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## The Effect of Diclofenac Sodium on the Renal Parenchyma During Complete Unilateral Ureteral Obstruction of the Rats

Received: November 4, 1996

**Abstract:** An experimental study was designed to investigate the effect of diclofenac sodium (DS) on both renal parenchyma during complete unilateral ureteral obstruction. In 40 adult rats, left ureteropelvic junction were completely obstructed. Rats were divided into 4 equal groups and treated with cefoperazone (Group 2), DS (Group 3), cefoperazone and DS (Group 4) for one week postoperatively. No drug was given to Group 1 (control). Then, both kidneys of all rats were removed and examined histopathologically. The parenchymal thickness of left kidneys were less than those of rights in all

groups. Renal capsuli were moderately thickened in all obstructed kidneys. There were congestion in glomeruli and parenchymas of all kidneys, dilatation in proximal and distal tubuli of obstructed kidneys, and focal lymphocytic infiltration in all kidneys except right kidneys in group 1 and 2. There was hemorrhage in all kidneys of Group 3 and 4. These findings support the fact that DS may cause renal complications during complete ureteral obstruction.

**Key Words:** Ureteral obstruction, hydronephrosis, diclofenac, cefoperazone.

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### Introduction

Obstruction of the urinary tract is a potential cause of renal failure. Acute unilateral obstruction of the kidney is associated with an increase in pelvic pressure followed by a decrease in ipsilateral renal blood flow (1). Concomitantly with these pressure changes the synthesis of renal vasoactive hormones is changed. There are different opinions about the effects of prostaglandins (PGs) on renal functions and the administration of PG synthesis inhibitors during acute urinary obstruction (AUO) (1-5). On the other hand, the lymphocytic infiltration and infection may occur in the renal parenchyma because of the decreased renal blood flow during AUO. Therefore, it is expected that prophylactic antibiotics are useful during the ureteral obstruction. This experimental study was planned to investigate the effects of diclofenac sodium (DS) which is a PGs and thromboxanes (TXs) synthesis inhibitor on both renal parenchyma during complete unilateral ureteral obstruction.

### Materials and Methods

#### Animals

Adult albino rats (Sprague-Dawley) weighing 200-

250g were used for the study. The animals were allowed at least 7 days for acclimation at a constant temperature with a 12-h light/dark cycle. They were provided with standart pellet food and water ad libitum before and after surgery.

#### Surgical Procedure

The rats were divided into 4 groups containing 10 rats in each group. By ketamine anaesthesia (5 mg/kg i.p), and by a midline laparotomy, left ureteropelvic junction was completely ligated with a 4-0 silk. Then, abdomen was closed with a 3-0 silk suture. No drug was given postoperatively to Group 1 (control). Cefoperazone (Cefobid-Pfizer, Istanbul) 100 mg/kg/day to Group 2, and DS (Voltaren-Ciba, Istanbul) 2 mg/kg/day to Group 3 were injected i.m. In Group 4, the same doses of both drugs were injected i.m. These medications were administrated for one week postoperatively in Groups 2,3 and 4. Finally, all rats were sacrificed and their both kidneys were removed.

#### Histological Examination

The kidneys were fixed with 10% neutral buffered formaline. After 24 hours fixation kidneys were bisected in corticomedullar plane and a 2 mm-thick tissue was processed and paraffin embedded routinely. Hematoxylin and eosin stained sections were examined

