Drug-induced renal disorder—A Mini Review

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ABSTRACT

Drug-induced kidney disorder/disease (DIKD) is an origin of kidney disease followed by acute renal failure. Drug-induced renal toxicity is more common in infants and young children in certain clinical circumstances where underlying renal dysfunction and cardiovascular diseases. Sometimes, administered drugs may cause acute renal injury, intra-renal obstruction, interstitial nephritis, nephrotic syndrome, and acid-base and fluid electrolytes disorders in patients. Certain drugs may cause alterations in intra-glomerular hemodynamics, inflammatory changes in renal tubular cells, leading to acute kidney injury (AKI), interstitial tubule disease, and renal scarring. Common risk factors include; pre-existing renal dysfunction, volume-depleted state, old age, and use of nephrotoxic drugs. Therefore, the prevention from the disease includes the knowledge about the nephrotoxicity, assessing considering the patient-related, kidney-related, and drug-related factors while prescribing medicines, using of alternative drugs, which are non-nephrotoxic, assessing the baseline of renal function before starting the treatment, monitor the renal function during the treatment and avoid the nephrotoxic drug combinations and withdrawing the offending drugs due to toxicity. The ADRs of the prescribed/administered are identified at the earliest to prevent the development of the last-stage renal disorder. This review discusses the risk factors associated with drug-induced renal disease, estimation of renal function, mechanism of drug-induced nephrotoxicity, and certain drugs that cause nephrotoxicity.

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INTRODUCTION

Nowadays, drug-induced renal disease is increased due to the rise in the usage of drugs and their availability in the market at easy (Jha and Chugh, 1995; Singh et al., 2003). Drug-induced nephrotoxicity is summed up as renal dysfunction or disease, which turns up as a consequence of indirect or direct exposure of the drug (Dhodi et al., 2014). The prevalence of drug-induced nephrotoxicity is 14-6% and 16% in adults and pediatrics, respectively. 50% or 0.5mg/dl rise in serum creatinine over 4 to 7 h time frame, and a minimum of 24 to 48 hr exposure to the drug is defined as nephrotoxicity, but it is not highly specific. Drug-induced kidney disorder can be classified into two types. Type A is dose-dependent, and type B is idiosyncratic reactions. Based on the pharmacological properties of the drug, the dose-dependent reactions are predictable, where idiosyncratic reactions are unpredictable. The Kidney Disease Improving Global Outcomes (Ostermann, 2018), categorized DIKD as acute, subacute and chronic the different mecha-
nisms can be explained as,

1. By modifying the intraglomerular hemodynamics

   E.g., Angiotensin-converting enzyme (ACE inhibitors), Non-steroidal Anti-inflammatory Drugs (NSAIDs), Angiotensin receptor blockers (ARB’S).

2. Renal tubular toxicity

   E.g., Aminoglycoside, amphotericin B, antiretrovirals.

3. Due to inflammation in the renal tubular cells, glomerulus, and surrounding interstitium

   E.g., Gold, allopurinol, lithium, aspirin.

4. Crystal nephropathy

   E.g., Antimicrobial agents, antivirals, methotrexate (Amoghimath and Majagi, 2017; Markowitz and Perazella, 2005; Palmer, 2002; Rossert, 2001)

**Risk factors, those increase the renal vulnerability to nephrotoxins**

The risk factors, which cause renal dysfunctions, are categorized into three, such as, Patient-related, kidney-related, and drug-related factors. (Dhodi et al., 2014; Naughton, 2008) The major risk factors which causing nephrotoxicity are mentioned in Table 1.

**Estimation of renal function**

The renal function should be evaluated before initiating nephrotoxic medication. During the cause of therapy, there is a need for monitoring renal function (Shahrbaf and Assadi, 2015; Schwartz et al., 1976).

**Renal function**

Glomerular filtration rate (GFR) is used to determine renal function. Both exogenous and endogenous substances are used as the markers in the measurement of GFR. But, to be used as a marker, the selected substance must be inert one, both pharmacologically and physiologically, and it should excrete completely only by glomerular filtration as an unchanged form.

The excreted rate of markers in urine will reflect the GFR, and the changes in the GFR indicates the dysfunction of the renal system.

**Insulin clearance**

The measurement of GFR by insulin clearance is an accurate method, but it is a tedious one.

**Creatinine**

It is an endogenous amine, and it is excreted only by glomerular filtration as an unchanged form. The serum creatinine level is determined by this method. Serum creatinine is used to calculate the creatinine clearance by various formulae because the production of creatinine varies with gender, age, and weight (Brahmankar and Jaiswal, 2005).

