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Drug Induced Nephrotoxicity: A Mechanistic Approach

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ABSTRACT
A common site for drug-induced toxicity is the kidney. In the clinical area, where the use of nephrotoxic medications is frequently inevitable, drug-induced nephrotoxicity continues to be a significant issue. This frequently results in Current issues including acute renal damage are discussed. The toxic effects of drugs that have been found to cause nephrotoxicity are produced by one or more common pathophysiological mechanisms. Understanding the toxic mechanisms for nephrotoxicity provides useful information on the development of drugs with therapeutic benefits with reduced side effects. The discovery and development of novel biomarkers that can diagnose kidney damage earlier and more accurately are needed for effective prevention of drug-induced nephrotoxicity. Drug-induced nephrotoxicity is more prevalent in some people and in particular therapeutic settings situations. Realistic strategies to prevent the last stage of renal failure include the early diagnosis of drug-induced nephrotoxicity and the decrease of therapeutic side effects.

KEYWORDS: Nephrotoxicity, Kidney Disease, Acute Tubular Necrosis, Apoptosis

I. INTRODUCTION

The primary focus on epidemiology of nephrotoxicity is drug-induced acute kidney Injury (AKI). According to prospective cohort studies of AKI, 14 - 26% of adult populations have drug-induced nephrotoxicity.[1-3] In paediatrics, nephrotoxicity is a major concern, with 16% of inpatient AKI occurrences being mostly drug-related.[4]The kidney is an essential organ in human body, receives an abundant blood flow of 25% of cardiac output and eliminates xenobiotic and metabolic products from the blood into the urine.[5] Three processes are involved during the formation of urine in kidneys, including glomerular filtration, tubular reabsorption and tubular secretion.[6] The glomerulus filtration is essential for the kidneys to rapidly remove waste products and toxins from the blood. The renal tubules are responsible for reabsorption and secretion of substances. [7]These compartments in kidneys are naturally exposed to high concentrations of metabolites as well as drugs, therefore causing it vulnerable to drug toxicity.[8] Drug-induced nephrotoxicity is one of the major pathogenic factors of AKI, chronic kidney disease (CKD), acute renal failure (ARF) and end-stage renal disease (ESRD). It was estimated that drug-induced renal failure is accounted for 25% of all cases of acute renal failure the incident in older patients is even as high as 60%.[9, 10]Nephrotoxicity is defining as rapid deterioration in the kidney function due to toxic effect of medications and chemicals. There are various forms, and some drugs may affect renal function in more than one way. Nephrotoxicity is also known as Kidney Damage which is referred as changes in the function or structure of the kidney, even in the absence of initial changes in the GFR. [10]

Mechanism of Drug induced nephrotoxicity

Nephrotoxicity caused by drugs is a frequent side effect of several drugs and diagnostic tools. It can appear in a variety of ways, ranging from a minor, reversible injury to severe renal disease, and is encountered in both inpatient and outpatient settings. The biochemical and molecular processes of nephrotoxicity have been the subject of several investigations. We now know more about the mechanisms by which nephrotoxicants cause renal cell death as a result of these investigations and bioinformatics-based methods.[11] Renal cells undergo all three primary kinds of cell death, including apoptosis, autophagy, and necrosis. The mechanisms of apoptosis include intrinsic and extrinsic pathways, and it is known that a number of cancer treatments, antibiotics, fungus, mould, metals like mercury, and oxidants can cause the death of renal cells. In the kidney, autophagy has not gotten as much attention as apoptosis. [12]

It has traditionally been assumed that nephrotoxic damage causes necrosis, which causes

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cell death. Apoptosis has recently been discovered to be a different mechanism of nephrotoxic cell death. In order to stop the spread of cells with defective genes, apoptosis is also a crucial mechanism for removing cells with damaged genetic material. Numerous cytotoxic substances have been discovered that kill cells both through necrosis and apoptosis. The concentration and length of exposure to the harmful substances may both affect the specific death mechanism. It is interesting to find out whether apoptosis is the mechanism of cell death in nephrotoxic damage because apoptosis has been shown to kill cancer cells in the case of cisplatin and many other chemotherapeutic drugs. Strategies reduce or avoid toxicity can be created by a better understanding of the precise mechanisms causing nephrotoxic cell injury. [13]

Hemodynamically mediated kidney injury

A decrease in intraglomerular pressure leads to kidney damage caused by hemodynamic mediated kidney injury. Common mechanisms include a reduction in renal blood flow, glomerular afferent arteriole vasoconstriction, or glomerular efferent arteriole vasodilation. In response to a reduction in renal blood flow, the kidney typically works to maintain glomerular filtration rate (GFR) by dilating the afferent arteriole and constricting the efferent arteriole. The juxtaglomerular apparatus enhances renin secretion when blood flow is diminished. Angiotensinogen is converted by plasma renin to angiotensin I, which is then converted by angiotensin-converting enzyme to angiotensin II (AII). The afferent and efferent arterioles are constricted by AII, increasing the intraglomerular pressure overall. Prostaglandin E2 (PGE2) in particular, which is generated by the kidneys, causes a net dilation of the afferent arteriole, which enhances blood flow into the glomerulus. Together, these actions preserve urine production and GFR. [19]

