

**RENAL EFFECTS OF SELECTIVE
CYCLOOXYGENASE-2 INHIBITORS IN RAT :
A LIGHT AND ELECTRON MICROSCOPIC STUDY**

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed classes of medication used extensively in the treatment of pain, fever and inflammation. The therapeutic efficacy of NSAIDs is probably mediated through their inhibition of cyclo-oxygenase enzyme. Two isoforms of cyclo-oxygenase (COX) had been identified named COX-1 and COX-2 (Kujubu et al., 1991; Rossat et al., 1999). A major drawback with nonselective NSAIDs has been the gastrointestinal (GI) erosions, bleeding, salt retention and occasionally acute renal failure. Such drawbacks were now attributed to the inhibition of COX-1 (Cryer, 1998; Brater, 1999). Therefore, specific inhibitors of COX-2 were introduced into widespread clinical use in 1999 (Hawkey, 1999). Two selective COX-2 inhibitors celecoxib and rofecoxib had become the most commonly prescribed medications worldwide. Structurally they both differ, celecoxib incorporates a sulphonamide moiety and have a CF3 group whereas rofecoxib does not (Wiholm, 2001). Clinical trials using these medications for treatment of arthritis and pain have uniformly demonstrated efficacy similar to that of nonselective NSAIDs together with marked reduction of GI toxicity and renal side effects (Bombardier et al., 2000; Silverstein et al., 2000).

Previous studies reported that COX-2 enzyme is constitutively expressed in renal tissues, and its expression in that organ can be upregulated in salt depleted animals (Komhoff et al., 1997) and in experimental heart failure (Tomasoni et al., 1998). These observations raised the possibility that selective COX-2 inhibitors rofecoxib and celecoxib may carry the same risk for renal adverse effect as do

nonselective NSAIDs. This was supported by the findings that selective COX-2 inhibitors in salt-depleted subjects induced qualitative changes in renal function similar to those seen with nonselective NSAIDs (Brater et al., 2001). Furthermore, studies comparing rofecoxib and celecoxib with respect to their cardiorenal side effects in hypertensive osteoarthritis patients reported higher frequency of edema and increased systolic blood pressure in patients treated with rofecoxib as compared with celecoxib (Catella-Lawson et al., 2001; Geba et al., 2001; Hennan et al., 2001; Whelton et al., 2001).

The nephropathological changes caused by rofecoxib and celecoxib were described in two isolated case reports (Rocha and Fernandez-Alonso, 2001; Henao et al., 2002). However, the patient in the first report was hypertensive and in the second was diabetic and they both received other medication beside the COX-2 inhibitors. Therefore, the purpose of this study was to describe and compare the effects of selective COX-2 inhibitors, celecoxib and rofecoxib, on the structure of kidney in normal healthy rats using both light and transmission electron microscopy.

MATERIAL AND METHODS

Animals :

Thirty male Sprague - Dawley rats weighing 200 - 225 g were used (supplied by the Animal house, King Saud University). The study was conducted in accordance with the standard establishment by the guide for the care and use of laboratory animals of the college of Medicine research Council (CMRC). The rats were housed individually in rack mounted with wire mesh cages to prevent coprophagia. They were housed at room temperature and allowed free access to water and food *ad libitum*. The animals were randomly divided into three groups :

Group I : (n = 10) untreated rats were used as control.

Group II : (n = 10) rats were treated with COX-2 inhibitor celecoxib (Celebrex, Searle, USA) in a dose of 10 mg / kg b.w. / day given by stomach tube for a period of 7 days.

Group III : (n = 10) rats were treated with COX-2 inhibitor rofecoxib (Vioxx, Merk, USA) in a dose of 10 mg / kg / b.w. / day by stomach tube for 7 days.

The oral administration of the drugs was well tolerated by all rats and no significant side effect was observed during the course of the study.

On day 7 of the study all animals were anesthetized with ether and their abdomen were opened to remove their kidneys.

The light microscopic study (LM) :

Kidneys were sectioned longitudinally to include both cortex and medulla. Specimens were fixed in 10% formalin, processed and embedded in paraffin. Thick sections (5 μ) were stained with hematoxylin and eosin (Hx. & E.) stain.

The electron microscopic study (EM) :

Renal cortical specimens were sliced into small pieces (1mm³) and were fixed in 2.5% glutaraldehyde in phosphate buffered saline PBS pH 7.4 for 4 hours. Specimens were then postfixed in 1% osmium tetroxide OS₄ in PBS for one hour, dehydrated in graded series of ethanol, cleared in xylene and embedded in araldite. Ultra-thin sections were doubly stained with lead citrate and uranyl acetate, examined and photographed using Jeol JEM - 1010 transmission electron microscope.

