

Drug-induced nephrotoxicity

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Received: 05 June 2014

Accepted: 02 July 2014

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ABSTRACT

Drug-induced nephrotoxicity is an extremely common condition and is responsible for a variety of pathological effects on the kidneys. Drug-induced acute renal failure (ARF) accounted for 20% of all ARF cases. Drugs showed to cause nephrotoxicity exert their toxic effects by one or more common pathogenic mechanisms. Although it is impossible to present all the drugs causing the nephrotoxicity, this article will summarize the mechanism of injury associated with particular common medications, discuss clinical presentations, renal markers, and evaluate strategies that prevent or minimize renal injury. Drug-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Therefore, successful prevention requires knowledge of pathogenic mechanisms of renal injury, patient-related risk factors, drug-related risk factors, and preemptive measures, coupled with vigilance and early intervention. General preventive measures include using alternative non-nephrotoxic drugs whenever possible; correcting risk factors, if possible; assessing baseline renal function before initiation of therapy, followed by adjusting the dosage; monitoring renal function and vital signs during therapy, and avoiding nephrotoxic drug combinations. Surprisingly, little information is available to guide us with respect to avoiding complications in critical illness; therefore, it is necessary to follow the guidelines.

Keywords: Medications, Nephrotoxicity, Pharmacovigilance, Renal biomarkers, Renal failure

INTRODUCTION

Drug-induced Nephrotoxicity is an extremely common condition and is responsible for a variety of pathological effects on the kidneys. It is defined as renal disease or dysfunction that arises as a direct or indirect result of exposure to drugs.¹ The incidence of drug-induced nephrotoxicity has been increasing with the increasing use of drugs and their easy availability as over-the-counter medications especially non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, etc.²

Drug-induced acute renal failure (ARF) accounted for 20% of all ARF cases in an Indian study.³ Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66%, due to a higher incidence of diabetes and cardiovascular diseases compelling them to take multiple medications. Although renal impairment is often reversible, it may still require multiple interventions and hospitalization.⁴

Most of the drugs which are found to be nephrotoxic exert toxic effects by one or more common pathogenic

mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Knowledge of offending drugs and their particular pathogenic mechanisms of renal injury is critical for recognizing and preventing drug-induced renal impairment.¹

RISK FACTORS

We are exposed to a variety of potential nephrotoxic substances on a rather frequent basis, in the form of therapeutic agents, while most of them are prescribed; many others are available to the general population as over-the-counter medication. Herbal remedies, natural products, and nutritional supplements that are widely available at most health food stores are also potentially nephrotoxic. More concerning are the harmful contaminants and chemicals contained in the products that are not listed on the label.^{5,6} Some of the risk factors are mentioned in Table 1.

Table 1: Risk factors that increase renal vulnerability to nephrotoxins.⁷

Patient-specific factors
Old age (>65 year)
Nephrotic syndrome
Cirrhosis/obstructive jaundice
Acute/chronic kidney disease
True or effective volume depletion
Metabolic perturbations
Immune response genes
Pharmacogenetics favoring drug toxicity
Kidney-specific factors
High rate of blood delivery (20-25% of cardiac output)
Increased toxin concentration in renal medulla and interstitium
Biotransformation of substances to reactive oxygen species
High metabolic rate of tubular cells (loop of Henle)
Proximal tubular uptake of toxins
Drug-specific factors
Prolonged dosing periods and toxin exposure
Potent direct nephrotoxic effects of the drug or compound
Combinations of toxins/drugs promoting enhanced nephrotoxicity
Competition between endogenous and exogenous toxins for transporters, increasing toxin accumulation within the tubular cell
Insoluble parent compound and metabolite with intratubular crystal precipitation

DRUGS CAUSING NEPHROTOXICITY⁷

Some drugs which are prescribed for various indications have a potential to cause nephrotoxicity and their mechanism by which they cause nephrotoxicity are listed in Table 2.

