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Histological and Ultrastructural studies on the kidneys of albino rat under the effect of tiaprofenic acid and the possibility of recovery after stoppage of the drug

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ABSTRAT

The present study was performed to evaluated the pathological effects of tiaprofenic acid (surgam) on the kidneys of adult male albino rat and the possibility of recovery after stoppage of the drug administration. 40 male albino rats divided into 4 equal groups were used in this study. Group I: (the control group) the animals were intramuscularly injected with 0.5 ml physiological saline solution. Group II, the animals were intramuscularly injected with the therapeutic dose of tiaprofenic acid (TA) (18 mg/kg b.w.) every 12 hours for 2 weeks. Group III, the animals were intramuscularly injected with double the therapeutic dose of (TA) (36 mg/kg b.w.) every 12 hours for 2 weeks. Group IV, the animals were intramuscularly injected with double the therapeutic dose of (TA) (36 mg/kg b.w.) every 12 hours for 2 weeks and then left without treatment for 4 weeks for the possibility of recovery. Animals of groups I,II,III were sacrificed 24 hours after the last dose, while animals of group IV were sacrificed 4 weeks after the last dose, and the kidney samples were obtained and processed for histological and ultrastructural examinations. Histological changes in the rat kidney induced by tiaprofenic acid (TA) included hypertrophied glomeruli, swelling of the parietal epithelial cells, proliferation of the mesangial cells, and narrowing of the urinary spaces. Moreover, the cells of the proximal and distal convoluted tubules showed marked cloudy swelling with hypertrophied nuclei ; some displayed signs of pyknosis and karyolysis. Many inflammatory cells invading the intertubular spaces were also seen.Ultrastructural observations revealed swollen of the parietal epithelial cells of Bowman's capsules , narrow urinary spaces, focal fusion of the visceral epithelial cells, thickened glomerular basement membrane and dilated glomerular capillaries with the prescence of amorphous materials as well as blood cells in the capillaries lumina. The proximal convoluted tubules showed erosion of the microvilli constituting the brush borders, with cell debris or cast in the lumina of the tubules; besides, degenerated mitochondria and lysosomes, fragmented rough endoplasmic reticulum and destruction of the basal infoldings were observed. The epithelial cells of the distal convoluted tubules manifested marked loss of some basal infoldings as well as degenerated mitochondria, and destructed endoplasmic reticulum. However, in the recovery group there was marked improvment in the kidney tissues which appeared more or less normal.

Keywords: Tiaprofenic acid, Rat kidney, Histology, Ultrastructure.

INTRODUCTION

Tiaprofenic acid (TA) or surgam is a new non-steroidal anti-inflammatory drug, which is derived from propionic acid; it is widely used in the treatment of rheumatoid

arthritis, musculoskeletal disorders, soft tissue injuries and acute pain of varying origins (Sorkin and Brogden, 1985; Day *et al*., 1989).

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed by physicians for rheumatic diseases (Craig and Stitzel, 1986); however, they may impair the renal functions through a variety of mechanisms arising from inhibition of renal prostaglandins (P. G.) synthesis (Linton, 1984). According to several researchers, the therapeutic abilities of the anti-inflammatory drugs, depend to a large extent on the inhibition of the cyclooxygenese enzyme responsible for the biosynthesis of prostaglandins (Roth and Siok , 1978 ; Higgs *et al*., 1980).

In a further comment on these drugs, Higgs *et al*. (1974) and Higgs and Flower (1981) mentioned that such drugs act to inhibit or interfere with the activities of a variety of other enzymes and cellular activities.

The kidneys are dynamic organs and represent the major control system maintaining body homeostasis by producing the urine in which various metabolic waste products are eliminated. The kidneys also regulate the fluid electrolyte balance of the body. Recent evidence has shown that oxygen free radicals (OFR) largely contribute to the complications observed in the end-stage renal disease (Canaud *et al*., 1999; Handelman, 2000).

The present study aimed to study the histopathological and ultrastructural changes of the kidney tissues of rats due to tiaprofenic acid injection and the possibility of recovery after stoppage of the drug.

MATERAL AND METHODS

Drug used

Tiaprofenic acid (TA) - which is also known under the name "surgam"- is used in vials. Each vial contains 393 mg of trometanol tiaprofenate as powder equivalent to 200 mg of TA; the solvent is 75 cm of butyl alcohol in 3 ml of water for injection. The therapeutic dose for rat was calculated relative to the human dose according to the formula of Paget and Barnes (1964). The doses were estimated according to the weight of each rat and given intramuscularly.

Experimental animals and design:-

40 male albino rats were used in this study; they were divided into four groups, 10 animals in each. Group I: served as control group and received 0.5 ml physiological saline solution as intramuscular injection every 12 hours for 2 weeks.

Group II: The animals were intramuscularly injected with the therapeutic dose of TA (18 mg/kg b.w.) every 12 hours for 2 weeks.

Group III: The animals were intramuscularly injected with double the therapeutic dose of TA (36 mg/kg b.w.) every 12 hours for 2 weeks.

Group IV: The animals were intramuscularly injected with double the therapeutic dose of TA (36 mg/kg b.w.) every 12 hours for 2 weeks, then left without injection for 4 weeks.

At the end of the experiment, the animals were anesthetized using ether inhalation and were sacrificed. Animals of groups I, II and III were sacrificed twenty four hours after the last dose while animals of group IV were sacrificed four weeks after the last dose, the kidneys were dissected out, and cut into small pieces that were taken and prepared for both light and electron microscopic studies.

For light microscopy, the small kidney pieces were fixed in 10% formalin, dehydrated in ethyl alcohol, cleared in xylene and embedded in paraffin wax. Sections of 5µm thick were stained with hematoxylin and eosin (Humason, 1979).

For electron microscopic studies very small kidney pieces were fixed in glutaraldehyde, then washed in buffer and post-fixed in 1% osmic acid (osmium tetroxide), dehydrated in ethanol, cleared in propylene oxide and embedded in Spurr`s resin (Weakley,1981). Semithin sections were stained with toluidine blue. Ultrathin sections (60-80 nm thick) were prepared, stained with uranyle acetate and lead citrate (Reynold, 1963) and examined on Philps 400 TEM in Ain Shams Specialized Hospital.

RESUTS

Histological results:-

Group I -The control group

Light microscopic examination of sections of renal cortex showed multiple glomeruli, each consists of a tuft of capillaries surrounded by capsular space and Bowman's capsule (Fig. 1).

The proximal convoluted tubules (PCT) are lined with pyramidal cells while the distal convoluted tubules (DCT) are lined with cuboidal cells (Fig.1), the lining epithelial cells of PCT and DCT have acidophilic cytoplasm and spherical basophilic nuclei (Fig. 1).