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blocking Agents

An ACEI or angiotensin II receptor blocker (ARB)-mediated kidney damage is brought on by a reduction in glomerular capillary hydrostatic pressure sufficient to reduce glomerular ultrafiltration. [15] Angiotensin II production is reduced when ACEI medication is started, which preferentially dilates the efferent arteriole. This lowers the glomerular capillaries' hydrostatic pressure and the glomerular outflow resistance, which modifies Starling's forces across the capillaries and lowers intraglomerular pressure and GFR and then frequently results in nephrotoxicity, especially in conditions of decreased renal blood flow or effective arterial blood volume, such as "prerenal" settings where glomerular afferent arteriolar blood flow is decreased and the efferent arteriole is constricted to maintain adequate glomerular capillary hydrostatic pressure for ultrafiltration.[15,16]

Nonsteroidal Anti-Inflammatory Drugs and Selective Cyclooxygenase-2 Inhibitors

By reducing the synthesis of vasodilatory prostaglandins from arachidonic acid, NSAIDs decrease cyclooxygenase-catalysed prostaglandin production and compromise renal function. Vascular endothelial and glomerular mesangial cells in the renal cortex and medulla produce renal prostaglandins. Their effects are primarily local and result in renal vasodilation (particularly prostacyclin and PGE2).[17] They have minimal activity when there is normal renal blood flow, but when there is decreased renal blood flow, their synthesis increases and they protect the kidneys from ischemia and hypoxia by inhibiting the angiotensin II, norepinephrine, endothelin, and vasopressin-induced renal vasoconstriction. Administration of NSAIDs in the setting of renal ischemia and compensatory increased prostaglandin activity may thus alter the balance of activity between renal vasoconstrictors and vasodilators. [10, 15] This leaves the activity of renal vasoconstrictors unopposed and promotes renal ischemia with loss of glomerular filtration. Combined NSAID or COX-2 inhibitor and ACEI or ARB therapy is also a concern and should be avoided in high risk patients. [18]

Calcineurin Inhibitors

The effectiveness of solid organ transplantation has been significantly improved by the calcineurin inhibitors cyclosporine and tacrolimus. However, nephrotoxicity continues to be a significant dose-limiting side effect of both medications.[19] Acute Hemodynamically-mediated kidney injury is the main cause of nephrotoxicity, despite reports of delayed chronic interstitial nephritis.[15, 20] While renal function rapidly improves after dose reduction, an initial dose-related hemodynamic mechanism is probably at effect during the first few months of therapy. It is possible that increased activity of thromboxane A2, endothelin, and the sympathetic nervous system, or

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decreased activity of nitric oxide or prostacyclin, is the cause of the reversible vasoconstriction and damage to the glomerular afferent arterioles.[21,22] Vasoconstriction due to increased renin angiotensin system activity may also contribute.Inversely, the main factors that appear to cause cyclosporine-induced chronic kidney disease include increased extracellular matrix synthesis, chronic renal ischemia, and renal arteriolar hyalinization.[22] Increased age, greater initial cyclosporine doses or serum concentrations, renal graft rejection, hypotension, infection, and concurrent use of nephrotoxic medications such aminoglycosides, amphotericin B, acyclovir, NSAIDs, and radio contrast agents are all risk factors.[23]

Acute Tubular Necrosis (ATN)

Direct toxic or ischemia pharmacological effects may result in damage to renal tubular epithelial cells. Acute tubular necrosis is the medical term for damage that most frequently affects the proximal and distal tubular epithelia and appears as cellular degeneration from basement membranes. [23] In osmotic nephrosis, swelling and vacuolization of proximal tubular cells may also be seen. The most typical inpatient manifestation of drug-induced nephrotoxicity is ATN. Aminoglycosides, radiocontrast media, cisplatin, amphotericin B, foscarnet, and osmotically active substances such immunoglobulin, dextrans, and mannitol are the primary causes linked to renal tubular epithelial cell injury. [10, 15]

Aminoglycosides

Since not all acute kidney injury that occurs during a course of therapy is caused by the aminoglycoside, aminoglycoside-associated nephropathy needs to be carefully assessed. Identification of the underlying cause or illness is frequently complicated by dehydration, sepsis, ischemia, and other nephrotoxic medications. ATN has been reported in 5–15% of patients receiving aminoglycoside therapy.[25]Patients on aminoglycosides typically have a decrease in GFR due to proximal tubular epithelial cell injury that causes tubular blockage and glomerular filtrate backleakage across the injured tubular epithelium.[26,27] The ability of cationic charge to enhance the binding of filtered aminoglycosides to the luminal membranes of renal tubular epithelial cells, followed by intracellular transit and concentration in lysosomes, may be connected to toxicity.[10,28]Reduced activity of membrane-bound enzymes, such as Na+-K+- ATPase, dipeptidyl peptidase IV, and neutral amino peptidase, can be caused by the release of lysosomal enzymes into the cytosol, production of reactive oxygen species, altered cellular metabolism, and changes in cell membrane fluidity. These factors can all contribute to cellular dysfunction and death. [25]