For children (between 1 to 20 years).

\[
Cl_{cr} = \frac{0.48H}{S_{cr}} \left[ \frac{W}{70} \right]^{0.7}
\]

For adults (above 20 years).

Males,

\[
Cl_{cr} = \frac{(140 - Age)W}{72S_{cr}}
\]

Females,

\[
Cl_{cr} = \frac{(140 - Age)W}{85S_{cr}}
\]

\[= 0.9Cl_{cr} \text{ of male}\]

Where,

- \( Cl_{cr} = \) Clearance of creatinine as ml/min,
- \( S_{cr} = \) Serum creatinine level in mg%,
- \( H = \) Height of the person in cm
- \( W = \) Weight of the person in kg.
- Age is noted in years.

The excreted amount of creatinine in 24 h in urine is the direct method to find out of the creatinine clearance. The blood samples, which were taken before and after the urine collection was analyzed to calculate the mean serum creatinine. It is calculated by using the following formula,

\[
C_{LR} = \frac{\text{Rate of creatinine excretion}}{\text{serum creatinine in mg%}}
\]

The normal clearance of creatinine is 120 to 130 ml/min. If the value becomes 20 to 50 ml/min indicates the renal failure was moderate level and values become less than 10 ml/min indicates the level of renal failure as severe. The renal function (RF) is calculated by using the following equation,

\[
RF = \frac{Cl_{cr} \text{ of patient}}{Cl_{cr} \text{ of a normal person}}
\]

**Mechanism of drug-induced nephrotoxicity**

The changes in glomerular hemodynamics, crystal nephropathy, thrombotic micro-angiopathy, tubular cell toxicity, inflammation, and rhabdomyolysis
Table 1: Risk factors that cause nephrotoxicity

<table>
<thead>
<tr>
<th>S. No</th>
<th>Category</th>
<th>Risk factors</th>
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| I     | Patient-related factors   | Age more than 65 years
Liver cirrhosis or obstructive jaundice
Acute or chronic kidney disorder
Effective or true volume depletion
Metabolic perturbations
Immune response genes |
| II    | Kidney related factors    | When the kidneys receive more than normal 20% to 25% of the cardiac output (about 1.0 to 1.1 liters per minute)
The increased concentration of toxins in the interstitium and renal medulla
Reactive oxygen species in the light of oxidative drug metabolism
The higher metabolism rate at the loop of Henle
Excessive uptake of toxins, (results in proximal tubular damage) |
| III   | Drug-related factors      | Continuous dosing and exposure to toxins
Substance or drug which causes potent nephrotoxic effects
Drugs/toxins, which increased nephrotoxicity while giving in combinations.
Accumulation of toxins in the loop of Henle due to transporters of exogenous and endogenous toxins.
Metabolite and/or parent compounds insolubility (results precipitation of crystals in intratubular) |

are the general mechanisms that cause nephrotoxicity (Kim and Moon, 2012).

Changes in glomerular hemodynamics
The kidney maintains intraglomerular pressure by regulating blood flow in efferent and afferent arteries and thus maintains a constant filtration rate and urine output. Prostaglandins are circulated for the expansion of afferent arteries (Kim and Moon, 2012). The anti-prostaglandin agents like NSAIDs, angiotensin receptor blockers (ARBs) ACE inhibitors, show nephrotoxicity in the glomerulus. Crystal nephropathy
Medicines that make insoluble crystals in the urine can also affect renal function disorder (Brahmankar and Jaiswal, 2005). Due to drug concentration and acidity of urine, insoluble crystals are formed
E.g., Ampicillin, antiviral agents (Perazella, 1999). Thrombotic microangiopathy
The direct toxicity in renal epithelial cells (or) organ damage through inflammation may result in drug-induced thrombotic microangiopathy (Kim and Moon, 2012; Pisoni et al., 2001).
E.g., Cyclosporine, Mitomycin-C, and Guanine Tubular cell toxicity
Drug toxicity is more prominent in proximal cells of renal tubular since these are exposed to the process of concentration and reabsorption through glomerular. The generation of free radicals may increase the oxidative stress, which will damage the mitochondria present in tubules and so the disturbed tubular transport system causes cytotoxicity.
E.g, Antifungal agents, aminoglycosides, anticancer drugs, antiretrovirals (Kim and Moon, 2012). Inflammation
The drugs which are nephrotoxic can cause the inflammation of proximal tubule, glomerulus, and
surrounding cellular matrix and then fiberize the kidney tissue. Chronic/acute interstitial nephritis, glomerulonephritis can induce toxicity in the kidney.

