cells, as well as degeneration and shedding of some of them inside the renal tubule lumen. There was also atrophy and lobulation of the renal glomeruli, as well as a rupture of Bowman's capsule for certain renal glomeruli, thickening of the Bowman's capsule basement membrane, and the presence of phagocytic and lymphatic cells with blood hemorrhage. This is similar to the findings of (Al-Shatti ,1992)who studied kidneys impacted by acute inflammation caused by the use of certain medicines. He demonstrated the existence of mononuclear inflammatory cells in the interstitium and that these cells were more abundant in the presence of larger doses of various hazardous chemicals. The study's findings revealed the development of rupture in certain renal cells, as well as degeneration and shedding of some of them inside the renal tubule lumen. There was also atrophy and lobulation of the renal glomeruli, as well as a rupture of Bowman's capsule for certain renal glomeruli, thickening of the Bowman's capsule basement membrane, and the presence of phagocytic and lymphatic cells with blood hemorrhage. This is similar to the findings of (Al-Shatti 1992) studied kidneys impacted by acute inflammation caused by the use of certain medicines. kidneys impacted by acute inflammation caused by the use of certain medicines.

He demonstrated the existence of mononuclear inflammatory cells in the interstitium and that these cells were more abundant in the presence of larger doses of the Chemicals is triggered

the irritation. Urinary molds were discovered as well cast.

It is also consistent with a research on renal failure patients done by Annamaraju and Baradhi in (2022). When a dialysis patient requires this medication, he begins with a low dose and progressively raises it while monitoring the patient for indications of toxicity and measuring the drug's concentrations in the mother's blood plasma and its metabolites. The medicine became hazardous after roughly six days of ingesting two-thirds of the average prescribed dose for adults.

According to Krishna and his group (2004), the causes of renal tubule necrosis as a result of poisoning are the death of the epithelial cells lining the renal tubules due to a lack of oxygen, as their metabolic effectiveness is dependent on the oxygen they receive through the blood vessels, and that any damage to the blood vessels caused by necrosis or narrowing of the arterioles leads to a disruption in blood flow. Toxic compounds cause enlargement of the renal tubules as a result of renal cell hypertrophy caused by the toxicity of the toxic substances.

According to Bicalho and his colleagues (2015), the pharmaceuticals that cause the most kidney damage are antibiotics and blood pressure medications, and these damages include renal tubule necrosis and interstitial tissue destruction. Nitro and amino chemicals are nephrotoxic, causing increased enzyme activity and degenerative alterations in the kidneys.

The study showed that there were no statistically significant differences in the levels of urea and creatinine between the two groups taking the drug at its two concentrations, the therapeutic dose and the double dose, and between the control group. These results are consistent with Aggelopoulou E, et al (2018). I disagreed with Ednell and his group (2011) who found an increase in the levels of both urea and creatinine in a woman poisoned with pentoxifylline who took 50 suicide pills, or about 20 grams. This result may be due to the large amount you consumed.

I have found sources that indicate the role of this drug in lowering creatinine levels. My First Aswadi and His Collection (2011)
Those who suffer from creatinine deficiency are advised not to take this medication. Annamaraju F et al. (2022).

Table 1: Urea and creatinine levels

Groups	Urea (mg/dL) (mean±s.d.)	Creatinine (mg/dl) (mean±s.d.)
control	50.66 ±11.52 a	1.26±0.32 A
Therapeutic dose	34.2±5.07 Ab	0.86 ± 0.13 Ab
overdose	46.62±16.40 Ab	1.15 ± 0.40 Ab

* Different letters indicate the presence of significant differences between the means of the coefficients at a significant level of $P \leq 0.05$

4. Conclusions

The study showed damage to kidney tissue The results showed some structural effects on kidney tissue, as the second group showed 52.9 mg/kg in the cortex, shedding of the lining of the urinary tubules with the presence of Cast, necrosis of renal cells and proliferation of inflammatory cells. The study also showed the presence of fibroblasts in the pulp with shedding of the urinary lining with necrosis in Urinary cells. The third group (105 mg/kg) was sloughing of the lining of the urinary tubules, necrosis of the urinary tubule cells with the presence of fibroblast cells, with the levels of creatinine and urea remaining within normal levels in all groups. that increased with increasing doses, while urea and creatinine levels remained within normal limits The study also recommends conducting more research on the drug's effect on albino rats at the molecular level, in addition to the drug's effect on other organs.

