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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 mechanisms 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,

$$Cl_{cr} = \frac{(140 - Age)\, W}{72 S_{cr}}$$

Females,

$$Cl_{cr} = \frac{(140 - Age)\, W}{85 S_{cr}}$$

$$= 0.9 Cl_{cr}\ of\ male$$

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,

$$C_{LR} = \frac{Rate\ of\ creatinine\ excretion}{serum\ creatinine\ in\ mg\%}$$

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,

$$RF = \frac{Cl_{cr}\ of\ patient}{Cl_{cr}\ of\ a\ normal\ person}$$

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

S. No	Category	Risk factors
I	Patient-related factors	Age more than 65 years Nephrotic syndrome 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.

Eg, 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/m^2 (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 interfusion, 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 sulphonamides 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.

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