

PROTECTIVE EFFECT OF CAPTOPRIL AGAINST CISPLATIN INDUCED NEPHROTOXICITY IN RATS

R.VIDHYA, M.JAYANTHI, U.KANAGAVALLI*

Department of Biochemistry, Adhiparasakthi college of Arts and Science,
kalavai-632 506, Tamilnadu, India.

Summary

Captopril, an Angiotensin- converting enzyme Inhibitor (ACE) containing sulfhydryl (-SH) group can protect against *Cisplatin*- induced Nephrotoxicity in rats. A single dose of Cisplatin (7.5mg/kg bwt) injected i.p. caused a significant increase in Blood Urea Nitrogen(BUN), Creatinine and Uric acid level as compared to control group. On the other hand, administration of Captopril (60mg/kgbwt) i.p. 1hr before cisplatin for 7 days, protected the kidney as indicated by restoration of BUN, Creatinine and Uric acid levels are significantly reduced. This reflects the beneficial role of *captopril* in treatment of Reno vascular hypertension and congestive heart failure; an effect that may be related to its free radicals scavenging and antioxidants effects which are sulfhydryl dependent.

Key words: Cisplatin, Captopril , Creatinine, Uric acid.

Corresponding author: U. Kanagavalli.
Adhiparasakthi college of Arts and Science,
Kalavai- 632 503. Vellore Dt. India
E-Mail; surya_fk81@rediffmail.com

Introduction

The kidneys are important organ actively involved in excretory and regulatory organs (1). The kidneys, in concert with hormonal and neural inputs that control their function, are the organs primarily responsible for maintains the stability of ECF volume, electrolyte composition and osmolarity (2). The kidney are also responsible for the role of Homeostasis, Excretion of waste product, Maintaining the water balance, acid-base balance, Hemopoietic function, endocrine function, Regulation of blood pressure and calcium level (3). Kidney injury due to chemicals or infectious agent may lead to Glomerulonephritis, Acute Renal Failure, Chronic Renal Failure and nephritic syndrome (4)(5).

Cisplatin, a widely used anti-neoplastic agent, is primarily used in the treatment of a variety of solid tumors (6). However the clinical usefulness of cisplatin has been seriously restricted because of its nephrotoxic side effects (7). The major site of renal injury is the s3 segment of the proximal tubule in the outer medulla of the kidney (8). Cisplatin has multiple intracellular effects, including regulating gene causing direct cytotoxicity with reactive oxygen species, activating mitogen – activated protein kinases, inducing apoptosis and stimulating inflammation and fibro genesis, these events cause tubular damage and tubular dysfunction with sodium, potassium and magnesium wasting (9) the BUN(10), Creatinine(11), Uric acid level was significantly increased(12). The present study is to examine the role of captopril in the protection of cisplatin – induced nephrotoxicity in rats.

Materials and Methods

Animals

Adult male albino rat of Wister strain weighing around 150 to 200 Gms were procured from Abdul Hakeem College Melvisharam, Tamilnadu, Vellore district. The animals were kept in polypropylene cages at an ambient temperature of 25±2°C AND 55-65% Relative humidity. A 12±1hr light and dark schedule was maintained in the animal house till the animals were acclimatized to the laboratory conditions, and were fed with commercially available rat chow (Hindustan Lever Ltd., Bangalore. India) and had free access to water. The experiments were designed and conducted in accordance with the institutional animal ethics committee.

Chemicals

Lyophilized cisplatin (cisplatyl 50, Laboratoire Roger Bellon, France) and captopril (Sigma-Aldrich Chemical CO., Bangalore) were dissolved in normal saline and given i.p. in doses of 7.5mg/kg (13) and 60mg/kg, respectively. All the other chemicals were of the highest available commercial grade.

Experimental design

Group 1: received 0.5ml saline, injected i.p. and served as control group. Group 2: received a single dose of captopril (60mg/kg). Injected i.p. Group 3: injected with a single dose of cisplatin (7.5mg/kg bwt), i.p. Group 4: injected i.p. with captopril (60mg/kg bwt) 1hr prior to a single i.p. injection of cisplatin (7.5mg/kg bwt). Seven days after treatment, the animals were anesthesia with ether, Blood samples were withdrawn by heart puncture, centrifuged and plasma was separated. Plasma urea nitrogen, creatinine and uric acid were determined according to the method of Dam-tsc method, jaff's method and phospho tungstic acid method respectively.

Result and Discussion

Table 1 show that injection of cisplatin (i.p) in a dose of 7.5mg/kg bwt caused significant increases in the level of plasma urea nitrogen, creatinine and uric acid respectively after seven days of treatment as compared to control group. On the other hand pretreatment of animals with captopril significantly reduced the elevated levels of urea and creatinine in plasma by 75% and levels of urea and creatinine in plasma by 75%

and 83% respectively(in comparison with cisplatin treated group) which returned to the normal value. While administration of captopril (60mg/kg) before cisplatin decreases the plasma level when comparison with cisplatin treated group.

This study shows that single injection of cisplatin in rats resulted in deterioration of renal function as indicated by elevation in plasma creatinine, urea and uricacid (14). The result reveal that creatinine, blood urea and uricacid returned approximately to the normal control level when animals were injected with captopril 1hr before cisplatin(15). Cisplatin nephrotoxicity primarily cause tubular interstitial lesions. In animal models cisplatin damages the proximal tubules. Specifically the s3 segment of the outer medullary stripe. Mitochondrial swelling and nuclear pallor occur in the distal nephron. The glomerulus's has no obvious morphologic changes (16) (17) (18).

Captopril is an angiotensin-converting enzyme inhibitor (ACEI) which is prescribed for the treatment of hypertension and congestive heart failure and also progression of chronic renal failure and of diabetic nephropathy (19). The potentiation of free radical scavenging action by ACEI'S has also been postulated (20). Captopril was found to increase antioxidants enzymes and non-enzymatic antioxidant defenses in several mouse tissues (21).

Table-1; Effect of captopril treatment on cisplatin- induced increase in plasma urea, uricacid and creatinine of male albino rats.

parameter	Urea (mg/dl)	Creatinine(mg/dl)	Uricacid(mg/dl)
Animal groups			
Control	48.1 ± 0.029	0.31 ± 0.02	7.99 ± 0.02
Captopril	45 ± 3.10	0.42 ± 0.04	5.87 ± 0.22
Cisplatin	291 ± 4.5*	6.21 ± 0.02*	5.61 ± 0.02*
Cisplatin+ captopril	57.1 ± 4.35 [#]	0.47 ± 0.07 [#]	4.83 ± 1.55 [#]

Data are expressed as mean values ± SEM. Captopril was administered i.p. in a single dose of 60mg/kg bwt 1h before a single dose of cisplatin(7.5mg/kgbwt, I.p.)

Multiple comparison were done using oneway ANOVA followed by SPSS

*Significantly different from control group at $p \leq 0.001$

Significantly different from cisplatin treated grou at $p \leq 0.001$

Captopril competes with angiotensin I for binding at the angiotensin-converting enzyme, blocking the conversion of angiotensin I to angiotensin II. Lower angiotensin II levels results in a decrease in blood pressure, an increase in rennin activity (19). From the table I it was evident after induced cisplatin, the plasma level was significantly increased after treated captopril was able to reduce all the elevated biochemical parameters due to nephrotoxicity.

Conclusion

Captopril an ACEI could have a protective effect against cisplatin-induced nephrotoxicity. This reflects the beneficial role of captopril in treatment of Reno vascular hypertension and congestive heart failure, an effect that may be related to its free radicals scavenging and antioxidants effects which are sulphhydryl dependent.

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