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Effect of Albendazole on microscopic anatomy of Kidney in Rabbits

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Albendazole is widely used anthelmintic drug against many parasitic infestations. A case of acute renal failure is seen in human due to albendazole treatment. The present study was designed to investigate the renal histological changes in rabbits after exposure to albendazole. For this purpose, 15 rabbits were randomly divided into 3 groups (n=5). One control group was untreated while other two experimental groups were treated with daily dose of 10 and 50mg/kg albendazole, for 10 days. Animal from each group was slaughtered on alternate days and kidney tissue sections were fixed in formalin and processed for histopathological studies. Observation of Histopathological sections of kidney from animal groups treated with albendazole revealed glomerular changes including shrinkage, atrophy and nephritis; cellular changes including tubular epithelium disruption, vacuolation, pyknosis, apoptosis and necrosis of interstitial cells; and other changes including narrowing of tubular lumen, fibrosis and hemorrhages. These changes were more severe in group treated with higher dose of 50mg/kg albendazole than those of other group (10mg/kg). With the passage of time, these changes went on increasing. It is concluded that albendazole cause severe damage to kidney structure, so should be prescribed wisely in kidney patients.

Keywords: Albendazole, histopathology, kidney,

INTRODUCTION

The kidneys are roughly bean-shaped (with few exceptions), paired organs, located in the abdominal cavity and play regulatory roles in vertebrate animals. This filtration machinery of the body participates in the whole-body homeostasis by (i) regulating acid-base balance, electrolyte concentrations, and extracellular fluid volume (ii) regulating blood pressure (iii) reabsorption and (iv) secretion of wastes. These physiological activities are taken place in basic unit of kidney called nephron. Formation of urine is also the function of kidney (Li *et al*., 2012). Each kidney has 3 morphological parts; pelvis, medulla and cortex. Pelvis is wide portion of ureter in the kidney which collect urine from collecting tubules. Medulla is middle portion of kidney, seen as striated region. Outer to medulla is cortex, in which histological units, nephrons reside. Nephron is composed of bowman's capsule, proximal tubule, loop of Henle and distal tubule which opens into collecting duct (Frandson, Wilke, & Fails, 2009) This anatomical and histological structure/features make kidneys perfect for the functioning described earlier.

Albendazole drug is most widely used anthelmintic in animals and humans as well. This is also part of deworming protocols and prescribed for many parasitic infestations. Albendazole is a drug of choice against hydated

cyst (Shams-Ul-Bari *et al.*, 2011), echinococcosis, and neurocysticercosis. It is equally effective against ascariasis but not against trichuriasis (Legesse, Erko, & Medhin, 2004). Albendazole has also significant role against soil transmitted helminths and improves nutritional status in children (Sungkar, Ridwan, & Kusumowidagdo, 2017). It also has synergistic effect with rifampicin against filariasis (Turner *et al*., 2017). Drug has also been found effective against giardiasis in children (Yereli *et al*., 2004)

Although, Albendazole is very useful drug but due to poor absorption from digestive tract i.e. there is low bioavailability of albendazole, make albendazole unsuitable for systemic parasites (Torrado *et al*.,1997). So, it can also not be a good option for brain cysticercosis when used alone (Garcia et al., 2016) Albendazole is known to cause teratogenic effects in cattle and sheep. This is avoided in pregnant females, as in case of dogs it can cause cleft palate and reduced weight of litter. In birds, albendazole can affect performance and egg hatchability. Albendazole is contra-indicated in animals suffering from hepatic disorders. This drug belongs to benzimidazole group which are associated with toxic effects to liver, testicles and gastrointestinal tract (Siroka & Svobodova, 2013). Other adverse effects mainly include Epigastric pain, Diarrhea, Headache, Nausea, Abdominal pain, Dizziness, Vomiting, Lethargy, and Constipation (Horton, 2000). A case of acute kidney failure in human has been seen when albendazole was used against Trichinella (Batzlaff, Pupaibool, & Sohail, 2014). This depicts the toxic effect of albendazole on kidney.

Kidneys are among the most sensitive body organs in their histopathological and functional responses. A vast research has been conducted on parasitic use of albendazole, its toxicity and its effect on different organs of body. As per our best knowledge, little is explained about the histopathological effects of albendazole on the kidney, so this study has been planned to check this effect of albendazole on kidney of rabbit.