Group II- Animals treated with the therapeutic dose of tiaprofenic acid (18 mg /kg b. w.)

Examination of the kidney of rat injected with the therapeutic dose of tiaprofenic acid (18 mg/kg b.w.) every 12 hours for 2 weeks, revealed variable degrees of histopathological alterations. The glomeruli had undergone hypertrophy, hypercellularity of the mesangial cells and narrowing of the urinary spaces. Basides, swelling of the parietal epithelial cells of Bowman's capsules was also seen (Figs. 2, 3).

The lining epithelial cells of the proximal and distal convoluted tubules showed cloudy swelling; the nuclei of such cells were hypertrophied; some displayed signs of pyknosis and karyolysis. Moderate interstitial mononuclear cell infiltration and interstitial haemorrhage were also seen in the intertubular spaces (Figs. 2, 3).

Group III- Animals treated with double the therapeutic dose of tiaprofenic acid (36mg /kg b. w.)

Examination of the kidney of rat injected with double the therapeutic dose of TA (36 mg/kg) every 12 hours for 2 weeks revealed marked damage of the glomeruli represented by congestion of the glomerular capillaries. Dilatation of the urinary spaces, degeneration of the parietal layer of Bowman's capsules were also seen (Figs. 4, 5).

The lining epithelial cells of proximal and distal convoluted tubules showed vacuolated cytoplasm with pyknotic nuclei. Marked accumulation of hyaline cast in the tubules lumina were also seen. Moreever, the intertubular spaces were infiltrated with inflammatory cells as shown in Figs. 4, 5& 6.

Group IV- The recovery group

Examination of kidney of rat injected with double the therapeutic dose of TA (36 mg/kg) every 12 hours for 2 weeks then left without injection for 4 weeks, revealed marked improvement of the kidney tissues, in spite of the presence of little pathological changes in renal corpuscles and the cells of the renal tubules (Fig. 7).

The glomeruli of the examined kidney tissues manifested clear signs of recovery. The urinary spaces had a rather normal widening, the parietal layer of Bowman's capsules appeared nearly normal (Fig. 7).

The proximal convoluted tubules almost restored their normal structure saving the presence of a few degenerative changes and the lumina of these tubulues had little cell debris (Fig. 7). The same figure shows regeneration of the distal convoluted tubules; the cytoplasm of their lining cells was slightly hypertrophied and their lumina appeared rather narrowed and contained fewer cell debris or hyaline cast. The nuclei of these cells displayed features of pyknosis (Fig. 8); the same figure shows some inflammatory cells infiltrating the intertubular spaces.

Ultrastructural results

Group I: The control group

As well known, the renal glomerulus, surrounded by a double-walled epithetlial capsule namely Bowman's capsule. The internal leaflets of the capsule enveloping the glomerular capillaries is the visceral layer, whereas the outer limit of the renal glomerulus is the parietal layer of Bowman's capsule. The space between the two leaflets is the urinary space. The wall of each glomerular capillary is formed of the glomerular basement membrane (GBM) and an inner endothelial lining. The glomerular basement membrane is surrounded by a discontinuous layer (the visceral layer) composed of the podocytes, each has a cell body from which extends several primary foot processes that give rise to numerous secondary processes embracing the glomerular capillaries. The secondary processes of the podocytes are interdigitated, delimiting elongated spaces called the filtration slits between the adjacent processes (Fig. 9). The lumina of the glomerular capillaries have certain cells, known as the mesangial or supporting cells adhering to their walls in places where the basal lamina forms a sheath that is shared by two or more capillaries (Fig.9). The proximal convoluted tubules (PCTs) have their lumina mostly occupied with the microvilli or brush border extending from the apical portion of their lining cells. The cytoplasm of these cells contains many cytophagic apical vacuoles as well as some pinocytotic vesicles, many spherical or elongated mitochondria, Golgi apparatus, endoplasmic reticulum and scattered lysosomes (Fig. 10). The nuclei of these cells lie in the centre of their basal parts. The cell membrane at the base of each cell displays multiple invaginations or folding to increase the cellsurface at the basal regions of such cells (Fig. 10).

The distal convoluted tubules have larger diameter than that of the proximal tubules and the luminal borders of their lining cells lack the brush borders and possess small microvilli (Fig. 11). The apical regions of these cells have small vesicles, besides the presence of few vacuoles. The basal regions of the cells have distinct basal infoldings that are almost similar to those of the lining cells of the proximal tubules (Figs. 11, 12). The cytoplasm of these cells possess many mitochondria and prominent endoplasmic reticulum (Fig. 12).

Group II: Animals treated with the therapeutic dose of tiaprofenic acid (18 mg /kg b. w.)

The renal glomeruli of rats injected with the therapeutic dose of tiaprofenic acid (18 mg/kg) every 12 hours for 2 weeks had irregular thickening of the glomerular basement membrane, the glumerular capillaries displayed dilatation and were filled with blood cells as well as flocculant materials. Moderate swelling and fusion of some podocyte foot processes were also seen (Fig.13).

The proximal convoluted tubules showed loss of the basal membrane infoldings, erosion of the microvilli of the apical brush border of the lining cells (Figs. 14, 15).

The mitochondria appeared swollen with degenerated cristae as well as ruptured membranes (Fig. 15).

The rough endoplasmic reticulum showed fragmentation with partial loss of ribosomes. Also, marked increase in the number of lysosomes was also seen in the proximal tubules of this group. The nuclei of the proximal tubules cells showed abnormal distribution of both euchromatin and heterochromatin (Fig. 14).

The lining epithelial cells of the distal convoluted tubules of rats of this group were swollen Fig. (18).

The basement membrane of these tubules cells displayed marked loss of some basal infoldings Fig. (16). The mitochondria of these cells were markedly degenerated (Figs. 16, 17). Fig. 17 shows fragmentation of the rough endoplasmic reticulum into small rod-like saccules with loss of ribosomes.

The nuclei of the lining cells of the distal convoluted tubules showed homogeneous distribution of euchromatin.

Group III: Animals treated with double the therapeutic dose of tiaprofenic acid (36mg /kg b. w.)

The renal corpuscles of rats injected with double the therapeutic dose (36 mg/kg b. w.) of Tiaprofenic acid every 12 hours for two weeks exhibited massive thickening of the glomerular basement membrane in some areas Fig. (18). The lumina of the glomerular capillaries were dilated and congested with many blood cells as well as flocculent materials. (Fig. 18). The mesangial cells and mesangial matrix were massively proliferated. Figs. 18&19 show enlarged urinary space filled with flocculent material as well as marked flattening and fusion of foot processes of the visceral epithelial cells.