Features of some common nephrotoxic drugs are as follows:

Aminoglycosides (AMG)

AMG are prototype drugs having nephrotoxicity as major side-effect. Nephrotoxic risk increases with Na⁺ and K⁺ depleted state, renal ischemia, increasing age, liver disease, diuretics, concomitant use of nephrotoxic agents and with duration of therapy reaching, 50% when given for 14 days or more.⁸

Relative toxicity: neomycin > gentamicin > tobramycin > netilmicin > amikacin > streptomycin.

Clinical features

It presents as acute tubular necrosis, showing features such as non-oliguric ARF, proximal tubular dysfunction,

proteinuria, glycosuria, hypokalemia, hypocalcemia and hypomagnesaemia.⁸

Mechanism of toxicity

AMG gets actively concentrated in the renal cortex and proximal tubular cells. It then binds to lysosomes, leading to the formation of myeloid bodies/secondary lysosomes, which is believed to interfere with the phosphatidyl-inositol pathway. Thus, momentary high drug concentrations as achieved immediately after intravenous injection result in saturation of the uptake mechanism. Hence, multiple dosing is more deleterious than single-dose bolus injection.^{8,9}

Prevention and precautions

To prevent AMG-induced nephrotoxicity in clinical practice, the following points need emphasis:¹⁰⁻¹⁸

- AMG nephrotoxicity is directly dependent on the dose and duration of therapy. Thus, nephrotoxicity is more likely to occur if large doses are given over prolonged periods, or usual doses are given to patients with underlying renal disease. Hence, use the lowest dose and shortest possible course of therapy.
- Use AMG as a once daily dose rather than divided dose especially in high-risk individuals.
- Serial monitoring of renal function (serum creatinine every other day) should be carried-out for early detection of nephrotoxicity.
- Avoid combination of AMGs with other potential nephrotoxins (amphotericin, cisplatin, diuretics, contrast material, etc.).
- During AMG therapy, ensure adequate hydration, especially in the elderly.

NSAIDS

Over-the-counter availability of these drugs puts a large population at risk. Higher than usual dose, volume depletion, congestive heart failure, nephrotic syndrome, cirrhosis particularly with ascites, preexisting renal disease and age >65 years are the factors which increase its toxicity.^{4,19}

Clinical features

It presents with oliguric ARF, hypokalemia, sodium and water retention, hypertension, heavy proteinuria, fever, rash, eosinophilia, etc. Classically seen with consumption of any NSAID for over 20 years especially with aspirin.¹⁹

Mechanism of toxicity

Nephrotoxicity is due to delayed hypersensitivity response with shunting of arachidonic acid metabolites to lipoxygenase the pathway. Leukotrienes mediate chemotaxis for white blood cells leading to cellular infiltrates (T-cell and