MATERIALS AND METHODS

Fifteen adult rabbits were purchased from local market. The animals were kept in the animal house of Zoology department, Govt. Post Graduate Islamia College for Women, Cooper Road, Lahore, Pakistan. They were provided with standard feed and water *ad libitum*. Cage floor was covered with wood shaving litter. The rabbits were divided into 3 groups and were acclimatized with comfortable environment. One was control group (untreated), and groups 1 and 2 were treated with 10 and 50mg/kg body weight of albendazole (Zentel® GlaxoSmithKline), respectively for 10 days. At days 2, 4, 6 ,8 and 10 of trial, animals were slaughtered according to (ethical rule or committee) and kidney tissue samples were taken in to 10% formalin for histological studies. Histological processes were carried out after fixation of tissues (Bancroft & Stevens, 2008). Micrometer was used for histological effects.

RESULTS

Control Group

Kidney did not show any histopathological changes in the kidney at the 2nd, 4th, 6th, 8thand 10th day of the experiment. The kidney showed no evidence of glomerular, tubular or interstitial damage. There was normal morphology of Bowman's capsule and glomerulus was intact. Epithelial cell and lining of renal tubules had no proliferation (Figure 1).

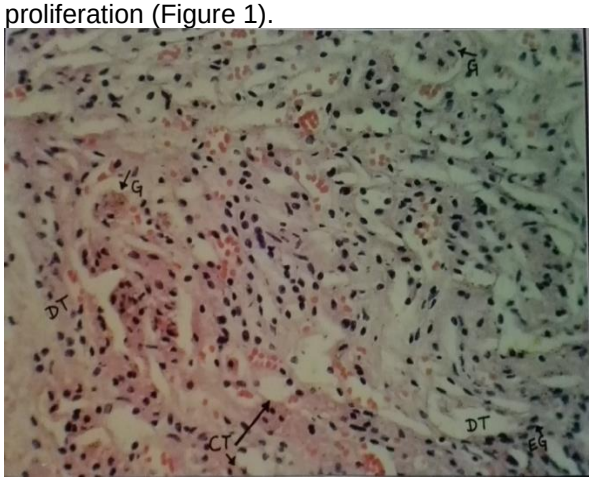

Figure 1: T.S. of kidney of control group (H&E 400X).
Glomeruli or Bowman's capsule (G), Distal tubules (DT), Convoluted tubules (CT), Hematopoietic tissues (HT), Epithelial cells lining renal tubules (EG).

Experimental group 1

Mild histopathologiacal changes were caused by the albendazole dose in the kidney day by day. There was slight infiltration, pyknosis, intertubular hemorrhages, slight narrowing acute tubular dilation and inter tubular dilation (Table 1).

Table 1: Histological changes in T.S. of kidney of animals (experimental group 1 and 2)

HISTOLOGICAL CHANGES IN KIDNEY	Day 2	Day 4	Day 6	Day 8	Day 10
Narrowing of tubular lumen	✓	✓	✓	✓	
Tubular epithelium disruption	✓	✓	✓	✓	✓
Vacuolation		✓	✓		
Fibrosis	✓	✓	✓	✓	✓
Hemorrhages		✓	✓	✓	✓
Glomerular atrophy			✓	✓	✓
Glomerular shrinkage			✓	✓	✓
Glomerular nephritis			✓	✓	✓
Pyknosis			✓	✓	✓
Apoptosis		✓	✓	✓	✓
Necrosis			✓	✓	✓

While in the later days of treatment, there was observed narrowing of the tubular lumen due to hypertrophy of endothelial cells, there were focal areas of vacuolation in the endothelial cells. The pyknotic nuclei, Intertubular infiltration of the neutrophils, swelling and proliferation of the endothelial cell living the glomerulus capillaries were seen. The thickening of the glomerular basement membrane (Crescent formation) and slight proliferation of the mesangial cells was evident. The glomeruli were appearing to be shrunken. The diffused glomerulonephritis and acute tubular necrosis were also observed (Figure 2a & 2b).