References :

Aggelopoulou E, Tzortzis S, Tsiourantani F, Agrios I, Lazaridis K. Atrial Fibrillation and Shock: Unmasking Theophylline Toxicity. *Med Princ Pract.* 2018;27(4):387-391. doi: 10.1159/000490145. Epub 2018 Jun 22. PMID: 29936503; PMCID: PMC6170900.

Al-Kuraishy, H. M., Al-Gareeb, A. I., & Hussien, N. R. (2019). Synergistic effect of berberine and

pentoxifylline in attenuation of acute kidney injury. *International journal of critical illness and injury science*, 9(2).

Al-Shatti, Muhammad Iyad. (1992). "Foundations of Pathology." Dar Al-Bashaer for Printing, Publishing and Distribution, 231- 612 - Damascus, p. 239

Annamaraju P, Baradhi KM. Pentoxifylline. [Updated 2022 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559096>.

Asvadi I, Hajipour B, Asvadi A, Asl NA, Roshangar L, Khodadadi A. Protective effect of pentoxifylline in renal toxicity after methotrexate administration. *Eur Rev Med Pharmacol Sci.* 2011 Sep;15(9):1003-9.

Bicalho, M. D., Soares, D. B., Botoni, F. A., Reis, A. M. M., & Martins, M. A. P. (2015). Drug-induced nephrotoxicity and dose adjustment recommendations: agreement among four drug information sources. *International journal of environmental research and public health*, 12(9), 11227-11240.

Chandan, N., Boen, M., Lake, E. P., & Aronson, I. (2018). Successful treatment of two individual cases of generalized granuloma annulare with amoxicillin/clavulanic acid and a combination of doxycycline and pentoxifylline. *Dermatology online journal*, 24(8).ISO 690

Delanian, S., Porcher, R., Rudant, J., & Lefaix, J. L. (2005). Kinetics of response to long-term treatment combining pentoxifylline and tocopherol in patients with superficial radiation-induced fibrosis. *Journal of clinical oncology*, 23(34), 8570-8579.

Edenl G, et al. Successful treatment of life-threatening pentoxifylline intoxication by high-flux hemodialysis. *Clinical Nephrology* 75: 171-173, No. 2, Feb 2011. Available from: URL: <http://dx.doi.org/10.2379/cn106385> - Germany

- Frampton, J. E., & Brogden, R. N. (1995). Pentoxifylline (oxpentifylline) A review of its therapeutic efficacy in the management of peripheral vascular and cerebrovascular disorders. *Drugs & Aging*, 7, 480-503.
- Hammad, M. A. M., Soltanzadeh Zarandi, S., Barham, D. W., & Yafi, F. A. (2022). Update on Treatment Options for Stuttering Priapism. *Current Sexual Health Reports*, 14(4), 140-149.
- Ibrahim, A., Gazzard, L., Alharbi, M., Rompré-Brodeur, A., Aube, M., & Carrier, S. (2019). Evaluation of oral pentoxifylline, colchicine, and penile traction for the management of Peyronie's disease. *Sexual Medicine*, 7(4), 459-463.
- Krishna, V. (2004). Text book of pathology, printed in India by offset himayatnager.
- Law, Y. X. T., Tai, B. C., Tan, Y. Q., Lata, R. N. M., & Lee, K. C. J. (2020). A small group randomized double-blind placebo-controlled study to evaluate the efficacy of daily pentoxifylline in the management of patients with erectile dysfunction with suboptimal treatment response to sildenafil. *Sexual Medicine*, 8(1), 14-20.
- Patton, C. J. and Crouch, S. R. (1977). Spectrophotometric and kinetics investigation of berthelot reaction for the determination of ammonia. *Anal. Chem.*, 49(3):464-4-96.
- Rasyid, A., Harris, S., Nurhayati, E., & Prihartono, J. (2018). Pentoxifylline in acute ischemic stroke patients with blood hyperviscosity. *International Journal of Applied Pharmaceutics*, 10(Special Issue 1), 307-310. ISO 690
- Tietz, N. M. (1987). Textbook of clinical chemistry. 3 ed C. Burtis, E. R. Ashwood, W. B. Saunders. PP: 919-861, 1245-1250.
- Whitfield, K., Rambaldi, A., Wetterslev, J., & Gluud, C. (2009). Pentoxifylline for alcoholic hepatitis. *Cochrane database of systematic reviews*, (4).