Chronic use of some cytotoxic drugs, immunomodulators, lithium, analgesics can cause chronic interstitial nephritis. Acute interstitial nephritis is caused by NSAIDs and antibiotic drugs such as rifampicin. Glomerulonephritis is caused either by hematuria or proteinuria (Naughton and Friesner, 2012)

**Rhabdomyolysis**

The skeletal muscle injury results in the release of myoglobin and serum creatinine kinase (Kim and Moon, 2012) muscle fiber contents into the bloodstream. The tubular obstruction alternations in GFR and renal injury next to direct toxicity (Kang et al., 2013) are caused by myoglobin. Rhabdomyolysis may be induced by drugs, either directly or indirectly. The direct method involves the toxic effect of drugs on myocytes' function and the indirect method by causing myocytes injury. Tea-colored urine, myalgia, and weakness are the symptoms of rhabdomyolysis (Huerta-Alardín et al., 2005; Naughton and Friesner, 2012).

E.g., Statins, Cocaine, Methamphetamine.

**Drugs causing nephrotoxicity**

**Aminoglycosides (AMG)**

The common ADR of aminoglycosides is ototoxicity and nephrotoxicity. In conditions like renal ischemia, sodium and potassium depleted state, lower disease, increasing age, use of diuretics, the nephrotoxic risk increases to 50% when given for 14 days or more (Luft, 1984; Singh et al., 2003).

**Clinical features**

The clinical feature includes proteinuria, hypomagnesemia, hypokalemia, proximal tubular dysfunction, glycosuria, and hypocalcemia.

**Mechanism**

It is actively concentrated in proximal tubular cells and renal cortex to achieve maximum concentration. It binds to lysosomes and forms myeloid body or secondary lysosomes. Aminoglycosides bind to receptors on the 30S subunit of bacterial ribosomes and induce misreading of the genetic code on the messenger RNA template (Maddison et al., 2008).

**Prevention**

The use of the lowest dose and shortest possible cause of therapy can minimize its toxicity. Also, avoiding the combination of AMG’s with other nephrotoxic drugs can limit its adverse effect.

**NSAIDs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are mainly used as pain relievers and in inflammatory conditions. As it is available as OTC drugs, large populations are at risk. Factors that increase the toxicity are volume depletion, cardiac heart failure, cirrhosis, higher than the usual dose.

**Clinical features**

Hypokalemia, sodium water retention, fever, rash, eosinophilia, etc.

**Mechanism**

It is due to reduced renal plasma flow caused by a decrease in prostaglandins, which regulate vasodilation at the glomerular level (Dixit et al., 2010)

**Prevention**

During the therapy with NSAIDs continuously monitor patient renal function. Habitual use of NSAIDs should be avoided and also avoid combination with other analgesics (Dhodi et al., 2014; Singh et al., 2003).

**Cisplatin**

Cisplatin is a common drug for the treatment of various solid organ tumors regimens. The common side effect of cisplatin is dose-related nephrotoxicity.

**Clinical features**

Azotemia and fluid loss are the symptoms of the tubulointerstitial disease (Palmer, 2002).

**Prevention**

Detoxification by antioxidant drugs plays an important role in cisplatin-induced renoprotection (Dhodi et al., 2014; Hajian et al., 2014).

**Acyclovir**

Intravenous administration of acyclovir at high doses can induce Acute kidney injury (AKI). The nephrotoxicity occurs when the iv dose is 500mg/m² (Krieble et al., 1993). Intratubular precipitation with symptoms like hematuria and obstructive uropathy occurs due to its lower solubility. Birefringent needle-shaped crystals are seen in urine analysis. The pre-existing renal insufficiency, volume depletion, and rapid bolus infusion, etc. are the risk factors. The normal renal function restores within 10-14 days after prompt withdrawal of therapy (Singh et al., 2003).

**Sulfonamides**

Sulfonamides are synthetic bacteriostatic antibiotics. By the emergence of AIDS, the use of sulfonamides has increased. Sulfadiazine is a prototype drug causing ARF and crystaluria. Its acetylated byproduct is toxic. The crystals of acetylsulfadiazine and sulfadiazine are identified by inspect-
ing urine sediments as they resemble as "sheaves of wheat."

**Mechanism**
The crystals of acetyl sulfadiazines and sulfadiazines are transmitted through a tubular lumen causing local abrasion and chemical irritation of collecting duct epithelium, as a result, occurs peritubular hemorrhage, obstruction, and tubular necrosis (Singh et al., 2003).

