Effect of Loratadine on the Renal Cortex of Mother and Offspring of Albino Rats

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Abstract: The aim of the present study is to evaluate the effect of administration of loratadine on the renal cortex of mothers and offspring of albino rats. Loratadine use in pregnancy is not associated with a large risk for offspring. Therefore this study is warranted to confirm these findings. Sixty albino rats of pregnant mothers and off spring. The animals were designed into two main groups: the control group divided into two subgroups (Ia, Ib). The experimental group divided into two subgroups (IIa, IIb).Each group consisted of 15 rats. Groups (Ia & Ib) served as control, while rats in groups (IIa & IIb), group (IIa) treated mother rat received oral daily single dose of 0.15 mg/kg b.w of loratadine for 3 weeks while group (IIb) are the offspring of the group (IIa). Histological examination showed fragmented glomerulus with focal necrosis. However proximal convoluted tubules showed atrophy, necrosis, cytoplasmic degeneration with brush border damage and cellular infiltration. Group (IIb) showed shrinkage of the glomerular tufts with thickening and wrinkling of basement membrane, tubular atrophy and necrosis. In addition, TEM showed irregular basement membrane with atrophy and effacement of podocytes with interspersed subendothelial deposits. The results of the present study suggest that use of Loratadine (0.15 mg/kg) could affect the renal cortex in both mother and offspring rats.

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1.Introduction

The histamine H1 receptor antagonists (antihistamines) are an important class of medications used for the relief of common symptoms associated with hyper histaminic conditions occurring in children and adults. This group of drugs may be subdivided into 3 generations, based upon their propensity to induce sedation and cardiotoxicity. The first generation (classical) antihistamines are highly effective in treating hyper histaminic conditions. However, they frequently induce sedation and may adversely affect a child's learning ability. First generation antihistamine-induced sedation has been described to occur in more than 50% of patients receiving therapeutic dosages. Serious adverse events are unusual following overdoses of first generation antihistamines although life-threatening adverse events have been described. When the so-called 'second generation' antihistamines terfenadine and astemizole were introduced they were widely embraced and quickly used by clinicians of all specialties, including paediatricians, as nonsedating alternatives to the first generation compounds. These new agents were found to be equally or more effective than first generation antihistamines in relieving symptoms associated with hyperhistaminic conditions without the soporific effects of the first generation agents. Loratadine, fexofenadine, mizolastine, ebastine, azelastine and cetirizine are the first of the new third generation antihistamines. These drugs have been shown to be efficacious with few adverse events including no clinically relevant cytochrome P450 mediated metabolic-based drug-drug interactions or QT interval prolongation/cardiac dysrhythmias (1).

The anti allergic and anti inflammatory activities of H_1-antihistamines occur through a variety of mechanisms (2-6). Antiallergic activities such as the inhibition of the release of mediators from mast cells and basophils probably involve a direct inhibitory effect on calcium-ion channels that reduces the inward calcium current activated by the depletion of the intracellular store of calcium. Anti inflammatory effects such as the inhibition of the expression of cell adhesion molecules and the chemotaxis of eosinophils and other cells may involve down-regulation of the H_1-receptor–activated nuclear factor-κB, a ubiquitous transcription factor that binds to the promoter and enhancer regions of many genes that regulate the production of pro inflammatory cytokines and adhesion proteins (3,4).

H1-antihistamines, the mainstay of treatment for urticaria, were developed from anticholinergic drugs more than 70 years ago. They act as inverse agonists rather than antagonists of histamine H1-receptors which are members of the G-protein family. The older first generation H1-antihistamines penetrate readily into the brain to cause sedation, drowsiness, fatigue and impaired concentration and memory causing detrimental effects on learning and

examination performance in children and on impairment of the ability of adults to work and drive. Their use should be discouraged. The newer second-generation H1-antihistamines are safer, cause less sedation and are more efficacious. Three drugs widely used for symptomatic relief in urticaria, desloratadine, levocetirizine and fexofenadine are highlighted in this review. Of these levocetirizine and fexofenadine are the most potent in humans *in vivo*. However, levocetirizine may cause somnolence in susceptible individuals, whereas fexofenadine has a relatively short duration of action and may be required to be given twice daily for all round daily protection. Although desloratadine is less potent, it has the advantages of rarely causing somnolence and having a long duration of action (7).

