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Original Research Article

Study on nephroprotective effect of Ebselen in cisplatin induced renal damage in rats

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ABSTRACT

Background: Renal dysfunction arises as a result of exposure to medicines, industrial or environmental chemicals. Cisplatin is a major antineoplastic drug used for the treatment of solid tumors. Its chief dose limiting side effect is nephrotoxicity; 20% of patients receiving high-dose cisplatin have severe renal dysfunction. Ebselen a promising antioxidant, was used to explore the nephroprotective effect.

Methods: The rats were divided into five groups; each group consisting of 6 animals. The experimental design included one control group and four experimental groups. The study was carried out for a period of 7 wks. The test drug Ebselen in group 4 and 5 and the reference standard drug Amifostine in group 3 was administered once a week intraperitoneally for 5 weeks. Nephrotoxicity was induced by cisplatin (5mg/kg IP) in the 6th week, following this the drug Amifostine in group 3 and Ebselen in group 4 and 5 will be continued twice a day for 5 consecutive days post induction. Urine samples were collected and sent for determination of urine creatinine and albumin.

Results: The Urine creatinine level and albumin level estimation in group II show significant renal damage as compared to control group. The statistical reduction in urine creatinine and urine albumin level in Ebselen treated group I (10mg/kg), Ebselen group V (20mg/kg) as compared to Cisplatin group II show a potential reduction in renal damage. Ebselen treated group V showed a reduction in urine creatinine and urine albumin as same as in group III.

Conclusions: This study brings to a close that Ebselen lessens Cisplatin induced renal damage.

Keywords: Amifostine, Cisplatin, Ebselen, Nephro-protective effect

INTRODUCTION

Kidney diseases are considered a public health issue worldwide, Nephrotoxic drugs (ND) as therapeutic agents that have the potential to cause adverse effects on renal function as a result of direct toxicity or compromised renal perfusion and this toxicity may depend on the clinical context involved.[1] The types of kidney dysfunction that are induced by ND include acute tubular necrosis, glomerular and tubulointerstitial injury, hemodynamically mediated damage and obstructive nephropathy.[2] Ebselen, a seleno-organic compound catalyzes the reduction of reactive oxygen species similar to glutathione peroxidase.

Numerous study reported that Ebselen has anti-inflammatory, anti-atherosclerotic, anti-mutagenic properties in both in vitro and in vivo studies. Hence the objective of our study was to evaluate the Nephroprotective effect of Ebselen in Cisplatin induced renal damage in rats. Cisplatin is a highly effective antitumor agent whose clinical application is limited by the inherent nephrotoxicity.[3] The current measures of nephroprotection used in patients receiving cisplatin are not satisfactory, and studies have focused on the investigation of new possible protective strategies.[4] Many pathways involved in cisplatin nephrotoxicity have been delineated and proposed as targets for nephroprotection, and many new potentially protective

agents have been reported.[5] The multiple pathways which lead to renal damage and renal cell death have points of convergence and share some common modulators. Unbound cisplatin is freely filtered at the glomerulus and taken up into renal tubular cells mainly by a transport-mediated process.[6] The drug is at least partially metabolized into toxic species. Cisplatin has multiple intracellular effects, including regulating genes, causing direct cytotoxicity with reactive oxygen species, activating mitogen-activated protein kinases, inducing apoptosis, and stimulating inflammation and fibrogenesis.[7] These events cause tubular damage and tubular dysfunction with sodium, potassium, and magnesium wasting. Most patients have a reversible decrease in glomerular filtration, but some have an irreversible decrease in glomerular filtration. Volume expansion and saline diuresis remain the most effective preventive strategies.[8] The most frequent event among all the described pathways is the oxidative stress that acts as both a trigger and a result. The most exploited pathways, the proposed protective strategies, the achievements obtained so far as well as conflicting data are summarized and discussed in this review, providing a general view of the knowledge accumulated in the past and recent research on this subject.[9,10]

METHODS

The study was undertaken at Central Animal House, Rajah Muthiah Medical College, and Hospital, Annamalai University. All studies were conducted in accordance with the National Institute of Health "Guide for the care and use of Laboratory Animals".[11] Ebselen and Cisplatin was purchased from MP Biomedical India Private Limited, Mumbai, Maharashtra. Amifostine was purchased from Sun Pharmaceuticals Ltd, Chennai, Tamilnadu. Cisplatin and Amifostine were dissolved in normal saline.

Ebselen was dissolved in dimethyl sulfoxide were administered. Healthy adult male rats of Wistar strain weighing 180 to 200 grams were used and purchased from Central Animal House, Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalai Nagar, Tamilnadu. Animals were housed in polypropylene cages, bedded with husk in groups of five under controlled environmental conditions at Central Animal House, Rajah Muthiah Medical College and Hospital, Annamalai University. Animals were fed with standard pellet diet, ad libitum, and water. Urine samples were sent for determination of creatinine and albumin. Urine creatinine was estimated by modified Jaffe's method and urine albumin was estimated by Reinhold's Biuret method. Values of Urine parameters were expressed as means±SD for six rats in each group.

Statistical analysis

The Data were analyzed by Duncan's Multiple Range test (DMRT), Using SPSS software version 17.0 (SPSS, Inc., Chicago, Illinois).