Table 2: Drug causing nephrotoxicity and their proposed mechanism of action.⁷

Drug class	Examples	Patho-physiological mechanism of renal injury
Analgesics	NSAIDs	Acute interstitial nephritis, Altered intraglomerular hemodynamics, Chronic interstitial nephritis, Glomerulonephritis
Antidepressants or mood stabilizers	Amitriptyline, doxepin, fluoxetine Lithium	Rhabdomyolysis Chronic interstitial nephritis, glomerulonephritis, rhabdomyolysis
Antihistamines	Diphenhydramine	Rhabdomyolysis
Antimicrobials	Acyclovir Aminoglycosides Amphotericin B Beta lactams Foscarnet Ganciclovir Pentamidine Quinolones Rifampin Sulfonamides Vancomycin	Acute interstitial nephritis, crystal nephropathy Tubular cell toxicity Tubular cell toxicity Acute interstitial nephritis Crystal nephropathy, tubular cell toxicity Crystal nephropathy Tubular cell toxicity Acute interstitial nephritis, crystal nephropathy (ciprofloxacin) Acute interstitial nephritis Acute interstitial nephritis, crystal nephropathy Acute interstitial nephritis
Antiretrovirals	Indinavir Adefovir, cidofovir	Acute interstitial nephritis, crystal nephropathy Tubular cell toxicity
Benzodiazepines		Rhabdomyolysis
Calcineurin inhibitors	Cyclosporine Tacrolimus	Altered intraglomerular hemodynamics, Chronic interstitial nephritis, Thrombotic microangiopathy Altered intraglomerular hemodynamics
Cardiovascular agents	ACE I, ARBs Clopidogrel, ticlopidine Statins	Altered intraglomerular hemodynamics Thrombotic microangiopathy Rhabdomyolysis
Chemotherapeutics	Cisplatin Interferon-alfa Methotrexate Mitomycin-C	Chronic interstitial nephritis, tubular cell toxicity Glomerulonephritis Crystal nephropathy Thrombotic microangiopathy
Diuretics	Loops, thiazides Triamterene	Acute interstitial nephritis Crystal nephropathy
Drugs of abuse	Cocaine, heroin, ketamine, methadone, methamphetamine	Rhabdomyolysis
Proton pump inhibitors	Omeprazole, pantoprazole	Acute interstitial nephritis
Others	Allopurinol Haloperidol Phenytoin Quinine Ranitidine	Acute interstitial nephritis Rhabdomyolysis Acute interstitial nephritis Thrombotic microangiopathy Acute interstitial nephritis

NSAIDs: Non-steroidal anti-inflammatory drugs, ACE I: Angiotensin-converting enzyme inhibitor, ARBs: Angiotensin II receptor blockers

eosinophils). Analgesic nephropathy is a chronic interstitial nephritis associated with capillary sclerosis of the vessels of renal pelvis and renal papillary necrosis, followed by

calcification. It is due to medullary ischemia induced by loss of vasodilatory effects of prostaglandins on vasa recta. Non-contrast computed tomography scan of the abdomen

showing bumpy contour of the kidney, decreased length of both the kidneys and papillary calcification are the feature of analgesic nephropathy.¹⁹

Prevention and management

- Recognize the risk (situational factors) for causation of nephrotoxicity and take corrective action to minimize nephrotoxic potential.
- Avoid chronic (habitual) use of NSAIDs.
- Avoid combinations of analgesics and monitor use of drugs when consumption is mandatory.
- All available analgesics have a nephrotoxic potential and should be carefully considered before usage.
- Early intervention can prevent its progression. Stop NSAIDs if patients develop any evidence of renal insufficiency and ensure adequate hydration before and during therapy.

Cisplatin

Nephrotoxicity is the major side effect of this drug, but it is cumulative and dose-related ($>25-33 \text{ mg/m}^2/\text{week}$).¹⁸

Clinical features

Acute tubular necrosis or tubulointerstitial disease with symptoms of azotemia and fluid loss. Biochemical tests usually show tubular proteinuria with prominent tubular casts. Increase in blood urea nitrogen (BUN), serum creatinine and low serum Na^+ , K^+ , Mg^{+2} , Ca^{+2} occur due to proximal tubular damage, especially at S3 portion.²⁰

*Prevention and management*¹⁸

- Prevention of toxicity is by avoidance of other nephrotoxic drugs like AMG.
- Diuresis should be started immediately after drug administration; maintaining urine output of 100 mL/hr, can decrease the nephrotoxicity. Mannitol may be helpful.
- When administered with hypertonic saline, cisplatin is better tolerated.
- Sodium-thiosulfate intravenous should be added if $>200 \text{ mg/m}^2$ of cisplatin is used.³
- Anti-oxidant drugs causing free radical scavenging may play an important role in renoprotection.¹⁸

Cyclosporine (CS-A)

Acute reversible and chronic irreversible nephrotoxicity are the two forms of cytotoxicity known with CS.

