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Review **Article**

A SYSTAMIC REVIEW ON DRUG INDUCED NEPHROTOXICITY

Abhay Ligade*[1], Dr. Vishnu A. Kangralkar[2]

*[1]PG Scholar, Department of pharmacology, Maratha Mandal's College of Pharmacy,
Email:abhayligade2001@gmail.com
[2]Department of Pharmacology, Maratha Mandal's College of Pharmacy.

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ABSTRACT:
The kidneys play a crucial role in maintaining physiological balance, including pH regulation, hormonal activity, blood pressure, and waste elimination. Drug-induced nephrotoxicity is a common cause of kidney injury, particularly among older adults and patients with multiple health conditions. It accounts for up to 20% of acute renal failure cases and may affect as many as 66% of older patients. This summary reviews different disease associated with kidney such as usually Crystal Nephropathy, Rhabdomyolysis, Thrombotic Microangiopathy, Acute Interstitial Nephritis (AIN)**,** Chronic Interstitial Nephritis, Acute Tubular Necrosis (ATN), Chronic Interstitial Nephritis, Acute Tubular Necrosis (ATN), Nephrotic Syndrome. As systematic review has been done on the drugs associated with nephrotoxicity and mechanism related to nephrotoxicity.

KEY WORDS: Nephrotoxicity, Crystal Nephropathy, Acute Tubular Necrosis, Nephrotic Syndrome, Nephrotoxic agents, Gentamicin

INTRODUCTION

The kidneys are essential organs responsible for a variety of important roles in the human body, such as balancing the body's pH levels, managing hormonal activity, regulating blood pressure, and aiding in the production of red blood cells.[1] One of the most common kidney issues is nephrotoxicity, which happens when the body is exposed to a toxin or medicine. The body's ability to eliminate waste products and extra urine, as well as blood electrolytes (including potassium and magnesium), will all rise when kidney disease develops.[2] Acute renal damage is frequently caused by drugs. The average patient now is older, has more comorbidities, and undergoes more diagnostic and treatment procedures that might damage kidney function. Certain patients and medical environments are more likely to experience drug-induced nephrotoxicity. About 20% of acute renal failure events that occur in hospitals and the community are brought on by drugs. [3,4,5] Up to 66 percent of older persons may have drug-induced nephrotoxicity.[6] Over the past 15 years, the prevalence of renal failure has nearly doubled. Currently, more than a million individuals worldwide are surviving because of kidney transplants, dialysis, or a variety of medications.[7] This article summarizes the drugs associated with nephrotoxicity most common mechanisms behind drug-induced nephrotoxicity

CRYSTAL NEPHROPATHY

Drugs that create crystals that are insoluble in human urine might cause renal damage. The crystals block urine flow and cause an interstitial response when they precipitate, generally in the distal tubular lumen.[8] Antibiotics (such as ampicillin, ciprofloxacin [Cipro], sulfonamides), antivirals (such as acyclovir, foscarnet, and ganciclovir [Cytovene]), indinavir, methotrexate, and triamterene (Dyrenium) are all commonly used medications known to cause crystal formation.[9,8,10] Both the drug's concentration in the urine and the pH of the urine affect the probability of crystal precipitation.[10] Volume depletion and underlying renal insufficiency put patients at the highest risk of developing crystal nephropathy.[10] Renal failure has also been linked to chemotherapy for lymphoproliferative disease, which causes tumor lysis syndrome with calcium phosphate crystal deposition and uric acid.[11]

RHABDOMYOLYSIS

A condition known as rhabdomyolysis occurs when skeletal muscle damage causes myocytes to lyse, releasing intracellular components such as creatine kinase and myoglobin into the plasma. Myoglobin causes renal

Address for Correspondence: Abhay Ligade. PG Scholar, Department of pharmacology, Maratha Mandal's College of Pharmacy, Rajiv Gandhi University of Health Sciences, Karnataka, Bengaluru 4th block Jaynagar, Bengaluru-560041, Email: abhayligade2001@gmail.com.

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damage as a result of tubular blockage, direct toxicity, and changes in GFR.[12] Drugs can cause rhabdomyolysis directly by impairing myocyte function or indirectly by making the myocyte more vulnerable to damage.[12,13] Tea-colored urine, myalgia, and weakness are clinical signs of rhabdomyolysis.[13] Although more than 150 drugs and poisons have been linked to rhabdomyolysis, statins are the most well-known cause.[12] The average documented incidence of rhabdomyolysis with statin monotherapy is 0.44 per 10,000 person-years of medication, making it an uncommon occurrence.[14] Rhabdomyolysis has been linked to a number of substances of abuse, including cocaine, heroin, ketamine (Ketalar), methadone, and methamphetamine.[12,13] Up to 81 percent of rhabdomyolysis cases are caused by drugs or alcohol, and up to 50 percent of patients go on to experience acute renal failure.[15]

