



## EFFECT OF TAURINE ON RENAL PATHOPHYSIOLOGY IN EXPERIMENTAL ANIMALS

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### ABSTRACT

Taurine, an essential amino acid (2-amino ethanesulfonic acid) and endogenous antioxidant agent has been studied as an antioxidant agent in renal impairment however the efficacy is not very well documented and its impact on exogenous supplementation in normal renal physiology has conflicting results. Therefore the present study has been undertaken to evaluate the role of Taurine supplementation in normal physiology and impaired kidney status due to high dose Diclofenac in rat models. Albino rats were divided into groups of 4 animals each. Test I(Diclofenac only), Test II( Taurine only), Test III(Diclofenac + Taurine), Test IV(Diclofenac + Taurine + N-acetylcysteine). Diclofenac 13.5mg/kg bw/day i.m. given for 10 days. Taurine(7.5mg/kg/day) and N-acetylcysteine(NAC(40 mg/kg) were given orally for 2 wks starting from day 5 of induced nephrotoxicity in respective groups. Serum urea and creatinine levels were measured after 1wk and 2wks of test drug administration and histopathological examination conducted. High dose of Diclofenac i.m. produced biochemical and histopathological features of nephrotoxicity. Biochemical and histopathological parameters also revealed features of nephrotoxicity in taurine only treated group. The group treated with Taurine + NAC for 2wks had significantly lowered nephrotoxic features compared to only Taurine treated group in nephrotoxic models.

**KEY WORDS:** Taurine, N-acetylcysteine, Diclofenac, Nephrotoxicity



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## INTRODUCTION

Taurine is an essential amino acid (2-amino ethanesulfonic acid) and endogenous antioxidant agent. Taurine has several beneficial physiological and biochemical effects in vitro and in vivo in experimental animals. It has cardiogenic actions, participates in osmoregulation, stabilizes the membrane potential in skeletal muscle, affects calcium ion kinetics, has antioxidant and anti-inflammatory properties and acts as a neurotransmitter.<sup>1,2,3</sup> It has been studied of its role in renal physiology and its metabolism has been documented as excretion of the compound as such or in the form of taurocholate or related bile salts. It has been studied of its effect on renal pathology however due to complex metabolism in the body, use of the compound at variable doses in normal physiological condition has been of questionable and variable results.<sup>4,5</sup> The renal has very high susceptibility to nephrotoxic injury and occurs in response to a number of pharmacological compounds.<sup>6,7,8</sup> N-acetylcysteine (NAC), a cysteine molecule having antioxidant properties has been explored to have nephroprotective potential. Hence the study has been conducted to evaluate the effect of taurine in normal renal physiological condition and compromised renal status in experimental animal models.

Groups	Drugs
Test I	Diclofenac
Test II	Taurine
Test III	Diclofenac + Taurine
Test IV	Diclofenac +Taurine + NAC

**Nephrotoxicity induction: Diclofenac 13.5mg/kg/day i.m for 10 days in the gluteus muscle.<sup>9</sup> Taurine : 7.5 mg/kg/day for 2 wks per oral. N-acetylcysteine : 40 mg/kg/day for 2 wks per oral.**

### Test drug Administration

Test drugs (Taurine and NAC) were started from day 5 of induced nephrotoxicity in Test III, IV and given for 2 weeks at the respective test groups.

### Parameters assessed

Serum Urea and Creatinine and Histopathology of Kidney

### Statistical analysis

The tests of significance of the results of serum urea and creatinine were calculated using one way ANOVA test followed by Dunnett's 't' test. P value less than 0.05 was considered significant. (spss 16)

## METHODS

### Study design

Albino rats were taken for the study and divided into test groups as Test I, Test II, Test III, Test IV of 4 animals each (total 16 animals). The number of animals and the procedures to be conducted were approved by the Institutional Animal Ethics Committee (IAEC) 1596/GO/a/12/CPCSEA

### Inclusion and exclusion criteria

The albino rats of either sex weighing 150 to 250gm were chosen for the study. Animals with baseline serum urea and creatinine level in the range of 10-45 mg/dl and 0.5-1.4 mg/dl respectively were considered for the study.

