ORIGINAL ARTICLE

MECHANISM OF NEPHROPROTECTION BY *PICRORHIZA KURROA*

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Background: Humans are exposed either deliberately or unintentionally to a variety of diverse chemicals that harm the kidney. To reduce the alarming high incidence of nephrotoxicity, some chemical as well as herbal alternatives are needed. Nimesulide belongs to a group of anti-inflammatory drugs that are in common use in our society. Like all non-steroidal anti-inflammatory drugs, it carries a potential threat of nephrotoxicity especially when other risk factors are present in user. The objective of this study was to find herbal alternative with anti-inflammatory and nephroprotective qualities and to bring into light its mechanism of nephroprotection. **Method:** This experimental study was conducted on mice at National Institute of Health, Islamabad from Feb 2013 to March 2014. Nimesulide was given in a dosage of 750 mg/kg body weight for 3 days to induce nephrotoxicity and protective effect of *Picrorhiza kurroa* was noted in two doses of 250 mg/kg and 500 mg/kg for 14 days. Renal function tests were done and urinary PGE_2 was measured to assess the effect of nimesulide and Pk on kidneys. **Results:** In our study, significant improvement was seen in serum urea and creatinine levels in mice receiving low and high dose *Picrorhiza kurroa*. However, no significant improvement was noted in urinary PGE_2 showing that the mechanism of nephroprotection is not by vasodilatory effect of Pk. **Conclusion:** This study showed nimesulide nephrotoxic potential and Pk is a good herbal anti-inflammatory and nephroprotective alternative for nimesulide but its mechanism of nephroprotection is not by PGE_2.

Keywords: Nimesulide; *Picrorhiza kurroa*; PGE2; Cisplatin

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INTRODUCTION

Nimesulide is one of many drugs that are available over the counter in our setup. Due to its high therapeutic effectiveness in variety of pains, it is ranked as one of the commonly used pain killers. Nimesulide is a member of NSAID group with anti-inflammatory, analgesic and anti-pyretic effects, having a multifactorial pharmacodynamic mechanism of action which exceeds its preferential inhibitory action on the COX-2 enzyme and also has unique pharmacokinetic properties.[1]

Nimesulide may cause hepatobiliary, renal, cutaneous & gastrointestinal adverse effects. Fulminant hepatic failure, acute hepatitis, multiple enterocolic perforations, cholestatic liver injury, & end stage renal failure has been reported with nimesulide use. Due to some fatal adverse effects nimesulide has been banned in many countries however it is still available in Pakistan as NIMS and NISE.[2]

Regarding toxic effect of nimesulide on kidneys, recent studies report that after repeated doses of nimesulide, there is an elevation of Tamm-Horsfall glycoprotein (uromodulin) and beta-N-acetyl glucosamindase in urine which are nephrotoxic compounds. This indicates that nimesulide is a possible nephrotoxic agent.[3] Nephrotoxicity induced by nimesulide has been demonstrated by many animal studies as well. In one study nimesulide in a dose of 2 mg/kg b.i.d was found to be toxic in dogs, causing development of gastric ulcers and mild nephrotoxicity on a four-day course of treatment.[4]

Prostaglandin inhibition mediated by nimesulide explains many of its renal complications including altered renal function tests. Prostaglandin induced renal vasodilation is critical for maintaining adequate renal perfusion. NSAIDs impair this renal vasodilation and alter renal hemodynamic. This effect is magnified in patients who are hypovolemic or are concomitantly using angiotensin converting enzyme (ACE) inhibitors.[5]

So, in general adverse effects related to NSAIDs are due to generation of oxidative stress and decreased antioxidant levels, immunological and idiosyncratic reactions, inhibition of prostaglandin synthesis, build-up of renal vascular resistance with a concomitant decrease in diuresis, GFR, and renal blood flow leading to a stage of acute reversible renal failure.[6]

Picrorhiza kurroa is a famous nephroprotective medicinal plant in Ayurvedic medicine. Roots and rhizomes extract provides protection against various renal toxins. Picroliv (standardized glycoside mixture isolated from roots of (*Picrorhiza kurroa*) has demonstrable nephroprotective effect in a renal ischemia-reperfusion induced injury model in rats. Seven days

pre-treatment of rats orally with Picroliv before commencement of experimental ischemia-reperfusion induced damage lowered renal lipid peroxidation, reduced apoptosis, and increased the viability of renal cells.[7]

Animal studies support the possible clinical benefit of Picroliv as nephro-protectant. I have established Pk nephroprotective effect in my previous published study which showed marked rise in serum urea and creatinine levels and significant changes in renal histopathology in mice.[8] However little work is done to evaluate the exact mechanism of nephroprotection of Pk. Yamgar *et al* demonstrated the nephroprotective and nephron-curative effect of herb against cisplatin induced nephrotoxicity in rats that was found to be significant. They proposed its mechanism due to its antioxidant property.[9]

Therefore, as a continuation of my previous study I aimed to evaluate Pk's nephroprotective mechanism and to see whether prostaglandins are involved or not.

