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Drug Induced Nephrotoxicity Treatment: Synthetic and Herbal Drugs

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Abstract

The evolution in the field of medicine is to develop new drugs to treat an ailment. So, it is never that the finding a better drug for treatment can stop. But the debate on picking a natural or synthetic system of medicine with the better ability to treat will be eternal. This creates dilemma in the treatment of different diseases and disorder and so in the nephrotoxicity. As we go through the literatures, we find different ways and drugs for the treatment of nephrotoxicity. Every system has advantages and corresponding disadvantages within itself corresponding to that of drugs. This article is all about the different nephroprotective drug used or present in literature, there advantages (nephroprotection ability) and disadvantages (side effects and less efficacy).

Key words: Nephroprotective, Nephrotoxicity treatment, Synthetic nephroprotective, Herbal nephroprotective.

INTRODUCTION

The medicine or drug to treat kidney issues are numerous. These drugs are specific in their action and provide relief by different mechanism or ways. The drug which has the action of improving a body condition also associates additional effects to it called as adverse or side effects. One of the dominant conditions with the concern of risk of life if untreated is nephrotoxicity. Nephrotoxicity is alteration or adverse functioning of kidney. It is known to all of us that the function of the kidney is to remove the toxic waste produced in the body. The two bean shaped structures with numerous numbers of nephron cells as the functioning unit performing the function of categorization of waste and nutrients. The nutrients or the required ingredients are withdrawn from the waste by filtration. Toxicity due to drugs in different parts of nephron can lead to improper functioning. Similarly, the inability of the nephron functioning can be due to the inflammation. The cause of inflammation can be an allergic reaction or the accumulation of solid masses (crystals) in the passage way obstructing the easy movement.[1-3]

There are many drugs as nephroprotective agent. Different class of drugs can modify the functioning of nephron at different stages. The ability in the present ailment diagnoses is to capture the changes and identify the worsening conditions. The indications such as change in the glomerular filtration rate (GFR), increase in the Serum creatinine (sCr) value and increased Blood urea nitrogen (BUN) ([1]) if diagnosed in the early stages halt to spread in toxicity is possible by different treatment procedure. In nephrotoxicity the glomerular filtration rate decreases to the value of 60mL/min/1.73m^2[4] intrarenal obstruction, interstitial nephritis, nephrotic syndrome, and acid-base and fluid electrolytes disorders. Certain drugs can cause alteration in intraglomerular hemodynamics, inflammatory changes in renal tubular cells, leading to acute kidney injury (AKI) and the values of sCr and BUN reach above 1.4mg/dL and 25mg/dL respectively. The drugs responsible for such changes are NSAIDs, Angiotensin converting enzyme (Captopril), Cyclosporin, methotrexate, Cisplatin, Aminoglycoside.[5]

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Treatment of nephrotoxicity

Currently nephrotoxicity is in the list of high patient records with around 60% of the patients in need of intensive care hospitalization. The cause of the nephrotoxicity can be intrinsic or the extrinsic toxic material. In both causes adverse effect of the drug has the greatest number of cases recorded.[3] With the increase in new ways of treatment, diagnosis and other therapeutic procedure the number of incidents with nephrotoxicity has elevated. Looking at different drugs available for the treatment they can be broadly grouped as synthetic drugs and herbal drugs.

Synthetic drugs

Loop diuretics

The use of diuretics in the treatment of ARF is generally with an idea or thought to subside the oliguria or anuria pathological condition. The results obtained from the clinical studies by Weinstein *et al*. Solomon *et al*. Stevens *et al*. and Lasing *et al*. and prophylactic use of furosemide or torsemide on the patients had increased urine output. But the condition of the kidney of ARF patient deteriorated. This shows the use of loop diuretics was better in the management of ARF patients to improve cardiac and lung functioning.[6]

The clinical evaluation of the effect of furosemide and torsemide was made along with a placebo in the patient of ARF. The study was on 92 patients receiving the dose of loop diuretics 3mg/kg body weight in the time gap of 6 hr for 21 days. The results obtained increased in the urine outflow in the patients with administration of loop diuretics in comparison with that of placebo in the first 24 hr. The results also show that patients with a higher extent of ARF had the highest mortality rate. The loop diuretics did not show a significant effect on the improvement of the patient's condition but was useful as the management therapy for the patients of ARF with the symptoms of oliguria or Anuria.[7]

Ionotropic agents (Dopamine)

Dopamine is an ionotropic agent that acts as the renal vasodilator, increases the sodium excretion in urine (natriuretic), increases the overall urine output (diuretic) and also have the Reno protective effect. The dopamine also has a property to increase blood flow in the renal region depending on the dose. Various studies on healthy humans indicate the beneficial effect of the dopamine on the kidney, whereas drugs did not show any significant improvement when administered to the patients of ARF. The studies on the low dose potential of dopamine were further required as the dopamine is a potent drug to improve various kidney functions and the use of it in the ARF is in small doses and is carried out in the limited strength.[8]

Of the total 2149 patients studied in 58 different experimentations mortality of the patients reported in the experiments was 508 of the 11 experimental trials. The dopamine had no progressive effect and 15.3% of the patients developed ARF receiving the dose of dopamine.[8] The dopamine alone did not have any positive effect on the humans with ARF but the need for further studies on the combination of dopamine with diuretics and other renoprotective agents can help to develop the required preventive dose regimen against ARF.

