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Preclinical Animal Models of Renal Disease

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Abstract

Acute Renal Failure (ARF) is a serious condition where the kidneys suddenly stop working, commonly caused by drug-related injury. This article aims to give a detailed explanation of different animal models used to study ARF, focusing on the biomarkers linked with this condition. When administering drugs to animals, it is essential to be mindful of the potential for ARF to occur. Nephrotoxic drugs like cisplatin, methotrexate, acyclovir, Cyclosporine, folic acid, amphotericin B, and amikacin can induce ARF if the dosage and duration of exposure are not adequately regulated to match the clinical scenario. Careful monitoring is crucial to ensuring the safety and well-being of the animals under our care. This article contains various screening models for ARF caused by various allopathic drugs like glycerol, acyclovir, amikacin, amphotericin B, Isoniazid-Rifampicin, cisplatin, folic acid, diclofenac, and lithium. The intrinsic toxicity of these medications also plays a significant role in the ensuing Acute Kidney Injury (AKI), and the kidney is probably more vulnerable to damage than other organs. These medications can be hazardous and their effects on the glomerulus and/or tubules can be caused by oxidative damage, hypersensitivity responses, altered hemodynamics, and tubule blockage. This article aims to provide a thorough description of the model used and to examine the findings in relation to that particular model. This approach can yield valuable insights and help ensure the findings' accuracy and relevance.

Keywords: Acute Renal Failure, Acyclovir, Amikacin, Amphotericin B, Cisplatin

1. Introduction

Acute Kidney Injury (AKI) is a serious medical issue that has an increased rate of mortality. It may immediately follow an injury or silently, with symptoms only appearing after its onset. Rhabdomyolysis-induced AKI is a type of AKI that often develops after physical, thermal, ischemic, infective, metabolic, or toxic causes of skeletal muscle trauma. This type of AKI releases toxic levels of myoglobin and other intracellular proteins into the bloodstream[1]. AKI can cause various symptoms such as reduced urine output (oliguria), swelling in the legs, ankles, and feet (edema), tiredness (fatigue), difficulty breathing (dyspnea), and loss of appetite (anorexia)[2]. Children experienced an incidence of community-acquired AKI of 8.3% and hospital-acquired AKI of 20.9%, compared to adults who experienced an incidence of AKI of 21.6% and 33.7%, respectively[3].

The renal tubular cells, glomerular cells, and vascular endothelium can all be impacted by AKI. Various factors like ischemia, toxins, infections, or inflammation can cause damage to these targets, resulting in impaired kidney function and potential harm to the kidney tissues. The specific targets and mechanisms involved can differ based on the underlying cause of AKI[4].

ARF can raise a patient's chance of dying after receiving specific medication treatments, such as acyclovir, methotrexate, amphotericin B, amikacin,

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Table 1. List of Animal models of renal disease

Sr. No	Inducer	Animal	Route of Administration and Dose	Duration of Study	Reference
1.	Glycerol	Rats, Mice	10 ml/kg *im*	8 days	[5]
2.	Acyclovir	Rats	150 mg/kg *ip*	8-9 days	[8,9]
3.	Methotrexate	S.D Rats	20 mg/kg *po*	5 days	[12]
4.	Amphotericin B	Mice	2/4 mg/kg *iv*	8 days	[14]
5.	Amikacin	S.D. Rats	100/500 mg/kg *sc*	10 days	[17]
6.	Ischemic Reperfusion	Rats	ARF is more frequently inducedby 45 minutes of ischemia followedby 24 hours of reperfusion.	1-2 days	[20]
7.	Diclofenac	Rats	15 mg/kg *ip*	3 days	[4]
8.	Cyclosporine	Rabbits	25 mg/kg *sc*	31 days	[28]
9.	Lithium	Rats	80 *mg/kg ip*	1 day	[29]
10.	Folic acid	Rats	250 mg/kg *ip*	1-2days	[30]
11.	Cisplatin	Rats	5-40 mg/kg *ip*	72 hrs	[21,22]
12.	Isoniazid-Rifampicin	Rats	50/100 mg/kg *po*	21-28 days	[31]

cyclosporine, cisplatin, and more allopathic drugs. Different animal models for the ARF have been created by researchers to better understand its pathogenesis and explore possible pharmacological treatments. This review discuss the different animal models of AKI, as summarized in Table 1[5].

2. Animal Models of Renal Failure

2.1 Glycerol-Induced ARF

2.1.1 Principle

The pathophysiology of glycerol-induced ARF involves myoglobin toxicity and also reactive oxygen species, inflammation, and apoptosis. Glycerol administration through the muscle causes the release of myoglobin and other muscle contents into the circulation[5,6].

2.1.2 Procedure

Prior to receiving the glycerol injection, rats fasted for a period of 24 hours. Then, 10 ml/kg of 50% glycerol was administered intramuscularly to both hind limbs of the rats. Rats were kept in metabolic cages so that urine could be collected continuously for 24 hours. Blood is collected from the retroorbital venous plexus into clean, heparinized tubes before and after the injection of glycerol to measure Blood Urea Nitrogen (BUN) and creatinine levels[7].