THROMBOTIC MICROANGIOPATHY

In thrombotic microangiopathy, platelet thrombi in the microcirculation induce organ damage, similar to thrombotic thrombocytopenic purpura. Drug-induced thrombotic microangiopathy can cause kidney damage by direct endothelial toxicity or immune-mediated reactions.[16] The medications most often implicated to this pathogenic mechanism of nephrotoxicity include quinine (Qualaquin), cyclosporine, mitomycin-C (Mutamycin), and antiplatelet medicines (e.g., clopidogrel [Plavix], ticlopidine [Ticlid]).[16,17]

ACUTE INTERSTITIAL NEPHRITIS

Previously linked to a number of conditions (such as enterococcal and diphtheria), acute interstitial nephritis is now more frequently related to medication therapy. Although it appears in only 1 to 2% of all renal biopsies, it accounts for 10 to 14% of cases of unexplained acute renal failure in patients who undergo biopsy. There are more than 50 medications known to cause acute interstitial nephritis, and the number is continually rising. Antibiotics and NSAIDs are the medication groups most frequently associated with acute interstitial nephritis. The disease's clinical characteristic is a sudden decrease in renal function, which typically happens 15 days (with a range of 2 to 44 days) following drug exposure. Common symptoms of an allergic response include fever, rash, or arthralgia in 10–40% of instances; eosinophilia in 35–100% of patients; and, with thorough search (using a particular stain), eosinophils in the urine in up to 40–100% of patientsIt is crucial to understand that an important number of patients may not exhibit these clinical characteristics; consequently, their absence should not rule out acute interstitial nephritis as the cause of unexplained acute renal failure. 30% of patients sustain diuresis, while the majority are oliguric. Erythrocyturia and sterile leucocyturia are commonly observed, while proteinuria is typically mild (19/24 hours). Isosthenuria and (often) a urine sodium level more than 40 mmol/L are indicated by urinary indices. Hemodialysis is necessary in up to 35% of patients.

A extensive interstitial infiltration of mononuclear cells characterizes the histological appearance; recovery has been noted following steroid therapy. Patients with pre-existing renal disease have been reported to develop progressive allergic interstitial nephritis (without allergy symptoms) as a result of diuretics. This provides a challenging diagnostic issue and, as a result, is a circumstance that is usually ignored.[18]

DRUGS INVOLVED IN ACUTE INTERSTITIAL NEPHRITIS[18]

ANTIBIOTICS

Amoxycillin Benzylpenicillin (penicillin G) ,Carbenicillin, Cefalexin, Cefalothin, Cefoxitin, Cefradin , Ciprofloxacin, Cotrimoxazole (trimethoprim plus sulfamethoxazole), Erythromycin, Methicillin, Nafcillin, Norfloxacin, Oxacillin, Rifampicin, Sulphonamides, Tetracyclines, Vancomycin

NSAID'S

Fenclofenac, Fenoprofen, Ibuprofen, Indomethacin, Mefenamic acid, Naproxen, Phenylbutazone Piroxicam, Sulindac, Tolmetin

DIURETICS

Chlorthalidone, Furosemide (frusemide), (Hydro)chlorothiazide, Antiepileptic drugs, Carbamazepine, Phenobarbital, Phenytoin (diphenylhydantoin) , Tolmetin Tienilic acid, Triamterene

OTHERS

Allopurinol, para-Aminosalicylic acid, Azathioprine,Captopril, Cimetidine, Naproxen, Glafenine, Isoniazid, a-Methyldopa, Propranolol

CHRONIC INTERSTITIAL NEPHRITIS

Compared with acute interstitial nephritis, chronic interstitial nephritis is less likely to be drug-induced, has a mild start, and frequently shows no symptoms of hypersensitivity.[19]Lithium, Chinese herbal remedies that include aristocholic acid, calcineurin inhibitors (such as cyclosporine and tacrolimus), and several chemotherapy drugs are medications associated to this mechanism of nephrotoxicity.[19,20,21]Chronic interstitial nephritis has been documented with analgesics such as acetaminophen, aspirin, and NSAIDs when taken persistently at high dosages (i.e., more than 1 gram daily for more than two years) or in individuals with underlying renal disease.[22,23] Because chronic interstitial nephritis can develop into end-stage renal disease, early detection is

crucial.[19] Due to failing to report of frequency of use and the fact that most patients do not view over-the-counter remedies as medications, diagnosis may be challenging.[24]

DRUGS INVOLVED IN CHRONIC INTERSTITIAL NEPHRITIS[24]

Acetaminophen
Aspirin
NSAIDs
Lithium

ACUTE TUBULAR NECROSIS

Acute tubular necrosis (ATN) is the most common form of drug-induced kidney injury, primarily resulting from the direct toxic effects of certain drugs on tubular epithelial cells—particularly those in the proximal tubules. A wide range of medications can lead to ATN, with notable examples including aminoglycoside antibiotics, amphotericin B, radiographic contrast agents, and cyclosporin.

