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NEPHROPROTECTIVE ASSAY MODELS: A REVIEW

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ABSTRACT

Nephrotoxicity is one of the major cause that affects the mankind resulting from the use of medications or from the use of diagnostic agents. It is mainly due to the accumulation of toxic chemicals and delayed excretion of the same from the body by the kidneys. It may lead to several other diseases and even can be fatal. Nephrotoxicity can be assessed by using different study models so that the safe dose of drugs can be determined to be used safely in the humans. Animals are used for the assessment and from the studies the effective and toxic doses of the chemicals can be found out.

KEYWORDS: Nephrotoxicity, animals, drug.

INTRODUCTION

Kidneys are bean shaped organs which are constituted by the functional unit called nephrons. Nephrons consists of a renal corpuscle and a renal tubule. The main functions of kidney are excretion, filtration of the blood plasma, maintenance of the homeostatis etc. Kidneys also play an important role in the detoxification of blood plasma.[1] When the excretion and detoxification by the kidneys do not work properly, it gets accumulated, leading to kidney specific toxicity known as nephrotoxicity.[2] Renal problems are a common occurrence in people. Nephrotoxicity may occur due to the consumption of chemicals, drugs or diagnostic agents. Drug induced nephrotoxicity is the common type of nephrotoxicity.[3]

Drug-induced nephrotoxicity is usually predisposed. They are more common in certain patients, and in specific clinical situations. As a result, successful prevention requires the knowledge of pathogenic mechanisms of kidney damage, patient related risk factors, drug related risk factors, preventive measures, alertness etc.[4] Drugs that induce nephrotoxicity includes aminoglycosides, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), anti-cancer drugs, sulfonamides, anti-histamines, anti-depressants etc.[5] The mechanisms included in the drug-induced nephrotoxicity are altered hemodynamics of the glomerulus, inflammation, crystal nephropathy, thrombotic microangiopathy, rhabdomyolysis, and tubular cell toxicity.[2,5]

NEPHROTOXIC MODELS

The various *in-vivo* models of the nephroprotective assay include:

a. Cisplatin model
b. Gentamicin model
c. Paracetamol model
d. Bromobenzene model
e. Doxorubicin model
f. Glycerol-induced model

The commonly used drugs for inducing nephrotoxicity are cisplatin and gentamicin.

Cisplatin Model

Cisplatin is chemically Cis-diaminedichloroplatinum-II. It is a DNA alkylating anti-cancer drug. Cisplatin gets accumulated in the kidney in the proximal and distal convulated tubules and produces free radicles which finally leads to renal damage by apoptosis or by generation of reactive oxygen species.[4]

In this study design, the experimental animals used are male Wistar albino rats with a body weight ranging from 120 g to 200 g. Cisplatin is administered as a single intraperitoneal administration with a dose of 5mg/kg.[3,6,7,8]

Gentamicin Model

Gentamicin is an aminoglycoside drug which mainly affects the kidney by causing tubular necrosis. It produces dose-dependent nephrotoxicity. It also works

by creating reactive oxygen species which causes lipid peroxidation leading to necrosis.[4]

In this model, male Wistar rats with a body weight of 150-200g are used for the experimentation. The drug is administered either via intramuscular route[8] or through oral route.[9] Gentamicin is given at a dose of 80 mg/kg.

Naveed Ullah et al performed a study using gentamicin by giving the drug to adult male rabbits weighing about 1-1.5 kg.[10]

Paracetamol Model

Acetaminophen, commonly known as Paracetamol, is a commonly used analgesic and antipyretic drug. It mainly causes hepatotoxicity, but produces renal damage in a dose-dependent manner; mainly in overdose. The symptoms of hepatotoxicity can be differentiated from that of nephrotoxicity. Pathophysiology of nephrotoxicity is due to cytochrome P-450 mixed function isoenzyme in the kidney.[11,12]

In paracetamol model, the animals used for the study are albino Wistar rats weighing from 120-150g. The drug is administered through intraperitoneal route at a dose of 200mg/kg[11] and 500mg/kg.(4,11-13)K.S Gopi performed the experiment on Wistar Kyoto rats weighing from 200-250g.[13]

Doxorubicin Model

Doxorubicin is an anthracycline containing antibiotic which is used as a chemotherapeutic drug. Doxorubicin is also called adiramycin. The exact mechanism of the drug producing nephrotoxicity is not completely known. It may be due to the formation of free radicles which leads to apoptosis and lipid peroxidation of the membranes. Also the drug gets accumulated in the kidney leading to direct nephrotoxicity.[14-17]

In doxorubicin model, adult male Wistar rats of body weight between 180-350g are used to conduct the study. The drug is administered through intraperitoneal route mainly. Also it is administered as intravenous injection. Doxorubicin is administered at a dose of 15mg/kg.[14-17]

Bromobenzene Model

Bromobenzene is an industrially used toxicant for the synthesis of many drugs. In large doses, bromobenzene causes renal necrosis. The secondary metabolites of bromobenzene like benzophenol, benzoquinol produces this nephrotoxicity. The exact mechanism is not known.

For the studies, adult male Swiss mice with a body weight of 30g are used. Drug is administered as intraperitoneal injection (2ml/kg) in peanut oil at a dose ranging from 0 to 9.4mmol/kg.[18,19]

Glycerol-induced Model

Glycerol induced nehrotoxicity or acute renal failure (ARF) in rats is similar to the human myoglobinuric ARF. The mechanisms involved are tubular nephrotoxicity, action of cytokines which is released followed by rhabdomylosis and ischemic renal injury.