RESULTS

The light microscopic study (LM) :

A) The control rats (group I) :

The cortex of the kidney displayed numerous globular structures, the renal corpuscles. Each corpuscle appeared as a dense rounded structure, the glomerulus, surrounded by a narrow Bowman's (urinary) space. A single layer of flat squamous cells, the Bowman's capsule, lined the renal corpuscle. The glomerulus was formed of a network of densely packed anastomotic capillaries and numerous nuclei of capillary endothelium, mesangial cells and epithelial cells (podocytes). An area of closely packed cells, the macula densa, appeared at the vascular pole of the glomerulus. Such cells were part of the lining of the distal convoluted tubules. The cortical tubules consisted mainly of proximal convoluted tubules and some distal convoluted tubules lined with cuboidal cells having rounded nuclei (Fig. 1). The renal medulla showed the renal tubules, and the vasa recta and delicate interstitial supporting tissue (Fig. 2).

B) The treated rats (groups II and III) :

The glomerular tuft in the celecoxib treated rats was hypercellular with apparent dilatation of the capsular space. As a result of such hypercellularity it was difficult to identify the capillary lumina (Fig. 3). On the other hand, the glomeruli of the rofecoxib treated rats showed normal cellularity, clear capillary lumina and normal capsular spaces. Moreover, the capsular epithelia in both specimens showed focal thickening. Although the cortical tubules of the celecoxib and rofecoxib treated rats showed segmental tubular dilatation together with focal areas of tubular atrophy, yet this atrophy was more prominent in the rofecoxib treated rats. Atrophic tubules were lined either by cells having vacuolated cytoplasm or by swollen cells with granular cytoplasm protruding into the tubular lumen. In other tubule cells were seen desquamated in their lumen. Moreover, the cortical interstitium in the rofecoxib treated rats showed dense infiltration by inflammatory cells (Fig. 4).

The corticomedullary junction in the celecoxib treated rats showed extensive dense cellular infiltration clearly interstitial and obscuring the tubular morphology as compared with the lighter infiltrate encountered in the rofecoxib treated rats (Figs. 5 & 6).

The renal papilla in the celecoxib treated rats showed prominent areas of hyalinosis and extensive eosinophilic patches with discrete interstitial cells, necrosis of the wall of the renal tubules and blood vessels of the renal medulla. Focal sloughing and hyperplasia of the cellular epithelium were also evident (Fig. 7). However, the renal papilla in the rofecoxib treated rats was more or less similar to the control (Fig. 8).

The electron microscopic study (EM) :

A) Control rats (group I) :

The glomerulus showed capillary lumina lined by flat endothelial cells. The endothelial cytoplasm was only prominent around the nucleus and elsewhere it formed a thin discontinuous layer, the lamina fenestrata. The epithelial cells (the podocytes) had branching trabeculae spreading out from the body and terminating as foot processes on the basement membrane of the glomerular capillary. The nuclei of the podocytes appeared larger and with lighter chromatin disperse than those of the endothelial cells. The mesangial cells existed in between the capillaries and within the basement membranes. They had dark round indented nuclei and abundant cytoplasm. The mesangial matrix (mesangium) was referred to the mesangial cytoplasm and the intercellular material (Fig. 9).

B) Treated rats (groups II & III) :

The glomerulus in the celecoxib treated rats showed focal effacement of foot processes of podocytes on the capillary basement membrane that showed irregular thickening. Capillary lumena were filled by proteinaceous material. Mesangial matrix was interposed between the basement membrane and the endothelial cytoplasm. Such matrix appeared also migrating peripherally into the capillary (Fig. 10). The glomeruli of the rofecoxib treated rats showed similar changes yet focal effacement of foot processes of podocytes was more prominent than that described with celecoxib (Fig. 11). Furthermore, numerous electron dense deposits appeared in the mesangium (Fig. 12). Mesangial proliferation and interposition between the basement membranes and the endothelial lining of the capillary was evident (Fig. 13).

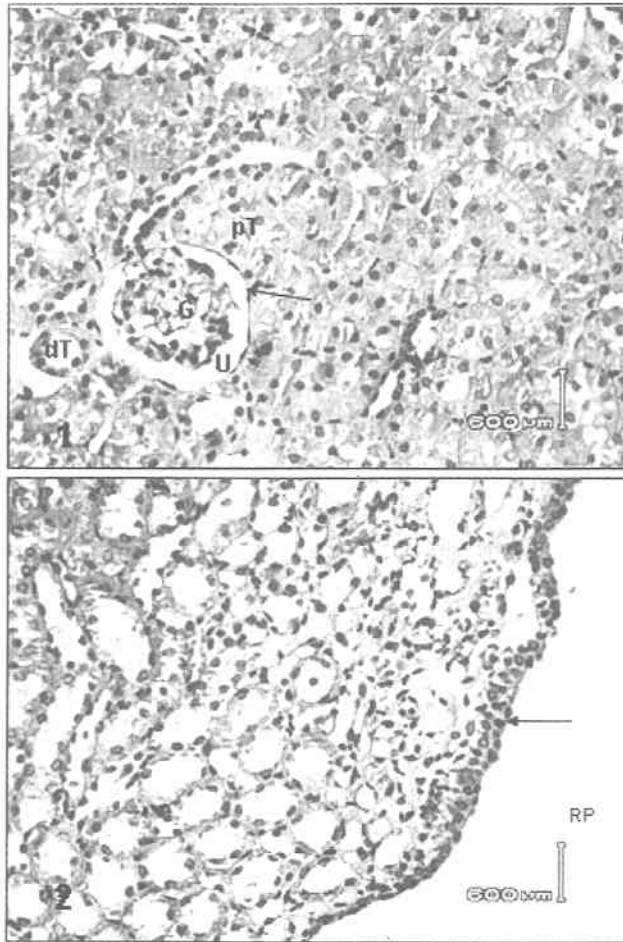


Plate I (Figs. 1 & 2) : Light photomicrographs of kidney of control rats.

