DRUG-INDUCED NEPHROTOXICITY AND ITS
MANAGEMENT - AN OVERVIEW

*M. LEENA¹, SUBASH VIJAYAKUMAR², A.Y. RAO³

ABSTRACT

Drug-induced renal failure is common and responsible for a variety of pathological effects on the kidney. Many medications can lead to renal dysfunction through various mechanisms, which can cause significant morbidity. Our review article mainly focused on drugs associated with nephrotoxicity and its prevention strategies. We developed a search strategy to find publications on drug induced nephrotoxicity and its management so; we searched Science Direct, Medline and PubMed bibliographic databases, and renal texts to identify relevant articles. Our review suggested that proper understanding the mechanisms involved, and recognizing the clinical presentations of renal dysfunction arising from use of commonly prescribed medications are important if injury is to be detected early and prevented. As it is impossible to list all drugs associated with 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.

KEY WORDS

Nephrotoxicity, Renal biomarkers, Renal toxicity, Renal injury and Medications.

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INTRODUCTION

Medication-induced nephrotoxicity has been cited, a major cause for acute renal failure in humans, and antibiotics especially aminoglycoside antibiotics, have been among the most common offending agents.\(^1\) Drugs causes approximately 20 percent of community and hospital acquired episodes of acute renal failure. Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 percent.\(^2\) Most episodes of renal dysfunction are reversible, with function returning to baseline when the medication is discontinued. Chronic renal injury can however be induced by some medications, leading to chronic tubulo-interstitial inflammation, papillary necrosis or prolonged proteinuria.\(^3\)

Incidence of acute renal failure in the newborn

Acute renal failure in the new born may be caused by a failure of renal perfusion (pre-renal failure), damage to the renal parenchyma (intrinsic renal failure) or obstruction of the urinary tract (post-renal failure). Most cases of intrinsic renal failure in the newborn are due to asphyxia, often in combination with sepsis and nephrotoxic drugs.\(^4\) Exposure to nephrotoxic drugs separately, or in combination precede most episodes of ARF in the newborn. Antibacterial-induced nephrotoxicity is an important parameter to be considered when treating the newborn and this is particularly true when use of a combination of different antibacterials and/or drugs with a nephrotoxic potential is being considered.\(^5\)

Epidemic Nephrotoxicity

Nephrotoxicity can also induced by 'atypical' or 'unconventional' agents, such as environmental agents (metals, minerals & animals), food agents (mushrooms, medicinal traditional herbs, dietary supplement & melamine), drugs, and other products (ethylene glycol). Nephrotoxicity varies according to local background, dependent on different food and cultural customs, as well as to differences in local fauna and flora.\(^6\) Recent outbreaks of nephrolithiasis and acute kidney injury among children in China have been linked to ingestion of milk-based infant formula contaminated with melamine. The USFDA has twice amended its assessment of melamine toxicity for infants, and concluded that only foods with less than 1 p.p.m. of melamine are safe for infants.\(^7\)

Mechanism of toxicity

Toxicity is a relative phenomenon that depends on the inherent structure and properties of a chemical and on its dose. Exogenous chemicals are absorbed after ingestion, inhalation, or skin contact and then distributed to various organs. Chemicals are frequently metabolized, often by multiple enzymatic pathways; to produce that may be more toxic, less toxic than the parent chemical. One or more of these products then interacts with the target macro molecules, resulting in a toxic effect.\(^8\)
Figure 1: Absorption and distribution of toxicities.

**Biotransformation of toxicants**

- **Toxicants**
  - Phase I reactions
  - Primary metabolites
  - Phase II reactions
  - Secondary metabolites

Elimination in urine, bile, or feces
Why the kidney is vulnerable to toxins

Kidney excretes many drugs, it is routinely exposed to high concentrations of drugs or their metabolites or both. Furthermore, the kidney has several features that allow nephrotoxins to accumulate. The proximal renal tubule presents a large area for nephrotoxin binding and transport into the renal epithelium. Reabsorption of the glomerular filtrate progressively increases intraluminal nephrotoxin concentrations, while specific transport pathways in the kidney may engender site-specific toxicity.9

Pathogenic mechanism of drug induced nephrotoxicity

Most drugs found to cause nephrotoxicity by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. 2

