Pharmacological Reports
2012, 64, 31–44
ISSN 1734-1140

Review

Animal models of acute renal failure

Amrit Pal Singh[1], Arunachalam Muthuraman[1], Amteshwar Singh Jaggi[1], Nirmal Singh[1], Kuldeep Grover[1], Ravi Dhawan[2]

[1]Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala 147002, India

[2]Khalsa College of Pharmacy, Amritsar (Punjab), India

Correspondence: Nirmal Singh, e-mail: nirmal_puru@rediffmail.com

Abstract:
The animal models are pivotal for understanding the characteristics of acute renal failure (ARF) and development of effective therapy for its optimal management. Since the etiology for induction of renal failure is multifold, therefore, a large number of animal models have been developed to mimic the clinical conditions of renal failure. Glycerol-induced renal failure closely mimics the rhabdomyolysis; ischemia-reperfusion-induced ARF simulate the hemodynamic changes-induced changes in renal functioning; drug-induced such as gentamicin, cisplatin, NSAID, ifosfamide-induced ARF mimics the renal failure due to clinical administration of respective drugs; uranium, potassium dichromate-induced ARF mimics the occupational hazard; S-(1,2-dichlorovinyl)-L-cysteine-induced ARF simulate contaminated water-induced renal dysfunction; sepsis-induced ARF mimics the infection-induced renal failure and radiocontrast-induced ARF mimics renal failure in patients during use of radiocontrast media at the time of cardiac catheterization. Since each animal model has been created with specific methodology, therefore, it is essential to describe the model in detail and consequently interpret the results in the context of a specific model.

Key words:
acetaminophen, acute renal failure, cisplatin, gentamicin, glycerol, ischemia-reperfusion injury

Abbreviations: ARF – acute renal failure, ATN – acute tubular necrosis, ATSDR – Agency of Toxic Substances and Disease Registry, Bcl-xL – B-cell lymphoma-extra large, BUN – blood urea nitrogen, CAA – chloroacetaldehyde, Cisplatin – cis-diaminedichloroplatinum(II), CLP – cecal ligation and puncture, CM and/or CT – contrast media, CYP – cytochrome-P, DCVC – S-1,2-dichlorovinyl-L-cysteine, DNA – deoxyribonucleic acids, *E. coli* – *Escherichia coli*, FA – folic acid, Fe–NTA – ferric-nitrilotriacetate, GFR – glomerular filtration rate, GSH – reduced glutathione, $HgCl_2$ – mercuric chloride, *im* – intramuscular, *ip* – intraperitoneal, *iv* – intravenous, I/R – ischemia and reperfusion, IFO – ifosfamide, LPS – lipopolysaccharide, MPTP – mitochondrial permeability transition pore, NaCl – sodium chloride, NADPH oxidase – nicotinamide adenine dinucleotide phosphate-oxidase, NSAIDs – non-steroidal anti-inflammatory drugs, NTA – nitrilotriacetic acid, *po* – per oral, ROS – reactive oxygen species, *sc* – subcutaneous, SHR – spontaneous hypertensive rats, TCE – trichloroethylene, TNF-α – tumor necrosis factor-α, UN – uranyl nitrate

Introduction

Acute renal failure (ARF) is characterized by a rapid, potentially reversible, decline in renal function including rapid fall in glomerular filtration rate (GFR) and retention of nitrogenous waste products over a period of hours or days. The mortality rate of patients with ARF has remained 25–70% despite the use of various pharmacologic agents. Therefore, it continues to be a frequent threatening complication following trauma, complex surgical procedures, and in patients hospitalized in intensive care units [73]. ARF increases the risk of death in patients after thoracoabdominal aortic surgery, bone marrow transplantation, amphotericin B therapy, in patients with liver cirrhosis and in cardiac surgery [30]. The various factors

Tab. 1. List of animal models for ARF in an experimental laboratory

S. No.	Animal models	Dose, route and duration	References
1	Glycerol	• Single dose 8–10 ml/kg, *im* is used for induction of ARF • Single dose 8 mg/kg, *im* is more commonly used for the induction of ARF	[61, 107, 127] [107]
2	Ischemia -reperfusion	• Clamping of both renal artery for 60 min (I) and 24 h (R). • Left renal artery clamping for 45 min (I) and 24 h (R) • Right renal artery and vein for 60 min (I) and 60 min (R) • Left renal artery and vein for 45 min (I) and 2 week (R) • Infra-renal aortic 150 min (I) and 180 min (R) • Left renal pedicle for 40 min (I) and 24 h (R) • 45 min ischemia followed by 24 h reperfusion is more commonly used for the induction of ARF	[15, 19, 36, 49,80, 87, 93, 140] [36, 80]
3	Gentamicin	• Dose range 40–200 mg/kg for 4–10 days • Dose 100 mg/kg, *ip* for 5 days is more commonly used for the induction of ARF	[21, 44, 99, 128, 137] [44]
4	Cisplatin	• Dose range 5–40 mg/kg, *ip* single dose • Dose 100 mg/kg is more commonly used for the induction of ARF	[6, 7, 61, 74, 76, 79, 81, 83, 89, 104] [89]
5	Radiocontrast media	**Diatrizoate** • Single dose range 2–10 ml/kg, *iv* • Dose 7 and 10 ml/kg, *iv* is more commonly used for the induction of ARF	[33, 45, 50, 141, 144] [33, 141]
		Ioxaglate • Dose 1 ml/min, intra aortic injection for 3 min is used for the induction of ARF	[122]
		Iohexol • Dose range 1.5–3 g of iodine/kg, *ip* injection is used for the induction of ARF	[75]
		Sodium iothalamate • Dose 6 ml/kg intra aortic administration for 2–3 min is used for the induction of ARF	[3]
6	NSAIDs	**Acetaminophen** • Dose range 375–3000 mg/kg, *ip* single dose. • Dose 750 mg/kg, *po* and 600 mg/kg, *ip* single dose is more commonly used for the induction of ARF.	[2, 27, 29, 69, 78, 100] [78, 100]
		Diclofenac sodium • Dose 15 mg/kg, *ip* injection for 3 day is used for the induction of ARF	[42]
7	Osmotic nephrosis	• Single dose 4–27% w/v sucrose, *ip* is used for the induction of ARF	[55, 144]
8	Ifosfamide	• Dose range 50–1100 mg/kg, *ip* 1–5 days • Dose 550 mg/kg, *ip* single dose is more commonly used for the induction of ARF	[14, 145] [145]
9	Uranium	**Uranyl nitrate** • Dose range 0.5–20 mg/kg is used for the induction of ARF • Single dose 15 and 25 mg/kg, *iv* is more commonly used for the induction of ARF	[13, 32, 39, 40, 48, 77, 101, 121] [13]
		Uranyl acetate • Single dose 5 mg/kg, *sc* is used for the induction of ARF	[39, 40]
10	Mercuric chloride	• Dose range 1–10 mg/kg, is used for the induction of ARF • Single dose 6 mg/kg, *ip* and 10 mg/kg, *sc* are more commonly used model for the induction of ARF	[4, 12, 46, 106, 143, 147] [4, 46]
11	Potassium dichromate	• Single dose 15 mg/kg, *sc* is used for the induction of ARF	[9, 68]
12	Folic acid	• Single dose 250 mg/kg, *iv* is used for the induction of ARF	[129]
13	Ferric-nitrilotriacetate	• Dose range 1–15 mg of iron/kg, *ip* is used for the induction of ARF • Dose 12 mg/kg, *po* and 15 mg/kg, *ip* is more commonly used for the induction of ARF	[54, 58, 97, 125] [125]
14	S-(1,2-dichlorovinyl)-L-cysteine (DCVC)	• Dose range 5–30 mg/kg, *ip* is used for the induction of ARF • Single dose 25 mg/kg, *ip* is more commonly used for the induction of ARF	[37, 102, 136] [37]
15	Sepsis	• Ligation of cecum and and punctured three times for the induction of ARF • Administration of LPS 2.5–15 mg/kg is used for the induction of ARF • Single dose 15 mg/kg, *ip* is more commonly used for the induction of ARF	[139] [63, 64, 96, 105] [63]
16	Bipyridyls	• Dose range 108–680 mg/kg of paraquat is used for the induction of ARF • Dose range 7.5–680 μmol/kg of diquat is used for the induction of ARF	[82] [82, 103]

that predispose to ARF are hemodynamic instability, major vascular surgery, hypovolemia, atherosclerosis, diuretic therapy, preoperative starvation, congestive cardiac failure, peritonitis, ileus obstruction, biliary surgery, jaundice, diabetes mellitus, hypoxia, ischemia and reperfusion (I/R), pre-eclampsia/eclampsia, sepsis, major burns and pancreatitis [62].

ARF is classically divided into pre-renal, renal (intrinsic) and post-renal failure. Pre-renal ARF is a consequence of decreased renal perfusion (due to hypovolemia/shock or ischemia), which leads to a reduction in GFR. Intrinsic renal failure occurs when there is a damage to the structures of the nephron such as the glomeruli, tubules, vessels, or interstitium. The major cause of intrinsic ARF is acute tubular necrosis (ATN) that results from ischemic or nephrotoxic injury. Pre-renal ARF and ischemic ATN may occur as a continuum of the same pathophysiological process, and together account for 75% of the causes of ARF [73]. Post-renal ARF follows obstruction of the urinary collection system with an increase in pressure within the renal collecting systems resulting in reduced GFR and renal failure.