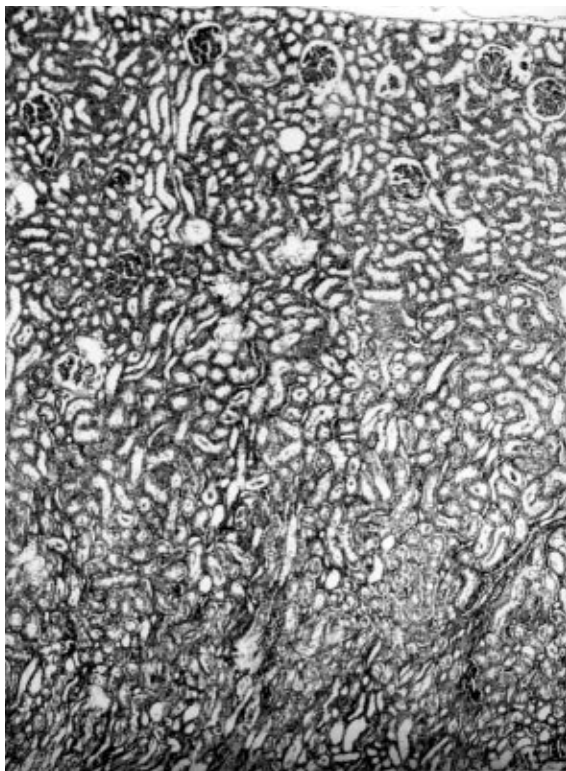


Figure 1. Histological view of normal kidney of the rat. (H-E, x40 original magnification)

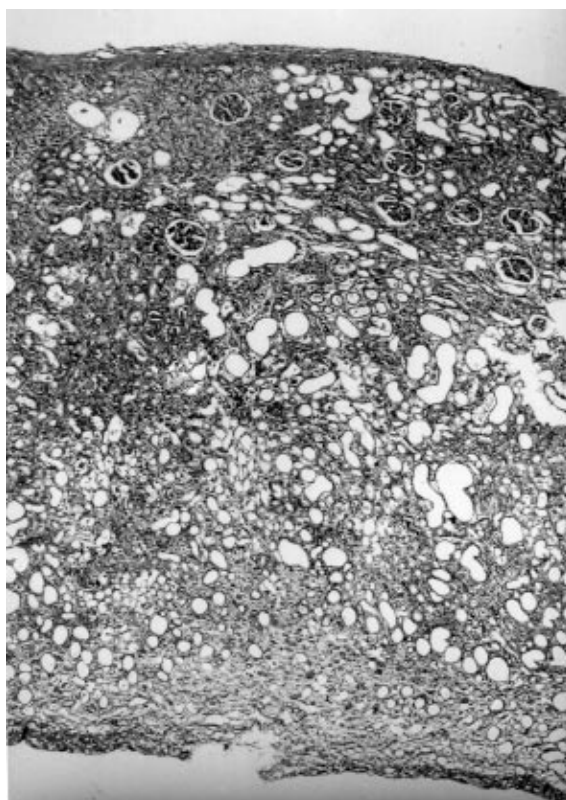


Figure 2. Capsular thicknesses: There are marked capsular fibrosis and moderate tubular dilatation in the rat kidney. (H-E, x40 original magnification)

by light microscope. The parenchymal and capsular thickness of the kidneys were measured by Carl Zeiss Jena screw ocular eyepiece micrometer.

#### Statistical Analysis

The differences between left and right kidney thicknesses were statistically evaluated with Student t test.

#### Results

In all groups the parenchymal thickness of left (obstructed) kidneys were less than those of rights as shown in Table I. The thickness of left and right kidneys were significantly different ( $p < 0.05$ ). The renal capsuli of right kidneys were normal in all groups, but there were moderate capsular thickening in all obstructed kidneys (Fig.2). Congestion was shown in glomeruli of all kidneys (Fig.4). Proximal and distal tubuli were dilated in obstructed kidneys (Fig.3), but normal in right kidneys. Focal lymphocytic infiltration

(FLI) were determined in all kidneys except right kidneys of Groups 1 and 2 (Fig.3). There was hemorrhage in all kidneys of Groups 3 and 4 (Figure 5). Congestion was shown in vessels of all kidneys. However, this finding was more severe in Groups 3 and 4 than the others.

#### Discussion

Acute unilateral obstruction of the kidney is a potential cause of renal failure. This condition may be associated with renal stones, ureteral kinking, intraluminal polyps or valves (6). However, total obstructions are rare in clinical practice, in contrast to partial ones. In this study, adult experimental rats were used and complete ureteral obstruction were performed. Therefore, to apply the results of this experimental model to congenital or chronic obstructive nephropathies as in ureteropelvic junction obstruction may be misleading.