The proximal convoluted tubules lining cells of rats treated with double the therapeutic dose of tiaprofenic acid showed swollen microvilli; degenerated or completely oblished microvilli were also seen in focal areas. Cell debris or casts were seen in the lumina of the tubules (Fig. 20). The same figure shows marked aggregation of many vacuoles especially near the apical parts of the cytoplasm; degeneration of the basal infoldings was also seen (Fig. 20). The mitochondria were swollen, displayed separation and detachment of their cristae and rupturing of their membranes (Fig. 20). The rough endoplasmic reticulum showed marked fragmentation with loss of ribosomes. The nuclei showed irregular nuclear membranes and abnormal distribution of chromatin (Fig. 20).

Electron microscopical examination of the distal convoluted tubule cells of the same specimens revealed marked loss of their apical microvilli (Fig. 21), marked thickening of their basement membranes with destruction or loss of the basal infoldings (Fig. 21). The mitochondria were degenerated with detachment of their cristae, loss of matrix as well as rupturing of their membranes (Fig. 21). The rough endoplasmic reticulum displayed fragmentation into small saccules. (Fig. 21).

Group IV: The recovery group

In the recovery group the parietal epithelial cells of Bowman's capsules looked more or less normal in appearance (Fig. 22); the urinary spaces were slightly narrowed and did not contain any flocculent materials as revealed in Fig. 22. This figure also illustrates fenestrated visceral epithelial cells with focal fusion of the foot processes. The glomerular capillaries basement membrane appeared with nearly normal structure. The lumina of the glomerular capillaries were empty (Fig. 22).

The lining cells of the proximal convoluted tubules showed restoration of the microvilli to their normal appearance (Fig. 23). The cytoplasm of these cells contained few vacuoles and numerous vesicles. The basement membranes of these

cells had a rather normal thickness, though they have lost parts of their basal infoldings (Fig. 23). The mitochondria showed partial restoration of their normal fine structure (Fig. 23).

The lining cells of the distal convoluted tubules of such recovering rats showed marked improvement in their structure; the cytoplasm contained few vacuoles, many mitochondria and some electron- dense lysosomes. The basement membrane had few basal infoldings (Fig. 24).

DISCUSSION

The excretion of tiaprofenic acid is predominantly renal in nature and is complete after 12 hours (Lucker *et al*., 1982). Tiaprofenic acid like many other non-steroidal anti-inflammatory drugs (NSAIDs), inhibits prostaglandin I_2 ($FPGI_2$) and prostaglandin E_2 (PGE_2) synthesis and has the same adverse effects on the renal functions (Lote *et al*., 1985).

Carmichael and Shankel (1985) reported as much as 274 cases of acute renal failure due to (NSAIDs) therapy. Prostaglandins appear to serve an important role in maintaining renal blood flow and adequate vasodilatation which is antagonised by NSAIDs.

The present study showed that tiaprofenic acid induced marked histopathological changes in rat kidneys and that these changes were apparent in both the glomeruli and the tubules.

The most promiment signs of devastation observed in the renal glomeruli were glomerular hypertrophy, mesangial proliferation, narrowing of the urinary spaces and irregular thickening of the glomerular basement membranes. Besides, vacuolar degeneration within the glomerular tissues, swelling of the parietal epithelial cells lining Bowman's capsules were also seen. The kidney tubules were markedly affected as indicated by swelling of the lining epithelial cells; the nuclei of such cells were hypertrophied with signs of pyknosis and karyolysis, together with peritubular inflammatory cells and interstitial haemorrhage with the presence of hyaline casts in the tubules lumina.

These findings confirm those described by Jackson and Lawrence (1978) who stated that treatment with a certain dose of either "Indomethacin" or "Phenylbutazone" caused renal papillary necrosis, degeneration in the renal tubules, as well as inflammatory cell infiltration. In the same direction. Marasco *et al*. (1987) indicated glomerular hypercellularity, necrosis in the renal tubules and focal inflammatory cell infiltration after "Ibuprofen" treatment. In the present study large foci of inflammatory cell infiltration were observed between the renal tubules; this observation is in agreement with Moussa and Abdel-Ghafar (1989) who detected similar peritubular inflammatory cell infiltration in rats treated with feldene (NSAID).

Similarly, the application of either analgesic drugs (El-Banhawy *et al*., 1989) or the analgesic narcotic drug "Flunitrazepam" (El-Banhawy *et al*., 1992) produced severe lesions in kidney tissues of the experimental rats.

The glomerular lesions observed in the present study were represented by thickening of the glomerular basement membrane, dilatation and congestion of the glomerular capillaries, focal fusion of foot processes of the visceral epithelial cells. The fusion of foot processes together with the thickened basement membrane means that renal dysfunction is expected. This finding confirms those reported by Hotta *et al*. (2001) and Rash *et al*. (2002). The importance of the glomerular basement membrane

is its role as the main barrier that normally prevents the passage of protein into urine; otherwise the development of proteinuria occurs (Cortan, 1987).

The proliferation of mesangial cells and matrix, presently illustrated are in accord with those described by Ebiad *et al*. (2007) who obtained similar findings in rats treated with piroxicam (NSAID). Al-Thani (1993) obtained similar findings in rats treated with the antibiotics daunomycin and chloramiphenicol.

The lesions of renal tubules observed in the present study were represented by destruction of the microvilli, formation of cell cast, vacuolation of the cytoplasm of the lining epithelial cells, destruction of the basal infoldings and prevalence of inflammatory cells in the intertubular spaces; these lesions agree with those obtained by Yousef (2007) in kidneys of rats treated with tamoxifen.

In agreement with the present results are those of Jackson and Lawrence (1978) who found papillary and tubular degeneration as well as inflammatory cell infiltration post-treatment with Indomethacin or phenylbutazone.

Also, in the present study there were dilatation and fragmentation of the rough endoplasmic reticulum, devastation of the mitochondria, increased lysosomes and pyknosis of some nuclei in the cells lining the proximal and distal convoluted tubules; this might be due to a defence mechanism exerted by these cells against the toxic effect of tiaprofenic acid keeping in consideration that the smooth and rough endoplasmic reticula have detoxifying effect on toxins reaching any cell in the body (Fawcett,1994)

The present results agree with those obtained by Murray and Brater (1997) who reported that patients who continue using NSAIDs pocessess acute necrosis in the renal tubules and permanent damage to the kidney. Similarly, Whelton (1999) stated that inhibition of renal prostaglandins produced by the use of NSAIDs can lead to fluid and electrolyte disorders, acute renal dysfunction, nephrotic syndrome, interstitial nephritis and renal papillary necrosis.

Our results also agree with those of Ten Jide *et al*. (1995) who reported a case of acute renal failure 3 weeks after starting intake of tiaprofenic acid. They added that after discontinuation of the drug and correction of electrolyte disturbance, renal function recovered almost completely within 6 months.