In clinical setup, the etiology of ARF is multifold and complex. Rhabdomyolysis is the syndrome characterized by breakdown of striated muscle with massive release of myoglobulin into the extracellular fluid and circulation leading to filtration of myoglobulin to renal tubules [126]. Rhabdomyolysis provokes ATN because myoglobin forms obstructing tubular casts and myoglobin also leads to intra-renal vasoconstriction due to nitric oxide scavenging and through hypovolemia. I/R-induced renal injury is also very important cause of ARF in clinical setup. Antibiotics such as gentamicin [92], anticancer agents such as cisplatin [61, 89, 94] and ifosfamide [145], radio contrast media, non-steroidal anti-inflammatory drugs (NSAIDS), osmotic changes, dietary or endogenous agents such as folic acid are the important causes of ARF [42, 51, 75, 129]. In order to understand the pathophysiology of onset of ARF in these different conditions and to explore the drug therapeutics, researchers have developed different animal models of ARF (Tab. 1). The present review discusses these different animal models of acute renal failure.

Animal models of ARF

Glycerol-induced ARF

Glycerol-induced ARF is characterized by myoglobinuria, tubular necrosis [66] and enhanced renal vasoconstriction. The pathogenic mechanisms involved in glycerol-induced renal failure include ischemic injury, tubular nephrotoxicity caused by myoglobin, and the renal actions of cytokines released after rhabdomylosis [34, 135]. The large numbers of disorders known to cause rhabdomyolysis include intrinsic muscle dysfunction (including trauma, burns, intrinsic muscle disease, and excessive physical exertion), metabolic disorders, hypoxia, drugs, toxins, infections, temperature extremes and idiopathic disorders [126]. Complications associated with rhabdomyolysis include disseminated intravascular coagulation, hyperkalemia and other metabolic imbalances, ARF and acute cardiomyopathy. In general, about 10–40% of cases with rhabdomyolysis develop ARF and it accounts for 2–15% of all cases of ARF. The model for studying this form of ARF is obtained in the rat by intramuscular injection of glycerol [119]. There is enhanced generation of hydrogen peroxide in renal cortex in rats with glycerol-induced acute renal failure.

A standard method of inducing renal failure is by intramuscular administration of 50% glycerol, v/v (8 ml/kg, *im*) [108]. The required amount of glycerol is administered as a deep *im* injection equally distributed to both hind legs. Rats are deprived of food and water for 24 h before glycerol administration after which they were sacrificed for kidney function evaluation [107]. Also, Vlahovic et al. [127] induced ARF by administration of glycerol (50% v/v in saline) *im* at a dose of 10 ml/kg. Injection volumes were divided equally between two hind limbs. The rats were dehydrated 18 h prior induction of myoglobinuric renal injury and sacrificed 48 h after injection of hypertonic glycerol without any restriction of diet or water [127]. Intramuscular injection of glycerol in the rabbit induces a model of ARF at a dose of 10 mg/kg that resembles the ARF caused by massive release of myoglobin in crush syndrome in humans [112, 123]. An intramuscular administration of single dose of 8 ml/kg of glycerol is the most appropriate animal model that clinically mimics the rhabdomyolysis-induced renal failure in humans.

Ischemia-reperfusion-induced ARF

Under the circumstances such as ischemia and nephrotoxins, ARF is characterized by "acute tubular necrosis" with flattened epithelia and tubular dilation and cast formation. In these conditions, the tubular damage and altered glomerular hemodynamics may

coexist or even lead to each other [57]. Although the detailed cellular and molecular mechanisms of cell injury and the subsequent recovery are not entirely known, yet, data from the previous studies have indicated that ARF may result from the necrosis and apoptosis of renal epithelial cells [35, 117, 131]. In the kidney, ischemia reperfusion injury is associated with cell death of tubular epithelial cells, localized in the stripe between the cortex and medulla; *via* necrosis or apoptosis that in-turn depends on the severity of the ischemic insult.

Experimentally, ARF is induced by clamping the left renal artery for 1 h followed by reperfusion in anesthetized uninephrectomized dogs and renal failure is noted to develop within 3 h [140]. Bhalodia et al. have reported the development of renal failure in rats within 24 h by clamping of both the kidneys for 60 min followed by 24 h of reperfusion [19, 93]. The development of I/S-induced ARF in rats has also been demonstrated by unilateral left renal artery clamping using a small non traumatic vascular clamp for 45 min followed by reperfusion for 24 h [36, 80]. Foglieni et al. have reported the development of renal failure in rats by clamping both right renal artery and vein for 60 min with a microsurgical clamp followed by reperfusion for 60 min [49]. Baker et al. have reported the development of renal failure in pigs by occluding infra-renal aorta with a standard angled arterial cross-clamp (palpation of distal aorta to confirm total aortic occlusion) for 150 min followed by reperfusion for 180 min [15]. Matthijsen et al. have reported the development of I/R-induced renal failure in mice by applying a non traumatic vascular clamp to the left renal pedicle for 40 min after 1.0 cm long midline abdominal incision to induce ischemia followed by reperfusion for 24 h [87]. Similarly, Susa et al. have reported the development of renal failure in mice by occluding left renal artery by an atraumatic microvascular clamp to induce ischemia lasting for 25–37 min with reperfusion of 24 h [115]. The ischemia of 45 min followed by 24 h reperfusion is more suitable and commonly used animal model to simulate the hemodynamic changes-induced alteration in renal function in humans.

Gentamicin-induced ARF

In humans, gentamicin has been used for the treatment of life threatening Gram negative infections. Clinically, the high dose of gentamicin (2.5 mg/kg, *im* every 12 h for 7 days) has been shown to produce nephrotoxicity [95]. It has been reported that 30% of patients treated with gentamicin for more than 7 days show signs of nephrotoxicity [85]. Gentamicin nephrotoxicity is one of the most common causes of ARF and promotes both increased morbidity and greater health care costs. The clinical trial reports of elder patients have documented that aminoglycosides levels above 2.5 μg/ml possess the major risk factors for aminoglycoside-associated nephrotoxicity [110, 116].

The mechanism of renal failure is that the polycationic aminoglycoside gentamicin is prefrentially uptaken by proximal tubular cells of the nephron by binding to negatively charged phospholipids on the brush border and is then quickly transferred to the transmembrane protein – megalin [88]. After internalization *via* endocytosis, the aminoglycoside is transported to the lysosome and tightly binds to acidic phospholipids in the lipid bilayer, causing reduced phospholipase activity and production of phospholipid metabolites. The ability of gentamicin to alter mitochondrial respiration has been well documented in reports of both *in vitro* and *in vivo* studies [59]. Other factors that contribute to the pathogenesis of gentamicin nephrotoxicity include generation of superoxide anion and hydroxyl radicals, alteration of anti-oxidant defense systems, depletion of reduced glutathione, Na^+-K^+-ATPase inhibition, opening of mitochondrial permeability transition pore and activation of renin-angiotensin system [8, 90, 92, 138].

Different methods have been employed to induce renal failure in rats that include *ip* administration of gentamicin sulfate at a dose of 100 mg/kg/day (in 0.9% NaCl) for 5–8 days and assessment of renal failure assessed 24 h after the last gentamicin injection [44]. Xie et al. reported the development of ARF in rats by administration of relatively higher dose of gentamicin sulfate at the dose of 150 mg/kg, *sc* route for five days [137]. On the other hand, in another variation, the development of ARF in rats has been shown by administrating gentamicin at a dose of 200 mg/kg twice daily for four consecutive days [99]. Volpini et al. have reported the development of ARF in rats by administration of gentamicin at a dose of 40 mg/kg, *im*, twice a day for nine days [128], while Bledsoe et al. reported the development of ARF in rats by administration of gentamicin at a dose of 80 mg/kg, *sc* for ten days with the assessment of renal failure on the eleventh day [21]. The administration of gentamicin 100 mg/kg, *ip*, for 5 consecutive days inducing renal

dysfunction is more commonly used model and closely mimics the antibiotic-induced changes in renal function in clinical setup.

Cisplatin-induced ARF

Cisplatin [cis-diaminedichloroplatinum(II)], an anticancer drug, is broadly used for the therapy of cancers such as ovarian, head and neck carcinomas, and germ cell tumors. Nephrotoxicity is frequent and is the major limitation in cisplatin-based chemotherapy. In humans, high dose of cisplatin (75 mg/m^2) has been used as baseline chemotherapeutic agent for the management of lung cancer. However, at this dose significant kidney damage has been seen in patients. The patients are administered saline infusion prior to and following cisplatin (total of 3.5–4.0 liters during 3–4 h) to prevent nephrotoxicity. The previous clinical studies had also reported that cisplatin in a dosage of 20 mg/m^2/day for 5 days causes significant changes in serum creatinine, creatinine clearance and 2.4 fold higher concentration of urine N-acetyl-β-D-glucosaminidase (an indicator of tubular damage) levels [134]. There are several mechanisms that contribute to renal dysfunction following exposure to cisplatin that include direct tubular toxicity in the form of apoptosis and necrosis that is mediated through inflammation, reactive oxygen species (ROS), calcium overload, phospholipase activation, depletion of reduced glutathione, inhibition of mitochondrial respiratory chain function, induction of apoptosis, opening of mitochondrial permeability transition pore (MPTP) and ATP depletion [10, 26, 67, 94].