Acute form

It is seen mostly in transplant recipients manifesting as ARF, due to vasoconstriction induced in the systemic circulation

and also due to vasospastic products of arachidonate metabolism specially thromboxane-A₂.^{4,19}

Clinical features

Sudden onset hypertension within weeks of transplant. Urine volume and Na^+ excretion are preserved, but glomerular filtration rate (GFR) and renal plasma flow are decreased with no change in the filtration fraction along with hypertension.²¹

Prevention and management

- Rapid improvement was seen with reduction of dose. GFR progressively reaches baseline as blood levels of CS-A fall to trough levels.
- Calcium channel blockers provide protection and ameliorate early and long-term CS toxicity and improve graft survival.
- Prostaglandin analog misoprostol also benefits in reversal of vasoconstrictive effects.

Chronic form

CS-A nephrotoxicity typically manifests after 1 year; mimics chronic rejection.

Clinical features

Hypertension, mild proteinuria, rarely hematuria, with a marked decline in GFR. Hemolytic uremia syndrome is a rare arteriopathy with severe renal impairment.

Mechanism of toxicity

It is due to obliterative arteriopathy, tubular atrophy and interstitial fibrosis. Tubular atrophy with diffuse fibrosis may appear as stripes (striped interstitial fibrosis - characteristic of CS-A). Severe lesions are seen in patients with cumulative dose of more than 1.8 g/kg over 6 months associated with thrombosis in the renal microcirculation along with thrombocytopenia and hemolytic anemia.³

Prevention and management^{3,4,19}

- Start CS-A on the 5th day post-surgery at the lowest dose with upward titration to reach ideal trough concentration in 1-2 months with meticulous monitoring of serum creatinine and blood pressure.
- Calcium channel blockers are beneficial in initial stages of acute hypertension.
- Avoid drugs such as cimetidine, ranitidine, diltiazem, verapamil, erythromycin, metoclopramide, anabolic steroids and oral contraceptives which raise CS-A concentration.

- Micronized forms of CS-A are beneficial as the total dose required less and also lower nephrotoxicity.

Amphotericin-B (Am-B)

It contains hydrophilic as well as lipophilic regions. Risk factors for toxicity remain the same as for any toxic nephropathy, but sodium deficiency is important especially in patients on diuretics and those with cumulative doses of 3-4 g have a greater risk.^{9,18}

Clinical features

Azotemia with inability to concentrate urine, increasing the urinary loss of K⁺ and Mg²⁺.

Mechanism of toxicity

It easily mingles with cellular membranes, disrupts them and damages the endothelium, which not only increases the permeability, but also causes vasoconstriction of afferent and efferent arteriole, decreasing GFR and leading to oliguric ARF, which may progress to tubular toxicity.⁴

Prevention and management⁴

- Prevention is the key in managing these patients.
- Dopamine agonist and salt supplementation may exert a protective role.
- Liposomal Am-B reduces the renal toxicity. A higher total dose of 5 mg/kg/day compared with a maximum of 0.5-1.5 mg/kg/day with hydrophilic Am-B can be achieved without risking the renal tissue.

GENERAL MEASURES TO PREVENT DRUG-INDUCED NEPHROTOXICITY²⁰⁻²²

- Adjust medication dosages using the Cockcroft-Gault formula (in adults) or Schwartz formula (in children).
- Assess baseline renal function using the modification of diet in renal disease equation, and consider patient's renal function when prescribing a new drug.
- Avoid nephrotoxic combinations.
- Correct risk factors for nephrotoxicity before initiation of drug therapy.
- Ensure adequate hydration before and during therapy with potential nephrotoxins.
- Use equally effective non-nephrotoxic drugs whenever possible.

BIOMARKERS OF DRUG INDUCED KIDNEY DAMAGE²³

Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. The existing biomarkers such as serum creatinine and BUN, to monitor renal safety are

insensitive and show limited specificity. In the past decade, several efforts have been undertaken to identify better markers of nephrotoxicity using genomics and proteomics approaches. These new markers are more sensitive and can detect damage earlier than BUN and creatinine levels. Some of these biomarkers are mentioned in Table 3.