In general, It was noticed that the alterations were more severe in rats treated with double the therapeutic dose of TA followed by rats treated with the therapeutic dose. In the recovery group, after stoppage of the drug, the renal tissues partially restored their normal structure.

From these findings it is concluded that the use of tiaprofenic acid (surgam) must be restricted to the urgent indications and it is advised to be given for a short duration with the proper dose.

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EXPLANATION OF FIGURES

Fig. (1): Photomicrograph of kidney section of control rat showing the normal structure of the renal corpuscles, proximal (PCT) and distal (DCT) convoluted tubules. Notice the glomerulus (GL), Bowman's capsule (BC) and the urinary space (*). (H&E- x 640)

Figs. (2-3): Photomicrographs of kidney sections of rats treated with the therapeutic dose of tiaprofenic acid (18 mg/kg b.w.) every 12 hours for 2 weeks.

Fig.(2): Showing expanded Bowman's capsule (BC), enclosing hypertrophied glomeruli (GL). The proximal (PCT) and distal (DCT) convoluted tubules show swelling and degeneration. Inflammatory cells (IC) are shown in the inter-tubular spaces. (H&E- x 320)

Fig. (3): Showing cloudy swelling of the parietal epithelial cells of Bowman's capsules (BC). The glomeruli (GL) manifest marked hypercellularity and narrowing urinary spaces. Besides, swelling, vacuolation and poorly defined cell boundaries of the lining cells of proximal (PCT) and distal (DCT) convoluted tubules are shown. Inflammatory cells (IC) are seen invading the inter-tubular spaces. (H&E- x 640)

Figs. (4-6): Photomicrographs of kidney sections of rats treated with double the therapeutic dose (36 mg/kg b.w.) of tiaprofenic acid every 12 hours for 2 weeks.

Fig. (4): Showing disrupted and congested glomeruli (GL), besides degenerative changes of the proximal (PCT) and distal (DCT) convoluted tubules. (H&E - x 320)

Fig. (5): Showing signs of necrosis of the glomeruli (GL) with disrupted capillaries. The proximal (PCT) and distal (DCT) convoluted tubules display necrosis of their lining cells. Their nuclei (N) show signs of karyolysis. (H&E- x 640)

Fig. (6): Showing marked occlusion of Bowman's capsules (BC) and proliferation of mesangial cells. The proximal (PCT) and distal (DCT) convoluted tubules show vacuolated cytoplasm and their lumina are occluded with hyaline casts (HC). The nuclei (N) of these cells show distinct features of karyolysis. Inflammatory cells (IC) are seen in the inter-tubular spaces. (H&E- x 320)

Figs. (7-8): Photomicrographs of kidney sections of rats treated with double the therapeutic dose of tiaprofenic acid (36 mg/kg b.w.) every 12 hours for 2 weeks and then left without treatment for 4 weeks.

Fig. (7): Showing signs of regeneration of the renal tissues; the glomeruli (GL) have the usual number of mesangial cells. The regenerating proximal (PCT) and distal (DCT) convoluted tubules partialy restored the normal organization of their lining cells; their lumina contain few cell debris. (H & E- x 640)

Fig. (8): Showing clear regeneration of both proximal (PCT) and distal (DCT) convoluted tubules. (H& E- x 640)

Figs. (9-12): Electron micrographs of kidney sections of the control rats.

Fig. (9): Showing glomerular capillaries (GC) situated in the urinary space (US); the glomerular capillary are surrounded by glomerular basement membrane (GBM). Notice the Bowman’s capsule (BC), the podocyte (P) and the mesangial matrix (Mm). (x 3600)

Fig. (10): Showing a part of the proximal convoluted tubule. Notice the apical microvilli (MV), the central spherical nuclei and the basal infoldings (BI). (x 3600)

Fig. (11): Showing a part of the distal convoluted tubule. Notice the short microvilli (MV), basal infoldings (BI), mitochondria (M) and the spherical nucleus (N). (x 4600)

Fig. (12): Showing magnified part of a distal convoluted tubule revealing the basement membrane (TBM) which shows extention of the basal infoldings (BI). The cytoplasm possesses many elongated mitochondria (M). (x 17000)

Figs. (13-17): Electron micrographs of kidney sections of rats treated with the therapeutic dose of tiaprofenic acid (18 mg/kg b.w.) every 12 hours for 2 weeks.

Fig. (13): Showing glomerular capillaries (Gc) with irregular thickening of the glomerular basement membrane (GBM). The lumina of the capillaries are filled with blood cells (BC) as well as flocculent materials. The urinary spaces are markedly narrowed (US). Note the mesangial matrix (Mm) and the swollen and vacuolated podocyte (P). (x 3600)

Fig. (14): Showing a proximal convoluted tubule with disrupted and rarified apical microvilli (MV) and cell debris in its lumen. Notice the degenerated mitochondria of the lining cells (M), electron-dense lysosomes (LY) and the abnormal nuclear chromatin distribution (N). (x 2800)

Fig. (15): Showing magnified part of the proximal convoluted tubule; the basement membrane (TBM)_shows marked loss of basal infoldings and the mitochondria (M) display degenerative changes. (x 10000)

Fig. (16): Showing part of a distal convoluted tubule with swollen cells and narrow lumen (L). The cytoplasm of such cells has many degenerated mitochondria (M) and the nuclei display homogeneous distribution of chromatin (N). (x 3600)

Fig. (17): Showing magnified part of the distal convoluted tubule with highly degenerated mitochondria (M). The basement membrane (TBM) of the tubule is markedly devoid of basal infoldings. (x 10000)

Figs. (18-21): Electron micrographs of kidney sections of rats treated with double the therapeutic dose (36 mg/kg b.w.) of tiaprofenic acid every 12 hours for2 weeks.

Fig. (18): Showing Bowman's capsule (BC) and dilated glomerular capillaries with blood cells (BC) and flocculent material in the capillaries lumina (GC). Notice the urinary space (US), the swollen podocyte (P) and the mesangial cell (MC). (x 2800)

Fig. (19): A magnified part of the above figure showing irregular thickening of the glomerular basement membrane (GBM) and focal fusion of the podocytes (P). The glomerular capillaries (GC) display dilatation. (x 8000)

Fig. (20): Showing part of a proximal convoluted tubule illustrating degenerated microvilli (MV), cell debris or cast in the tubule lumen, fragmented rough endoplasmic reticulum (RER), many cytoplasmic vacuoles (V) and degenerated mitochondria (M). The cell nuclei show irregular nuclear envelope and abnormal chromatin distribution (N). (x 2800)