2.1.3 Advantages

- The glycerol takes less time to induce kidney injury by increasing serum creatinine and uric acid levels.
- Glycerol is easily available in the market.
- Cost effective due to cheaper price.

2.1.4 Disadvantage

- Skilled personnel are required for dosing because the route of administration of glycerol is IM in the hind limb of the rat where various nerves are also present. If they get injured, this may produce a disability for the rat's walking.
- The glycerol is hydrophobic in nature so it will produce muscle destruction and inflammation at the site of administration.
- Administration of glycerol the recovery of kidney damage starts which may interfere with the test drug activity.

2.2 Acyclovir-induced ARF

2.2.1 Principle

The antiviral drug acyclovir is efficacious and often used. However, high renal damage prevents it from being used in clinical settings. Because of its extremely slow *in-vivo* metabolism, acyclovir is mostly eliminated by glomerular filtration and tubular secretion. The two mechanisms

through which acyclovir is hypothesized to produce nephrotoxicity are oxidative stress and its direct impact on renal tubular cells[9].

2.2.2 Procedure

Comparing the untreated group of rats with the group that received acyclovir therapy allows for the screening of acyclovir-produced ARF. Rats representing the control group received 0.2 ml of water Intraperitoneally (IP) every day for 7 days. Acyclovir is given at 150600 mg/kg intravenously once a day for 7 days Rats were anesthetized on the eighth day of therapy, and either a retro-orbital or cardiac puncture was used to collect blood samples[9].

2.2.3 Advantages

- Inducer is easily available at cheap rates so it is a cost-effective induction model.
- The metabolism rate of acyclovir is very low and mainly excreted through glomerular filtration and tubular secretion hence it directly attacks renal tubular cells and produces damage to the kidneys.

2.2.4 Disadvantage

- The clinical use of acyclovir is oral and IV, but the induction models that are available for AKI are with IP and IV but not oral.
- Requires more than 8 days to produce kidney damage.
- Produces itching and swelling at the site of application.

2.3 Methotrexate Induced ARF

2.3.1 Principle

Methotrexate is known to be a potent anticancer and immunosuppressive agent. Nevertheless, one of the potential complications that may arise from its use is nephrotoxicity. The development of methotrexate nephrotoxicity is caused by various factors, such as oxidative stress and inflammation, which affect multiple pathways[10]. The damage to the kidneys caused by methotrexate may be due to a rise in adenosine levels in the plasma of extracellular fluid. This, in turn, could activate A1 receptors in the renal tissues, resulting in reduced renal blood flow and decreased excretion of salt and water[11].

2.3.2 Procedure

In this study, rats received a daily dosage of saline by oral gavage for a period of five days. They get an intraperitoneal injection of methotrexate at a dose of 20 mg/kg on the third day of the trial. Three days post-injection, ether is used to make the rats unconscious and then exposed to cervical dislocation for the purpose of sacrifice. The body weights at the beginning and end were noted, and the weight increase as a percentage of the beginning weight was computed. The kidneys were then taken out, washed, and dried[12].

2.3.3 Advantages

- Only 3 days are required to produce toxicity.
- Low dose required to produce toxicity.

2.3.4 Disadvantages

- It is a chemotherapeutic drug having major side effects i.e., hepatotoxicity which leads to the increased mortality rate of the animal.
- High in cost.

2.4 Amphotericin B-Induced ARF

2.4.1 Principle

Amphotericin B is an antibiotic that falls under the category of polyene macrolides. The most significant side effect of using amphotericin B is nephrotoxicity. The decrease in glomerular filtration rate was previously caused by amphotericin B-induced direct afferent arteriole contraction, Amphotericin B insertion into cell membranes, which results in the development of holes and H-ion return flow within cells, is what causes the renal tubules to become acidic. The suppression of the arginine vasopressin receptor signalling pathway by amphotericin B isthought to be the cause of resistance to the antidiuretic hormone polyuria[13].

2.4.2 Procedure

The research involved conducting two separate experiments, namely a one-time dosage experiment and a seven-day repeated dosage experiment. To prepare the correct dosage of Amphotericin B powder, it was dissolved in a 5% glucose solution. These dosing solutions were made right before use. The doses were given through a bolus dosage of 10 ml/kg given intravenously, depending on the animal's weight. In an experiment with a single dosage, a 5% glucose solution was given to the untreated group. Additionally, two groups each got a single dose of amphotericin B at either 2 or 4 mg/kg.

The animals were humanly killed 24 hours afterthe dose had been administered. In the seven-day repeated dosing experiment, three groups were used: A control group, two groups that received amphotericin B dosages of 1 or 2 mg/kg/day, and a third group. The sacrifice of the animals occurred on the eighth day[14].

2.4.3 Advantages

- The toxicity is produced at a low dose.
- Kidneys are damaged in less time interval.

2.4.4 Disadvantages

- Expensive.
- Produces hepatotoxicity.
- High mortality rate.