In rare cases, both first- and second-generation H_1-antihistamines are reported to cause adverse effects, the mechanisms for which are incompletely understood. These effects include fixed-drug eruption, photosensitivity, urticaria, fever, elevation of liver enzymes and hepatitis, and agranulocytosis (8).

First-generation antihistamines are small lipophilic molecules that are associated with numerous adverse events largely because of their propensity to cross the blood-brain barrier and their cholinergic activity. Second-generation antihistamines, being more lipophobic, offer the advantages of a lack of CNS and cholinergic effects such as sedation and dry mouth, which are commonly seen in first-generation antihistamines. Their longer duration of action also enables a more patient-friendly dosing regimen which increases patient compliance. The pharmacokinetic profiles of loratadine and cetirizine are reflective of the advantages of these agents as non-cardiotoxic antihistamines (9).

Antihistamines are widely used by dermatologists to help control the symptoms of a range of pruritic conditions, but also specifically for the treatment of urticaria and other mast cell-driven disorders. These drugs are considered safe, with few serious side-effects, so routine monitoring is rarely performed. report the case of a patient with acute interstitial nephritis (AIN) associated with the antihistamine cetirizine. Acute interstitial nephritis secondary to long-term use of cetirizine for the treatment of urticaria pigmentosa (10).

Loratadine is a powerful H_1 antagonist commonly employed in the treatment of allergic disorders. Increased extracellular Ca^{2+}concentrations reduced the inhibitory activity of loratadine, indicating that external $Ca^{2+}$and loratadine have antagonistic effects on basophil histamine release. These results indicate that loratadine, in addition to H_1 receptor blocking activity, has the capacity to inhibit histamine release from human basophils (11).

Loratadine reduce IgE-mediated histamine release. Terfenadine, cetirizine, and loratadine blocked allergen-induced hyper responsiveness to methacholine (12).

Loratadine is usually compatible with breast-feeding (classified category L-2 by theAmerican Academy of Pediatrics (Jasek 2007) In the U.S., it is classified as category B in pregnancy, meaning that animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women (8).

Loratadine (INN) is a second-generation H1 histamine antagonist drug used to treat allergies. Structurally, it is closely related to tricyclic antidepressants, such as imipramine, and is distantly related to the atypical antipsychotic quetiapine (13). Loratadine is a tricyclic antihistamine, which acts as a selective inverse agonist of peripheral histamine H_1-receptors. Histamine is responsible for many features of allergic reactions (14).

Loratadine is indicated for the symptomatic relief of allergy such as hay fever (allergic rhinitis), urticaria (hives), chronic idiopathic urticaria (15) and other skin allergies (5). For allergic rhinitis (hay fever), loratadine is effective for both nasal and eye symptoms: sneezing, runny nose, itchy or burning eyes. Loratadine could be also used to treat mild to moderate pain from headaches. Similarly to cetirizine, loratadine attenuates the itching associated with Kimura's disease. Patients with severe hepatic liver disorders may need to start with a lower dose. No dose adaptation is necessary for elderly or renal (kidney) impaired patients (14, 15).

As a “nonsedating” antihistamine, loratadine causes less (but still significant, in some cases) sedation and psychomotor retardation than the older antihistamines because it penetrates the blood/brain barrier to a smaller extent. Although drowsiness is rare at the common 10-mg dose. Other possible side effects include headache and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastrointestinal disturbances (14, 15).

Loratadine is usually compatible with breast-feeding (classified category L-2 by the American Academy of Pediatrics). In the U.S., it is classified as category B in pregnancy, meaning animal reproduction studies have failed to demonstrate a risk to the fetus, and no adequate and well-controlled studies in pregnant women have been conducted (16).

First-generation H_1-antihistamines, particularly those in the phenothiazine class, have been associated with the sudden infant death syndrome, although

causality has never been proved. Some oral H_1-antihistamines, including cetirizine and loratadine, are considered relatively safe for use during pregnancy (Food and Drug Administration category B) (17).

Women in their childbearing years often require drug therapy for allergic conditions. Loratadine, a newer non sedating antihistamine, is often used because of its preferred side effect profile. To date no published data exist on the safety of loratadine use in pregnancy (18).

