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ACECLOFENAC-INDUCED PHYSICOCHEMICAL ALTERATIONS IN TOXICITY AMONG MALE ALBINO RATS

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ABSTRACT

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with adverse renal effects caused by the reduction in synthesis of renal prostaglandins in sensitive persons or animal species, and potentially during long-term use in non-sensitive persons if resistance to side effects decreases with age. The effects of Aceclofenac sodium on the kidneys were studied during 4 1/2 hours in eight patients with normal renal function. Urinary output decreased within 10 min after the injection, and maximally by 80%. The renal plasma flow and the glomerular filtration rate initially diminished significantly, by 35%, but began to increase after only 2 hours. The dominant and persistent effect was a reduction of free water clearance, with maximum fall from 5.9 to 0.08ml/min after 2 1/2 hours. Aim: The aim of this study was to evaluate the effects of Aceclofenac-induced acute nephrotoxicity using biochemical parameters in rats. ***Methods****: 12 male Wistar rats allotted in 4 equal groups were intraperitoneally injected with 0, 10, 50 and 100mg/kg Aceclofenac, respectively and 12 hours after injection, blood serum samples were collected for assessment of basic renal function test parameters such as urea, creatinine, and uric acid, sodium, Potassium.* ***Results****: Rats treated up to 50mg/kg Aceclofenac were considered to be within normal range in rats. By increase in dose more than 50mg/kg showed significant increases in uremia were evidenced in intoxicated animals. Observed specifically in group IV Rats.* ***Conclusions****: In this study, uremia, as an indicator of kidney damage, was significantly increased depending on dose. Aceclofenac may cause kidney damage depending on dose and this effect may also be observed. NSAIDs-induced nephrotoxicity may be due to the inhibitory effect of these drugs on prostaglandin synthesis, thus causing kidney ischemia.*

KEY WORDS

Aceclofenac, Impaired renal function, Nephrotoxicity, Uremia

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most common classes of medications used worldwide, with an estimated usage of >30 million per day.1 NSAIDs exert anti-inflammatory, analgesic and antipyretic effects through the suppression of prostaglandin (PG) synthesis, by inhibiting the enzyme cyclooxygenase (COX). The gastrointestinal tract and the kidneys are important targets for untoward clinical events associated with the use of NSAIDs.2 Approximately 2.5 million Americans experience NSAID-mediated renal effects yearly. Nonselective NSAIDs inhibit both COX-1 (expressed constitutively in the kidney) and COX-2 (inducible in most tissues in response to injury or inflammation, but also present at detectable levels in normal adult mammalian kidneys), the rate-limiting enzymes for the production of PGs and thromboxane (TX) COX-2 is regulated in response to intravascular volume

COX-1 functions mainly in the control of renal hemodynamic and glomerular filtration rate (GFR), while COX-2 functions primarily affect salt and water excretion.3 Blockade of either or both of these enzymes can have, therefore, different effects on renal function. PGs regulate a wide variety of renal functions. PGE2 is

considered to be mainly a tubular PG and PGI2 a vascular PG. However, renal arterioles, tubules, medullary interstitial cells, and mesangial cells are able to produce both PGE2 and PGI2. PGE2 regulates sodium and chloride transport in the loop of Henle and modulates water transport and renal medullary blood flow.4 The physiological effects of PG2 are mediated through the four G-protein-coupled transmembrane prostaglandin receptors EP1, EP2, EP3, and EP4. PGI2 regulates renal vascular tone, GFR and renin release COX-2 activates the renin-angiotensin system, while an increased activity of the renin-angiotensin system inhibits COX-2. PGI2 and PGE2 increase potassium secretion primarily by stimulating the secretion of renin and activating the renin-angiotensin-aldosterone system.5 Macula densa sensing of tubule NaCl concentration at the distal end of the loop of Henle serves as a primary regulatory step in renin secretion and tubuloglomerular feedback. Sodium retention is a well-described feature of all nonselective NSAIDs due to inhibition of COX-2 by these drugs.6 Therefore, it is predictable that COX-2 selective inhibitors may have similar effects. Some serum parameters are used to evaluate organ damage. Increased serum urea and creatinine concentrations are accepted as indicators of kidney damage. It has been shown that Aceclofenac may cause nephrotoxicity in rodents and increased serum urea and creatinine concentrations are accepted as markers of infection- and chemical agent-induced nephrotoxicity in rats.7

METHODS

This prospective interventional study was conducted for a period of 3 months from August to November 2018 in the department of pharmacology which is attached to well-constructed animal house section in CIPRA LABS. Institutional animal ethical committee approval was given by the committee members on July 2015.Totally 12 male Wister rats of weight around 150-250 grams were divided into 4 equal groups. The animals were housed under 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.

- Group - I receive (0mg) of Aceclofenac.
- Group - II (10mg) of Aceclofenac.
- Group - III (50mg) of Aceclofenac.
- Group IV (100mg) of Aceclofenac.

Diclofenac was injected by intraperitoneally after 12 hours after injection, blood serum samples were collected for assessment of basic renal function test parameters such as urea, creatinine, and uric acid, sodium, Potassium. Biochemical analysis of renal parameters was analyzed by automated analyzer [ATICO Med Lab Analyser1781].