Izuwa et al. have reported that administration of 5 ml/kg cisplatin (0.1% of saline solution) in the abdominal cavity is associated with development of ARF in rats within 72 h of administration [61], while Roncal et al. reported the development of renal failure with the same dose of cisplatin after five days of drug injection [104]. Other reports have documented the development of renal failure with a single *ip* dose of 6 mg/kg [74], 20 mg/kg and 30 mg/kg cisplatin in rats within 72 h [79, 89]. The ARF model has also been developed in mice by injecting a single dose of cisplatin 16 mg/kg, *ip* and renal dysfunctioning has been observed after 72 h of injection [76]. On the other hand, Lu et al. have reported the induction of ARF in mice by injecting cisplatin at a dose of 30 mg/kg, *ip* [83]. Other research groups have also developed cisplatin-induced renal failure model in mice by varying the dose of cisplatin that include 12 mg/kg, *ip* [6]; 18 mg/kg, *ip* [7]; 40 mg/kg, *ip* [81].

Radiocontrast media-induced ARF

Clinically, radiocontrast media are very commonly used in radiology particularly for cardiac catheterization. Radiocontrast-induced nephropathy is a frequent clinical problem and is a major cause of acute renal failure [24]. Patients administered with radiocontrast media have been reported to exhibit an increased frequency of clinical adverse events including permanent impairment of renal function, longer hospital stay and increased mortality rate. The incidence of radiocontrast nephropathy approaches 30–50% in patients with volume depletion, congestive heart failure, preexisting renal failure, or diabetes mellitus [11]. In patients, isoosmolar radiocontrast (86% of iodixanol) and low-osmolar radiocontrast agent (14% of iohexol) induce acute renal failure [24, 132]. The pathogenesis of radiocontrast nephropathy appears to be multifactorial and includes a deleterious reduction of renal arteriolar blood flow and glomerular filtration rate as well as the direct renal tubular toxicity caused by the radiocontrast agents [43]. The pathophysiology of toxic renal injury caused by radiocontrast media involves changes in generation of free radicals, inflammatory mediators, alteration of anti-oxidant defense systems and development of apoptosis [142].

Different research groups have employed different contrast media to develop renal failure models in animals. Diatrizoate is a water-soluble organic iodide contrast medium (1-deoxy-1-(methylamino)-D-glucitol 3,5-diacetamido-2,4,6-triiodobenzoate) [50]. In the pure form, it contains 59.87% of organically bound iodine and 50% (w/v) solution contains 300 mg I/ml. It has an osmolality of 1550 mosm/kg, and is hypertonic to blood. Erley et al. [45] have reported the development of ARF in rats by administration of sodium ditriazoate at a dose of 2 ml/kg into the jugular vein over a period of 2 min. After the injection, three clearance periods are performed each lasting 30 min, in which urine and blood sampling is done to assess the renal failure [45]. Yen et al. have reported the development of ARF in rats within 1 h by administration of 10 ml/kg of ditriazoate with an iodine load of 3700 mg/kg *via* the tail vein [141], while Colbay et al. reported the development of ARF in rats within 24 h by *iv* injection of ditriazoate (7 ml/kg) over a period of 5 min [33].

Iohexol is commonly used as a non-ionic X-ray contrast media agent [98] and for the measurement of GFR. Iohexol does not bind to serum proteins and is 100% filtered through glomerulus, with no indications of tubular secretion or reabsorption. Touati et al. have reported the development of renal failure in rats, in which rats were uninephrectomized and six days later, the aorta was clamped above the renal artery and a low-osmolar contrast media (CM), ioxaglate, was injected (1 ml/min; 3 min) *via* an aortic puncture in the single remaining kidney. The parameters to assess the renal failure were determined 24 and 48 h after CM administration [122]. Lee et al. have reported the development of renal failure in mice within 24 h by *ip* administration of iohexol (350 mg iodine/ml, 1.5–3 g iodine/kg) [75].

Kwak et al. [72] have reported the development of renal failure in rats by administering three doses of the contrast medium named Ultravist *via iv* route: low dose (CT: 0.5 ml/kg = 0.15 g iodine/kg), standard (CT: 2 ml/kg = 0.6 g iodine/kg), and high-dose (CT: 8 ml/kg = 2.4 g iodine/kg). The blood sampling was done 48 h after the contrast injection to assess the renal failure [72]. Agmon et al. have reported the development of renal failure in rats by injecting sodium iothalamate (80%) through the arterial cannula over 2–3 min, at the dosage of 6 ml/kg. The blood samples were withdrawn 24 h after the contrast medium injection to assess the renal impairment [3]. Single dose administration of diatrizoate 7–10 ml/kg induced renal failure is more commonly used animal model to clinically simulate radiocontrast media-induced renal failure at the time of cardiac catheterization in patients.

NSAID-induced ARF

Acetaminophen-induced ARF

Acetaminophen is most widely used in the world as an analgesic and antipyretic drug that is safe at therapeutic dosages. However, it is also known to cause hepatic necrosis and renal failure in humans [56] and animals [52] in overdoses. In human, acetaminophen represents a growing cause of renal failure in current medical practice. Acetaminophen-induced renal insufficiency is consistent with acute tubular necrosis, an increase in the plasma creatinine level and a decrease in the GFR. The cumulative doses of acetaminophen and aspirin have been documented to induce the renal failure at the dose of 100–499 g and 500–2,999 g or ≥ 3,000 g, respectively, in patients [130]. Oxidative stress is reported to play a role in the pathogenesis of acetaminophen-induced renal damage whose metabolism occurs *via* cytochrome-P (CYP) 450 enzymes in both the liver and the kidneys. In renal tissues, prostaglandin synthetase and N-deacetylase enzymes play a key role in the formation of free radicals and their metabolites. At higher doses, acetaminophen is shunted through these pathways leading to the increased production of reactive oxygen/nitrogen metabolites, gradual GSH depletion, formation of lipid peroxidative products leading to cell death and renal failure [1, 17, 51, 52].

Palani et al. reported the development of ARF in rats within 24 h by administrating a single dose of acetaminophen (750 mg/kg, *po*) [100]. Adeneye et al. and Cekmen et al. have reported the development of ARF within 24 h in rats by administration of a single dose of acetaminophen 800 mg/kg, *ip*, which was dissolved in normal saline [2, 27]. Recently, Kheradpezhouh et al. have reported that ARF may be induced in rats within 18–24 h by *ip* administration of a single dose of acetaminophen (700 mg/kg), dissolved in propylene glycol and distilled water (50:50) [69]. Acetaminophen is also used to induce ARF in mice, as Li et al. have reported the development of ARF within 16 h in mice by administration of a single nephrotoxic dose of acetaminophen (600 mg/kg, dissolved in saline, 25 ml/kg, *ip*) [78]. In another study, Chen et al. have reported the development of ARF within 4 h in mice with different age groups, i.e., young ones with age of 3–31 month and old ones with age of 30–31 months, by administration of the same dose of acetaminophen (375 mg/kg, *ip*) dissolved in ethanol:propylene glycol (1:4) [29]. Single dose administration of acetaminophen (600–750 mg/kg) induced renal failure in rodents closely related to renal dysfunction due to overdose of acetaminophen in humans.

Diclofenac sodium-induced ARF

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most common prescription medicines and diclofenac is widely used NSAID for the management of pain and inflammation associated with arthritis. Unfortunately, one of the main side effects of NSAIDs administration is renal function damage [42]. Therefore, the research has been directed for exploring non-steroidal analgesics that do not exhibit the typical side effects associated with NSAIDS including renal

failure [30]. In human, diclofenac has been widely used NSAID for the management of pain and inflammation associated with arthritis [133]. A clinical trial report has documented that diclofenac (75 mg/day for six months) induces severe renal injury [60]. NSAIDs mediated abrogation of prostaglandin synthesis and resultant renal ischemia is the major mechanism and intra-renal ROS generation is also potential mechanism contributing to development of acute interstitial nephritis [42]. Experimentally, *ip* administration of diclofenac (15 mg/kg) injection for 3 day has been reported to induce renal failure in rats [42].

Osmosis-induced ARF

Osmotic nephrosis is described on the morphological basis and is characterized by vacuolization and swelling of the renal proximal tubular cells. Clinically, osmotic nephrosis is due to intravenous infusion of hypertonic sucrose, hydroxyethyl starch, dextrans, and contrast media to reduce intra-cranial pressure [84]. In preclinical studies, osmotic diuresis is produced by administering 20% sucrose solution in rabbits that produces renal failure within the hour, and is characterized by vacuolar degeneration and nuclear shrinkage of tubular cells [55]. Zhang et al. have reported that single dose administration of mannitol (4%, 9%, 19% and 27%) with dose of 5 ml/kg leads to induction of renal apoptosis and acute renal damage in spontaneous hypertensive rats [144].