### Procedures

#### Animal selection

Adult albino rats were obtained from the central animal house RIMS, Imphal. The animals were housed in standard conditions of temperature, relative humidity (55 ± 5%), and light (12 h light/dark cycles) were used. They were fed with standard pellet diet and water *ad libitum*. The animals were divided into 4 groups of 4 animals each and were treated with respective drugs as shown below

## RESULTS

The study showed that the changes in the body weight of the rats before and after administration of the drugs were not prominent. No changes in skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system and motor activity and behaviour pattern and also sign of salivation, diarrhoea, lethargy were noted. The onset of toxicity and signs of toxicity were also not observed. Serum was analysed for urea, creatinine and histopathology of the kidney were done.

### Biochemical parameters

Blood Urea levels were estimated by Direct Colorimetry method using Diacetyl Monoxime Reagent and Creatinine level by Alkaline Picrate Method.<sup>10</sup>

**Table1**  
**Serum Urea values**

Groups	Baseline values	After 1 wk	After 2 wks
Test I	19.25 ± 1.75	41.50 ± 1.84*	47.00 ± 0.91*
Test II	18.75 ± 2.05	25.00 ± 2.64	30.50 ± 2.50
Test III	20.50 ± 3.17	44.25 ± 1.10*	42.50 ± 0.50
Test IV	18.75 ± 1.65	34.75 ± 4.21	39.25 ± 1.38*
Between group	df = 11		
Within group	df = 36	F = 24.76	

Values are mean ± SEM, \*P<0.05, significant compared to baseline

**Table 2**  
**Serum Creatinine values**

Groups	Baseline values	After 1 wk	After 2 wks
Test I	0.75 ± 0.06	1.65 ± 0.06*	1.97 ± 0.07*
Test II	0.72 ± 0.02	0.80 ± 0.04	0.09 ± 0.00
Test III	0.70 ± 0.04	1.57 ± 0.06*	1.40 ± 0.09*
Test IV	0.77 ± 0.06	1.25 ± 0.09	0.97 ± 0.07
Between group		df = 11	
Within group	df = 36		F = 46.22

Values are mean ± SEM, \*P<0.05, significant compared to baseline

**Pathological Scoring**

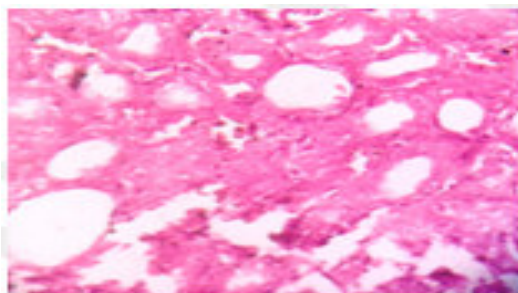
Animals were sacrificed under high dose ether and carcasses were buried deep in the ground covered with lime and disinfectants.<sup>11</sup> The histological scoring was performed as a combined score of the following

parameters assessed (Tubular degeneration, Necrosis, Tubular dilatation, Hyaline protein casts, Interstitial leucocytic infiltration and glomerular congestion) and graded(FDA guidelines).

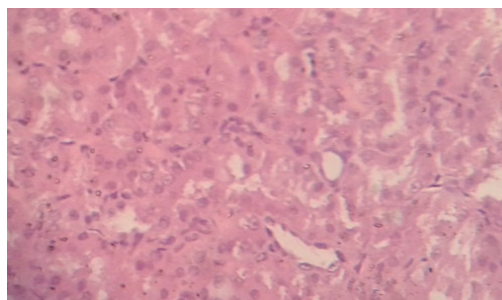
**Table 3**  
**Histopathological scoring**

Histological parameters	Taurine	Diclofenac	Diclofenac + taurine	Diclo+NAC+Taurine
Tubular degeneration	-	+++	+	-
Tubular necrosis	-	+++	+	-
Tubular dilatation	+	+++	++	+
Hyaline cast	+	+	+	+
Interstitial leucocytic infiltration	+	+++	+	+
Glomerular congestion	++	-	-	-

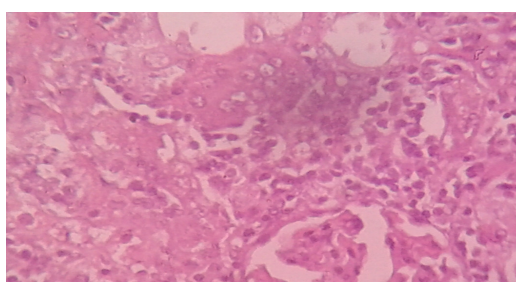
Scoring: (-)nil, (+) mild, (++)moderate, (+++) severe