Table 1: Drug Induced Nephrotoxicity and its Mechanism.10-37

<table>
<thead>
<tr>
<th>Nephrotoxic drugs</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs, Cyclosporins, Tacrolimus, ACE Inhibitors.</td>
<td>Intraglomerular hemodynamics</td>
</tr>
<tr>
<td>Antimicrobials, Amphotericin B, Betalactum antibiotics, s Rifampicin, Adefovir, Cidofovir, Contrast dye, Zoledronate.</td>
<td>Tubular Cell Toxicity</td>
</tr>
<tr>
<td>Foscornet, Methotrexate, Triamterene, Ganciclovir.</td>
<td>Crystal nephropathy</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Acetaminophen, Aspirin, Acyclovir, Betalactum antibiotics, Quinolones, Rifampicin, Sulfonamides, Cisplatin, Allopurinol, Loops &amp; thiazide diuretics, Chinese medicines.</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Amitryptiline, Diphenhydramine, Doxylamine, Benzodiazepines, Statins, Methodone.</td>
</tr>
<tr>
<td>Thrombocytic Microangiopathy</td>
<td>Cyclosporin, Clopidogrel, Mitomycin C, Quinine.</td>
</tr>
</tbody>
</table>
Figure 2: General Nephrotoxic factors.¹⁰

Figure 3: Clinical Features of Drug Induced Nephrotoxicity.¹¹

- General
  - Costo–vertebral angle edema
  - Elevated serum creatinine
  - Fever
  - Hypertension
  - Malaise

- Glomerulo nephritis
  - Foamy urine
  - Marked facial and lower extremity pitting edema
  - Oliguria

- Acute interstitial nephritis
  - Arthralgia
  - Eosinophilia
  - Eosinophiluria
  - Pyuria

- Acute tubular necrosis
  - Magnesium wasting

- Nephrolithiasis
  - Renal colic
  - Hematuria
ASSESSMENT OF RENAL FUNCTION TESTS

According to the ICH S7A Harmonized tripartite Guideline (Safety Pharmacology Studies for Human Pharmaceuticals), most of the parameters suggested to assess renal function includes urinary volume, specific gravity, Osmolality, pH, fluid/electrolyte balance, proteins, cytology, blood urea nitrogen, plasma creatinine and plasma proteins.\(^{12}\)

Renal function test is given in the figure: 4.\(^{13}\)

**Table 2: Normal Ranges of blood and urine biochemistry.**

<table>
<thead>
<tr>
<th>Blood Chemistry</th>
<th>Urine Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium 132–144 mmol/l</td>
<td>Sodium 100–200 mmol/24 h</td>
</tr>
<tr>
<td>Potassium 3.5–5.5 mmol/l</td>
<td>Potassium 30–90 mmol/24 h</td>
</tr>
<tr>
<td>Urea 3.5–7.4 mmol/l</td>
<td>Protein &lt; 0.15 g/24 h</td>
</tr>
<tr>
<td>Creatinine 44–80 μmol/l</td>
<td>Creatinine 9–17 mmol/24 h</td>
</tr>
<tr>
<td>Chloride 95–110 mmol/l</td>
<td>Creatinine Clearance -120 ml/min</td>
</tr>
<tr>
<td>Plasma osmolality 275–295 m osmol/kg</td>
<td>(HCO(^{-3}) + Cl(^{-})) 12–16 mmol/l</td>
</tr>
</tbody>
</table>

Urine Analysis

Urinalysis by definition refers only to the chemical analysis of urine. Routine urinalysis refers to

1. Macroscopic analysis which includes assessment of physical characteristics and chemical analysis

2. Microscopic analysis for formed elements.\(^{15}\)

Assessment of kidney function and identification of the site of injury within the nephron is the best performed through the examination of urine. Injury can be assessed by examination of cellular enzymes which are preferentially leaked into the urine.\(^{12}\)

Renal function and glomerular filtration rate\(^{14}\)

Glomerular filtration rate (GFR) is the rate (volume per unit of time) at which ultrafiltrate is formed by the glomerulus.\(^{16}\) and it is calculated by the clearance of specific substances.

Characteristics of an ideal marker for GFR Measurement\(^{17}\)
- Constant rate of production (or for exogenous marker can be delivered intravenously at a constant rate)
- Freely filterable at the glomerulus (minimal protein binding)
- No tubular reabsorption
- No tubular secretion
- No extra renal elimination or metabolism
- Availability of an accurate and reliable assay
- For exogenous marker: safe, convenient, readily available, inexpensive, and does not influence GFR (physiologically inert)

**Causes of interpatient variability include:**

- Body size: GFR conventionally factored by 1.73 m$^2$
- Sex: GFR approximately 8% higher in males
- Race
- Age: age-related decline in GFR, 0.75 to 1.0 mL/min/1.73 m$^2$ (0.01 to 0.02 mL/s/ 1.73 m$^2$) per year
- Pregnancy: GFR elevated as much as 50% in first trimester and onward; returns
- Toward normal by 4 to 8 weeks postpartum
- Protein intake: GFR higher in patients on high-protein diet
- Diurnal variation: values tend to be about 10% higher in afternoon than at night.