Ifosfamide-induced ARF

Ifosfamide (IFO), a synthetic analog of cyclophosphamide, is an alkylating oxazaphosphorine and is widely used as first-line combination therapy for a variety of malignancies including metastatic germ-cell testicular cancer and some sarcomas [28]. High-dose chemotherapy using IFO leads to hemorrhagic cystitis, Fanconi syndrome and ARF [28]. Ifosfamide has been documented to induce the renal failure in patients at higher cumulative doses of 73.5 g/m^2 [47]. The other clinical trial report has documented that cumulative ifosfamide dose of 9–128 g/m^2/course induces severe renal failure in pediatric osteosarcoma patients [16]. In another study, ifosfamide dose of 12 g/m^2 for 6 consecutive days has been shown to develop nephrotoxicity in 45.46% of patients that required hemodialysis and subsequently 36.36% of patients were reported to die [18]. IFO mustard reacts with deoxyribonucleic acids (DNA) molecules to form intra-and inter-strand cross-links, causing the DNA strand to break and ultimately cell apoptosis and/or necrosis [145, 146]. Ifosfamide has also been shown to inhibit glutathione synthesis, generate reactive oxygen species, mitochondrial damage and apoptosis leading renal failure [28, 109, 145]. Chloroacetaldehyde (CAA, a metabolite of ifosfamide) causes depletion of protein thiol and mitochondrial ATP, DNA cross-links and inhibition of DNA synthesis [65, 113]. Badary has demonstrated that *ip* administration of ifosfamide at a dose of 50 mg/kg for 5 consecutive days induces the renal damage in rat [14]. ARF has been shown to develop in mice by *ip* injection with different range of doses such as 350, 550, 800 or 1100 mg/kg of ifosfamide. However, the dose of 550 mg/kg of ifosfamide was reported to produce reproducible ARF within 72 h [145]. Single dose administration of ifosfamide, 550 mg/kg, *ip*, induced renal failure in more commonly employed animal model to study various aspects of renal dysfunction due to anticancer agents-induced renal failure in cancer patients.

Uranium-induced ARF

The kidney is being particularly sensitive to uranium. In chronically exposed uranium workers, the reduction in renal proximal tubular reabsorption of amino acids and low molecular weight proteins consistent with uranium nephrotoxicants has been reported [120]. Uranium nephrotoxicity has been extensively studied in experimental animals using uranyl nitrate (UN) and uranyl acetate, and is characterized by an increased serum creatinine and blood urea nitrogen (BUN) accompanied by abnormal electrolyte excretion, proteinuria, glucosuria and tubular necrosis [20]. As with many nephrotoxins, uranyl-mediated pathologic damage is most evident in the straight position of the proximal tubule [25].

Avasthi et al. reported the development of renal failure in rats by *iv* administration of two doses of uranyl nitrate 15 mg/kg and 25 mg/kg [13]. Later, researchers have reported the development of renal failure in rats within 5 days by *ip* administration of single dose of uranyl nitrate (0.5 and 10 mg/kg) dissolved in 0.9% of saline [101, 121]. Fleck et al. reported the development of renal failure in rats by administration of single dose of uranyl nitrate (5 mg/kg, *ip*) which was dissolved in 0.9% NaCl [48]. It has been reported that single injection of 1 ml/kg (5 mg/kg) into the tail vein

of rat induces renal failure [70, 71]. The plasma levels of urea nitrogen and creatinine increase significantly from third day to fifth day after intravenous administration of uranyl nitrate [71, 77]. Choi et al. have reported the development of renal failure in rats within 5 days by *iv* administration of uranyl nitrate at a dose of 5 mg/kg [32]. Subcutaneous injection of uranyl acetate dihydrate (5 mg/kg) has also been reported to generate ARF within 72 h [39, 40].

Mercuric chloride-induced ARF

Mercuric chloride ($HgCl_2$) is a well-known renal toxicant that causes ARF. A single injection of $HgCl_2$ into rats results in necrosis of the tubular epithelial cells of the kidney [124]. Early tubular epithelial injury induced by mercuric chloride consists of fragmentation of the plasma membrane, swelling of the mitochondria and disruption of the nucleus and cytoplasmic organelles. Oxidative stress, which occurs after the metabolic generation of ROS, seems to play an important role in the pathogenesis of $HgCl_2$-induced ARF [22]. Zimmermann et al. have reported the development of ARF in rat within 24 h by administration of a single *sc* injection of $HgCl_2$ at a dose of 2.5 and 4.7 mg/kg [147]. Yoneya et al. have reported the development of ARF in rats within 24 h by *ip* administration of $HgCl_2$ (1 mg/kg) dissolved in saline (1 mg/ml) [143]. Ewald et al. have also been reporting the development of ARF in mice within 24 h by administration of a single *ip* injection of $HgCl_2$ at a dose of 6 mg/kg [46]. Ahn et al. has developed renal failure in rabbits within 24 h by administration of a single *sc* dose of $HgCl_2$ at 10 mg/kg [4]. The development of ARF in rats within 24 h by administration of a single *sc* dose of $HgCl_2$ at 4.0 mg/kg and 5.0 mg/kg has also been described [12, 106]. The administration of mercuric chloride 6 mg/kg, *ip* (single dose) in rabbit and 10 mg/kg, *sc* in mice (single dose) induced renal failure models more commonly used to clinically mimic the chemical industrial hazard associated with ARF in human.

Potassium dichromate-induced ARF

Chromium is a naturally occurring element found in volcanic dust, rocks, soil, plants and animals. The most common forms of chromium in the environment are hexavalent (Cr^{6+}) and trivalent (Cr^{3+}). Cr^{6+} and Cr^{3+} are widely used in industrial and chemical processes such as leather tanning, printing, in hair dyes, steel manufacturing and wood preservative production. In some regions, waste disposal of chromium compounds to the environment contributes to increase its presence and potential toxicity [111]. In biological systems, the soluble forms of Cr^{6+} are absorbed more easily than Cr^{3+} and are reduced to Cr^{3+} *via* Cr^{5+} by glutathione, ascorbate and hydrogen peroxide [5]. Once chromium is absorbed, it is distributed in the liver, lung, spleen, kidney and heart. Appel et al. have reported the development of non-oliguric pattern of ARF in rat within 24 h by administration of a single *sc* injection of potassium dichromate ($K_2Cr_2O_7$) 15 mg/kg [9]. Recently, Khan et al. have demonstrated that a single injection of potassium dichromate (15 mg/kg, *sc*) causes development of ARF within 48 h [68].

Folic acid-induced ARF

Folic acid (FA) induced ARF is a conventional animal model of human ARF [118]. FA-induced renal injury is associated with the rapid appearance of FA crystals within renal tubules and subsequent acute tubular necrosis, followed by epithelial regeneration and renal cortical scarring [23, 91]. The molecular mechanisms by which FA induces ARF remain poorly understood. FA-induced renal failure is characterized by necrosis and apoptosis of tubular epithelial cells. In FA treated animals there is marked reduction in the expression of anti-apoptotic protein B-cell lymphoma-extra large (Bcl-xL) in kidneys along with marked elevation of tumor necrosis factor-α (TNF-α) in blood and kidneys [129]. An *iv* injection of folic acid (250 mg/kg) is reported to induce ARF after 48 h in mice [129].

Ferric-nitrilotriacetate-induced ARF

Nitrilotriacetic acid (NTA), a synthetic chelating agent, is used as a household and hospital detergent in various countries. NTA is a low-toxic agent [54, 97]; however, the ferric-nitrilotriacetate (Fe-NTA) complex causes acute nephrotoxicity in animals as well as in humans [54, 86]. Fe-NTA-induced generation of free radicals, including superoxide anions and hydroxyl radicals, is a major mechanism of renal toxicity [125]. Hamazaki et al. have reported that the administration of single dose of Fe-NTA (15 mg iron/kg) induces the acute tubular necrosis and renal failure in rats [54], while Umemura et al. reported that oral administration of Fe-NTA (12 mg Fe/kg) in rats causes

ARF [125]. Furthermore, administration of the single dose of Fe-NTA (8 mg iron/kg, *ip*) has also been reported to induce renal failure in rats [53]. ARF is induced within 24 h in mice by *ip* injection of Fe-NTA with different doses such as 1, 2, and 4 mg/kg [58].

S-(1,2-dichlorovinyl)-L-cysteine-induced ARF

S-(1,2-Dichlorovinyl)-L-cysteine (DCVC) is a potent nephrotoxicant and is a metabolite of trichloroethylene (TCE), a ground water contaminant listed as one of the most hazardous chemicals by Agency of Toxic Substances and Disease Registry (ATSDR) [38]. DCVC selectively damages the proximal tubules of the kidneys and causes mortality by ARF [37, 136]. Administration of DCVC (30 mg/kg, *ip*) in mice is reported to cause loss of renal architecture within 24 h [102]. Darnerud et al. have reported that administration of single dose of DCVC at the lower dose of 5 mg/kg and higher dose of 25 mg/kg produces ARF in mice in a dose dependent manner. Administration of DCVC 5 mg/kg is reported to induce moderate lesions in the straight proximal tubules within 24 h. Furthermore, administration of 25 mg/kg of DCVC is documented to produce more pronounced lesions in the tubular segment that extend to other segments such as sub-capsular region [37]. Wolfgang et al. [136] have reported that two stereoisomers L-DCVC (at 10^{-5} M) and D-DCVC (at 10^{-5} M) produce renal injury *in vitro* system using rabbit renal cortical slices. Furthermore, administration of 25 mg/kg was also reported to produce ARF within 24 and 48 h in rabbits [102, 136].