Loratadine is a second generation histamine H1 receptor antagonist, that has high potency anti allergic properties and is associated with low adverse effects compared with other antihistamines. Acute interstitial nephritis is a cause of acute renal failure that is most often induced by drugs or, less frequently, infection or sarcoidosis. Although the number of drugs associated with acute interstitial nephritis is too large, the antihistaminic loratadine have never been reported before.A case report of an interstitial nephritis with acute renal failure that suggesting hypersensitivity reaction in a 77 old man who had received loratadine (10 mg/day) during ten days before his assessment to our hospital by disseminated pruritic syndrome (19).

2. Material and Methods

Animals

The present study was based on materials obtained from 60 albino rats of pregnant mothers and off spring. The body weight mother rats from 180-200 gm. The animals were designed into two main groups: the control group divided into two subgroups (Ia, Ib). the experimental group divided into two subgroups (IIa, IIb). Each group of mother rats was isolated in a single cage and kept in the same conventional condition of diet and environment in the animal house.

The control group was divided into two sub groups:

Group Ia: included 15 control mother rats.

Group Ib: included 15 control offspring of the control mother rats at ages of four days postnatal.

The experimental group was divided into two sub groups:

Group IIa: included 15mother rats treated orally with a single dose of Loratadine 0.15 mg/kg /day from first day of gestation to delivery.

Group IIb: included 15 offspring of the mother rats treated by single dose of Loratadine0.15 mg/kg /day from first day of gestation to delivery.It ages of four days postnatal.

Drug administration

Loratadine (Claritin) is available as a 10 mg tablet, is taken once a day. Loratadine was administered orally by gavage to pregnant rats group IIa at dose of 0.15mg/kg from first day of gestation to delivery.

The Control group (Ia) were given orally distilled water throughout the experiment. Thereafter, during the entire experiment, all animals were checked daily for state of health and behavior. After 4 days of delivery all animals of groups (Ia, Ib) and groups (IIa, IIb). The kidneys were excised and divided into small pieces for histological examination.

Light microscopy

Small slices of kidney tissue were taken and fixed in 10 %formalin for 24 hours, and were imbedded in paraffin. Five-micron thick sections were routinely stained with hematoxylin and eosin (20).

Electron microscopy

Samples of kidney were fixed in 2.5% glutaraldehyde and 0.25 M sodium cacodylate, post fixed in 1% osmium tetroxide and embedded in Spurr's epoxy. Ultrathin sections were picked up on nickel grids, stained with uranyl acetate/lead citrate **(21)**

3. Result

The Kidney of control mother rats in group Ia have normal structure of renal cortex which displayed the renal corpuscle, proximal convoluted tubules and distal convoluted tubules.The renal corpuscle containing a tuft of glomerular (G) capillaries, surrounded by a double-walled epithelial (Bowman) capsule. The internal (visceral) layer closely envelops the glomerular capillaries composed of modified epithelial cells called podocytes. The outer (parietal) layer forms the surface of the capsule composed of simple squamous epithelial cells.Between the capsular layers is the capsular space. (plate 1-a,b).The electron microscopic examination shows the internal lining of the glomerular capsule composed of complex epithelial cells called podocytes. From the cell body of podocyte several primary processes. Each primary process give rise a secondary processes (pedicle). Between the pedicles are slit pores. Between the fenestrated endothelial cells of the capillieries and the covering podocytes is the glomerular basement membrane (plate.3-a).

The proximal convoluted tubules (PT) are lined with simple cuboidal epithelium with eosinophilic granular cytoplasm and round nuclei in the center, or near the base of the cells.Their lateral cell borders are indistinct. The cell apex has many long microvilli

that form a prominent brush border in the lumen (plate 1 -c) However, electron microscopic examination confirm the cell of convoluted tubule contain euchromatic nucleus with apical cytoplasm has numerous vesicles near the the bases of the microvilli.Long mitochondria concentrated along the basal membrane having normal cristae (plate.3-b).

The distal convoluted tubules (DT) show considerably smaller cuboidal epithelium,having no brush border and more empty lumens, (plate.1-c). However, electron microscopic examination confirm the cell of convoluted tubule contain euchromatic nucleus, and fewer mitochondria with normal cristae (plate.3-c).