Fig. (1) : Renal cortex. Note the renal corpuscle formed of a glomerulus (G) surrounded by urinary space (U) and lined by flattened squamous cells (arrow). Note the proximal convoluted tubules (pT) and the distal convoluted tubule (dT) separated by delicate interstitium..

(Hx. & E.; x 400)

Fig. (2) : Renal papilla (RP) showing medullary tubules and blood vessel and the covering epithelium (arrow).

(Hx. & E.; x 400)

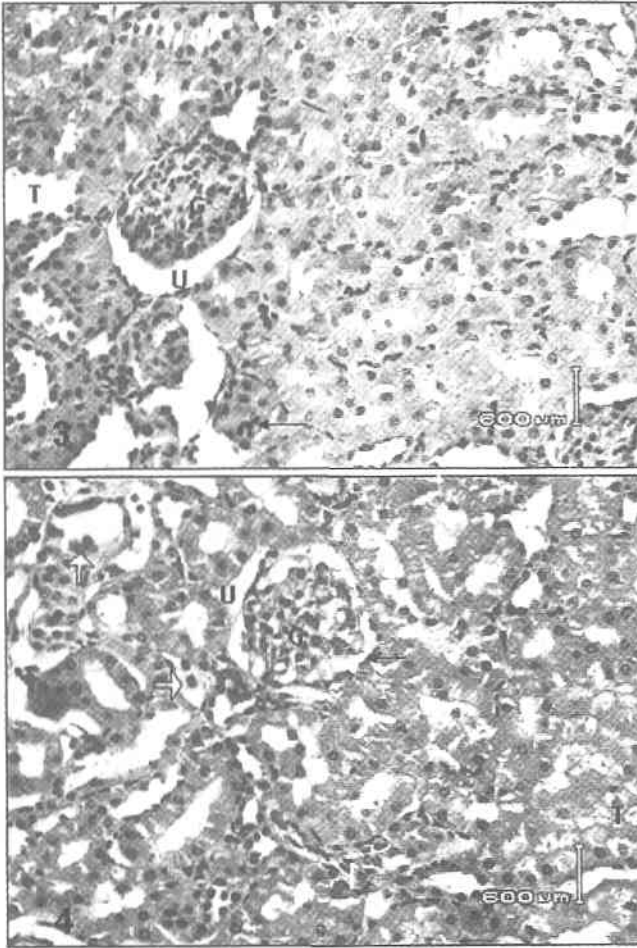


Plate II (Figs. 3 & 4) : Light photomicrographs of the renal cortex of the celecoxib and rofecoxib treated rats.

Fig. (3) : Rats treated with celecoxib. Note the hypercellular glomerulus (G) obscuring the capillary lumina with wide urinary space (U) and focal thickening of the capsular epithelium. Dilated tubules (T) were evident.

(Hx. & E.; x 400)

Fig. (4) : Rats treated with rofecoxib showing the glomerulus (G) and urinary space (U). Note the focal thickening of the capsular epithelium (arrow). Cortical tubules lined by cells having vacuolated cytoplasm (T) were evident. Note other tubules lined by granular necrotic cells or having desquamated cells in their lumen (white arrow). The interstitium shows extensive cellular infiltration (I).

(Hx. & E.; x 400)

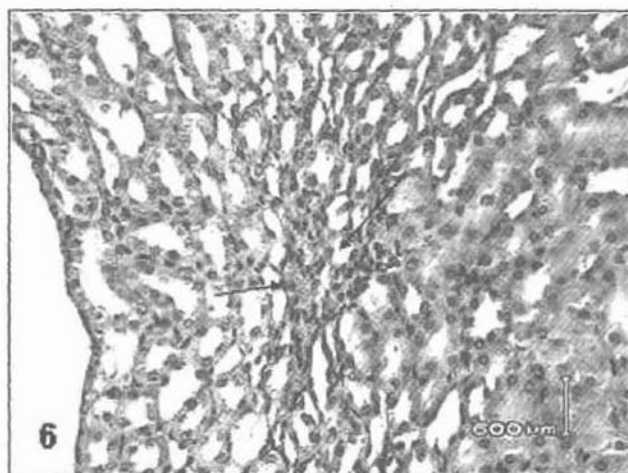
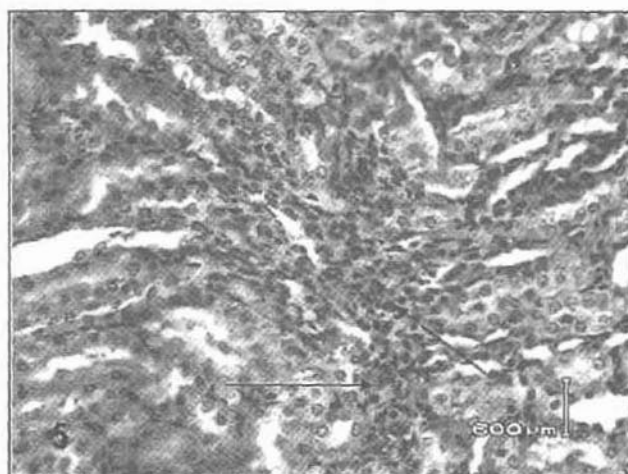