Sepsis-induced ARF

Cecal ligation and puncture (CLP) induced polymicrobial sepsis is also employed to induce ARF in rats. The rats are anesthetized and a 2 cm ventral midline incision is made to expose and ligate the cecum with a 4.0 silk just distal to the ileocecal valve to avoid intestinal obstruction. Thereafter, ligated cecum is punctured three times with a 16 gauge needle followed by drainage with 3 mm wide latex slice twice and 5 mm width latex slice once. After this procedure, animals are fluid resuscitated with sterile saline (40 ml/kg) and within 24 h the animals develop renal failure as detected by an increase in creatinine levels along with extreme lethargy, diarrhea, piloerection and tachypnea [139]. Ruetten et al. have demonstrated that intravenous infusion of lipopolysaccharide (LPS) (10 mg/kg) for 30 min in the the left femoral vein induces ARF in rat [105]. Johannes et al. have reported that 30 min infusion of LPS (2.5 mg/kg) induces endotoxemia associated renal failure in rat [64]. Jesmin et al. have demonstrated that single *ip* injection of LPS derived from *Escherichia coli* (*E. coli* 055:B5) (15 mg/kg) induces the potential ARF in rats [63]. Recently, the renal artery occlusion along with *sc* injections of *Escherichia coli* in 4 week old rats is reported to cause renal failure [96]. An *ip* administration of bacterial toxic protein, i.e., LPS 15 mg/kg (single dose) induced renal failure in rats is more commonly employed animal model that mimics the infection-induced renal failure in humans.

Bipyridyls-induced ARF

Paraquat and diquat dibromide are commercially available herbicides and are extensively used worldwide. Diquat is useful for studying the effects of ROS *in vivo* particularly in renal system [114]. It stimulates cellular production of ROS by undergoing cyclic reduction-oxidation processes, in which the diquat dication is reduced to the monocation radical, which inturn reduces molecular oxygen to superoxide. Lock and Ishmael has demonstrated that administration of paraquat (680 μmol/kg, *po*, and 108 μmol/kg, *sc*) cause the renal tubular damage after 6 and 24 h, respectively, in rats [82]. Diquat (680 μmol/kg, *po*)-induced renal tubular damage is characterized by urinary proteinuria and glucosuria within 6 to 24 h in rats [82]. It has been reported that a single oral dose of diquat (540 μmol/kg) induces the renal functional changes and kidney damage in rats [103]. Rogers et al. [103] have demonstrated that cumulative dose 0–50 μmol/kg of diquat *ip* during the period of 6 h induces the ARF in glutathione reductase-deficient mice, with the dose of 7.5 μmol/kg diquat, renal injury is mainly demonstrated in proximal tubules within 1 h and tubular necrosis is observed within 2 h [103].

Conclusions

The development of different animal models of acute renal failure, especially those closely simulating clinical conditions, has contributed immensely in under-

standing the pathophysiology underlying the onset of renal failure. Since the etiology for induction of renal failure is multifold, therefore, a large number of animal models have been developed to mimic the clinical conditions of renal failure. Glycerol-induced renal failure closely mimics the rhabdomyolysis; ischemia-reperfusion-induced ARF simulate the hemodynamic changes-induced changes in renal functioning; drug-induced such as gentamicin, cisplatin, NSAID, ifosfamide-induced ARF mimics the renal failure due to clinical administration of respective drugs; uranium, potassium dichromate-induced ARF mimics the occupational hazard; S-(1,2-dichlorovinyl)-L-cysteine-induced ARF simulate contaminated water-induced renal dysfunction; sepsis-induced ARF mimics the infection-induced renal failure and radiocontrast-induced ARF mimics renal failure in patients during use of radiocontrast media at the time of cardiac catheterization.

Acknowledgment:
The authors are grateful to Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, India for providing technical facilities.

References:

1. Abdel-Zaher AO, Abdel-Hady RH, Mahmoud MM, Farrag MM: The potential protective role of alpha-lipoic acid against acetaminophen-induced hepatic and renal damage. Toxicology, 2008, 243, 261–270.
2. Adeneye AA, Olagunju JA, Benebo AS, Elias SO, Adisa AO, Idowu BO, Oyedeji MO et al.: Nephroprotective effects of the aqueous root extract of *Harungana madagascariensis* (L.) in acute and repeated dose acetaminophen renal injured rats. Int J Appl Res Nat Prod, 2008, 1, 6–14.
3. Agmon Y, Peleg H, Greenfeld Z, Rosen S, Brezis M: Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. J Clin Invest, 1994, 94, 1069–1075.
4. Ahn CB, Song CH, Kim WH, Kim YK: Effects of *Juglans sinensis* Dode extract and antioxidant on mercury chloride-induced acute renal failure in rabbits. J Ethnopharmacol, 2002, 82, 45–49.
5. Aiyar J, Berkovits HJ, Floyd RA, Wetterhahn KE: Reaction of chromium(VI) with glutathione or with hydrogen peroxide: identification of reactive intermediates and their role in chromium(VI)-induced DNA damage. Environ Health Perspect, 1991, 92, 53–62.
6. Ajith TA, Abhishek G, Roshny D, Sudheesh NP: Co-supplementation of single and multi doses of vitamins C and E ameliorates cisplatin-induced acute renal failure in mice. Exp Toxicol Pathol, 2009, 61, 565–571.
7. Aleksunes LM, Augustine LM, Scheffer GL, Cherrington NJ, Manautou JE: Renal xenobiotic transporters are differentially expressed in mice following cisplatin treatment. Toxicology, 2008, 250, 82–88.
8. Ali BH: Gentamicin nephrotoxicity in humans and animals: some recent research. Gen Pharmacol, 1995, 26, 1477–1487.
9. Appel GB, Siegel NJ, Appel AS, Hayslett JP: Studies on the mechanism of non-oliguric experimental acute renal failure. Yale J Biol Med, 1981, 54, 273–281.
10. Arany I, Safirstein RL: Cisplatin nephrotoxicity. Semin Nephrol, 2003, 23, 460–464.
11. Asif A, Garces G, Preston RA, Roth D: Current trials of interventions to prevent radiocontrast-induced nephropathy. Am J Ther, 2005, 12, 127–132.
12. Augusti PR, Conterato GM, Somacal S, Sobieski R, Spohr PR, Torres JV, Charao MF et al.: Effect of astaxanthin on kidney function impairment and oxidative stress induced by mercuric chloride in rats. Food Chem Toxicol, 2008, 46, 212–219.
13. Avasthi PS, Evan AP, Hay D: Glomerular endothelial cells in uranyl nitrate induced acute renal failure in rats. J Clin Invest, 1980, 65, 121–127.
14. Badary OA: L-Histidinol attenuates Fanconi syndrome induced by ifosfamide in rats. Exp Nephrol, 1999, 7, 323–327.
15. Baker RC, Armstrong MA, Young IS, Mc-Clean E, O'Rourke D, Campbell FC, D'Sa AA, McBride WT: Methyl prednisolone increases urinary nitrate concentrations and reduces subclinical renal injury during infrarenal aortic ischemia reperfusion. Ann Surg, 2006, 244, 821–826.
16. Berrak SG, Pearson M, Berberoglu S, Ilhan IE, Jaffe N: High-dose ifosfamide in relapsed pediatric osteosarcoma: therapeutic effects and renal toxicity. Pediatr Blood Cancer, 2005, 44, 215–219.
17. Bessems J, Vermeulen N: Paracetamol (acetaminophen) induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. Crit Rev Toxicol, 2001, 31, 55–138.
18. Beyzadeoglu M, Arpaci F, Surenkok S, Ozyigit G, Oysul K, Caglar K, Ataergin S et al.: Acute renal toxicity of 2 conditioning regimens in patients undergoing autologous peripheral blood stem-cell transplantation. Total body irradiation-cyclophosphamide versus ifosfamide, carboplatin, etoposide. Saudi Med J, 2008, 29, 832–836.
19. Bhalodia Y, Kanzariya N, Patel R, Patel N, Vaghasiya J, Jivani N, Raval H: Renoprotective activity of *Benincasa cerifera* fruit extract on ischemia/reperfusion-induced renal damage in rat. Iran J Kidney Dis, 2009, 3, 80–85.
20. Blantz RC: The mechanism of acute renal failure after uranyl nitrate. J Clin Invest, 1975, 55, 621–635.
21. Bledsoe G, Shen B, Yao YY, Hagiwara M, Mizell B, Teuton M, Grass D Chao L, Chao J: Role of tissue kallikrein in prevention and recovery of gentamicin-induced renal injury. Toxicol Sci, 2008, 102, 433–443.
22. Bohets HH, Van Thielen MN, Van der Biest I, Van Landeghem GF, D'Haese PC, Nouwen EJ, De Broe ME: Cytotoxicity of mercury compounds in LLC–PK1, MDCK and human proximal tubular cells. Kidney Int, 1995, 47, 395–403.