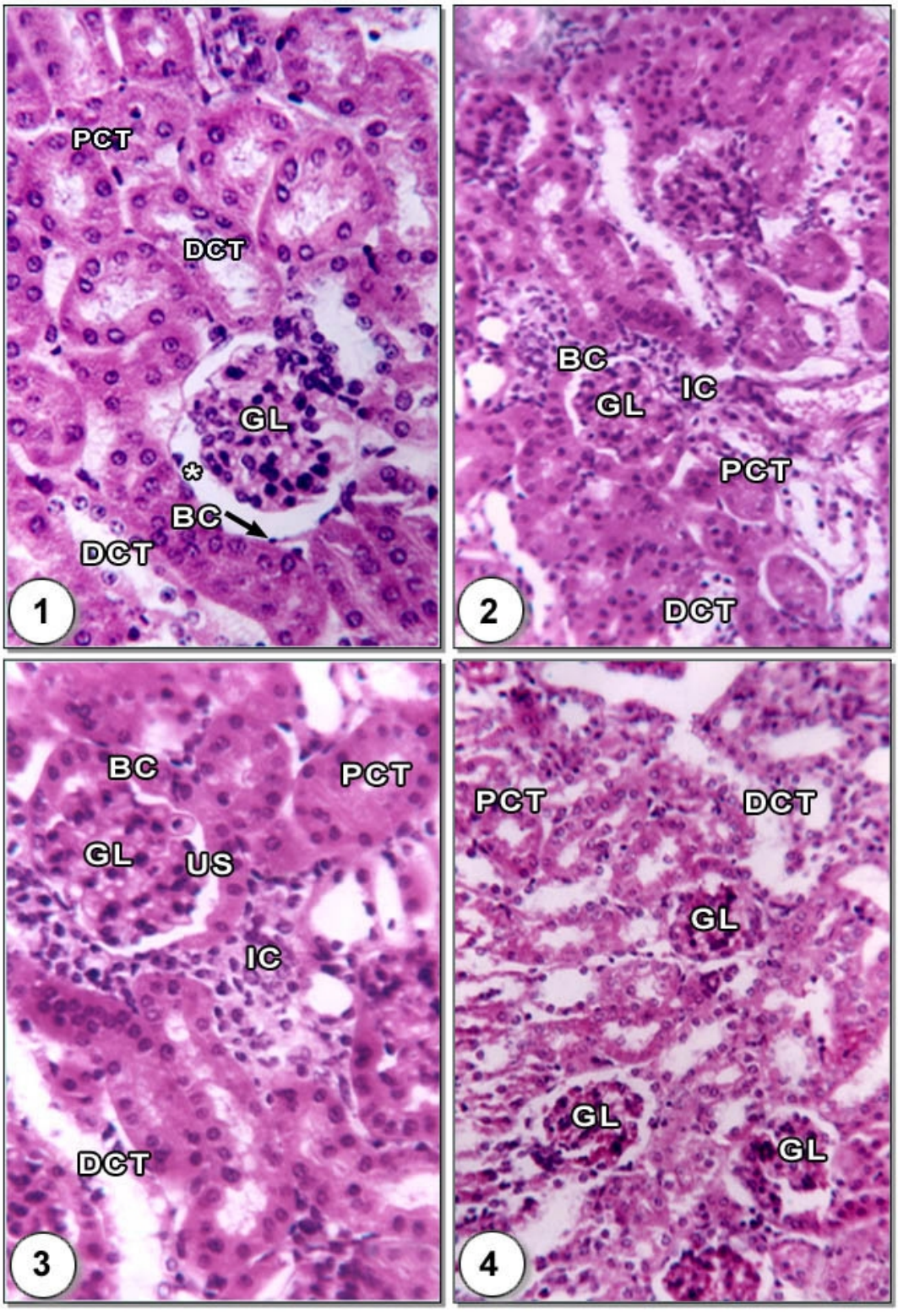
Fig. (21): Showing a distal convoluted tubule revealing detachment and extrusion of the apical part of the tubule cells into the lumen (L) of the tubule. The cytoplasm contains many vacuoles (V) as well as many destructed mitochondria (M), few basal infoldings (BI) and fragmented rough endoplasmic reticulum (RER). (x-2800)

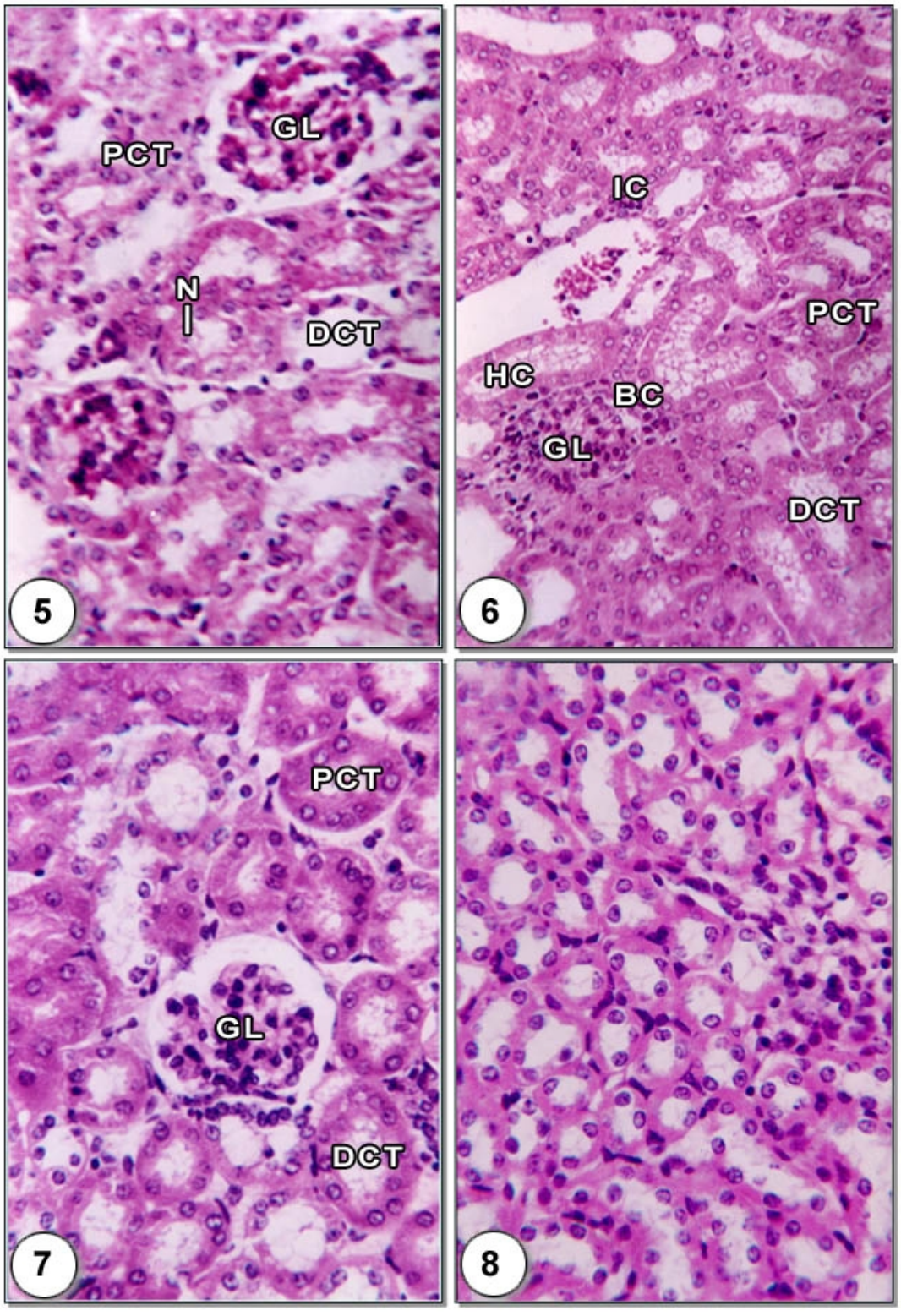
Figs. (22-24): Electron micrographs of kidney sections of rats treated with double the therapeutic doses (36 mg/kg. b. w.) of tiaprofenic acid every 12 hours for 2 week and then left without treatment for 4 weeks.