**Normal range for GFR**

The normal corrected GFR are

Male: 120±25 mL/min

Female: 95±20 ml/min.$^{19}$

Creatinine Clearance (C): creatinine concentration alone can be used to estimate GFR by a number of mathematical models.

The commonly used are

- Cockcroft-Gault equation,
• Modification of diet in renal disease (MDRD), and
• Schwartz equation.\textsuperscript{14}

Formulas to assess renal function.
and
Adjust Medication Dosages.

<table>
<thead>
<tr>
<th>MDRD equation</th>
<th>Schwartz equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( eGFR = 186 \times \text{serum creatinine (mg per dL)}^{-1.154} \times \text{age (years)}^{-0.203} \times (0.742 \text{ if patient is female}) \times (1.210 \text{ if patient is black}) \text{.}^2 )</td>
<td>( eCrCl = (\text{length [cm]} \times k) \div \text{serum creatinine (mg per dL)} )</td>
</tr>
<tr>
<td>( k = 0.55 \text{ (children one to 13 years of age)} )</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cockcroft and Gault equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male:</strong> ( eCrCl = ((140 - \text{age (years)}) \times \text{ideal body weight [kg]}) \div (\text{serum creatinine [mg per dL]} \times 72) \text{.}^2 )</td>
</tr>
</tbody>
</table>

**RENA\(LBIOMARKERS**

Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. According to the NIH working group, a biomarker is a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or a pharmacological response to a therapeutic intervention (Biomarkers Definitions Work Group, 2001).\textsuperscript{22}

**Ideal features of biomarkers used to detect drug-induced nephrotoxicity**

- Identifies kidney injury early (well before the renal reserve is dissipated and levels of serum creatinine increase)
- Reflects the degree of toxicity, in order to characterize dose dependencies
- Displays similar reliability across multiple species, including humans
- Localizes site of kidney injury
- Tracks progression of injury and recovery from damage
Is well characterized with respect to limitations of its capacities

Is accessible in readily available body fluids or tissues.\textsuperscript{23}

**Existing biomarkers for detecting kidney injury**

The current biomarkers, serum creatinine (SCr) and blood urea nitrogen (BUN), to monitor renal safety are late and insensitive and show limited specificity with the serious consequences that AKI can not be prevented or managed with appropriate tools.\textsuperscript{24}

**Second-generation biomarkers for acute kidney injury**

In the past decade, several efforts have been undertaken to identify better and earlier markers of nephrotoxicity using genomics and proteomics approaches (Amin et al. 2004; Devarajan 2008; Kramer et al. 2004; Thukral et al. 2005). Those new markers are more sensitive and can detect damage earlier than BUN and creatinine levels.\textsuperscript{25}

**Table 3: List of biomarkers of nephrotoxicity.\textsuperscript{26}**

<table>
<thead>
<tr>
<th>Urinary protein with enzymatic activity</th>
<th>Filtered low-molecular proteins</th>
<th>Heart-type fatty acid binding protein</th>
<th>Liver type fatty acid binding protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine amino peptidase</td>
<td>( \alpha )-Microglobulin\textsubscript{1}</td>
<td>Interleukin-18</td>
<td>Microalbumin</td>
</tr>
<tr>
<td>( \alpha )-Glutathione-S-tranferase</td>
<td>( \beta )-Microglobulin\textsubscript{2}</td>
<td>Kidney injury molecule-1</td>
<td>Neutrophil gelatinase-associated lipocalin</td>
</tr>
<tr>
<td>( \gamma )-Glutamyl transpeptidase</td>
<td>Cystatin-C</td>
<td>Retinol binding protein</td>
<td></td>
</tr>
<tr>
<td>( \eta )-Glutathione-S-tranferase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Acetyl-( \beta )-D-glucosaminidase</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MANAGEMENT OF NEPHROTOXICITY.**

Most patients with ARF recover with conservative management which includes

- Fluid monitoring,
- Protein restriction,
- Drug adjustments,
- Dietary or potassium control, and
- Dialysis (usually temporary).\textsuperscript{27}
Main metabolic abnormalities in patients with renal failure.\textsuperscript{28}