23. Bosch RJ, Woolf AS, Fine LG: Gene transfer into the mammalian kidney: direct retrovirus-transduction of regenerating tubular epithelial cells. Exp Nephrol, 1993, 1, 49–54.
24. Brown JR, Thompson CA: Contrast-induced acute kidney injury: The at-risk patient and protective measures. Curr Cardiol Rep, 2010, 12, 440–445.
25. Bulger RE: Renal damage caused by heavy metals. Toxicol Pathol, 1986, 14, 58–65.
26. Buzzi FC, Fracasso M, Filho VC, Escarcena R, del Olmo E, San Feliciano A: New antinociceptive agents related to dihydrosphingosine. Pharmacol Rep, 2010, 62, 849–857.
27. Cekmen M, Ilbey YO, Ozbek E, Simsek A, Somay A, Ersoz C: Curcumin prevents oxidative renal damage induced by acetaminophen in rats. Food Chem Toxicol, 2009, 47, 1480–1484.
28. Chen N, Aleksa K, Woodland C, Rieder M, Koren G: N-Acetylcysteine prevents ifosfamide induced nephrotoxicity in rats. Br J Pharmacol, 2008, 153, 1364–1372.
29. Chen TS, Richie JP, Nagasawa HT, Lang CA: Glutathione monoethyl ester protects against glutathione deficiencies due to aging and acetaminophen in mice. Mech Ageing Dev, 2000, 120, 127–139.
30. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. Am J Med, 1998, 104, 343–348.
31. Choi BM, Chen XY, Gao SS, Zhu R, Kim BR: Anti-apoptotic effect of phloretin on cisplatin-induced apoptosis in HEI-OC1 auditory cells. Pharmacol Rep, 2011, 63, 708–716.
32. Choi YH, Lee I, Lee MG: Slower clearance of intravenous metformin in rats with acute renal failure induced by uranyl nitrate: contribution of slower renal and non-renal clearances. Eur J Pharm Sci, 2010, 39, 1–7.
33. Colbay M, Yuksel S, Uslan I, Acarturk G, Karaman O, Bas O, Mollaoglu H et al.: Novel approach for the prevention of contrast nephropathy. Exp Toxicol Pathol, 2010, 62, 81–89.
34. Curry SC, Chang D, Connor D: Drug-and toxin-induced rhabdomyolysis. Ann Emer Med, 1989, 18, 1068–1084.
35. Dai RP, Dheen ST, Tay SS: Induction of cytokine expression in rat post-ischemic sinoatrial node (SAN). Cell Tissue Res, 2002, 310, 59–66.
36. Damianovich M, Ziv I, Heyman SN, Rosen S, Shina A, Kidron D, Aloya T et al.: ApoSense: a novel technology for functional molecular imaging of cell death in models of acute renal tubular necrosis. Eur J Nucl Med Mol Imaging, 2006, 33, 281–291.
37. Darnerud PO, Brandt I, Feil VJ, Bakke JE: S-(1,2-dichloro-[^{14}C]vinyl)-L-cysteine (DCVC) in the mouse kidney: correlation between tissue-binding and toxicity. Toxicol Appl Pharmacol, 1988, 95, 423–434.
38. De-Rosa CT, Johnson BL, Fay M, Hansen H, Mumtaz MM: Public health implications of hazardous waste sites: findings, assessment and research. Food Chem Toxicol, 1996, 34, 1131–1138.
39. Domingo JL: Chemical toxicity of uranium. Toxic Ecotoxic News, 1995, 2, 74–78.
40. Domingo JL, de la Torre A, Bellés M, Mayayo E, Llobet JM, Corbellab J: Comparative effects of the chelators sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron) and diethylenetriaminepentaacetic acid (DTPA) on acute uranium nephrotoxicity in rats. Toxicology, 1997, 118, 49–59.
41. Edelstein CL, Schrier RW: Pathophysiology of ischemic acute renal injury, in diseases of the kidney and urinary tract. Lippincott Williams and Wilkins, Philadelphia, 2007, 930–961.
42. Efrati S, Berman S, Siman-Tov Y, Lotan R, Averbukh Z, Weissgarten J, Golik A: N-acetylcysteine attenuates NSAID induced rat renal failure by restoring intrarenal prostaglandin synthesis. Nephrol Dial Transplant, 2007, 22, 1873–1881.
43. Epstein FH, Brezis M, Silva P, Rosen S: Physiological and clinical implications of medullary hypoxia. Artif Organs, 1987, 11, 463–467.
44. Erdem A, Gundogan NU, Usubutun A, Kilinc K, Erdem SR, Kara A, Bozkurt A: The protective effect of taurine against gentamicin-induced acute tubular necrosis in rats. Nephrol Dial Transplant, 2000, 15, 1175–1182.
45. Erley CM, Heyne N, Burgert K, Langanke J, Risler T, Osswald H: Prevention of radiocontrast-induced nephropathy by adenosine antagonists in rats with chronic nitric oxide deficiency. J Am Soc Nephrol, 1997, 8, 1125–1132.
46. Ewald KA, Calabrese EJ: Lead reduces the nephrotoxicity of mercuric chloride. Ecotoxicol Environ Saf, 2001, 48, 215–218.
47. Ferrari S, Pieretti F, Verri E, Tolentinis L, Cesari M, Versari M, Zolezzi C et al.: Prospective evaluation of renal function in pediatric and adult patients treated with high-dose ifosfamide, cisplatin and high-dose methotrexate. Anticancer Drugs, 2005, 16, 733–738.
48. Fleck C, Scholle T, Schwertfeger M, Appenroth D, Stein G: Determination of renal porphyrin handling in rats suffering from different kinds of chronic renal failure (CRF): Uranyl nitrate (UN) induced fibrosis or 5/6-nephrectomy (5/6NX). Exp Toxic Pathol, 2003, 54, 393–399.
49. Foglieni C, Fulgenzi A, Ticozzi P, Pellegatta F, Sciorati C, Belloni D, Ferrero E, Ferrero ME: Protective effect of EDTA pre administration on renal ischemia. BMC Nephrol, 2006, 7, 5–16.
50. Fountaine H, Harnish P, Andrew E, Grynne B: Safety, tolerance, and pharmacokinetics of iodixanol injection, a nonionic, isosmolar, hexa-iodinated contrast agent. Acad Radiol, 1996, 3, 475–484.
51. Gamal el-din AM, Mostafa AM, Al-Shabanah OA, Al-Bekairi AM, Nagi MN: Protective effect of arabic gum against acetaminophen-induced hepatotoxicity in mice. Pharmacol Res, 2003, 48, 631–635.
52. Ghosh J, Das J, Manna P, Sil PC: Acetaminophen induced renal injury via oxidative stress and TNF-α production: therapeutic potential of arjunolic acid. Toxicology, 2010, 268, 8–18.
53. Gupta A, Sharma S, Chopra K: Reversal of iron-induced nephrotoxicity in rats by molsidomine, a nitric oxide donor. Food Chem Toxicol, 2008, 46, 537–543.
54. Hamazaki S, Okada S, Ebina Y, Midorikawa O: Acute renal failure and glucosuria induced by ferric nitrilotriacetate in rats. Toxicol Appl Pharmacol, 1985, 77, 267–274.
55. Helmholz HF: Renal changes in the rabbit resulting from intravenous injection of hypertonic solution of sucrose. J Pediat, 1933, 3, 144–157.