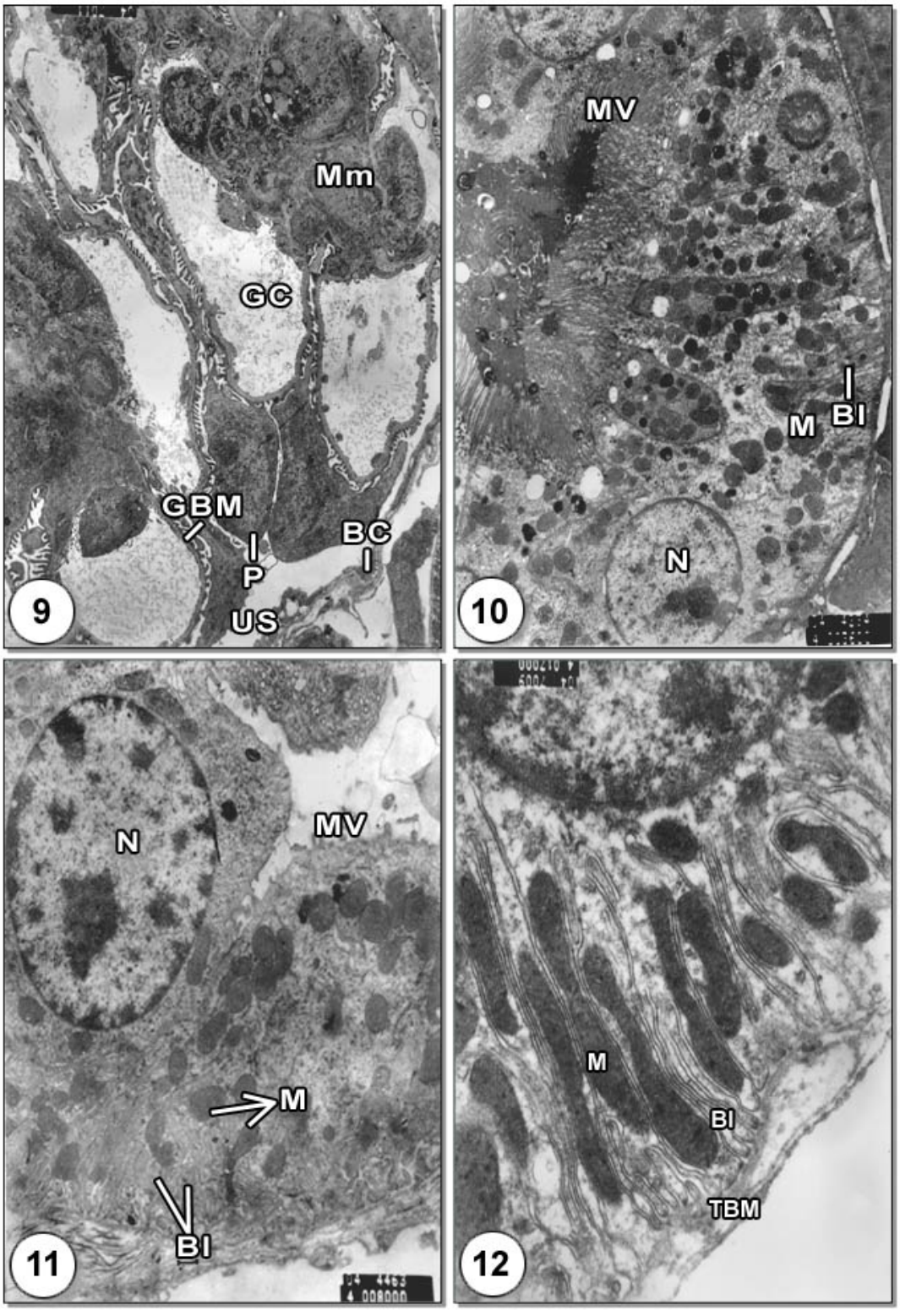
Fig. (22): showing almost normal picture of glomerular capillaries wall (GBM) and foot processes (arrowheads). (x-3600)