The results of light microscopic examination in the kidney of mother rats treated with Loratadine group (IIa) showed that there were many areas of tubular damages ranged from mild to severe in the kidney were observed in all treatment animals. These renal damages appeared as cytoplasmic vacuolation and necrosis of epithelial lining of renal tubules. A few renal tubules showed single epithelial cells desquamated to their lumen and focal infilteration with inflammatory cells. Also showed fragmented the glomerulus with focal necrosis surrounded by dilated capsular space and focal necrosis of glomerulus. (plate.1-d,e,f) However, electron microscopic examination of the group (IIa) confirm the finding the podocytes, appeared atrophy, with irregular thickeness of basement membrane with interspersed subendopithelial deposits (plate.4-a).

The cells of the proximal convoluted tubule showed euchromatic nuclei (N), with area of lost of microvilli with disarray of cytoplasmic organells (plate.4-b).

The Kidney of control offspring rats in group (Ib) have normal renal structure of cortex. The glomerulus (G) is formed of anastomsing capillaries, surrounded by a double-walled epithelial (Bowman) capsule. The internal (visceral) layer closely envelops the glomerular capillaries. The outer (parietal) layer forms the surface of the capsule composed of simple squamous epithelial cells.Between the capsular layers is the capsular space (CS).The proximal convoluted tubules (PT) are lined with simple cuboidal epithelium with eosinophilic granular cytoplasm and rounded nuclei with apical brush border. The distal convoluted tubules (DT) show considerably smaller cuboidal epithelium, less acidophilic cytoplasm (plate.2-a,b).

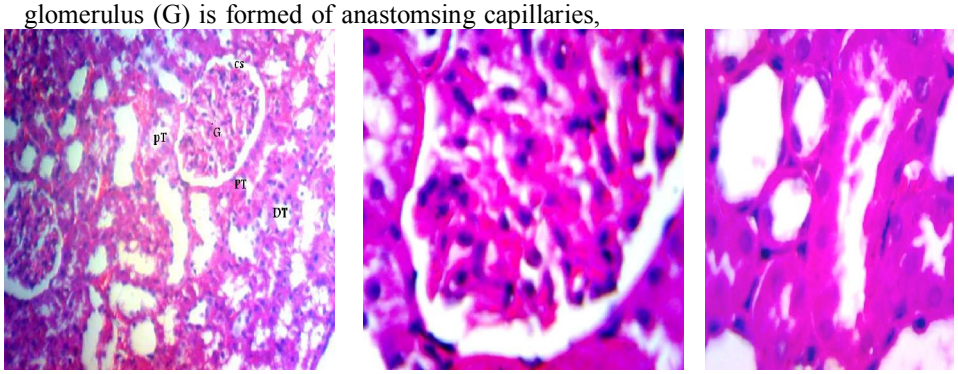
Electron microscopic examination of renal cortex of control offspring (I b) showed glomeruli of renal corpuscles were made up of capillary loop segments, podocytes within Bowman space; organelles in the podocyte cytoplasm (plate.5-a).

The proximal convoluted tubules with euchromatic nuclei, many mitochondria with normal cristae and long dense apical microvilli (plate.5-b).

Light microscopic examination in the kidney sections of an offspring of mother treated rats group (IIb) showing multifocal interstitial edema with inflammatory cells infilterate with variable eosinophilic cells; shrinkage the glomerular tufts with thickening and wrinkling of basement membrane, tubular atrophy and necrosis (plate.2-c,d).

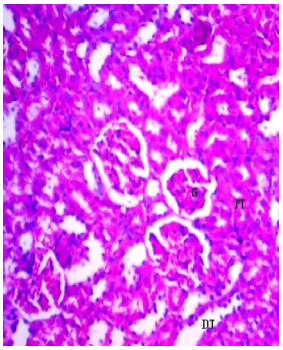
However, electron microscopic examination of the group (IIb) confirm the finding the podocytes. appeared atrophy, with irregular thickness of basement membrane with subendothelial intra membranous deposits, atrophy and effacement of podocytes (plate.6-a).

The cells of the proximal convoluted tubule showed dentate hyperchromatic nucleus, few organelles displaced toward the basolateral side and dys morphic mitochondria (plate.6-b).