Plate III (Figs. 5 & 6) : Light photomicrographs of the corticomedullary junction of the kidneys in celecoxib and rofecoxib treated rats.

Fig. (5) : Rat treated with celecoxib shows dense cellular infiltration (arrow) that obscures the tubules. (Hx. & E.; x 400)

Fig. (6) : Rat treated with rofecoxib shows moderate cellular infiltrations arrow). (Hx. & E.; x 400)

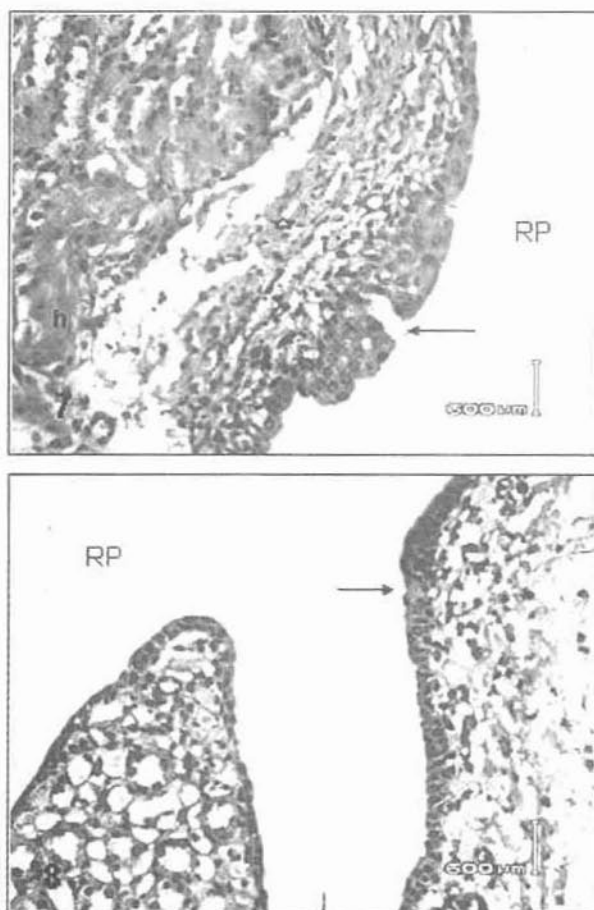


Plate IV (Figs. 7 & 8) : Light photomicrographs of the renal papillae of the celecoxib and rofecoxib treated rats.

Fig. (7) : renal papilla (RP) of rat treated with celecoxib showing eosinophilic materials (*) and focal deposition of hyaline material (h). Note the hyperplasia of the covering epithelium and the focal area of sloughing (arrow).

(Hx. & E.; x 400)

Fig. (8) : renal papilla (RP) of rat treated with rofecoxib showing apparently normal tubule and vasa recta. Note the normal thickening of the epithelial covering (arrow).

(Hx. & E.; x 400)