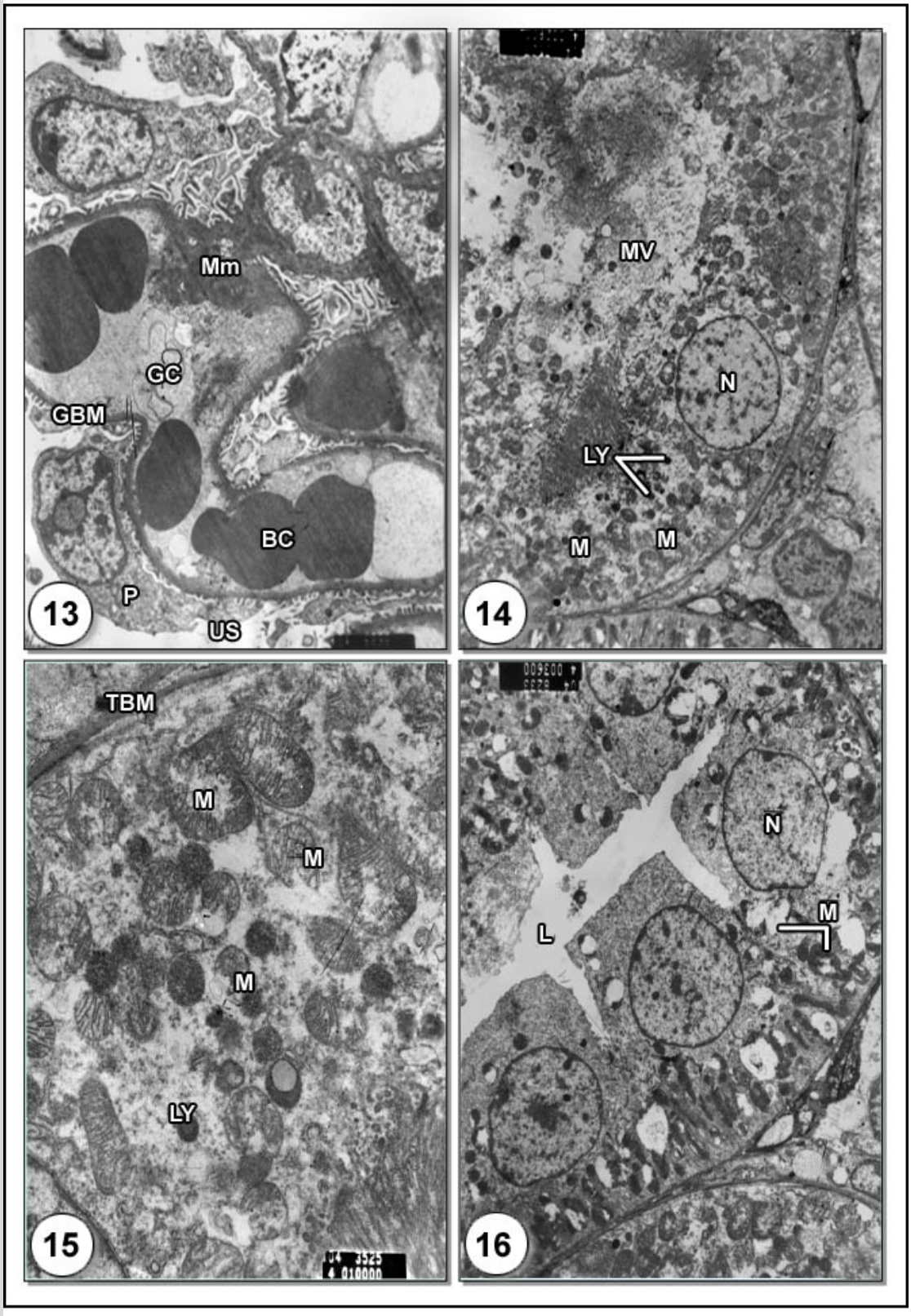
Fig. (23): Showing a proximal convoluted tubule with well-developed microvilli (MV), few lysosomes (LY), the nuclei at the basal portion of the cells (N), mitochondria (M) as well as endocytotic vacuoles (V). (x 2800)

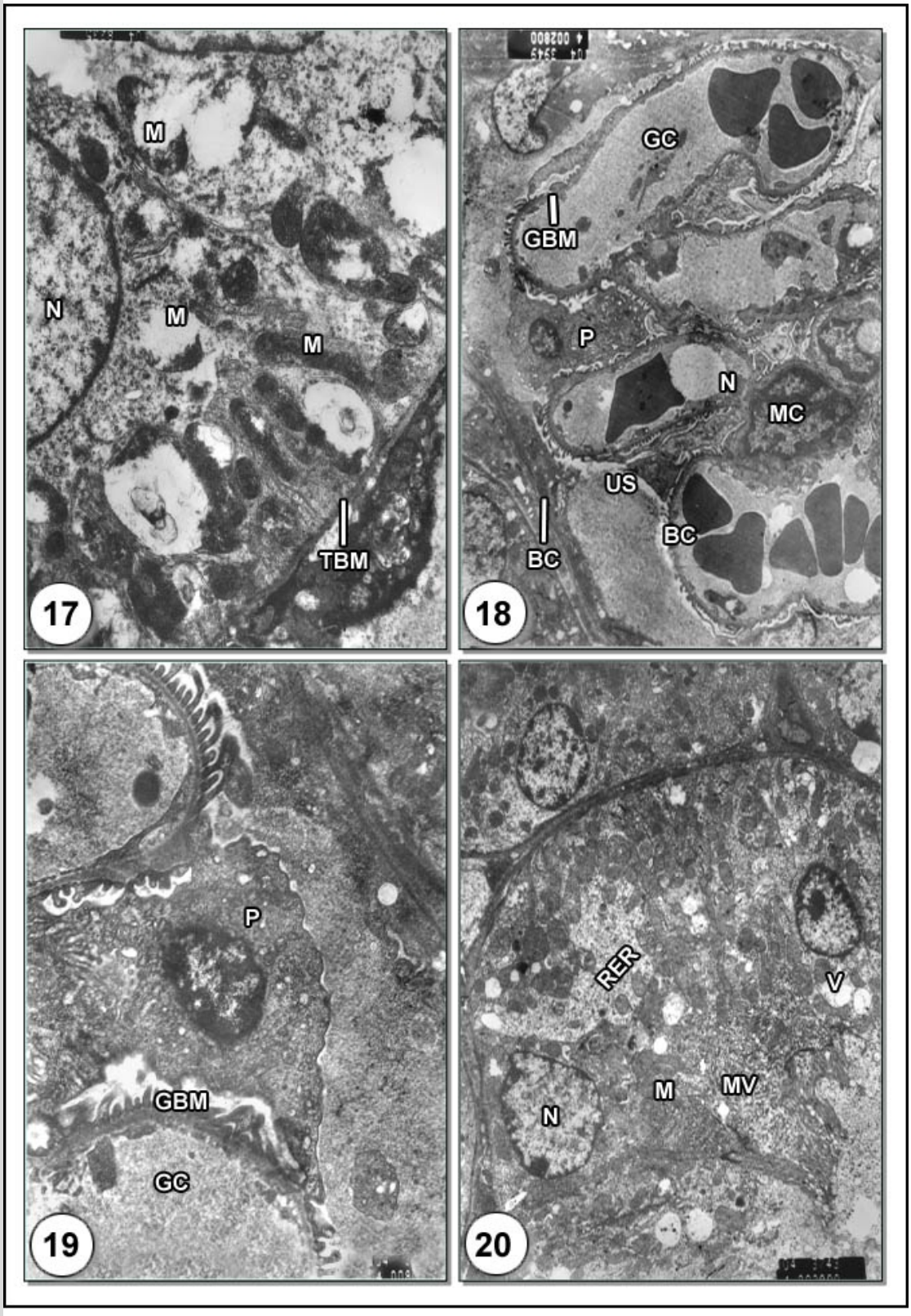
Fig. (24): Showing a distal convoluted tubule; the cells have basal infoldings (BI), elongated mitochondria (M) and nuclei in the apical cytoplasmic region (N). (x 2800)