A B C

Plate 1: The micrographs of kidney (cortical part) of mother rats; H&E**. (a-b-c):** kidney sections of control mother rats group (Ia): (**a**): showing the normal histological structure of the glomerulus (G), proximal convoluted tubules (PT) and distal convoluted tubules (DT) in the cortical portion; x100. (**b**): High power from previous section showing the glomerulus surrounded by capsular space, covered by the simple squamous parietal layer of Bowman capsule; x400 **(c)**: proximal convoluted tubules (PT)and distal convoluted tubules (DT) in the cortical portion; x400.



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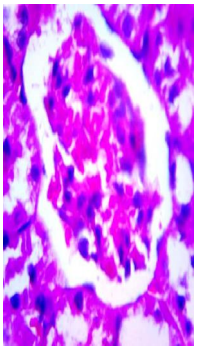

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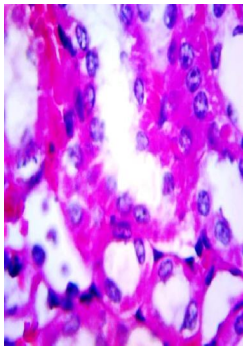
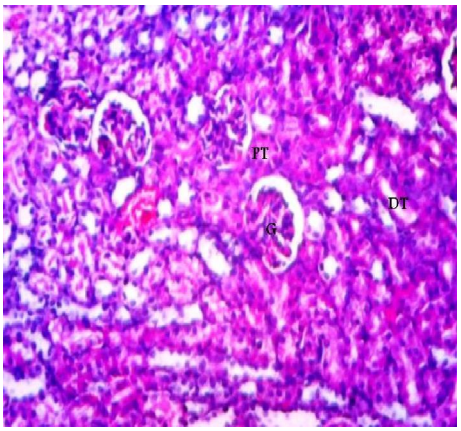
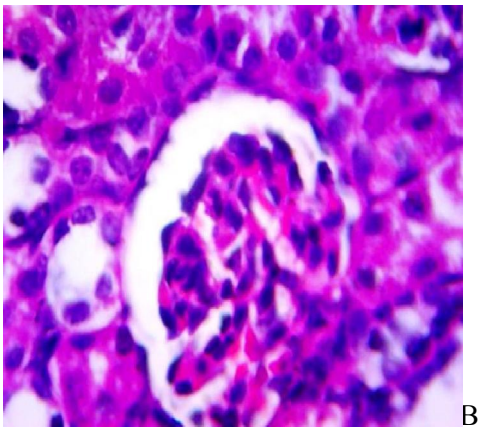


F

Plate 1(d-e-f) sections of mother treated kidney group (II a): **(d):** showing a fragmented glomeruli (G), with dilated the capsular spaces.Also some glomerular tufts was observed with focal necrosis. and tubular atrophy; x100 **(e):** High power from previous section showing fragmented the glomerulus with focal necrosis surrounded by dilated capsular space, x400 **(f):** showing tubular atrophy with cytoplasmic vacuolation, cellular necrosis and and focal infilteration with inflammatory cells, partial loss of bruch dorder of (PT), x400.



A



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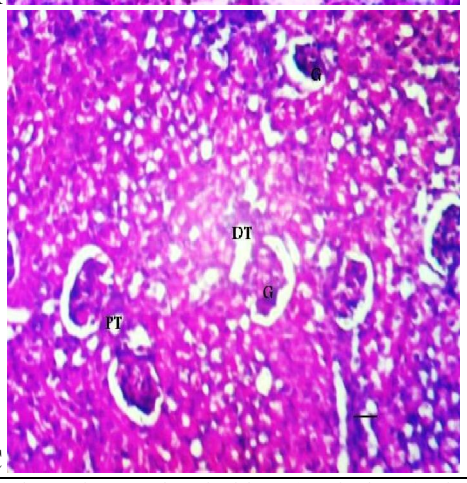