MATERIAL AND METHOD

This study was conducted at animal house of National Institute of Health, Islamabad from Feb 2013 to March 2014. Adult Balb C mice were used as experimental animals. They were kept in proper ventilated rooms and given standard laboratory diet. Glycosidal extract of Pk was synthesized by Stas Ottos method for glycoside extraction.[10] 20 mice were grouped in four. Group 1 was given Pk in a dose of 250 mg/kg for 14 days, group 2 were given nimesulide 750 mg/kg for 3 days[11], group 3 were given 750 mg/ kg nimesulide for 3 days followed by 250 mg/kg[12] Pk for 14 days and group 4 were given 750 mg/ kg nimesulide for 3 days followed by 500 mg/kg Pk for 14 days. At the end of study renal function tests and urinary PGE2 were measured by using ELISA.

RESULTS

Animal model of nephrotoxicity was created by giving nimesulide in toxic doses of 750 mg/kg for 3 days to mice. Administration of nimesulide led to significant (p-value <0.001) rise in serum urea from 16 mg/dl of control group to 61 mg/dl of nimesulide group and serum creatinine (p-value <0.000) from 0.31 mg /dl of control group to 0.50 mg/dl of nimesulide group. With administration of nimesulide urinary PGE_2 levels decreased from mean value of 1.62 pg/ml in control group to 0.58 pg/ml in group 2 (Table-1). Group vise comparison was made by Tukey's test for urinary PGE_2. Tukey's test showed significant difference with p-value (0.000) when comparison was made between control group (Group 1) and nimesulide group 2 (Table-1). Curative effect of Pk was established where results showed reversal of serum urea and creatinine. Mean serum urea was significantly (p-value <0.001) lowered to 14 mg/dl of group given low dose of Pk and 16 mg/dl in group given high dose of Pk. Similarly, mean serum creatinine was significantly (p-value <0.001) lowered to 0.22 mg/dl of group given low dose of Pk and 0.24 mg/dl in group given high dose of Pk. However, for urinary PGE_2 insignificant p-value was noted when comparison of nimesulide group 2 was made with low and high dose Pk groups with p-values (0.502) and (1.000) respectively (Table-1)

Table-1: Comparison of PGE_2 between different groups

Groups	Mean PGE_2 (pg/ml)	p-value
Control	1.62	0.000
Nimesulide	0.58	
Nimesulide	0.58	0.502
Low dose Pk	0.43	
Nimesulide	0.58	1.00
High dose Pk	0.45	

DISCUSSION

Medicinal plants have nephroprotective properties due to the presence of various complex chemical substances like flavanoids, alkaloids, tannins, glycosides, phenol, saponins and terpenoids.[13]

In literature, we can find vast experienced based evidence and animal based studies on the nephroprotective activity of *Picrorhiza kurroa*. The exact mechanism of nephroprotection by Pk is unknown. In this study, we try to find out the vasodilatory effect of Pk by measuring PGE_2. A confirmation for mechanisms of renal damage such as involving Prostaglandins was done by estimating urinary PGE_2 level which is a good indicator of renal damaged. PGE_2 levels were measured by ELISA and it was seen that PGE_2 levels decreased to 0.58 pg/ml in nimesulide treated group 2 from 1.6 pg/ml of control group 1 in which only Pk extract in a dose of 250 mg/kg was given, showing a decrease of approximately 64%. This showed that nimesulide has induced ischemic insult to kidneys.

However, in groups 3 and 4 which were administered low and high dose of PK respectively, only a slight but not significant improvement in PGE_2 values was noted and these remained at 0.45 pg /ml.

Our results showing rise in serum urea and creatinine concur with Yamgar S and Sali L who also studied the nephroprotective effect of crude extract of *Picrorhiza kurroa* in mice against cisplatin induced kidney damage but showed its nephroprotective to be by its antioxidant activity and prostaglandin levels were not measured.[9]

Seth P *et al* have demonstrated nephroprotective effect of picroliv in a dose of 12

mg/kg in rats against ischemia induced acute renal failure through modulation of free radical induced renal damage. This again supports our study reflecting the nephroprotective effect of *Picrorhiza kurroa*.[14]

However, no studies and relevant data regarding Pk nephroprotective effect through PGE_2 have been conducted until now. By noticing our results of Pk on serum urea and creatinine levels we can conclude that though *Picrorhiza kurroa* is a potent nephroprotective agent, but the possible effective mechanism for this protection is not by vasodilatory effect of its glycosides on kidneys. Therefore, for nephroprotection the proposed mechanism was not PGE_2 mediated. Further studies are needed to evaluate other mechanisms of nephroprotection especially its antioxidant effect.

CONCLUSION

This study showed nimesulide nephrotoxic potential and Pk is a good herbal anti-inflammatory and nephroprotective alternative for nimesulide but its mechanism of nephroprotection is not by PGE_2

AUTHORS' CONTRIBUTION

AS: Supervision, concept, manuscript preparation, data collection, ZN: Statistical analysis. H: Contributed in review. SSA: Proof reading. ST: Proof reading.

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