Vasodilators (Fenoldopam)

The probable mechanism for the nephrotoxic behavior by a potent immunosuppressant or any such drug was the vasoconstriction leading to the decrease in blood flow to the renal region. The use of selective Dopamine A1 receptor agonist fenoldopam with the property of vasodilation was to identify its potential to normalize the function of the kidney. Cyclosporin an immunosuppressant in the organ transplant produced vasoconstriction leading to the ailments of nephrotoxicity. Thus, the usage of cyclosporine is limited in the present days.[9]

In a study potency and efficacy of fenoldopam tested against the nephrotoxic cyclosporine A inducing agent on rats. The dose of 100mg/kg i.p. administration of cyclosporine increased the para amino hippuric acid and inulin content in the body. This was the sign of nephrotoxicity by cyclosporine. The use of fenoldopam in the dosage of 10μg/kg per min increased the clearance of PAH and inulin from the body of rats. The fenoldopam is a vasodilator and acts on the glomerular arterioles. The relaxation of efferent and afferent arteriole was evident by the increase in the flow and glomerular filtration rate. The nephrotoxicity reversal was evident in the study and the fenoldopam a selective Dopamine A agonist provides relief from the nephrotoxicity. The study also indicates the better ability of the selective dopamine agonist over the general dopamine in the nephroprotective activity.[10]

Calcium channel blockers (CCB)

There are various internal body changes or modifications leading to nephrotoxicity. Hypertension is a high blood pressure condition with its effect also on the excretory organ kidney. Hypertension can be induced within the body by various internal body changes or external drug intake. There are various changes in renal tissues promoting the use of calcium channel blockers in nephrotoxicity. The use of antihypertensive supplements in nephrotoxicity is not novel making the researches to be more on the study of its action. The gentamicin a potent antibiotic and a popular nephrotoxic drug causes shedding of tubular cells and death of the cells (necrosis). The use of verapamil a calcium channel blocker on the rats with gentamicin induced nephrotoxicity shows various changes in the kidney. The size of nephrons increased in the rats dosed with verapamil, the coagulative necrosis was subsided by the CCB. The verapamil had a little effect on the gentamicin induced nephrotoxicity.[11] Ultrastructural and functional alteration with blood urea nitrogen and serum creatinine increase leading to acute renal insufficiency (ARI).

Doxorubicin an anticancer agent is a nephrotoxic drug. The use of different CCB belonging to the group of dihydropyridine has a different effect. Amlodipine used in this study had a positive effect on reducing the serum creatinine and BUN values increased by the doxorubicin-induced nephrotoxicity. The nifedipine and nitrendipine used in the study did not show many changes also on the glutathione, glutathione-s-transferase and superoxide dismutase which were altered by doxorubicin. Even though few beneficial effects observed by nifedipine against cisplatin-induced nephrotoxicity its activity was null against the doxorubicin nephrotoxic behaviour.[12]

Herbal drugs

Natural drugs having many complex structure and compounds in a single plant has several medicinal properties in it. With the development of the traditional system, its use with the particular mechanism chemistry and the structure responsible for providing relief is understood. In the nephroprotection when the modern or synthetic system is unable to deliver relief from the conditions of nephrotoxicity and related issues. Herbal drugs or the traditional system also joins hands to provide the desired protection and relief from the toxic condition.[13,14]

The structural elucidation and evaluation suggest the use of polyphenolic compounds to deliver the Renoprotective, Anti-inflammatory and Diuretics property. The use of phenols as antioxidants is not new.[15] Developing a synthetic form of the polyphenols is a tedious step. The extraction of the

constituents of interest from the plant part is a better alternate. Various herbal drugs with the different properties and mechanisms of nephroprotection are *Desmodium canadense*, *Saliba miltiorrhiza*, *Tribulus Terrestris*, *Tinospora cardifolia*, *Zingiber officinale* and *Coriandrum sativum*.

The herbal medicines have a different mechanism of action compared to synthetic drugs in nephroprotection. They usually show antioxidant property which is evident by a reduction in ROS count. The increased concentration of serum creatinine and blood urea nitrogen in nephrotoxicity is also neutralized by various drugs such as *Coriandrum sativum*,[16] L-carnitine,[17] and *Boerhaavia diffusa*.[18] There are many drugs which also show a reduction in glutathione as a symbol of antioxidant. The drugs also improved the morphological condition of the kidney which was evident by the histopathological studies.

The use of Punarnava, Keokand, *Fumaria indica* and such other drugs show a great nephroprotective activity. The anti-inflammatory effect of these agents also helps to regain the structure of the kidney and from various other complications associated with it.[19] The proven activity of Punarnava also makes it a standard to compare in the nephroprotection of other herbal drugs to it in the animal and clinical studies.

CONCLUSION

From different studies, it is evident that the activity of nephron is important. The study in the present time is to find the drugs which can act as nephroprotective. In this study, the comparison of the different drugs from synthetic and herbal origins was made to understand the better acting drugs. Synthetic drugs were specific in the treatment and multiple doses delivered the required action. In comparison, the herbal drugs had the action of antioxidant, anti-inflammatory and other mechanisms in a single drug. The study reveals that the nephroprotective drugs need more experimentations to understand its effect. The potency of synthetic drugs make it more convenience for the immediate relief from the symptoms of nephrotoxicity. There can also be a combination of herbal and synthetic drugs. The combined drugs need to be studied which can act in a better way.

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CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

GFR: Glomerular filtration rate; **sCr:** Serum creatinine; **BUN:** Blood Urea Nitrogen; **AKI:** Acute Kidney Injury; **NSAID's:** Non Steroidal Anti-inflammatory Drugs; **ARF:** Acute Renal Failure; **PAH:** Para Amino Hippurate.

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