- Anorexia – reduced oral nutrient intake
- Gastrointestinal consequences of uraemia
- Restrictive diets
- Uremic toxicity – inadequate dialysis prescription
- Metabolic acidosis
- Endocrine factors (PTH, insulin resistance etc.)
- Peripheral insulin resistance
- Impairment of lipolysis
- Low grade inflammatory state _activation of protein catabolism
- Augmented catabolic response to intercurrent disease
- Metabolic acidosis
- Hyperparathyroidisms, uremic bone disease
- Impairment of vitamin D3 activation

**Conservative management**

**Fluid balance**

Adequate hydration is important to maintain renal perfusion and avoid drug-induced renal impairment. Whenever possible, volume status should be assessed and corrected, if necessary, before initiation of nephrotoxic agents. This is particularly true when prescribing medications such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and NSAIDs, which induce alterations in renal hemodynamics in patients who are significantly volume depleted.\textsuperscript{29}

**Nutrition**

Nutrition is an important consideration in ARF. Adequate energy must be provided in order to promote anabolism and prevent catabolism, which potentiates hyperkalemia, hyperphosphatemia and acidosis. The purpose of nutritional management is to prevent or treat malnutrition, to reduce accumulation of waste products, potassium and phosphorus, and to prevent complications of uremia.\textsuperscript{30}
Table 4: Vitamin supplementation in acute renal failure.\(^{31}\)

<table>
<thead>
<tr>
<th>Vitamins</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>4mg/wk</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10iu/d</td>
</tr>
<tr>
<td>Thiamine Hcl (B(_1))</td>
<td>2mg/dl</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>10iu/d</td>
</tr>
<tr>
<td>Riboflavin (B(_2))</td>
<td>2mg/d</td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>10mg/d</td>
</tr>
<tr>
<td>Ascorbic acid (C)</td>
<td>70-100mg/d</td>
</tr>
<tr>
<td>Biotin</td>
<td>200mg/d</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1mg/d</td>
</tr>
<tr>
<td>Vitamin B(_{12})</td>
<td>4µg/d</td>
</tr>
<tr>
<td>Folic acid</td>
<td>1mg/d</td>
</tr>
<tr>
<td>Vitamin B(_{12})</td>
<td>4µg/d</td>
</tr>
</tbody>
</table>

Renal replacement therapy.

Renal replacement therapy is indicated in a patient with ARF when kidney function is so poor that life is at risk. The common types of renal replacement therapy includes:

- Haemodialysis
- Haemofiltration
- Haemodiafiltration
- Peritoneal dialysis.\(^{27}\)

Common indications for dialysis in acute renal failure.\(^{30}\)

- Hyperkalemia
- Severe metabolic acidosis
- Hyperphosphatemia/hypocalcemia
- To make space for nutrition and drug administration
- Failure to improve with conservative management

Specific Prevention Strategies for Selected Agents
### Table 5: Drugs altering intraglomerular hemodynamics.

<table>
<thead>
<tr>
<th>Medications</th>
<th>Prevention strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Use analgesic with less prostaglandin activity</td>
</tr>
<tr>
<td>Angiotensin receptor blockers, NSAIDs</td>
<td>Correct volume depletion before initiation of drug especially if used on chronic basis.</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Monitor renal function and vital signs, following initiation or dose escalation especially if used in-at risk patient</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Use low effective dose.</td>
</tr>
</tbody>
</table>

### Drugs associated with tubular cell toxicity

<table>
<thead>
<tr>
<th>Medications</th>
<th>Prevention strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Use extended-interval dosing, administer during active period of day, limit duration of therapy, monitor serum drug levels and renal function 2-3 times/week, maintain trough levels ≤1mcg/ml.</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>Saline hydration before and after dose administration, consider administering as a continuous infusion over 24 hours, use liposomal formulation, limit duration of therapy.</td>
</tr>
<tr>
<td>Contrast dye</td>
<td>Use low-osmolar contrast in the lowest dose possible and avoid multiple procedures in 24 to 48 hours, 0.9% saline or sodium bicarbonate (154mEq/L) infusion before and after procedure, with hold NSAIDs and diuretics at least 24 hours before and after procedure, monitor renal function 24 to 48 hours post-procedure, consider acetylcysteine pre-procedure.</td>
</tr>
</tbody>
</table>