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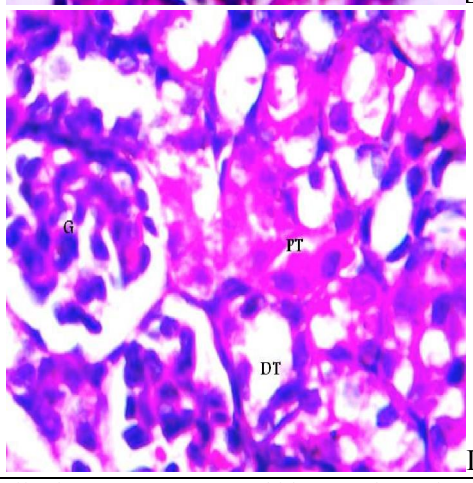
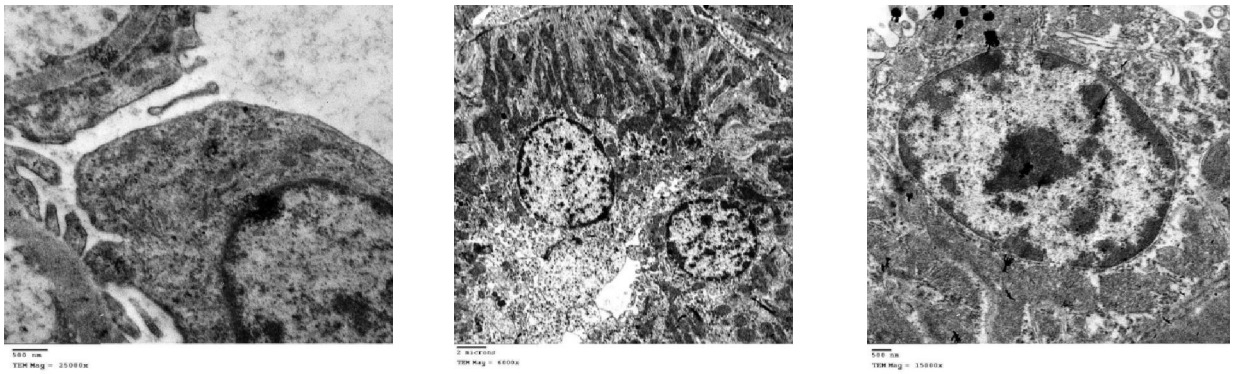


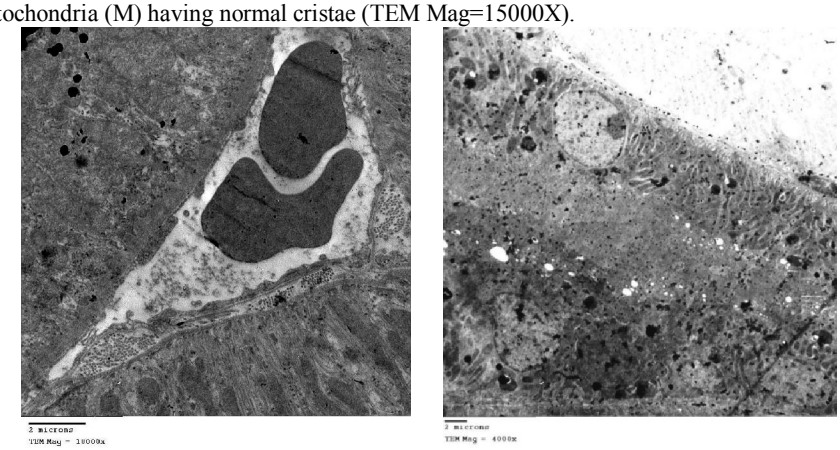
D

Plate 2: photomicrographs of Kidney (cortical part) of an offspring rats. H&E**. (a-b):** kidney sections of control offspring rats group (Ib). **(a):** showing the normal histological structure of the glomerulus (G), proximal convoluted tubules (PT) and distal convoluted tubules (DT); x100. (**b**): High power from previous section showing the glomerulus surrounded by capsular space, covered by the simple squamous parietal layer of Bowman capsule; x400. **(c-d):** kidney sections of an offspring of mother treated rats group (IIb): **(c):** showing mutifocal interstitial edema with inflammatory infilterate (w) with variable eosinophils cells; shrinkage of the glomerular tufts x100. **(d):** High power from previous section showing shrinkage of the glomerulus with thickening and wrinkling of basement membrane, tubular atrophy and necrosis; x400.