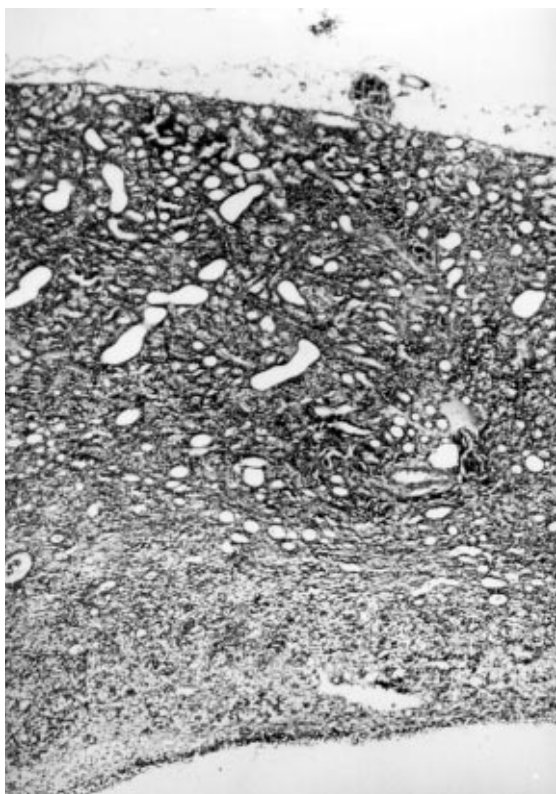


Figure 3. Tubular dilatation: There are marked tubular dilatation and focal lymphocytic infiltration in this kidney. (H-E, x40 original magnification)

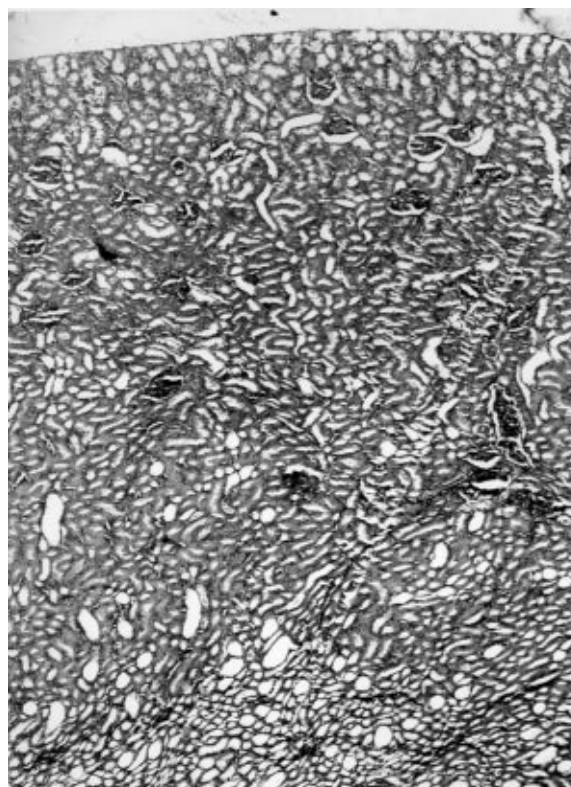


Figure 4. Congestion: There are severe vascular congestion, minimal tubular dilatation in this picture. (H-E, x40 original magnification)

Table 1. Results of histopathological examination

Groups	*	Parenchymal thickness(mm)	Capsular thickness**	Glomeruli	Tubuli	Int. FLI***	Rate of hemorrhh(%)	Vessels ****
1	R	5.9	N	Normal	Normal	-	-	+
	L	2.5	++	Congestion	Dilated	++	-	+
2	R	5.6	N	Normal	Normal	-	-	+
	L	2.5	++	Congestion	Dilated	++	-	+
3	R	6.0	N	Congestion	Normal	++,H	70	++
	L	3.4	+	Congestion	Dilated	+++,H	80	+++
4	R	5.5	N	Congestion	Normal	+,H	60	++
	L	2,9	+	Congestion	Dilated	+++,H	80	++

(\*)R:right, L: left kidney.