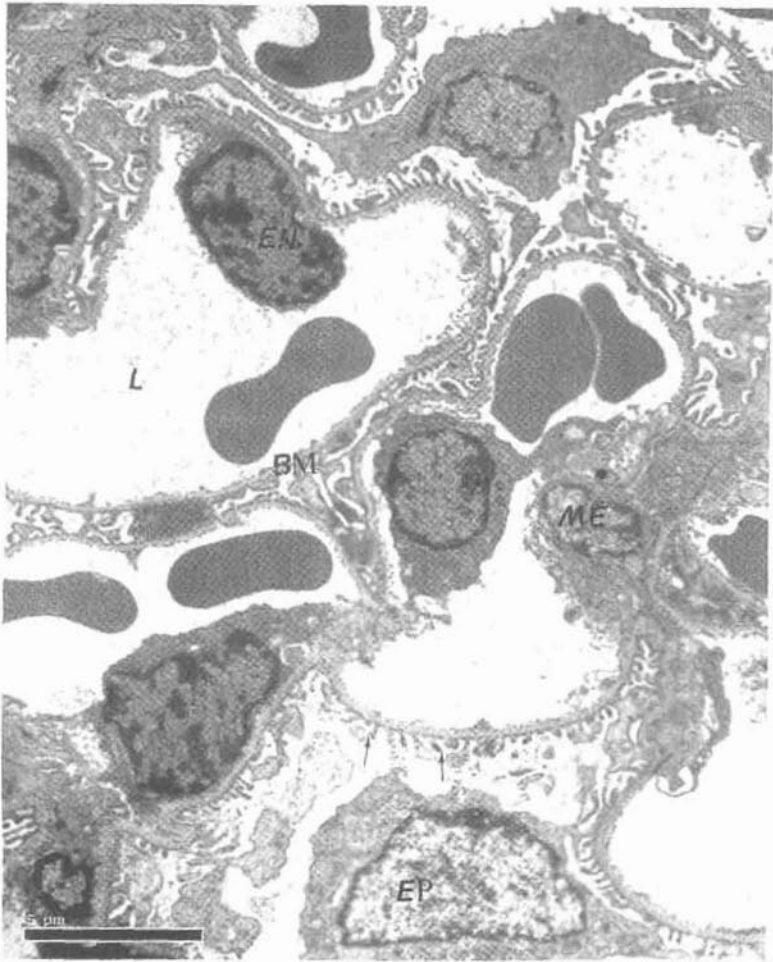


Fig. (9) : Electronmicrograph of the glomerulus of control rat. Note the trabeculae and the foot processes (arrow) of the epithelial cells (EP). Endothelial cells (EN) lined the capillary (L) which is also surrounded by the basement membrane (BM). Mesangial cells (ME).

(x 400)

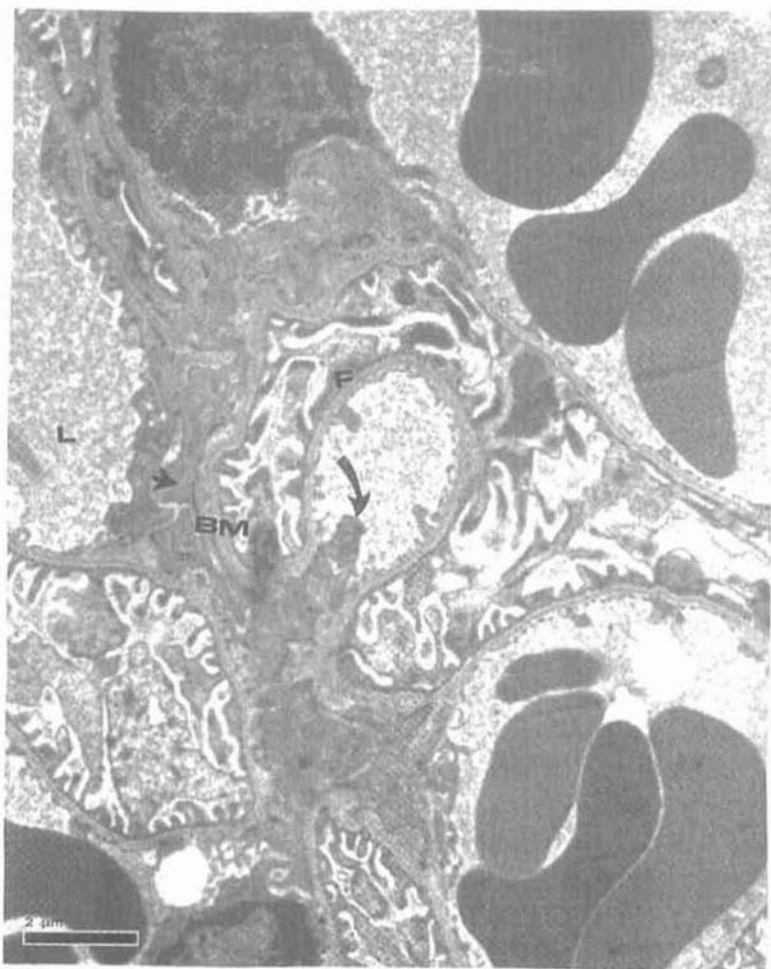


Fig. (10) : Electronmicrograph of the glomerulus of the celecoxib treated rats showing focal effacement of the foot processes of podocyte (F). Note the mesangial migration into the capillary (arrow) and the mesangial interposition (arrowhead) between the thickened basement membrane (BM) and the endothelial lining the capillary which appeared filled with proteinaceous material (L).