Renal failure is induced by administering glycerol 50% in rats through intramuscular injections. The dose of the drug is 8 ml/kg. The drug is administered mainly in the hind paw of the rats.[20]

CONCLUSION

Albino Wistar rats were used for the experimentation in majority of the nephroprotective models but the body weight of animals varied accordingly in each of the study modes. Apart from the albino Wistar rats, rabbits and mice were also included in the study in different models. The dose is calculated and administered with respect to the body weight of the animals selected. After the drug administration, blood is withdrawn from the animals for analyzing the blood parameters like blood urea nitrogen(BUN), serum urea, serum creatinine, WBC count, total protein etc is determined. The body weight of animals is also determined in the due course of the experiment. The animals are then anaesthetized and sacrificed. Kidneys are removed and analyzed. The effect of the study is confirmed thorough histopathological examinations.

REFERENCES

1. Tortora GJ, Derrickson B. Principles of Anatomy and Physiology. Wiley. 14th Edition, 2014; 981-984.
2. Kim S-Y, Moon A-R. Drug-Induced Nephrotoxicity and Its Biomarkers. Biomol Ther, 2012; 20(3): 268–272.
3. Swathi N, Sreedevi A, Bharathi K. Evaluation of Nephroprotective Activity of Fruits of *Ficus hispida* on Cisplatin-Induced Nephrotoxicity. Pharmacogn J, 2011; 3(22): 62–68.
4. Chatterjee P, Chakraborty B, Nandy S. Review On Nephroprotective Activity Study By Different Plant Extract. Adv J Pharm Life Sci Res, 2014; 2(2): 24-40.
5. Naughton CA. Drug-Induced Nephrotoxicity. American Family Physician, 2008; 78(6): 743-750.
6. Abdel-Hady H, El-Sayed MM, Abdel-Hady AA, Hashash MM, Abdel-Hady AM, Aboushousha T, et al. Nephroprotective Activity of Methanolic Extract of *Lantana camara* and Squash *(Cucurbita pepo)* on Cisplatin-Induced Nephrotoxicity in Rats and Identification of Certain Chemical Constituents of *Lantana camara* by HPLC-ESI- MS. Pharmacogn J, 2017; 10(1): 136–147.
7. Seena Xavier, Haneefa MS, Anand RD, Maheshwari R, Shetty MM. Antioxidant and Nephroprotective Activities of the Extract and Fractions of *Homonoia riparia* Lour. Pharmacogn Mag, 2017; 13(49): 25–30.
8. Aparna M, Deepika MY, Nagaraju B, Prasad K. Evaluation of Nephroprotective Activity of Ethanolic Extract of *Annona reticulata* in

Gentamicin and Cisplatin Induced Nephrotoxicity in Rats. J. Pharm. Sci. & Res, 2016; 8(9): 995-1007.
9. Padmalochana K, Rajan MSD. *In-Vivo* Nephroprotective Potential From Leaves Extracts of *Andrographis paniculata*. World J Pharm Pharm Sci, 2015; 4(03): 1414-1425.
10. Ullah N, Khan MA, Khan T, Ahmad W. Nephroprotective potentials of *Citrus aurantium*: A prospective pharmacological study on experimental models. Pak J Pharm Sci, 2014; 27(3): 505-510.
11. Chinnappan SM, George A, Thaggikuppe P, Choudhary Y, Choudhary VK , Ramani Y, Dewangan R. Nephroprotective Effect of Herbal Extract *Eurycoma longifolia* on Paracetamol-Induced Nephrotoxicity in Rats. Evidence-Based Complementary and Alternative Medicine, 2019; 2019: 1-6.
12. Mazer M, Perrone J. Acetaminophen-Induced Nephrotoxicity: Pathophysiology, Clinical Manifestations, and Management. Journal of Medical Toxicology, 2008; 4(1): 1-6.
13. Gopi KS, Reddy GA, Jyothi K, Kumar AB. Acetaminophen-induced Hepato- and Nephrotoxicity and Amelioration by Silymarin and *Terminalia chebula* in Rats. Toxicology International, 2010; 17(2): 64-66.
14. Ayla S, Seckin I, Tanriverdi G, Cengiz M, Eser M, Soner BC, et al. Doxorubicin Induced Nephrotoxicity: Protective Effect of Nicotinamide. Int J Cell Biol, 2011; 2011: 1–9.
15. El-Sheikh AAK, Morsy MA, Mahmoud MM, Rifaai RA, Abdelrahman AM. Effect of Coenzyme-Q10 on Doxorubicin-Induced Nephrotoxicity in Rats. Adv Pharmacol Sci, 2012; 2012: 1–8.
16. Refaie MMM, Amin EF, El-Tahawy NF, Abdelrahman AM. Possible Protective Effect of Diacerein on Doxorubicin-Induced Nephrotoxicity in Rats. Journal of Toxicology, 2016; 2016: 1-9.
17. Ren X, Bo Y, Fan J, Chen M, Xu, D, Dong Y, He H, Ren X et al. Dalbergioidin Ameliorates Doxorubicin-Induced Renal Fibrosis by Suppressing the TGF-β Signal Pathway. Mediators of Inflammation, 2016; 2016: 1-10.
18. Rush GF, Kuo C-H, Hook JB. Nephrotoxicity of bromobenzene in mice. Toxicol Lett, 1984; 20(1): 23–32.
19. Rush GF, Newton JF, Maita K, Kuo C-H, Hook JB. Nephrotoxicity of phenolic bromobenzene metabolites in the mouse. Toxicology, 1984; 30(3): 259–272.
20. Glycerol-Induced Acute Renal Failure Model [Internet]. Glycerol-Induced Acute Renal Failure Model - Creative Biolabs. [cited 2020 Feb4]. Available from: https://www.creative-biolabs.com/drug-discovery/therapeutics/glycerol-induced-acute-renal-failure-model.htm.