RESULTS

The rat was divided into 5 groups of six each (n=6). They were kept in the animal house for 7 weeks. The experimental design included one control group and 4 experimental groups. The test drug Ebselen in group 4 and 5 and the reference standard drug amifostine in group 3 was administered once a week intraperitoneally for 5 weeks. Nephrotoxicity was induced by Cisplatin (5mg per kg IP) in the sixth week, following this the drug amifostine in group 3 and ebselen in group 4 and 5 was continued twice a day for 5 consecutive days post induction. The first dose was given two hours prior to induction and the next dose two hours post induction. Urine samples were collected for 24 hours following Cisplatin dose from each group keeping animals separately in special metabolic ages.
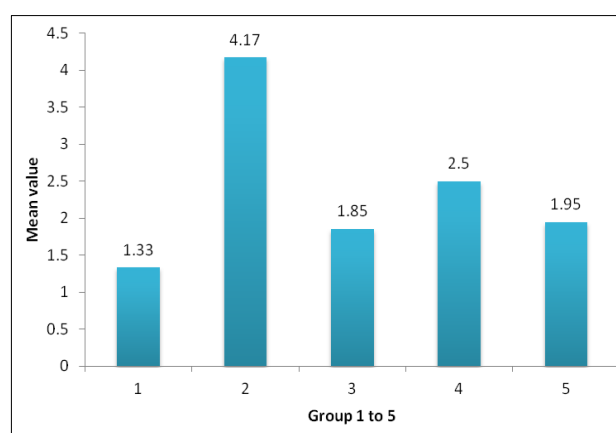

Figure 1: The effect of Ebselen on urine creatinine in Wistar rats.
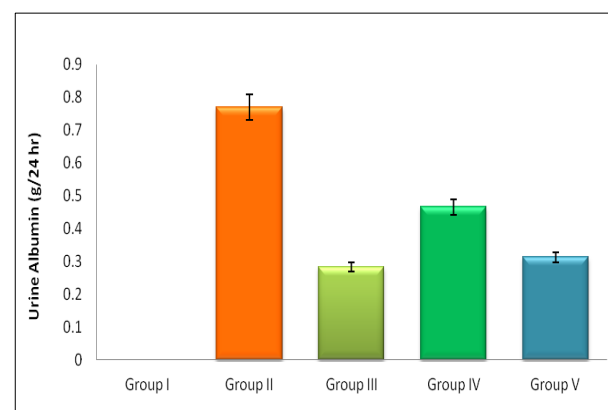

Figure 2: The effect of Ebselen on urine albumin in Wistar rats.

Urine creatinine level estimation in group II show significant renal damage as compared to control group I, III, IV, V. The statistically significant reduction in urine creatinine levels in Ebselen treated group IV (10mg/kg), Ebselen group V 20mg/kg) as compared to Cisplatin group II show a significant reduction in Nephrotoxicity. Ebselen

treated group V showed a significant reduction in urine creatinine in III (Figure 1).

Urine albumin level estimation in group II show significant renal damage as compared to control group I, III, IV, V The statistically significant reduction in urine albumin levels in Ebselen treated group IV (10mg/kg), Ebselen group V 20mg/kg) as compared to Cisplatin group II show a significant reduction in Nephrotoxicity. Ebselen treated group V showed a significant reduction in urine albumin as same as in group III (Figure 2).

DISCUSSION

Our present study with Ebselen showed a significant improvement in kidney function. The Urine levels of Creatinine and albumin level was elevated in group 2.[11] This increase implicates renal injury impairing renal tubular function. Amifostine group 3 was comparable to normal control, while Ebselen group 5 at a dose of 20mg/kg showed statistically significant improvement in the recovery from renal injury.[12] Several in vivo studies of Cisplatin Induced Nephrotoxicity have recognized apoptosis as an important mode of cell death in the normal and pathologic state. Caspase 1,8 and 9 are initial Caspases that activate Caspase-3, the principle execution Caspase in renal tubular apoptosis. Also, Caspase-1 directly activates caspase-3 in Cisplatin induced renal injury model.[13] Cisplatin induced apoptosis and ATN are reduced in Caspase 1 deficient mice. Several studies elucidated that enhanced peroxidative damage caused by ROS especially the hydroxyl radical may contribute to the Cisplatin induced renal failure. Mitochondrial dysfunction is a central component of Cisplatin Nephrotoxicity of proximal tubules in-vivo and in-vitro.[14] The role of Amifostine in protecting in normal tissues from radiotherapy and alkylating platinum agent toxicity has been shown to be due to both a modification of the DNA target of the chemotherapeutic agents and to its well-known oxygen free radical scavenger activity (Meyers et al, 1977). Pre-clinical greater in the normal than in the malignant tissues.

Amifostine acts as a potent free radical scavenger, preferentially target highly reactive OH radicals.[15] The free radical Scavenger Ebselen is a lipid soluble Seleno-organic compound having glutathione peroxidase activity in vitro.[16] Several studies reported that Ebselen attenuates Neuronal death induced by ischemic perfusion. In Rodent models, Ebselen has shown to provide significant protection against ischemic damage in both gray and white matter.[17]

Cisplatin induced Nephrotoxicity was associated with an increase in urine creatine and albumin. On the day of inducing renal toxicity with Cisplatin, the dose of Ebselen was administered twice a day for 5 days.[18] There was a significant improvement in urine creatinine and albumin in 20mg/kg treated group, which is suggestive of a renoprotective action of this drug.

CONCLUSION

From this study, we conclude that Ebselen, mimics glutathione peroxidase activity. As nephroprotective activity has been evaluated in several molecular studies. Our study clearly reveals that at a dose of 20mg/kg/day, offers significant protection against the nephrotoxic effect of Cisplatin in Wister rats which have compared to that of amifostine.

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