56. Hengy B, Hayi-Slayman D, Page M, Christin F, Baillon JJ, Ber CE, Allaouchiche B, Rimmelé T: Acute renal failure after acetaminophen poisoning: report of three cases. Can J Anaesth, 2009, 56, 770–774.
57. Heyman SN, Lieberthal W, Rogiers P, Bonventre JV: Animal models of acute tubular necrosis. Curr Opin Crit Care, 2002, 8, 526–534.
58. Hsu DZ, Wan CH, Hsu HF, Lin Y, Liu M: The prophylactic protective effect of sesamol against ferric–nitrilotriacetate-induced acute renal injury in mice. Food Chem Toxicol, 2008, 46, 2736–2741.
59. Humes HD, Sastrasinh M, Weinberg JM: Calcium is a competitive inhibitor of gentamicin-renal membrane binding interactions and dietary calcium supplementation protects against gentamicin nephrotoxicity. J Clin Invest, 1984, 73, 134–147.
60. Inoue M, Akimoto T, Saito O, Ando Y, Muto S, Kusano E: Successful relatively low-dose corticosteroid therapy for diclofenac induced acute interstitial nephritis with severe renal failure. Clin Exp Nephrol, 2008, 12, 296–299.
61. Izuwa Y, Kusaba J, Horiuchi M, Aiba T, Kawasaki H, Kurosaki Y: Comparative study of increased plasma quinidine concentration in rats with glycerol and cisplatin induced acute renal failure. Drug Metab Pharmacokinet, 2009, 24, 451–457.
62. Jacob R: Acute renal failure. Indian J Anaesth, 2003, 47, 367–372.
63. Jesmin S, Gando S, Zaedi S, Prodhan SH, Sawamura A, Miyauchi T, Hiroe M, Yamaguchi N: Protease-activated receptor 2 blocking peptide counteracts endotoxin-induced inflammation and coagulation and ameliorates renal fibrin deposition in a rat model of acute renal failure. Shock, 2009, 32, 626–632.
64. Johannes T, Ince C, Klingel K, Unertl KE, Mik EG: Iloprost preserves renal oxygenation and restores kidney function in endotoxemia-related acute renal failure in the rat. Crit Care Med, 2009, 37, 1423–1432.
65. Kandala JC, Mrema JE, DeAngelo A, Daniel FB, Guntaka RV: 2-Chloroacetaldehyde and 2-chloroacetal are potent inhibitors of DNA synthesis in animal cells. Biochem Biophys Res Commun, 1990, 167, 457–463.
66. Karam H, Bruneval P, Clozel JP, Loffler BM, Bariety J, Clozel M: Role of endothelin in ARF due to rhabdomyolosis in rats. J Pharmacol Exp Ther, 1995, 274, 481–486.
67. Kawai Y, Nakao T, Kunimura N, Kohda Y, Gemba M: Relationship of intracellular calcium and oxygen radicals to cisplatin-related renal cell injury. J Pharmacol Sci, 2006, 100, 65–72.
68. Khan MR, Siddiqui S, Parveen K, Javed S, Diwakar S, Siddiqui WA: Nephroprotective action of tocotrienol-rich fraction (TRF) from palm oil against potassium dichromate ($K_2Cr_2O_7$)-induced acute renal injury in rats. Chem Biol Interact, 2010, 186, 228–238.
69. Kheradpezhouh E, Panjehshahin MR, Miri R, Javidnia K, Noorafshan A, Monabati A, Dehpour AR: Curcumin protects rats against acetaminophen-induced hepatorenal damages and shows synergistic activity with N-acetylcysteine. Eur J Pharmacol, 2010, 628, 274–281.
70. Kim SH, Shim HJ, Kim WB, Lee MG: Pharmacokinetics of a new carbapenem, DA-1131, after intravenous administration to rats with uranyl nitrate induced acute renal failure. Antimicrob Agents Chemother, 1998, 42, 1217–1221.
71. Kim YG, Yoon EJ, Yoon WH, Shim HJ, Lee SD, Kim WB, Yang J, Lee MG: Pharmacokinetics of DA-125, a new anthracycline, after intravenous administration to uranyl nitrate-induced acute renal failure rats or protein-calorie malnutrition rats. Biopharm Drug Dispos, 1996, 17, 183–195.
72. Kwak HS, Lee YH, Han YM, Jin GY, Kim W, Chung GH: Comparison of renal damage by iodinated contrast or gadolinium in an acute renal failure rat model based on serum creatinine levels and apoptosis degree. J Korean Med Sci, 2005, 20, 841–847.
73. Lameire N, Van Biesen W, Vanholder R: The changing epidemiology of acute renal failure. Nat Clin Pract Nephrol, 2006, 2, 364–377.
74. Lee DW, Kwak IS, Lee SB, Song SH, Seong EY, Yang BY, Lee MY, Sol MY: Post-treatment effects of erythropoietin and nordihydroguaiaretic acid on recovery from cisplatin-induced acute renal failure in the rat. J Korean Med Sci, 2009, 24, 170–175.
75. Lee HT, Jan M, Bae SC, Joo JD, Goubaeva FR, Yang J, Kim M: A1 adenosine receptor knockout mice are protected against acute radiocontrast nephropathy in vivo. Am J Physiol Renal Physiol, 2006, 290, F1367–F1375.
76. Lee S, Ahn D: Expression of endothelin-1 and its receptors in cisplatin-induced acute renal failure in mice. Korean J Physiol Pharmacol, 2008, 12, 149–153.
77. Lee YH, Park KH, Ku YS: Pharmacokinetic changes of cyclosporine after intravenous and oral administration to rats with uranyl nitrate-induced acute renal failure. Int J Pharm, 2000, 194, 221–227.
78. Li C, Liu J, Saavedra JE, Keefer LK, Waalkes MP: The nitric oxide donor, V-PYRRO/NO, protects against acetaminophen induced nephrotoxicity in mice. Toxicology, 2003, 189, 173–180.
79. Li S, Gokden N, Okusa MD, Bhatt R, Portilla D: Anti-inflammatory effect of fibrate protects from cisplatin-induced acute renal failure. Am J Physiol Renal Physiol, 2005, 289, 469–480.
80. Lieberthal W, Levine JS: Mechanisms of apoptosis and its potential role in renal tubular epithelial cell injury. Am J Physiol, 1996, 271, F477–F488.
81. Liu M, Chien CC, Burne-Taney M, Molls RR, Racusen LC, Colvin RB, Rabb H: A pathophysiologic role for T lymphocytes in murine acute cisplatin nephrotoxicity. J Am Soc Nephrol, 2006, 17, 765–774.
82. Lock EA, Ishmael J: The acute toxic effects of paraquat and diquat on the rat kidney. Toxicol Appl Pharmacol, 1979, 50, 67–76.
83. Lu LH, Oh DJ, Dursun B, He Z, Hoke TS, Faubel S, Edelstein CL: Increased macrophage infiltration and fractalkine expression in cisplatin induced acute renal failure in mice. J Pharmacol Exp Ther, 2008, 324, 111–117.
84. Massermann JH: Effects of the intravenous administration of hypertonic solution of sucrose with special reference to cerebrospinal fluid pressure. Bull Johns Hopkins Hosp, 1935, 57, 12–17.
85. Mathew TH: Drug-induced renal disease. Med J Aust, 1992, 156, 724–728.

86. Matsuura R: Uptake of iron and nitrilotriacetate (NTA) in rat liver and the toxic effect of Fe-NTA. Acta Med Okayama, 1983, 37, 393–400.
87. Matthijsen RA, Huugen D, Hoebers NT, Vries B, Peutz-Kootstra CJ, Aratani Y, Daha MR et al.: Myeloperoxidase is critically involved in the induction of organ damage after renal ischemia reperfusion. Am J Pathol, 2007, 171, 1743–1752.
88. Mingeot-Leclercq MP, Tulkens PM: Aminoglycosides: nephrotoxicity. Antimicrob Agents Chemother, 1999, 43, 1003–1012.
89. Mitazaki S, Kato N, Suto M, Hiraiwa K, Abe S: Interleukin-6 deficiency accelerates cisplatin-induced acute renal failure but not systemic injury. Toxicology, 2009, 265, 115–121.
90. Morales AI, Detaille D, Prieto M, Puente A, Briones E, Arévalo M, Leverve X et al.: Metformin prevents experimental gentamicin-induced nephropathy by a mitochondria- dependent pathway. Kidney Int, 2010, 77, 861–869.
91. Mullin EM, Bonar RA, Paulson DF: Acute tubular necrosis. An experimental model detailing the biochemical events accompanying renal injury and recovery. Invest Urol, 1976, 13, 289–294.
92. Muthuraman A, Singla SK, Rana A, Singh A, Sood S: Reno-protective role of flunarizine (mitochondrial permeability transition pore inactivator) against gentamicin induced nephrotoxicity in rats. Yakugaku Zasshi, 2011, 131, 437–443.
93. Muthuraman A, Sood S, Gill NS, Arora R: Therapeutic potential of *Emblica officinalis* L. fruit extract on ischemia reperfusion injury induced acute renal failure in rat. Lat Am J Pharm, 2010, 29, 1208–1214.
94. Muthuraman A, Sood S, Singla SK, Rana A, Singh A, Singh A, Singh J: Ameliorative effect of flunarizine in cisplatin-induced acute renal failure via mitochondrial permeability transition pore inactivation in rats. Naunyn Schmiedebergs Arch Pharmacol, 2011, 383, 57–64.
95. Mwengee W, Butler T, Mgema S, Mhina G, Almasi Y, Bradley C, Formanik JB, Rochester CG: Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis, 2006, 42, 614–621.
96. Nakamura A, Niimi R, Yanagawa Y: Protection from sepsis-induced acute renal failure by adenoviral-mediated gene transfer of β_2-adrenoceptor. Nephrol Dial Transplant, 2010, 25, 730–737.
97. Okada S: Iron-induced tissue damage and cancer: the role of reactive oxygen free radicals. Pathol Int, 1996, 46, 311–332.
98. Olsson B, Aulie A, Sveen K, Andrew E: Human pharmacokinetics of iohexol. A new nonionic contrast medium. Invest Radiol, 1983, 18, 177–182.
99. Ortega A, Ramila D, Izquierdo A, González L, Barat A, Gazapo R, Bosch RJ, Esbrit P: Role of the renin-angiotensin system on the parathyroid hormone–related protein overexpression induced by nephrotoxic acute renal failure in the rat. J Am Soc Nephrol, 2005, 16, 939–949.
100. Palani S, Kumar RP, Kumar BS: Effect of the ethanolic extract of *Indigofera barberi* (L.) in acute acetaminophen induced nephrotoxic rats. New Biotechnol, 2009, 25, S14–S14.
101. Priyamvada S, Khan SA, Khan MW, Khan S, Farooq N, Khan F, Yusufi ANK: Studies on the protective effect of dietary fish oil on uranyl nitrate induced nephrotoxicity and oxidative damage in rat kidney. Prostaglandins Leukot Essent Fatty Acids, 2010, 82, 35–44.
102. Reddy RN, Latendresse JR, Mehendale HM: Colchicine antimitosis causes progression of S-(1,2-dichlorovinyl)-L-cysteine-induced injury leading to acute renal failure and death in mice. Toxicology, 2006, 220, 147–159.
103. Rogers LK, Bates CM, Welty SE, Smith CV: Diquat induces renal proximal tubule injury in glutathione reductase-deficient mice. Toxicol Appl Pharmacol, 2006, 217, 289–298.
104. Roncal CS, Mu W, Croker B, Reungjui S, Ouyang X, Tabah-Fisch I, Johnson RJ, Ejaz AA: Effect of elevated serum uric acid on cisplatin induced acute renal failure. Am J Physiol Renal Physiol, 2007, 292, 116–122.
105. Ruetten H, Thiemermann C, Vane JR: Effects of the endothelin receptor antagonist, SB 209670, on circulatory failure and organ injury in endotoxic shock in the anaesthetized rat. Br J Pharmacol, 1996, 118, 198–204.
106. Sarwar Alam M, Kaur G, Jabbar Z, Javed K, Athar M: *Eruca sativa* seeds possess antioxidant activity and exert a protective effect on mercuric chloride induced renal toxicity. Food Chem Toxicol, 2007, 45, 910–920.
107. Sauriyal DS, Jaggi AS, Singh N, Muthuraman A: Investigating the role of endogenous opioids and K_{ATP} channels in glycerol-induced acute renal failure. Fundam Clin Pharmacol, 2011, (in press). DOI: 10.1111/j.1472-8206.2011.00936.x
108. Savic V, Vlahovic P, Djordjevic V, Mitic-Zlatkovic M, Avramovic V, Stefanovic V: Nephroprotective effects of pentoxifylline in experimental myoglobinuric acute renal failure. Pathologie Biologie, 2002, 50, 599–607.
109. Sehirli O, Sakarcan A, Velioglu-Ogunc A, Cetinel S, Gedik N, Yegen BC, Sener G: Resveratrol improves ifosfamide-induced Fanconi syndrome in rats. Toxicol Appl Pharmacol, 2007, 222, 33–41.
110. Selby NM, Shaw S, Woodier N, Fluck RJ, Kolhe NV: Gentamicin-associated acute kidney injury. Q J Med, 2009, 102, 873–880.
111. Sheehan PJ, Meyer DM, Sauer MM, Paustenbach DJ: Assessment of the human health risks posed by exposure to chromium-contaminated soils. J Toxicol Environ Health, 1991, 32, 161–201.
112. Solez K, Morel-Maroger L, Sraer JD: The morphology of "acute tubular necrosis" in man: Analysis of 57 renal biopsies and a comparison with the glycerol model. Medicine, 1979, 58, 362–376.
113. Sood C, O'Brien PJ: Molecular mechanisms of chloroacetaldehyde induced cytotoxicity in isolated rat hepatocytes. Biochem Pharmacol, 1993, 46, 1621–1626.
114. Spalding DJ, Mitchell JR, Jaeschke H, Smith CV: Diquat hepatotoxicity in the Fischer-344 rat: the role of covalent binding to tissue proteins and lipids. Toxicol Appl Pharmacol, 1989, 101, 319–327.
115. Susa D, Mitchell JR, Verweij M, Van de Ven M, Roest H, Van den Engel S, Bajema I et al.: Congenital DNA repair deficiency results in protection against renal ischemia reperfusion injury in mice. Aging Cell, 2009, 8, 192–200.