(x 6000)

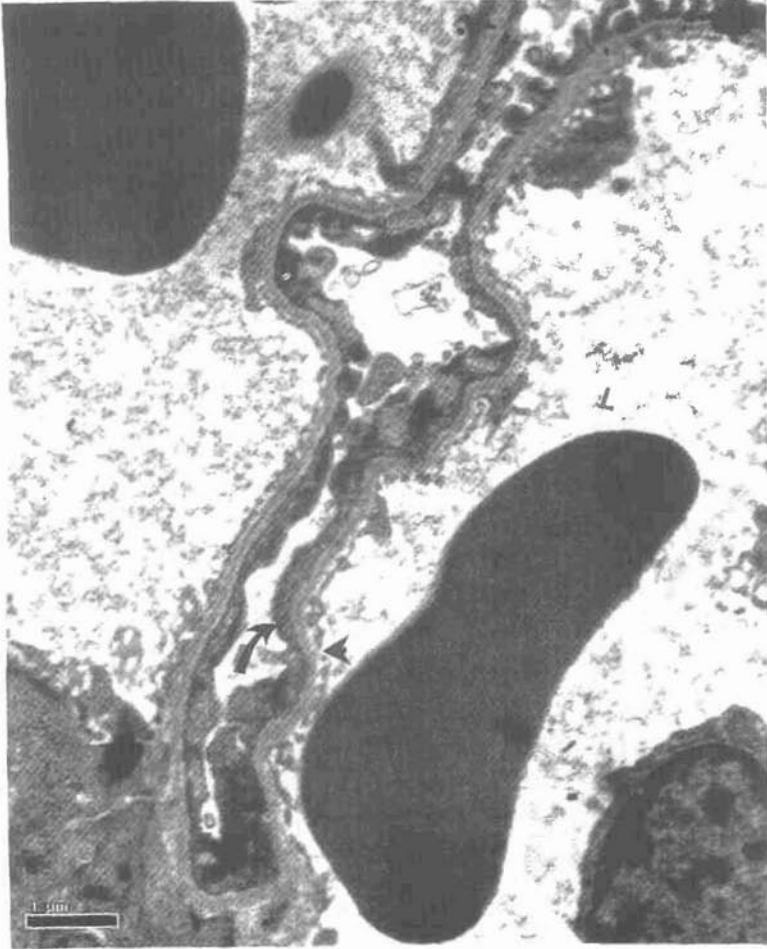


Fig. (11) : Electronmicrograph of the glomerulus of the rofecoxib treated rats showing the effacement of the foot processes of podocytes (arrow). Note the lamina fenestrata (arrowhead) lining the capillary (L).
(x 10000)

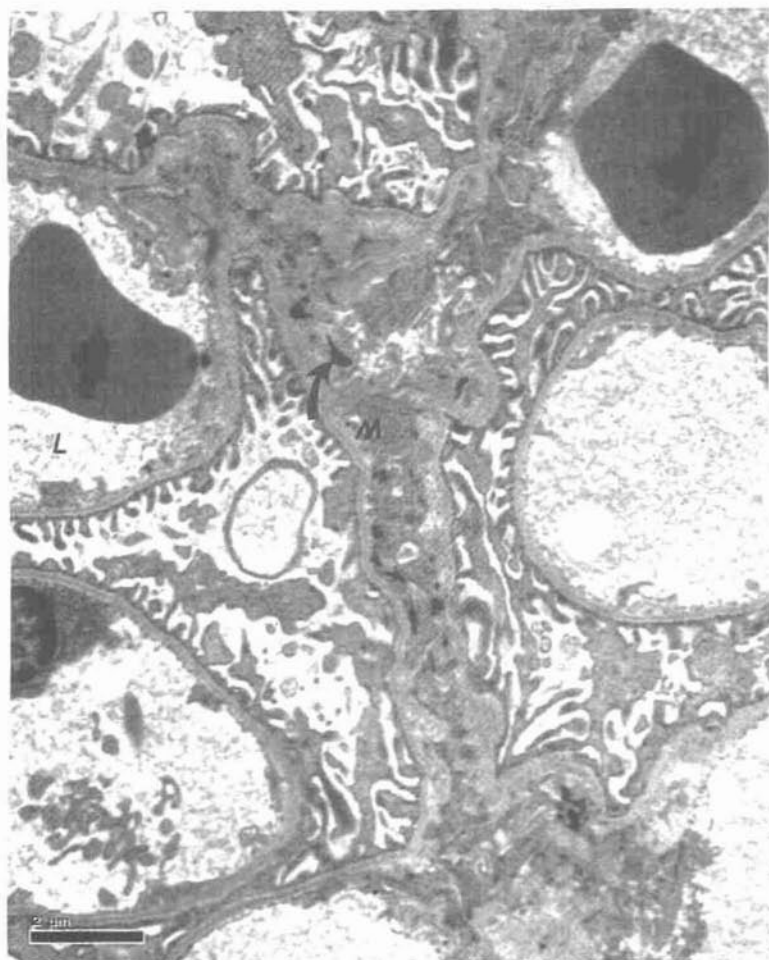


Fig. (12) : Electronmicrograph of the glomerulus of the rofecoxib treated rats showing numerous electron-dense deposits (arrow) in the mesangium (M). Capillary lumen (L).