RECOGNITION AND EARLY INTERVENTION

Most episodes of drug-induced renal impairment are reversible. Renal function generally returns to baseline provided the impairment is recognized early, and the offending medication is discontinued.²⁴ Failure to act on available information relating to clinical findings or laboratory results was the most common monitoring error, occurring in 37% of preventable adverse drug events, including those affecting the kidney, in older ambulatory patients.²⁵ A decrease in renal function as evidenced by a rise in serum creatinine levels following the initiation of a drug signals the possibility of drug-induced renal injury. The exception to this is an increase in serum creatinine following the initiation of cimetidine or trimethoprim, because they compete with creatinine for tubular secretion and are not associated with kidney damage or urine abnormalities.²⁴ Although there are no standard guidelines used to interpret changes in serum creatinine, 50% rise from baseline, an increase of 0.5 mg/dL (40 μmol/L) or more when baseline serum creatinine is <2 mg/dL (180 μmol/L), or an increase of 1 mg/dL (90 μmol/L) or more if baseline creatinine is >2 mg/dL have been used as biochemical criteria of ARF.²⁶⁻²⁸

At the first sign of renal dysfunction, the patient's medication list should be reviewed to identify offending agents. If multiple medications are present and the patient is clinically stable, physicians should start by discontinuing the drug most recently added to the patient's medication regimen. Attention should then be directed at avoiding further renal insults by supporting blood pressure, maintaining adequate hydration, and temporarily discontinuing all other possible nephrotoxins.²⁹

CONCLUSION

Emerging data demonstrate that even small reversible changes in renal function in critically ill patients are associated with adverse outcomes. Medication-related renal dysfunction is common in the critically ill for a number of possible reasons, including increased patient complexity with other coexistent risk factors for acute kidney injury (e.g., sepsis, hypotension); polypharmacy; overestimation of preexisting renal function, particularly in elderly patients; and inaccurate and insensitive methods of assessing acute changes in renal function. Surprisingly little information is available to guide us with respect to avoiding these complications in critical illness; therefore, we must follow this guideline.

Table 3: Biomarkers of nephrotoxicity.²¹

Nephron segment	Drug induced nephrotoxicity	Biomarkers
Glomerulus	ACE inhibitor, ARB, NSAIDs, Mitomycin-C Antiplatelet agents, Cyclosporin, Quinone	Proteinuria Albumin, transfer in, immunoglobulin G, β 2-microglobulin, α 1-microglobulin, Cystatin C Retinol binding protein Cytokines Interferons, Interleukins, TNF, CSFs Type IV collagen
Proximal tubule	Aminoglycoside antibiotics Am-B, Adefovir Cisplatin, Foscarnet Contrast stain, Cocaine, Heroin, Methadone Methamphetamine	Urinary proteins with enzymatic activity α -GST, N-Acetyl-D-Glucosaminidase Proteinuria Albumin, Transferrin, Immunoglobulin G, β 2-microglobulin, α 1-microglobulin, Cystatin C Retinol binding protein Cytokines, Interferons, Interleukins, TNF, CSFs KIM-1, NGAL, Clusterin, Osteopontin
Distal tubule	Am-B, Lithium Acyclovir, Indinavir, Sulfonamides	NGAL, Clusterin, Osteopontin

ACE: Angiotensin-converting enzyme, ARB: Angiotensin II receptor blockers, NSAIDs: Non-steroidal anti-inflammatory drugs, TNF: Tumor necrosis factor, CSFs: Colony-stimulating factors, GST: Glutathione S-transferase, Am-B: Amphotericin-B, NAGL: Neutrophil gelatinase-associated lipocalin

“Always be Precautious and Preventive.”

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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doi: 10.5455/2319-2003.ijbcp20140826

Cite this article as: Dhodi DK, Bhagat SB, Pathak D, Patel SB. Drug-induced nephrotoxicity. *Int J Basic Clin Pharmacol* 2014;3:591-7.