2.5 Amikacin-induced ARF

2.5.1 Principle

Amikacin is one of the number of aminoglycoside antibacterial drugs that are often prescribed to treat severe Gram-negative bacterial infections[15]. Aminoglycosides are drugs that accumulate in the lysosomes of proximal tubular cells, a process known as adsorptive pinocytosis. This accumulation leads to phospholipidosis, which has been studied both *in vivo* and *in vitro*. Humans have also been observed to develop similar phospholipidosis. The nephrotoxicity of aminoglycosides is caused by their ability to bind to phospholipids and the extent of their uptake by the kidneys. This can lead to focal necrosis, tubular degeneration, and interstitial proliferation even at low, therapeutic doses. Therefore, the potential for nephrotoxicity is related to the development of phospholipidosis in patients taking aminoglycosides[16].

2.5.2 Procedure

Both male and female rats were included in the study. Every rat was administered either 100 or 500 mg/kg of amikacin once a day for a maximum of ten days via subcutaneous injection. Serum creatinine was evaluated in each sample of blood after blood samples were collected. The medical condition known as nephrotoxicity is identified by an increase in the creatinine level. After the study concluded, the rats' kidneys were collected and sorted based on their results. The analysis of the concentration of amikacin in these tissue samples was also conducted[17].

2.5.3 Advantages

- Cost-effective induction model.
- Route of administration is quite easy.

2.5.4 Disadvantages

- Requires maximum days and multiple doses to produce nephrotoxicity.
- Produces neuromuscular paralysis.
- Produces irreversible ototoxicity.

2.6 Ischemic Reperfusion-Induced ARF

2.6.1 Principle

Ischemia-reperfusion-induced AKI is a frequently used AKI model in mice and rats. However, there is often a significant amount of variability in the results, and mortality rates are frequently high and not reported[18]. Renal ischemia followed by the restoration of blood flow, known as reperfusion, can initiate a cascade of signal pathways that lead to kidney cell death, inflammation, and AKI[19].

2.6.2 Procedure

The rats were given a regular diet of pellets and water, with no restrictions on intake. To anesthetize the rats, they were given an intraperitoneal injection of ketamine (60 mg/kg) and diazepam (5 mg/kg). Both renal pedicles were discovered through a central incision and blocked for exactly 60 minutes using a microvascular clamp. After this time, the clamps were removed, and the kidneys were allowed to reperfusion. The abdomen was then closed using continuous sutures in two layers. After a 24-hour reperfusion period, all rats were humanely euthanized and both kidneys were removed for antioxidant and histological analysis[20-24].

2.6.3 Advantages

- No chemical is required for kidney damage.
- Cost-effective.
- Less time required for induction.

2.6.4 Disadvantages

- Skilled professionals are required.
- Mortality rate is high.
- Chances of contamination are higher.
- Continuous evaluation is required.

2.7 Cisplatin-Induced ARF

2.7.1 Principle

Cisplatin is a potent chemotherapeutic agent commonly used to treat various solid tumors. However, its effectiveness is dependent on the dosage administered, and nephrotoxicity is the primary limiting factor in its use. Cisplatin nephrotoxicity is caused by several mechanisms such as renal vasoconstriction, oxidative stress, inflammatory responses, and activation of apoptotic pathways[25]. Cisplatin can enter renal epithelial cells primarily through the OCT2 transporter, and to a lesser extent through the Ctrl transporter. Once inside, cisplatin can causeharm to both nuclear and mitochondrial DNA, as well as produce reactive oxygen species. These effects lead to the activation of both mitochondrial and non-mitochondrial pathways ofapoptosis and necrosis[26].

2.7.2 Procedure

The animals received a one-time injection of cisplatin through the ip route, with doses ranging from 5-40 mg/kg. Blood samples were collected 24 and 72 hours after the injection, The levels of creatinine and blood urea nitrogen were evaluated, and the rats' kidneys were removed after 72 hours. For histopathological evaluation[27].

2.7.3 Advantages

- Less time required for induction.
- Cost effective.
- Used drug for a variety of disease induction.

2.7.4 Disadvantages

- It is chemotherapeutic thus it has many side effects.
- It has dose-dependent neurotoxicity.
- Drug resistance can occur.

3. Conclusion

The review provides a thorough analysis of various allopathic drugs and their effectiveness intreating ARF in animal models. The examination of various animal models helps researchers better understand the pathophysiology of ARF and evaluate potential therapeutic interventions.

The limitations of these drugs have also been discussed, which can guide future research and drug development in the field of nephrology. Overall, this evaluation adds to the existing knowledge and understanding of ARF. The importance of using animal models in preclinical studies is emphasized, as this allows researchers to test specific aspects of the disease and potentially find new treatments that could be applied in clinical settings. It's encouraging to see that research is ongoing and that there is a concerted effort to find new and effective treatments for ARF.

I found this review article to be incredibly helpful for anyone interested in researching or treating acute renal failure in animals. It provides valuable insights into the use of allopathic drugs in different animal models and can pave the way for further advancements in the understanding and management of this condition. Ultimately, this knowledge can lead to improved patient outcomes and a better quality of life.

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