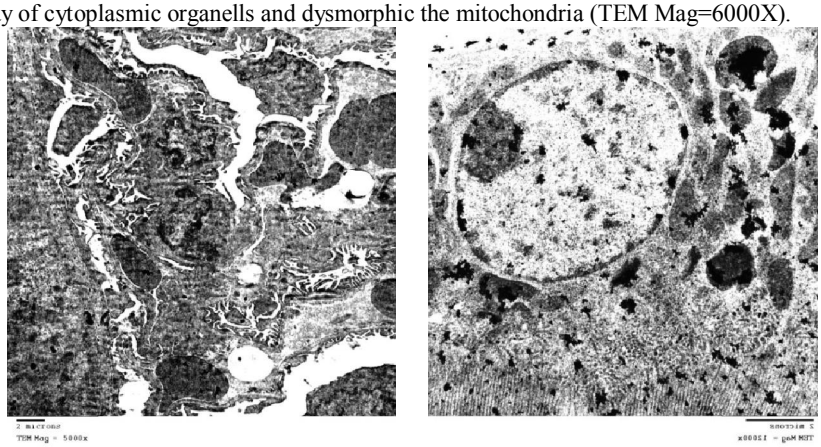
A B C

Plate3: Transmission electron microscopic picture of a section of kidney of control mother rats group (Ia) **(a)**:showing the glomerular basement membrane (BM), foot processes and filtration slits were observed and cell body of podocyte in capillary space with abundant cytoplasm containing an assortment of organelles (TEM Mag=25000x). **(b):** showing the cells of the proximal convoluted tubule with euchromatic nuclei (N), many mitochondria (M) having normal cristae. The brush border of the cells has normal microvilli (Mv) (TEM Mag=6000X). **(c):** showing the cell of the distal convoluted tubule with euchromatic nuclei (N), many mitochondria (M) having normal cristae (TEM Mag=15000X).



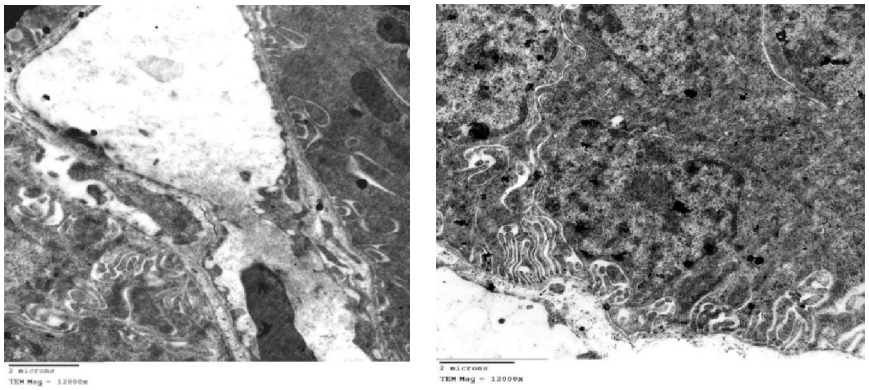
A B

Plate 4: Transmission electron microscopic picture of a section of kidney of treated mother rats group (IIa) **(a):** showing the irregular thickening of glomerular basement membrane with interspersed subendopithelial deposits, atrophy of podocytes (TEM Mag=10000x). **(b):** showing the cells of the proximal convoluted tubule with euchromatic nuclei (N), with area of lost apical microvilli with disarray of cytoplasmic organells and dysmorphic the mitochondria (TEM Mag=6000X).



A B

Plate5: Transmission electron microscopic picture of a section of kidney of control of an offspring rats groug (Ib): **(a)**: showing capillary loop segments, podocytes within Bowman space; organelles in the podocyte cytoplasm (TEM Mag=5000X). **(b):** proximal convoluted tubule with euchromatic nuclei (N), with intact apical microvilli (TEM Mag=12000X).



A B

Plate6: Transmission electron microscopic picture of a section of kidney of an offspring of treated mother rats group(IIb): **(a):** showing the irregular thickening of glomerular basement membrane subepithelial and intramembranous deposits atrophy and effacement of podocytes (TEM Mag=12000X). **(b):**proximal convoluted tubules with dentate hyperchromatic nucleus, few organelles displaced toward the basolateral side and dys morphic mitochondria loss of brush border (TEM Mag=20000X).