**Prevention**
Preventive measures include proper hydration up to 3 liters/day. Ensure urine pH at 7.5, by urinary alkalinization with sodium bicarbonate at the dose of 6-12 g of per day. In hematuric patients, ultrasonography is advised (Singh et al., 2003; Hardesty et al., 1960).

**β-Lactams and vancomycin**
Methicillin may cause acute interstitial nephritis (AIN). The current vancomycin preparations are free from adverse effects, but the early vancomycin preparations had considerable nephrotoxic potential due to impurities (Guo and Nzerue, 2002; Schetz et al., 2005). The combination of aminoglycoside and vancomycin has synergetic toxicity.

**Rifampicin**
In all acute renal failure cases, the nephrotoxicity induced by rifampicin varies from 1.8% to 16%. Generally, rifampicin related kidney failures are next to drug-induced hemolytic anemia (Singh et al., 2003). Most of the withdrawal case of therapy and sustain management makes the recovery of the patient within 3 weeks (Power et al., 1983; Singh et al., 2003).

**Gold and D- penicillamine**
Gold
In 30% of patients with renal pathology have proteinuria of which membranous glomerulopathy is most common. Proteinuria is normally less than 3.5 g/dl. It is commonly caused by parenteral gold.

**Penicillamine**
7% of people develop nephrotic syndrome with kidney biopsy demonstrating membranous nephropathy (Singh et al., 2003). Acute kidney injury is caused due to polymyxins (polymyxin B and colistin) by toxic, toxic tubular injury (Justo and Bosso, 2015; Shirali and Pazhayattil, 2014).

**Chemotherapeutic agents**
Chemotherapeutic drugs play an important role in the treatment of different neoplasm. However, it leads to serious complications for patients. Nephrotoxicity disorder is commonly found in many chemotherapeutical agents; these lead to comprehensive renal complications (Shirali and Pazhayattil, 2014).

**Cyclosporine (CS-A)**
The two types of cytotoxicity caused by cyclosporine are acute and chronic. Acute is reversible, and chronic produce irreversible nephrotoxicity.

**Acute form**
It is mostly found in transplant recipients with acute renal failure (ARF) due to arachidonate metabolism and also because of vasoconstriction induced in the systemic circulation. When the dose is reduced, rapid improvement is seen.

**Chronic form**
CS-A renal toxicity usually shows after one year and is similar to chronic rejection. The mechanism of toxicity includes obliterative-arteriopathy, interstitial fibrosis, and tubular atrophy (Dhodi et al., 2014).

**Amphotericin B (AMB)**
Amphotericin is usually used in the management of fungal infections. AMB causes dose-dependent nephrotoxicity. It is commonly used available as two forms; liposomal form and conventional form. Liposomal amphotericin is more safe when compared with conventional amphotericin (Mistro et al., 2012; Nankivell et al., 2003).

**Calcineurin inhibitors (CNIs)**
Cyclosporine and tacrolimus are generally used as immunosuppressants, and they are more important after organ transplantation surgery. They have numerous drug-drug interactions, which causes toxic serum drug levels (Naesens et al., 2009). Persistent calcineurin inhibitor exposure can cause interstitial and tubular atrophy, causing chronic kidney disease (Myers et al., 1988; Nankivell et al., 2003).

**Common measures to prevent drug-induced renal toxicity**
(Dhodi et al., 2014; Naughton, 2008) Before the initiation of therapy, correct risk factors for renal impairments and also consider the patient’s renal function. Adequate hydration of body before and during the therapy and, if possible, avoid the combination of nephrotoxic drugs. The dosages should be adjusted using the Schwartz formula in children’s Cockcroft-Gault formula in adults. Another important measure is the immediate withdrawal of offending drugs, which can help renal functions to return baseline (Guo and Nzerue, 2002; Palmer, 2002; Schetz et al., 2005).
CONCLUSION

Drug-induced nephrotoxicity is related to acute renal damage as well as with chronic kidney disorder. When symptoms of renal disorders are identified, the patient’s treatment chart should be checked thoroughly for the presence of any nephrotoxic drugs. If drug-induced acute interstitial nephritis is noted means the complete withdrawal of the compound is advisable one. Traditional nephrotoxicity assays such as measurement of blood urea nitrogen (BUN) or the measurement of serum creatinine concentration have not measured the progression of renal failure accurately. Early diagnosis may reduce economic costs, and therefore, recently developed biomarkers are used.

REFERENCES


