Alleviation of Ibuprofen induced Nephrotoxicity by vitamin supplementations

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ABSTRACT
The aim of the present study was to investigate the impact of the combined administration of vitamin B complex and ‘C’ on ibuprofen induced nephrotoxicity. Male albino rats were subdivided into five groups: the first was a control group, the second and third received Ibuprofen at a low and high dose of 1.5 mg and 3 mg/100g body weight /day respectively for 7 days, the fourth group received high dose and vitamin supplementation (B complex and C) at a dosage of ml/100g body weight, the fifth group rats received high dose (3 mg) of ibuprofen for seven days followed by withdrawal of drug for a further seven days. No significant changes were observed in the histopathology of kidney tissues in the control rats. The Ibuprofen treatment affects the histopathology of kidney. Low dose treatment group, minor glomerular abnormality (increase in size). In high dose also increase in size of glomerulus was observed. Many proximal convoluted tubules showed hydropic changes, coagulation necrosis and degeneration with inflammation treated group showed normalcy of the histoarchitecture of the kidney. Regeneration was started in the withdrawal group.

Key words: Ibuprophen, nephrotoxicity, B complex, Vitamin C.

INTRODUCTION
Non-steroidal anti-inflammatory drugs (NSAIDs) which are often used for the relief of non specific fever (Radwan, 2000), continue to be important for the palliation of pain (Simon, 1994). They are the most frequently used medications for the treatment of a variety of common chronic and acute inflammatory conditions (Manoukian et al., 1996). Ibuprofen is a new generation of non-steroidal anti-inflammatory drug, which is classified under non- narcotic analgesic (Kleinchknecht, 1985). It is sought as a safer, more effective alternative to either corticoids or aspirin for the use with rheumatoid arthritis and osteoarthritis.

Several studies have indicated that NSAIDs can generally prevent prostaglandin synthesis from arachidonic acid by inhibiting the activity
of the prostaglandin synthesis enzyme cyclooxygenase. The inhibition of cyclooxygenase activity removes the influence of cyclooxygenase products on cellular events (Brune, 1984). Prostaglandins are formed from dietary essential fatty acids (principally arachidonic acid) esterified to phospholipids and in some instances to triglycerides. These products have some potent biological activities affecting cell function in every organ. The high levels of NSAIDs also inhibit the activities of various enzymes, the proteoglycon synthesis from chondrocytes, the ionic exchange rate and the processes depend on prostaglandins (Rubatelli et al., 1979; Skoutakis et al., 1988 and Kayaalp, 1998). It will be worthwhile to study its effect on the histology of the kidney which contributes for excretion and metabolism.

**MATERIALS AND METHODS**

Mature adult albino rats of wistar strain weighing 150gm – 250gm were procured from Tamil Nadu Agricultural University, Coimbatore, India. The animals were maintained in an animal house with standard facilities having CPCSA approval (722/02a/ CPCSEA). They were kept under uniform conditions at light and water adlibitum. They were fed with rat feed. The animals were randomly divided into following five groups of 5 each; Group I: normal control group, Group II: low dose of Ibuprofen (1.5mg), group III: High dose of Ibuprofen (3mg) / 100g body weight / day for seven days, Group IV: High dose + vitamin supplementation (B complex and Vitamin C (0.05mg, Group V: High dose for seven days followed by withdrawal period of further seven days.

The animals were weighed before and after treatment schedule. Twenty four hours after the last treatment schedule the animals were sacrificed by decapitation method. The kidney was dissected out and cleaned off adhering connective tissues and blood strains, washed in cold physiological saline thrice, blotted on a filter paper and weighed using electronic balance. Small piece of kidney was fixed in formaldehyde (10%) for histological sections.

**RESULTS AND DISCUSSION**

The kidney is a vital organ concerned with metabolism and excretion of drugs (Passmore and Roboson, 1973). It is therefore important to study the effect of any pharmaceutical agent on this organ, if it is intended to be used for human use. The effects of NSAIDs in therapeutic doses on oxidative stress have been established (Kappus, 1986), but there is little knowledge on the effects of high doses of these drugs (Akdogan and Akkus, 1997). The kidney is another organ affected by the toxic effects of NSAIDs (Cliver and Stoff, 1984; Palmer, 1995). It is known to be important target organ for the unwanted effects of NSAID, which can produce acute, reversible permanent effects (Brune and Linder, 1992). The NSAIDs adversely change the kidney function (Goodman and Gilman, 1995) and may play a role in the induction of membranous nephropathy (Radford et al., 1996). During Ibuprofen metabolism the number of reactive oxygen species (ROS) can be increased. These products induced peroxidative damage in renal tissue. The increase in SOD levels and MDA activity in renal tissue may indicate peroxidative damage. Gokcimen et al., (2000) and (2001) reported that, in the renal tissue structural changes including reduction in GSH-PX and GR activities in the kidney and increased MDA levels in serum. The decrease in GSH-PX activity possibly destroys the process of \(H_2O_2\) conversion into \(H_2O\). Thus, in the present study also cell damage in kidney tissue was induced by increased levels of \(H_2O_2\).

Histological examination of the kidney tissues in the control group (fig 1) revealed no significant deviation from the normal histological structures. The changes in the histological structure of the kidney was significantly affected by the second, third, fourth and fifth Ibuprofen treatments. In the low dose drug treatment (fig - 2), kidney tissue showed minor glomerular abnormality. The glomerulus was slightly increased in size, and showed minor degree of increase in Mesangial cells. A few proximal convoluted tubules (PCT) showed hydropic changes and few were degenerated. In the high dose Ibuprofen treated group (fig - 3), thickening of basement membrane of the glomerulus, and increase in glomerular size and cellularity. Many proximal convoluted tubules showed changes with narrowed lumen. Many tubules revealed coagulation necrosis and degeneration with inflammation and infiltration of lymphocytes.

Vitamin B complex and vitamin C supplementation (fig 4 & 5) along with Ibuprofen showed reduced hydropic changes in proximal convoluted tubules. There was rather a diffuse glomerulonephritis brought about by a
high dose Ibuprofen treatment was withdrawn, the kidney histology showed considerable changes. There was a uniform thickening of the basement membrane of the glomerulus. In many proximal convoluted tubules, the diameter was reduced. Infiltration of glomerular tuft was also observed.

In the present study, degeneration in proximal convoluted tubules and hydropic changes was induced by Ibuprofen treatment especially very prominent in the high dose drug treated group suggesting an altered fluid homeostasis and cell injury. In the kidney, cellular swelling appears whenever cells are incapable of maintaining ionic and fluid homeostasis (Cotron et al., 1989). This effect of the drug appears to be permanent, since drug withdrawal (fig- 6) was not effective in restoring the histoarchitecture. The given dose of vitamin B complex could not restore the histoarchitecture of the tissue, since the diffuse glomerular nephritic condition was observed. Thus, in the present study, severe necrosis, glomerulo nephritis and segmental necrosis was brought about...
by Ibuprofen treatment suggesting nephrotoxicity of the drug. Similar nephrotoxicity has been induced by other NSAIDs like diclofenac in rats as humans in the form of nephritic syndrome, interstitial nephritis and renal failure (Robinson et al., 1990; Calvo Allen et al., 1994; Kulling et al., 1995 and Veena, 1996).

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