Histologically, ATN is marked by varying degrees of tubular epithelial cell necrosis, often exposing the underlying basement membrane. Evidence of tubular regeneration is typically present, including the formation of new epithelial cells and tubules. In some instances, mild interstitial changes such as edema and inflammatory cell infiltration may be observed, particularly in the cortico-medullary region. These overlapping features can sometimes make it challenging to distinguish ATN.[24]

NEPHROTIC SYNDROME

Proteinuria and the nephrotic syndrome are typically caused by glomerular abnormalities. This is also true for drug-induced nephrotic syndrome, where the most common lesion type is membranous glomerulonephritis. Apart from this, several cases of minimal glomerular changes have been reported, and associated focal segmental sclerosis has also been observed. Animal studies provide the majority of the evidence that the drug-induced nephrotic syndrome is immunologically mediated. Rats given intramuscular injections of gold or mercury develop a common form of membranous glomerulonephritis; in these tests, multiple autoantibodies have been identified, and the illness may be induced by a variety of delivery methods. Certain medications that can cause glomerulonephritis, including penicillamine, can also cause other autoimmune diseases. Although the exact processes of damage are unknown, three major concepts exist. First, the drugs may produce antibodies against glomerular components by acting as haptens. Secondly, Drugs may also work by attaching and altering the glomerular antigens, which would then trigger antibodies that target the altered antigens and result in the illness. Thirdly, Drugs may have an immunomodulatory impact, therefore creating an autoimmune disease. No matter the mechanism involved, it's evident that genetic factors play a major role in determining the effect. The HLA-B8 and DR3 antigens are commonly present in people with drug-induced nephrotic syndrome, for example, and a particular medication may cause distinct nephropathies in various persons.[25]

MECHANISM OF TUBULAR CELL DEATH[26]:

The key feature of the nephrotoxicity of amino glycosides is their cytotoxicity of tubules. Treatment of experimental animals with gentamicin result in necrosis and apoptosis of tubular epithelial cells. In culture, gentamicin causes both necrosis and apoptosis of these cells. The phenotype of death might depend on the concentration of the gentamicin as with other cytotoxic compounds such as hydrogen peroxide and cisplatin. It is also depending on concurrence of other predisposing factors such as specific point of renal parenchyma, degree of ischemia. Apoptosis in an ATP requiring process. When the cells ATP reverse drops, the death mode loses the typical characteristics of apoptosis and acquires those of necrosis. Hypoxia inhibits ATP production, respiration and sensitize cells to fas ligands and induce cell death. Gentamicin cytotoxicity occurs in those cells type in which the drug accumulates. In the kidney, these cells constitute the epithelial cells in the cortex, mainly in the proximal tubules of experimental animals and humans, and also in the distal and collecting ducts. A higher accumulation of gentamicin in these cells is consistent with the expression of a transporter of proteins and cat ion, mainly, the giant endocytic complex formed by megalin and cubilin, which is restricted to proximal tubules. This complex is known to transport gentamicin and in general aminoglycosides by endocytosis these drugs then traffic through the endosomal department and accumulates in mainly lysosome, endoplasmic reticulum, and golgi apparatus. Gentamicin bind to membrane phospholipids alter their metabolism and turn over, and as a consequence, cause a condition known as phospholipidis that has been observe in experimental animal and human treated with drug. Phospholipidosis corelates directly with level of toxicity.

Lysosomal phospholipidosis results from
Inhibition of A1, A2 and C1 phospholipases
Reduction in the availability of negative charge which needs for the correct function of phospholipases.

CONCLUSION

Acute renal damage is often caused by drugs, particularly in older patients with more comorbidities and more diagnostic procedures. Nephrotoxic drugs exploit common pathogenic pathways, and certain patients and clinical settings are more likely to experience drug-induced nephrotoxicity. Effective prevention requires understanding pathogenic processes, patient-related risk factors, and preventive strategies. Risk factors include age over 60, underlying renal insufficiency, diabetes, heart failure, and sepsis. Monitoring and early intervention are crucial for effective prevention. This review has outlined the the most common mechanisms of drug-induced nephrotoxicity and major drugs associated with nephrotoxicity, providing an alphabetical overview of commonly used agents and their potential renal effects. Although not exhaustive, it serves as a useful reference, underscoring the need for clinicians to consider the risk of drug-induced nephropathy when prescribing, particularly for vulnerable patients.

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