(\*\*)Capsular thickness: N (normal);<10micron, +:10-50 micron, ++:>50 micron

(\*\*\*)Interst, FLI (Interstitial Focal Lymphocytic Infiltration): +: minimal, ++: moderate, +++:severe. H: Hemorrhage

(\*\*\*\*)Renal vascular congestion: +minimal, ++:moderate, +++:severe

It was not amazing that parenchymal thickness of obstructed kidneys were decreased according to contra-

lateral ones in all groups. This finding was probably due to the increased intrarenal pressure and hydro-nephrosis of affected kidneys (7,8,9). The thickening

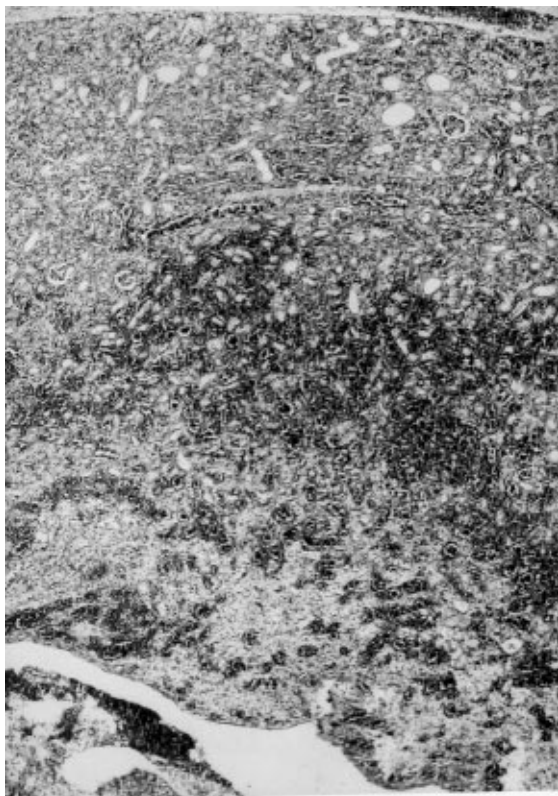


Figure 5. Hemorrhage: There are severe interstitial hemorrhage, some tubular dilatation and vascular congestion. (H-E, x40 original magnification)

of renal capsule in obstructed kidneys of all groups may be related to the fibrosis.

The PGs and TXs have major well-documented effects on smooth muscles and platelets. The non-steroidal anti-inflammatory drugs (NSAID) (eg, aspirin, indomethacin, ibuprofen, diclofenac sodium) block both PG and TX formation by inhibiting cyclooxygenase ac-

tivity (10,11). As a result, platelet aggregation is strongly inhibited. We consider that severe renal parenchymal congestion and hemorrhage seen in group 3 and 4 are due to PG and TX synthesis inhibition by DS. Indeed, hemorrhagic diathesis due to administration of DS has already been reported (12).

Interstitial FLI was seen in all obstructed kidney (Table 1). Because the neutrophilic infiltration rather than lymphocytic one are seen during the acute phase of infection, FLI must not probably due to the infection. We consider that FLI in obstructed kidneys was due to urinary obstruction rather than the infection. Therefore, cefoperazone was not useful during the first week in Groups 3 and 4.

On the other hand, by preventing arachidonic acid conversion via the cyclooxygenase pathway, NSAIDs may cause more substrate to be metabolized through the lipoxygenase pathway, leading to an increased formation of inflammatory leukotrienes (10). The leukotrienes are chemotactic and chemokinetic agents formed from eicosanoic acids in polymorphonuclear leukocytes, platelets and macrophages by the lipoxygenase pathway, in response to both immunologic and non-immunologic stimuli (13). We consider that the FLI in Groups 3 and 4 may also be explained by this mechanism together with urinary obstruction.

In conclusion, although the administration of DS has been recommended by some authors in the patients with renal colic (2,14,15), it can be predicted that DS may cause renal complications during complete ureteral obstruction.

### Acknowledgement

This study was supported by Research Fund of Research Fund of Erciyes University (Pr.No.95.01.036).

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