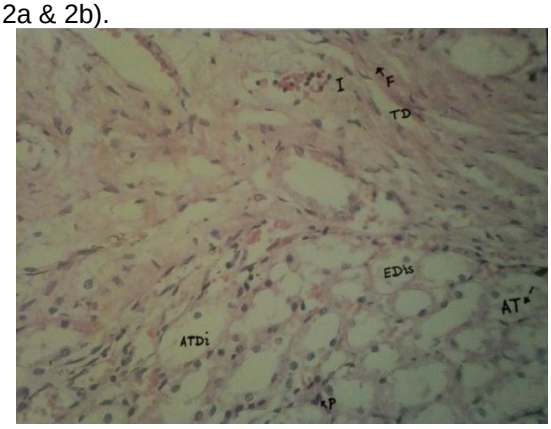

Figure 2a: T.S. of kidney of experimental group 1 (H&E 400X).
Slight infiltration (I), Slight pyknosis (P), Intertubular hemorrhage (H), Apoptosis (A), Slight narrowing of tubular lumen (NwL), Acute tubular dilation (ATDi), Intertubular dilation (TD), fibrosis (F), Atrophy of tubules (At), Narrowing of tubular lumen with proliferation of endothelial cells, Renal tubule epithelium showing disruption (EDis), Acute tubular necrosis (AN).

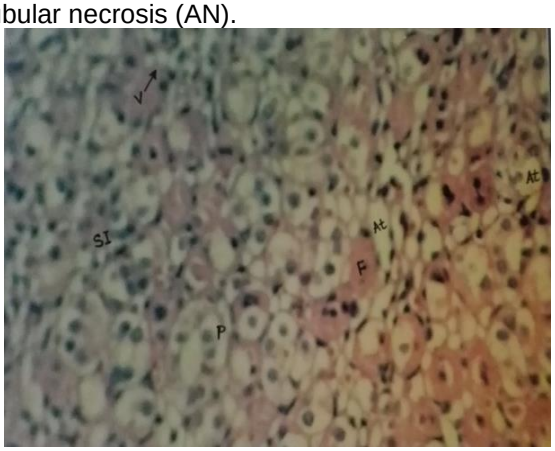

Figure 2 b: T.S. of kidney of experimental group 1 (H&E 400X).
Severe infiltration (SvI), severe tubular atrophy with cystically dilated tubules with proteinaceaous casts (At), interstitial spaces showing severe fibrosis (F), severe necrosis of interstitial cells (SvN), Pyknotic nuclei (P), hemorrhages in interstitial cells (H), Vacuolation (V).

Experimental group 2:

The animals of the experimental group 2 treated with high dose of Albendazole (50 mg/kg bwt), showed severe histological changes (Table 1). The histological changes included increased mononuclear infiltration and severe tubular atrophy with cystically dilated tubules (having proteinaceous casts). The interstitial spaces were showing severe fibrosis. Pyknotic nuclei were

observed. There was prominent necrosis of the interstitial cells, with hemorrhages and interstitial vacuolation being evident. Tubular epithelia were severely disruptive showing tubular atrophy. Glomeruli were showing diffused glomerulonephritis with thickening of the basement membrane. Glomerular tuft was severely disrupted intertubular spaces were having vacuolation. There were signs of pyknosis hyalinized and acellular glomeruli were observed. Shrinkage in glomerular tufts was seen (Figure 3a & 3b).

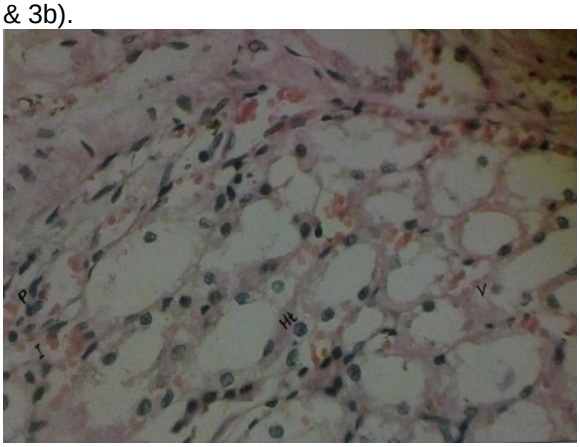

Figure 3a: T.S. of kidney of experimental group 2 (H&E 400X).
Vacuolation (V) in the endothelial cells, Pyknotic nuclei (P), Mononuclear Infiltration between the tubules and Infiltration of inflammatory cells in the glomeruli (I), Narrowing of lumen due to the hypertrophy of endothelial cells (Ht), Swelling and proliferation of endothelial cell living the glomerulus capillaries (Crescent formation), thickening of glomerular basement membrane (BM), Shrinkage of glomerulus (ShG), Diffused glomerulonephritis (DifGn), Acute tubular necrosis (N).