116. Susser Z, Raveh D, Yinnon AM: Safety of once daily aminoglycosides in the elderly. J Am Geriatr Soc, 2000, 48, 857–859.
117. Suzuki S, Maruyama S, Sato W, Morita Y, Sato F, Miki Y, Kato S et al.: Geranylgeranylacetone ameliorates ischemic acute renal failure via induction of Hsp70. Kidney Int, 2005, 67, 2210–2220.
118. Szczypka MS, Westover AJ, Clouthier SG, Ferrara JL, Humes HD: Rare incorporation of bone marrow-derived cells into kidney after folic acid induced injury. Stem Cells, 2005, 23, 44–54.
119. Thiel G, Wilson DR, Arce ML, Oken DE: Glycerol induced hemoglobinuric acute renal failure in the rat. Nephron, 1967, 4, 276–297.
120. Thun MJ, Baker DB, Steenland K, Smith AB, Halperin W, Berl T: Renal toxicity in uranium mill workers. Scand J Work Environ Health, 1985, 311, 83–90.
121. Tolson JK, Roberts SM, Jortner B, Pomeroy M, Barber DS: Heat shock proteins and acquired resistance to uranium nephrotoxicity. Toxicology, 2005, 206, 59–73.
122. Touati C, Idee JM, Deray G, Santus R, Balut C, Beaufils H, Jouanneau C et al.: Modulation of the renal effects of contrast media by endothelium derived nitric oxide in the rat. Invest Radiol, 1993, 28, 814–820.
123. Trillaud H, Degrze P, Combe C, Deminire C, Palussre J, Benderbous S, Grenier N: USPIO-enhanced MR imaging of glycerol-induced acute renal failure in the rabbit. Magn Res Imaging, 1995, 13, 233–240.
124. Troyer DA, Kreisberg JI, Venkatachalam MA: Lipid alterations in LLC-PK1 cells exposed to mercuric chloride. Kidney Int, 1986, 29, 530–538.
125. Umemura T, Hasegawa R, Sai-Kato K, Nishikawa A, Furukawa F, Toyokuni S, Uchida K et al.: Prevention by 2-mercaptoethane sulfonate and N-acetylcysteine of renal oxidative damage in rats treated with ferric nitrilotriacetate. Jpn J Cancer Res, 1996, 87, 882–886.
126. Vanholder R, Sever MS, Erek E, Lameire N: Rhabdomyolysis. J Am Soc Nephrol, 2000, 11, 1553–1561.
127. Vlahovic P, Cvetkovic T, Savic V, Stefanovic V: Dietary curcumin does not protect kidney in glycerol-induced acute renal failure. Food Chem Toxicol, 2007, 45, 1777–1782.
128. Volpini RA, Balbi APC, Costa RS, Coimbra TM: Increased expression of p38 mitogen activated protein kinase is related to the acute renal lesions induced by gentamicin. Braz J Med Biol Res, 2006, 39, 817–823.
129. Wan B, Hao L, Qiu Y, Sun Z, Cao Q, Zhang Y, Zhu T et al.: Blocking tumor necrosis factor-α inhibits folic acid-induced acute renal failure. Exp Mol Pathol, 2006, 81, 211–216.
130. Waring WS, Jamie H, Leggett GE: Delayed onset of acute renal failure after significant paracetamol overdose: A case series. Hum Exp Toxicol, 2010, 29, 63–68.
131. Wei Q, Wang MH, Dong Z: Differential gender differences in ischemic and nephrotoxic acute renal failure. Am J Nephrol, 2005, 25, 491–499.
132. Weisbord SD, Mor MK, Resnick AL, Hartwig KC, Sonel AF, Fine MJ, Palevsky PM: Prevention, incidence, and outcomes of contrast-induced acute kidney injury. Arch Intern Med, 2008, 168, 1325–1332.
133. Whelton A, Lefkowith JL, West CR, Verburg KM: Cardiorenal effects of celecoxib as compared with the nonsteroidal anti-inflammatory drugs diclofenac and ibuprofen. Kidney Int, 2006, 70, 1495–1502.
134. Willox JC, McAllister EJ, Sangster G, Kaye SB: Effects of magnesium supplementation in testicular cancer patients receiving cisplatin: a randomised trial. Br J Cancer, 1986, 54, 19–23.
135. Wolfert AI, Oken DE: Glomerular hemodynamics in established glycerol-induced ARF in the rat. J Clin Invest, 1989, 84, 1967–1973.
136. Wolfgang GH, Gandolfi AJ, Stevens JL, Brendel K: In vitro and in vivo nephrotoxicity of the L and D isomers of S-(1,2-dichlorovinyl)-cysteine. Toxicology, 1989, 58, 33–42.
137. Xie Y, Nishi S, Iguchi S, Imai N, Sakatsume M, Saito A, Ikegame M et al.: Expression of osteopontin in gentamicin-induced acute tubular necrosis and its recovery process. Kidney Int, 2001, 59, 959–974.
138. Yang CL, Du XH, Han YX: Renal cortical mitochondria are the source of oxygen free radicals enhanced by gentamicin. Ren Fail, 1995, 17, 21–26.
139. Yang Q, Liu D, Long Y, Liu HZ, Chai WZ, Wang XT: Acute renal failure during sepsis: Potential role of cell cycle regulation. J Infect, 2009, 58, 459–464.
140. Yatsu T, Arai Y, Takizawa K, Kasai-Nakagawa C, Takanashi M, Uchida W, Inagaki O, et al.: Effect of YM435, a Dopamine DA1 receptor agonist, in a canine model of ischemic acute renal failure. Gen Pharmacol, 1998, 31, 803–807.
141. Yen HW, Lee HC, Lai WT, Sheu SH: Effects of acetylcysteine and probucol on contrast medium-induced depression of intrinsic renal glutathione peroxidase activity in diabetic rats. Arch Med Res, 2007, 38, 291–296.
142. Yesilyurt A, Aydýn Erden I, Bilgic I, Erden G, Albayrak A: The protective effect of erdosteine on radiocontrast induced nephrotoxicity in rats. Environ Toxicol, 2011, 26, 395–402.
143. Yoneya R, Ozasa H, Nagashima Y, Koike Y, Teraoka H, Hagiwara K, Horikawa S: Hemin pretreatment ameliorates aspects of the nephropathy induced by mercuric chloride in the rat. Toxicol Lett, 2000, 116, 223–229.
144. Zhang J, Duarte CG, Ellis S: Contrast medium and mannitol induced apoptosis in heart and kidney of SHR rats. Toxicol Pathol, 1999, 27, 427–435.
145. Zhang J, Lu H: Ifosfamide induces acute renal failure via inhibition of the thioredoxin reductase activity. Free Radic Biol Med, 2007, 43, 1574–1583.
146. Zhang J, Tian Q, Chan SY, Li SC, Zhou SF, DuanW, Zhu YZ: Metabolism and transport of oxazaphosphorines and the clinical implications. Drug Metab Rev, 2005, 37, 611–703.
147. Zimmermann HD, Schmidt E, Weller E, Becker C, Dieker P: Intra- and extra renal vascular changes in the acute renal failure of the rat caused by mercury chloride. Virchows Arch A Pathol Anat Histol, 1977, 372, 259–285.

Received: April 21, 2011; **in the revised form:** September 18, 2011; **accepted:** October 25, 2011.