(x 6000)

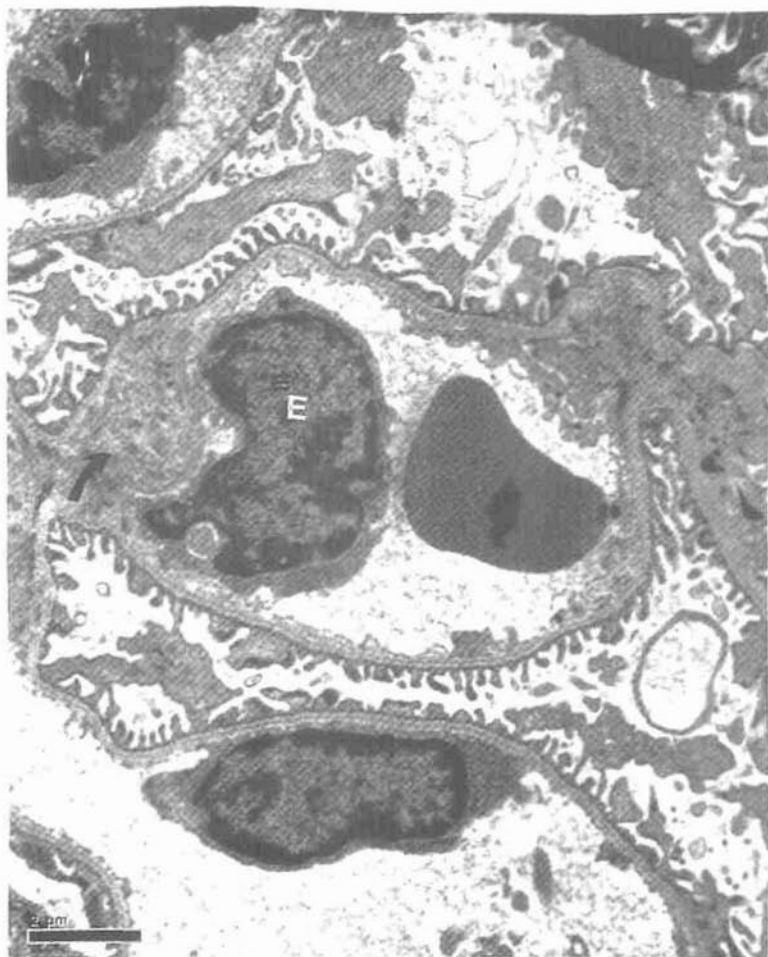


Fig. (13) : Electronmicrograph of the glomerulus of the rofecoxib treated rats showing the interposition of mesangium between the endothelial cells (E) and the capillary basement membrane (arrow). (x 6000)

DISCUSSION

It has recently been hypothesized that selective inhibition of COX-2 could provide the potent anti-inflammatory and analgesic effects of NSAIDs with fewer GI and renal side effects. COX-2 enzyme is mainly cytokine inducible and is expressed in inflammatory cells (Kujubu, 1991). Therefore, specific COX-2 inhibitors, celecoxib and rofecoxib, could enable treatment of pain and inflammation. Furthermore, COX-2 is constitutively expressed in the thick ascending limb of Henle, in glomerulus, in interstitial cells of the papilla and in the macula densa of the kidney in rats (Harris et al., 1994; Komhoff et al., 1997). Moreover, selective inhibition of COX-2 with celecoxib and rofecoxib caused sodium and potassium retention and reduced glomerular filtration rate and effective renal plasma flow (Rossat et al., 1999; Schwartz et al., 2002). Perazella and Tray (2001) suggested that selective COX-2 inhibitors, like NSAIDs could cause acute renal impairment in patients with risk factors that induce prostaglandin-dependent renal function.

The current study extended the previous observations by describing the effect of the selective COX-2 inhibitors celecoxib and rofecoxib on the structure of the kidney in rats. The main affection with celecoxib was in the glomerulus as evident by using both LM and EM. Moreover, dense interstitial cellular infiltration in the corticomedullary junction and prominent papillary necrosis were evident. Papillary necrosis was reported in nephrotoxicity induced by NSAIDs (Molland, 1978). The pathogenesis of papillary damage was either due to direct toxicity or to medullary ischemia. Furthermore and consistent with our findings is the report of a case of biopsy-proven acute interstitial nephritis in a 73 - year - old diabetic women who had taken celecoxib for more than one year (Henaio et al., 2002). Celecoxib also induced nonoliguric acute renal failure in a patient with rheumatoid arthritis (Alkhuja et al., 2002).

In the rofecoxib treated rats the most obvious lesions were in the cortical tubules and interstitium. Proximal tubular necrosis together with tubular hypertrophy and dilatation as a compensatory mechanism for tubular atrophy were evident. There was also diffuse interstitial infiltration with inflammatory cells. Molland (1978) stated that cortical lesions in analgesic nephropathy possibly occurred secondary to papillary necrosis. However, the current study showed that cortical lesion with rofecoxib occurred with sparing of the renal papilla. The EM showed focal effacement of foot processes of podocytes and extensive electron-dense deposits in the mesangium. This was partly in agreement with Rocha and Fernando-Alonso (2001)

reports about a case of biopsy-proven reversible acute interstitial nephritis resulting from rofecoxib treatment in a hypertensive woman with glomerular sparing and absence of electron-dense deposits in mesangium. The proliferation of mesangial cells and the mesangial interposition between the basement membrane and the endothelium observed in celecoxib and rofecoxib treated rats were described in cases of membranoproliferative glomerulonephritis (**Jennette et al., 1998**).