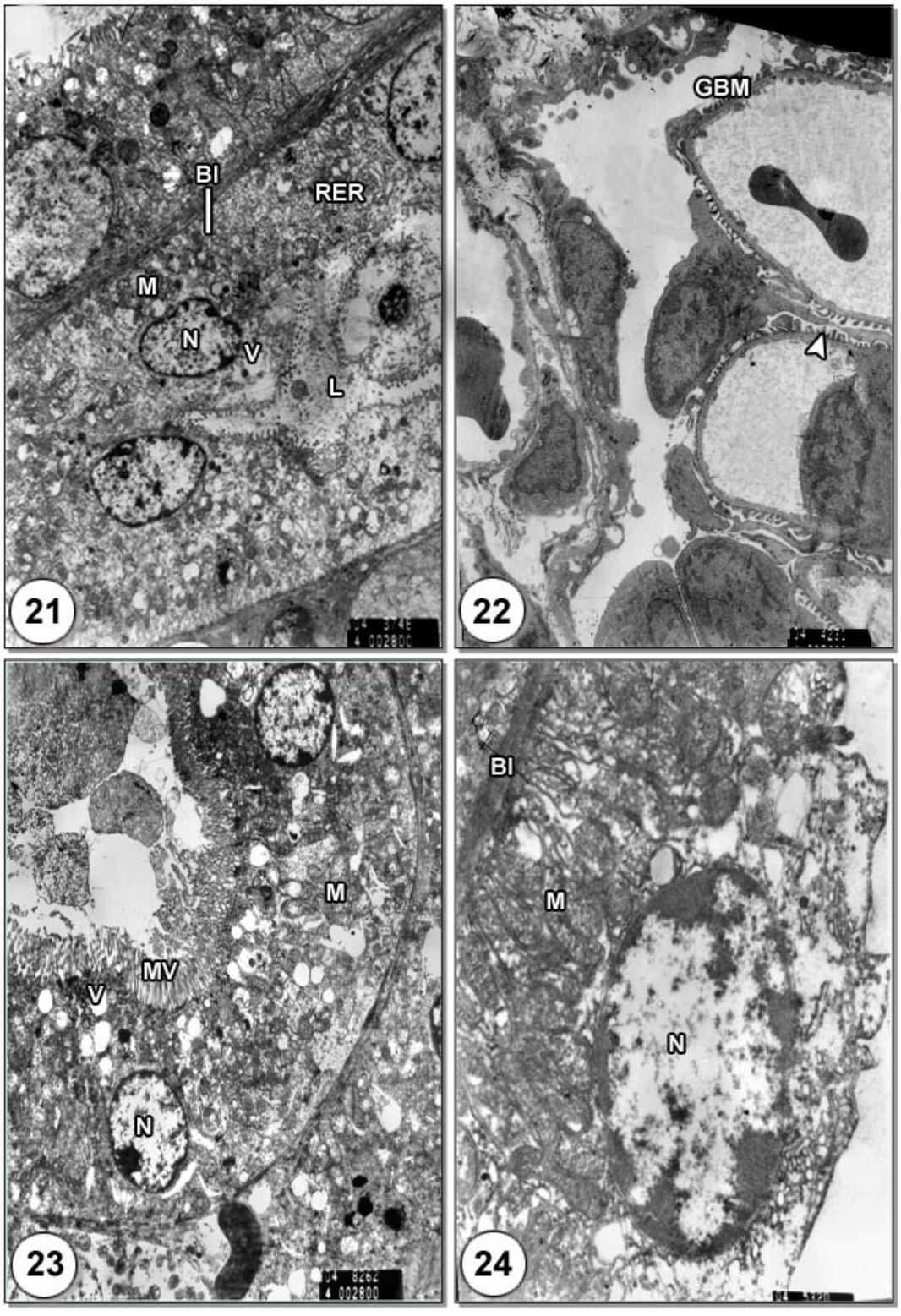












ARABIC SUMMARY

دراسات هستولوجية وتركيبية دقيقة على كلى الجرذ الأبيض تحت تأثيرحامض التيابروفينك ومدى إمكانية الشفاء بعد توقف المعالجة.

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يعتبر حامض التيبروفينك المعروف تجاريا بسم" سورجام" من أهم العقاقير المضادة للإلتهابات. وصممت هذه الدراسة لمعرفة مدى تأثير هذا العقارعلى كلى الجرذ الأبيض وإمكان الشفاء من هذه الآثارأوالحد منها بعد توقف المعالجة. وقد تم تقسيم الحيوانات إلى أربع مجموعات ، اعتبرت المجموعة الأولى مجموعة ضابطة ولم تعط أية جرعات، أما المجموعة الثانية فحقنت بجرعةعلاجية من العقار(مقدارها 18 مجم/ كجم من وزن الجسم) كل12 ساعة لمدة أسبوعين، وعولجت المجموعة الثالثة بضعف الجرعة العلاجية من العقار(مقدارها 36 مجم / كجم من وزن الجسم) كل 12 ساعةلمدة أسبوعين، أما المجموعة الرابعة فحقنت بضعف الجرعة العلاجية من العقار(مقدارها 36 مجم /كجم من وزن الجسم) كل 12 ساعة لمدة أسبوعين،ثم تركت دون معالجة لمدة أربعة أسابيع لبحث إمكانية الشفاء من تأثير العقار.
وأظهرت الدراسة أن حامض التيابروفينك قد أحدث تغيرات فى كلى الجرذ الأبيض، فقد لوحظ تضخم فى الكريات الكلويه وإنتفاخ في الخلايا المبطنه لمحفظة بومان وضيق في الساحات البولية. ولوحظ أيضا إنتفاخ سحابى للأنيبيبات الكلوية مع تنكرز وتحلل فى أنوية الخلايا المبطنه لها ووجود رشح خلوى فى تجاويف الأنيبيبات الكلويه إضافة إلى وجود خلايا إلتهابيه بين الأنيبيبات الكلويه.
وأظهرت الدراسه بالمجهر الإلكترونى زيادة فى سمك الغشاء القاعدى المبطن للأوعيه الدمويه للكريات الكلويه وتمدد فى النسيج المزنجيالى مع إنتفاخ وإلتحام للنتوءات القدميه ،كما أظهر الفحص إنتفاخ للأنيبيبات الكلويه وفقد الخملات الدقيقه وتهدم فى الثنيات القاعديه للأغشيه الخلويه مع تهدم ملحوظ فى الميتوكوندريا وتفتت فى الشبكه الإندوبلازميه الخشنه ووجود فراغات فى السيتوبلازم.
أما فى مجموعة الإستشفاء فقد لوحظ تحسن ملحوظ فى نسيج الكلى.
ونستنتج من هذه الدراسه أن حامض التيابروفينك له تأثير ضار على الكلي وهذا التأثير يزداد بزيادة الجرعه، وأنه يمكن الحد أو التخلص من هذه الآثار بعد توقف المعالجة لفترة مناسبة.