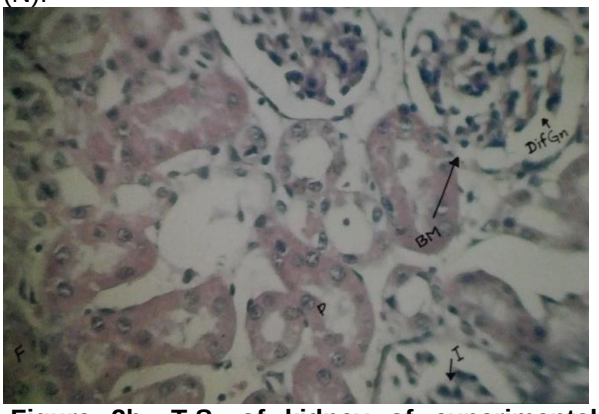

Figure 3b: T.S. of kidney of experimental group 2 (H&E 400X).
Narrowing of lumen (NwL), Moderate infiltration (I), Moderate Pyknotic nuclei (P), Moderate Swelling and proliferation of the endothelial cell living the glomerulus capillaries, Severe thickening of basement membrane (BM), (Crescent formation), Moderate shrinkage, Diffused glomerulonephritis (DifGn), Fibrosis (F).

DISCUSSION

Kidneys are homeostatic organs of the body, located in the abdominal cavity near lumber vertebrae. The basic unit of kidney is nephron, which is composed of bowman's capsule, proximal tubule, loop of Henle, and distal tubule. Kidney has very organized gross and histological structure and play active role in excretion of nitrogenous wastes and drug metabolites. During the excretion of drug metabolites, there are chances of kidney damage. There are many drugs which damage the kidney histological structure. Albendazole is potent anthelmintic against hydated cyst, echinococcosis, neurocysticercosis, ascariasis and filariasis. It has synergistic effect with many other drugs. Albendazole has even been tested as anticancer agent against ovarian cancer and its pharmacokinetic for this purpose has been meliorated using serum albumin nanoparticles (Noorani *et al.,*2015). Although, albendazole is a useful anthelmintic drug which is broadly used in the filed but has been seen damaging to kidneys. In this study, the effect of two different doses of albendazole on kidneys has been demonstrated through histopathological studies.

Histopathological analysis is an appropriate way to study the cellular damage of any organ. This technique has been utilized for this study of kidney damage. With the increase of albendazole dose and duration, there were increased glomerular changes including shrinkage, atrophy and nephritis; cellular changes including tubular epithelium disruption, vacuolation, pyknosis, apoptosis and necrosis of interstitial cells; and other changes including narrowing of tubular lumen, fibrosis and hemorrhages. Animals group which received 50 mg/kg dose of albendazole showed more severe disruption of kidneys as compared to animals receiving lesser dose of 10 mg/kg. These severe findings in this group were included diffused glomerulonephritis with the thickening of basement membrane, pyknosis hyalinized and acellular glomeruli, tubular atrophy with cystically dilated tubules having proteinaceous casts and fibrosis of interstitial cells. Batzlaff *et al.* (2014) has reported the acute

interstitial nephritis in humans within 2 days due to albendazole dosage of 400 mg bid. Albendazole increased the urea, creatinine, glucose and cholesterol in the serum of rats while reduced the albumin (Arise and Malomo, 2009). The significant changes in these parameters clearly indicate the damage to kidney. Treatment of rats with albendazole for consecutive fifteen days also altered the kidney alkaline phosphatase and aminotransferases which is considered due to damage of plasma membrane and change in amino acid metabolism of the kidney cells (Arise & Malomo, 2005). Different metabolic changes in the kidney are caused by albendazole, which may be associated with cellular damage. It has been observed that kidney isoenzymes CYP1A1 and CYP1A2 are increased in response to albendazole in goats, which allow the gentle elimination of florfenicol from the body (Alina *et al*., 2016). Ivermectin, another type of anthelmintic, has also shown similar histopathological changes including vacuolation of tubular cells and glomerular atrophy in the kidney of rabbit (Al-Jassim, Jawad, Al-Masoudi, Majeed, 2016)

Albendazole is widely used drug in veterinary field and in many cases of humans. As it has been seen that albendazole disrupt the kidney histology and cause change in metabolism.

CONCLUSION

In conclusion, albendazole toxicity to nephrons causes pathological changes in the glomeruli and in the proximal, distal and collecting tubules of the experimental animals. Thus, the use of this drug should be regulated properly specifically in kidney patients. Any excessive use may lead to the veterinary or medical complications affecting livestock and human health.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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