Conventional NSAIDs were associated with substantial renal toxicities including electrolyte disturbances, edema, hypertension, acute and chronic interstitial nephritis, papillary necrosis, glomerular lesions and acute haemodynamic renal failure (**Brater, 1999**). According to the official product circulars, peripheral edema may occur as an adverse event for celecoxib and rofecoxib at a rate higher than the placebo (**Celebrex, 2000; Vioxx, 2001**). Although previous analysis indicated that rofecoxib had significantly greater renal toxicity than celecoxib (**Zhao et al., 2001**) yet, the data comparing the COX-2 inhibitors were difficult to interpret as comparable doses have not been used in clinical trials (**Crafford, 2002**). This was supported by the histopathological finding in this study which showed that in a controlled setting in healthy rats the COX-2 inhibitors induced nephrotoxicity comparably similar to that of nonselective NSAIDs. Moreover, the early speculation that COX-2 inhibitors might represent a class of renal-sparing NSAIDs (**Bombardier et al., 2000; Silverstein et al., 2000**) was not consistent with our study.

In conclusion, we found that increased selectivity for COX-2 did not spare the kidney and on that basis it is recommended that clinicians would carefully follow the renal precautions for COX-2 selective inhibition that are present in their respective product circulars.

SUMMARY

Selective cyclooxygenase-2 inhibitors were recently used for the treatment of pain, fever and inflammation. Celecoxib and rofecoxib, the two COX-2 inhibitors, became the most commonly prescribed medication world wide. Clinical trials using these drugs showed that they had efficacy similar to NSAIDs with marked reduction of the gastrointestinal and renal side effects. The aim of this work was to describe the effects of selective COX-2 inhibitors, celecoxib and rofecoxib, on the structure of the kidney in rats. Thirty Sprague-Dawley rats weighing 200 - 225 g were used. They were divided into three groups 10 rats each. In group I the rats were untreated

and used as control, in group II the rats were treated with celecoxib (10 mg / kg b.w. / day) while in group III the rats were treated with rofecoxib (10 mg / kg b.w. / day). Treatment for the 2nd and 3rd groups was by stomach tube for seven days. Kidneys from rats of all groups were processed for light and electron microscopic examination. Although celecoxib induced hypercellularity of the glomerulus and dilatation of the renal space, yet the major changes were papillary necrosis and dense interstitial inflammatory cellular infiltration at the corticomedullary junction. The EM showed evidence of glomerulonephritis in the form of mesangial proliferation and interposition between the basement membrane and the endothelial cytoplasm. Rofecoxib primarily affected the proximal convoluted tubule which showed segmental dilatation and prominent focal atrophy. Moreover, the cortical interstitium showed extensive cellular infiltration. The EM showed electron-dense deposits in the mesangium. In conclusion, both celecoxib and rofecoxib affected the histological structure of the rat's kidney in a way similar to the analgesic nephropathy induced by NSAIDs.

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تأثير مثبطات السيكو او كسينيز ٢ الخاصة على الكلية فى الفأر :
دراسة باستخدام المجهر الضوئى والمجهر الإلكتروني

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الهدف من هذا البحث هو دراسة تأثير مثبطات سيكوأوكسبجنيز - ٢ الخاصة السيليكوكسيسب والروفيكوكسيسب والتي تم تداولها حديثا واستخدامها كمضادات للالتهابات على نسج الكلى فى الفأر الأبيض . وقد تم استخدام ثلاثون فأرا قسموا إلى ثلاث مجموعات كل واحدة عشرة فئران : المجموعة الأولى لم تتناول أى عقار حيث استخدمت كمجموعة ضابطة والثانية تمت معالجتها بعقار السيليكوكسيسب عشرة مجم لكل كجم من وزن الفأر يوميا لمدة سبعة أيام عن طريق انبوب المعدة . اما فئران المجموعة الثالثة فقد تمت معالجتها بعقار الروفيكوكسيسب عشرة مجم لكل كجم من وزن الفأر يوميا لمدة سبعة أيام عن طريق انبوب المعدة اضا . تم تشريح الفئران واستخراج الكلى ثم فحصها بالميكروسكوب الضوئى والإلكترونى لمعرفة التغيرات التى طرأت عليها حيث وجد الأتى :

كانت عينات فئران المجموعة الضابطة طبيعية ، أما الحالات التى عولجت بعقار سيليكوكسيسب فقد أظهرت تجمعات الخلايا المضادة للالتهابات وتأثر الحويصلات فى القشرة . أما الحالات التى تناولت الروفيكوكسيسب فكان معظم التأثير على القنوات البولية ونخاع الكلية . وهذا يثبت أن كلا من السيليكوكسيسب والروفيكوكسيسب لهما تأثيرهما على أنسجة الكلى فى الفأر الأبيض مما قد يؤثر على وظيفة الكلى مثلهم مثل العقاقير المضادة للالتهابات الغير المتخصصة .