Statistical analysis

The tests of significance of the results of basic renal parameters were calculated using one-way ANOVA test followed by students paired' test. P value less than 0.05was considered significant (SPSS 18.0).

RESULTS

Totally 12 male Wister rats of weight around 150-250 grams were divided into 4 equal groups. The animals were housed under 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.

Aceclofenac was injected by intraperitoneally after 12 hours after injection, blood serum samples were collected for assessment of basic renal function test parameters such as urea, creatinine, and uric acid, sodium, Potassium. In a group, I, II, II serum urea, serum creatinine, serum uric acid, sodium, and potassium level is found to be in within normal range which doesn't show gross variations of p-value <0.005which is not statically significant. In group IV serum urea level is found to be high than the normal range when compared to other groups of p-value <0.001 which is found to be statically significant.

Table: 1 The renal profile parameters among 4 groups of male Albino wistar rats after the specified dosage of Aceclofenac administration (n=12).

Renal profile parameters	Group-I (N=3) 0mg	Group-II (N=3) 10mg	Group-III (N=3) 50mg	Group-IV (N=3) 100mg
Urea (mg/dl)	18.11 ± 0.82	23.21±1.98	29.45±3.44	45.98±2.31
Uric acid (mg/dl)	8.76±8.9	14.54±5.6	19.12±9.0	22.90±0.7
Serum creatinine (mg/dl)	4.67±4.5	17.30±0.66	23.09±0.67	41.66±0.56
Sodium (mEq/L)	151.07±0.83	160.01±0.77	165±8.9	170.88±4.5
Potassium (mEq/L)	6.0 ±0.5	8.08±0.3	9.03±0.5	11.08±7.8

DISCUSSION

Aceclofenac, 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.8 This manifests as acute renal dysfunction, fluid, and electrolyte disorders and pathologically reveal renal papillary necrosis, interstitial nephritis.9 Serum analysis of urea, creatinine, uric acid, sodium, potassium was impaired and severe tubular damage was observed in the study. DCL sodium-induced nephrotoxicity was manifested by elevation in the serum levels of creatinine, urea, and uric acid, and was confirmed through oxidative stress disturbances that were previously reported by many authors.10 Creatinine is an anhydride of creatine and is formed by spontaneous and irreversible reaction during skeletal muscle metabolism. Serum creatinine is one of the kidney related variables that indicate renal toxicity. Creatinine may be indicative of kidney-specific physiological disorders.11 An increase in serum creatinine is a biomarker for renal damage. Urea is formed by the liver and considered the main end product of protein catabolism in carnivorous and omnivorous species. Plasma urea levels can be a reliable indication of renal function as a significant.12 Uric acid is produced by the breakdown of purines and by straight synthesis from 5-phosphoribosyl pyrophosphate (5-PRPP) and glutamine. Uric acid is passed in the urine in humans, but in other mammals, uric acid is further oxidized to allantoin before excretion. Another explanation of the elevated serum uric acid level in DCL group is the defence mechanisms against free radical-created oxidative damage causes an increase in the concentration of uric acid (electron donors) in order to reduce free radicals.13 This effect may aggravate the condition of renal damage resulted from uric acid. Chemokines such as monocyte chemoattractant protein-1 (MCP-1) are expressed in glomeruli of animals and humans with glomerulonephritis. MCP-1 is involved in the monocyte/macrophage infiltration into glomeruli and the renal interstitium.14 Mesangial cell production and release of MCP-1 is stimulated by cytokines and growth factors while dexamethasone or PGE reduces the glomerular MCP-1 expression, suggesting that endogenously formed PGs can modulate the formation of MCP-1 and influence the clinical outcome of experimental glomerulonephritis. In very rare cases, NSAIDs may induce glomerular disease, such as membranous nephropathy which is clinically complicated by nephrotic syndrome.15 Not only renal transplant patients but also patients with different forms of glomerulonephritis (e.g., membranous nephropathy, focal segmental glomerulosclerosis, steroid-resistant minimal change nephropathy) may be treated with a calcineurin inhibitor.16 The kidney is vulnerable toward adverse effects of the calcineurin inhibitors cyclosporine A and tacrolimus, including a decrease of GFR, tubular dysfunction, glomerulosclerosis, and renal interstitial fibrosis.17 When possible, selective and nonselective NSAIDs should be avoided in patients with CKD, congestive heart failure, or liver cirrhosis to prevent ARF. There is some evidence to support an increased incidence of adverse effects with increased dosing of selective and nonselective NSAIDs Some medications, such as ACE inhibitors, angiotensin II-receptor blockers, and β-blockers may increase NSAID-related renal complications.18

CONCLUSION

It is concluded that depending on the dose of Aceclofenac administered which increased urea concentrations, an indicator of kidney damage in serum, kidney damage cannot be evaluated using the

stereological method or by serum oxidative stress parameters despite slight variations of them mainly observed with 50 mg/kg Aceclofenac. More severe damage in organs is necessary in order to evaluate damage using the above-mentioned biochemical parameters.

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