### Drugs associated with chronic interstitial nephropathy

<table>
<thead>
<tr>
<th>Medications</th>
<th>Prevention strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen, aspirin, NSAIDs</td>
<td>Avoid long-term use, particularly of more than one analgesic, use alternate agents in patients with chronic pain.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Maintain drug levels within the therapeutic range, avoid volume depletion.</td>
</tr>
</tbody>
</table>
Drugs associated with crystal nephropathy

<table>
<thead>
<tr>
<th>Medications</th>
<th>Prevention strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir, methotrexate, sulfa</td>
<td>Discontinue or reduce ensure adequate hydration,</td>
</tr>
<tr>
<td>antibiotics, triamterene.</td>
<td>establish high urine flow. Administer orally</td>
</tr>
</tbody>
</table>

**General Goals to Prevent Drug-Induced Nephrotoxicity.**

1. Avoid simultaneous use of two or more different nephrotoxic drugs

2. Be careful with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patient who are taking drugs that induce afferent arteriole vaso constriction (e.g., contrast agents, calcineurin blockers).  

3. Adjust medication dosages using the Cockcroft-Gault formula (in adults) or Schwartz formula (in children).

4. Assess baseline renal function using the MDRD equation, and consider patient's renal function when prescribing a new drug.

5. Correct risk factors for nephrotoxicity before initiation of drug therapy.

6. Ensure adequate hydration before and during therapy with potential nephrotoxins

7. Use equally effective non-nephrotoxic drugs whenever possible.  

**Role of antioxidants in the prevention of drug nephrotoxicity**

Reactive oxygen species play a significant role in the pathogenesis of many chronic diseases such as diabetes mellitus, cancer, chronic renal failure etc. The primary event leading to renal failure is a free radical mediated injury to the endothelial cells in the outer medulla.

Antioxidants are first line defense against free radical damage and are critical for maintaining optimum health and well being. The administration of various natural or synthetic antioxidants has been shown to be of benefit in prevention and attenuation of renal scaring in numerous animal models of kidney diseases. These include vitamins, N-acetylcysteine, \( \alpha \)-lipoic acid, melatonin, dietary flavonoids and phytoestrogens, and many others. Supplementation of antioxidant vitamin C and vitamin E (500mg/day during 6 months) corrects plasma antioxidant status and attenuating the cardiovascular disease that accompanies kidney failure.

Administration of superoxide dismutase provides a marked protection against gentamicin-induced impairment of renal function.
Table 6: List of Antioxidants that ameliorate the nephrotoxicity of platinum compounds.\textsuperscript{36}

<table>
<thead>
<tr>
<th>Antioxidants</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Species</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C or E</td>
<td>100mg/kg</td>
<td>Intraperitoneal</td>
<td>Once</td>
<td>Rats</td>
<td>Kadikoylu et al. (2004)</td>
</tr>
<tr>
<td>Xanthorrhzhiol</td>
<td>200/kg</td>
<td>Per oral</td>
<td>4 days</td>
<td>Rats</td>
<td>Kim et al. (2005)</td>
</tr>
<tr>
<td>Lycopene</td>
<td>4mg/kg</td>
<td>Per oral</td>
<td>10 days</td>
<td>Rats</td>
<td>Atessahin et al. (2005)</td>
</tr>
<tr>
<td>Tomato juice + dried black grapes</td>
<td>Supplement to diet</td>
<td>–</td>
<td>6 days</td>
<td>Rats</td>
<td>Cetin et al. (2006)</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>10mg/kg</td>
<td>Per oral</td>
<td>6 days</td>
<td>Rats</td>
<td>Shimeda et al. (2005)</td>
</tr>
<tr>
<td>Quercitin</td>
<td>50mg/kg</td>
<td>Per oral</td>
<td>20 days</td>
<td>Rats</td>
<td>Francescato et al. (2004)</td>
</tr>
<tr>
<td>Desferrioxamine</td>
<td>250mg/kg</td>
<td>Intraperitoneal</td>
<td>Once</td>
<td>Rats</td>
<td>Kadikoylu et al. (2004)</td>
</tr>
<tr>
<td>Glutamine</td>
<td>300mg/kg</td>
<td>Per oral</td>
<td>Once</td>
<td>Rats</td>
<td>Mora et al. (2003)</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Drug-induced kidney injury is a common condition associated with considerable morbidity and mortality. Successful prevention requires assessing base line renal function before the initiation of the therapy, followed by adjusting the dosage, monitoring renal function and vital signs during therapy and avoiding nephrotoxic drug combinations. Additional characterization and validation of individual biomarkers and biomarkers panels will ultimately result in earlier diagnosis of kidney injury and improved prognosis of outcome.

**REFERENCES**