4. Discussion

Loratadine is a second generation histamine H1 receptor antagonist, that has high potency anti allergic properties and is associated with low adverse effects compared with other antihistamine (23).

The study finds of tubular damages ranged from mild to severe in the kidney were observed in all treatment animals. These renal damages appeared as degeneration and necrosis of epithelial lining of renal tubules. A few renal tubules showed single epithelial cells desquamated to their lumen and focal inflammatory cells infilterate with loss of microvilli. These findings are in general agreement with the observations in acute tubular necrosis,metabolic or toxic disturbance cause necrosis of renal tubular epithelial cells. A dacauses of renal tubular epithelium blockage of renal tubules by necrotic cells and a secondary reduction in glomerular blood flow. Drug induced acute interstitial nephritis, there is edema of interstitium with inflammatory infilteration.and degeneration or necrosis of tubular epithelium (22).

Acute interstitial nephritis is a cause of acute renal failure that is most often induced by drugs. A case report of an interstitial nephritis with acute renal failure that suggesting hypersensitivity reaction in a 77 old man who had received loratadine (10 mg/day) during ten days before his assessment to our hospital by disseminated pruritic syndrome (23). Acute interstitial nephritis is an important cause of acute renal failure resulting from immune-mediated tubule interstitial injury, initiated by medications (24).

Drugs that cause tubular cell toxicity do so by impairing mitochondrial function, interfering with tubular transport, increasing oxidative stress, or forming free radicals (25, 26).

The study finds also fragmented the glomerulus with focal necrosis surrounded by dilated capsular space and focal necrosis of glomerulus and effacement of podocytes with irregular thickness of basement membrane with interspersed sub endopithelial deposits. Many of the proximal tubules demonstrated loss or attenuation of the brush borders and dysmorphic mitochondria in renal cortex of treated mothers and their offspring. These findings are in general agreement with the observations of others.

Many of the proximal tubules demonstrated interstitial nephritis. Patient had a moderate interstitial mononuclear cell inflammatory infiltrate with a few scattered eosinophils and frequent tubulitis in many well-preserved tubules. This patient's medication list included acyclovir, phenytoin, aspirin, citalopram, loratadine, omeprazole, but the precise cause of interstitial nephritis remains uncertain entirely excluded, the prominent podocyte injury with extensive foot process effacement that was observed byEM in all three cases along with the absence of segmentally sclerotic glomeruli was most characteristic of minimal change disease (27).

The tubular cells of the kidney are particularly vulnerable to toxicant-mediated injury due to their disproportionate exposure to circulating chemicals and transport processes that result in high intracellular concentrations. It is generally thought that the parent chemical or a metabolite initiates toxicity through its covalent or non covalent binding to cellular macromolecules or through their ability to produce reactive oxygen species. In either case the activity of the macromolecule(s) is altered resulting in cell injury. For example, proteins and lipids in the plasma membrane, nucleus, lysosome, mitochondrion

and cytosol are all targets of toxicants. If the toxicant causes oxidative stress both lipid peroxidation and protein oxidation have been shown to contribute to cell injury.

In many cases mitochondria are a critical target and the lack of adenosine triphosphate (ATP) leads to cell injury due to the dependence of renal function on aerobic metabolism. The loss of ATP leads to disruption of cellular ion homeostasis with decreased cellular K+ content, increased Na+ content and membrane depolarization. Increased cytosolic free Ca2+ concentrations can occur in the early or late phase of cell injury and plays a critical role leading to cell death. The increase in Ca2+ can activate calcium activated neutral proteases (calpains) that appear to contribute to the cell injury that occurs by a variety of toxicants. During the late phase of cell injury, there is an increase in Cl- influx, followed by the influx of increasing larger molecules that leads to cell lysis. Two additional enzymes appear to play an importantrole in cell injury, particularly oxidative injury. Phospholipase A2consists of a family of enzymes in which the activity of the cytosolic form increases during oxidative injury and contributesto cell death. Caspases are a family of cysteine proteases that are activated following oxidative injury and contribute to cell death (28).

Conclusion

These findings indicate that administration of Loratadine may have some deleterious effects of the renal cortex of mother and offspring rats. Therefore be cautiously used in both man and animal.

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