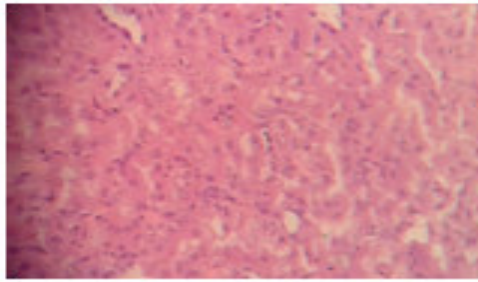
**Figure 1**  
**Effect of Taurine on Histopathology of Kidney**



**Figure 2**  
**Effect of Diclofenac on Histopathology of Kidney**



**Figure 3**  
**Effect of Diclofenac + Taurine on Histopathology of Kidney**



**Figure 4**  
**Effect of Taurine +Diclofenac + NAC on Histopathology of Kidney**

Serum urea values were significant in Diclofenac only treated group (Test I) at 1wk and 2wks compared to baseline values at  $P < 0.05$ . Also the urea levels were significant in Test IV group of animals treated with Taurine+Diclofenac+NAC at 2 wks compared to baseline values at  $P < 0.05$ . Serum creatinine values were significant in Diclofenac only treated group and animals treated with Diclofenac+Taurine (Test III) at 1wk and 2 wks compared to baseline values at  $P < 0.05$ . Histopathological features revealed mild changes in taurine group and severe nephrotoxic changes in diclofenac group. Test group treated with Taurine +NAC+Diclofenac shows only mild nephrotoxic changes compared to Diclofenac +Taurine treated group.

## DISCUSSION

Diclofenac, a non-steroidal anti-inflammatory drug, have an adverse effect on renal physiology. Inhibit renal prostaglandin production, limiting renal afferent vasodilation, increases afferent resistance; this causes the glomerular capillary pressure to drop below normal values and the GFR to decrease. This manifests as acute renal dysfunction, fluid and electrolyte disorders and pathologically reveal renal papillary necrosis, interstitial nephritis.<sup>9,12</sup> Serum analysis of urea and creatinine were impaired and severe tubular damage were observed in the study. In this study, Taurine only treated group shows mild tubular dilatation, hyaline cast, leucocytic infiltration and moderate glomerular congestion in histopathological examination of kidney. The findings could be correlated to some complex mechanism of ion transport across renal tissue.<sup>4</sup> Studies have shown that there has been wide variation in the fractional excretion of taurine from kidney.<sup>5</sup> In the present study, serum creatinine level was significantly reduced by Taurine in Diclofenac induced nephrotoxicity. This probably occurs in part due to scavenging of reactive oxygen species responsible for renal damage.<sup>13,14,15</sup> The reduction in the renal damage is characterized in histopathological examination of renal tissue by only mild changes in tubular

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degeneration, necrosis and leucocytic infiltration compared to severe changes observed in Diclofenac treated group.<sup>16,17</sup> Serum urea level is significantly reduced by NAC+Taurine in Diclofenac induced nephrotoxicity in this study. And the absence of tubular degeneration, necrosis and glomerular congestion suggests the potential role of NAC+Taurine to ameliorate the oxidative stress due to its antioxidant property.<sup>18,19</sup> Studies have demonstrated that the mechanisms regulating NAC-induced renoprotective effects involved, in addition to antioxidant effects, augmentation of PGE2 release by renal tissue and also by combating the compromised renal blood flow. It acts by inducing renal vasodilatation, decreasing oxidative stress via inhibition of intrarenal ROS content and, most importantly, restoration of intrarenal PGE2 release back to the normal levels.<sup>20,21</sup> In another study, acute kidney injury induced by oxidative stress due to warfarin-related nephropathy could be ameliorated by NAC.<sup>14</sup> Studies on Taurine has revealed that it removes Hypochlorous acid (HOCL) by reacting with it to form Chlorotaurine and that HOCl stress impairs Superoxide dismutase (SOD) activity, hence have an antioxidant role.<sup>22,23</sup> Hence in this study, the combined effect of NAC and Taurine could be attributed for reduction in the nephrotoxic changes observed. And the findings support the antioxidant property in compromised renal status in this study.

## CONCLUSION

It could be concluded that Taurine supplementation produced an adverse effect on normal renal physiology however Taurine attenuated the diclofenac induced nephrotoxicity more effectively by the simultaneous administration of Taurine and N-acetylcysteine. This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

## CONFLICT OF INTEREST

There is no actual or potential conflict of interest.

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