Radio contrast media

The third most common source of ATN that occurs in hospitals is the use of radiographic contrast agents like Iodine, Barium sulphate. [29]As the number of risk factors rises, the risk of contrast-induced nephrotoxicity increases, and diabetes individuals with CKD are at the highest risk. [31, 32] direct tubular damage and/or renal ischemia appear to be the etiology of contrast-induced nephrotoxicity. The frequent occurrence of renal tubular enzymuria and the biopsy results of proximal tubular epithelial cell vacuolization and acute tubular necrosis point to direct tubular toxicity. In contrast to these findings, it is frequently observed that renal tubular function is intact because of low urine salt concentrations and sodium fractional excretion. Renal ischemia may be caused by humoral factors such as prostaglandins, adenosine, atrial natriuretic peptide, nitric oxide, and endothelin that are out of balance, as well as systemic hypotension carried on by a contrast injection.[33]

Platin containing compound

Platin-containing compounds are important chemotherapeutic agents that frequently cause ATN. The incidence of cisplatin nephrotoxicity is 6–13%, down from the much higher rate of >50% observed in the 1980s. The total dose limit and decreased administration rate are the main causes of this decrease in toxicity. In high risk patients, carboplatin is typically recommended over cisplatin due to its decreased incidence of nephrotoxicity.[35]Plasmin-containing substances may bind to proximal tubular cellular proteins and sulfhydryl groups, impair cell energy production, alter cell enzyme function, and uncouple oxidative phosphorylation. These effects may cause acute injury to the proximal tubules. A progressive decrease of glomerular filtration and poor distal tubular function follow the initial proximal tubular injury. Renalbiopsies generally show sparing of glomeruli with necrosis of proximal and distaltubules and collecting ducts. Risk factors include increased age,

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dehydration,renal irradiation, concurrent use of aminoglycoside antibiotics. [36, 37]

Amphotericin B

ATN caused by amphotericin B can occur at cumulative doses as low as 300–400 mg, and when they reach 4 g, incidence rises to 80%. After the ingestion of 2-3 g, toxicity typically shows up as renal tubular potassium, sodium, and magnesium depletion, decreased urine concentration, and distal renal tubular acidosis as a result of hydrogen ions leaking back out of the tubular lumen. Direct tubular epithelial cell toxicity, increased tubular permeability, necrosis, arterial vasoconstriction, and ischemia injury are some of the processes of kidney damage. [37] Amphotericin B infusions given quickly may become more toxic. Overall, renal medullary tubular epithelial cell necrosis and kidney damage are the combined impacts of higher cellular energy and oxygen demand due to enhanced cell membrane permeability and lower cellular oxygen delivery due to renal vasoconstriction.[38,39]Risk factors include CKD, higher average daily doses, volume depletion, and concomitant administration of diuretics and other nephrotoxins. Rapid infusions of amphotericin B have the potential to increase toxicity. [39]

Osmotic Nephrosis

There are a number of medications, such as mannitol, low-molecular-weight dextran, radiographic contrast agents, or drug carriers like sucrose and propylene glycol, that have been linked to the vacuolization, swelling, and ultimately necrosis of proximal tubular epithelial cells with a decline in renal function. The hypertonic and osmotically active properties of these drugs could be the cause of the deterioration in renal function. [41]Intravenous immunoglobulin solutions contain hyperosmolar sucrose, which can lead to acute kidney injury and osmotic nephrosis. Generally, these adverse effects go away shortly after the medication is stopped. Rarely, mannitol may result in proximal tubular cell vacuolization on biopsy and oligo-anuric kidney damage. As a result of increased solute transport to the macula densa and subsequent tubuloglomerular feedback, it may potentially directly cause renal vasoconstriction or create an osmotic diuresis, both of which result in decreased renal blood flow. [42]

Acute allergic intestinal disease

Renal tubules and the interstitial tissue around them are both affected by tubulointerstitial disorders. [41] Up to 3% of all instances of AKI have acute allergic interstitial nephritis (AIN) as their underlying aetiology. AIN is characterized as a diffuse or focal interstitial infiltrate of lymphocytes, plasma cells, eosinophil's, and occasional polymorph nuclear neutrophils. With drug-induced AIN, granulomas and tubular epithelial cell necrosis are very typical. An allergic hypersensitive response is the aetiology. Occasionally, the presence of circulating antibodies against drug hapten-tubular basement membrane complexes, low serum complement levels, and the deposition of IgG and complement in the tubular basement membrane point to a humoral antibody-mediated mechanism. AIN has been linked to a number of medications, including numerous antimicrobials, analgesics, diuretics, and gastrointestinal medicines. [41, 42]

β-Lactams

Although methicillin-induced allergic interstitial nephritis served as the model for AIN, it is now known that almost all β-lactam antibiotics are linked to AIN. Signs of AIN include fever, maculopapular rash,and eosinophilia, associated with renal findings of pyuria and haematuria, low-levelproteinuria, and oliguria. Systemic hypersensitivity findings of fever, rash, eosinophilia,and eosinophiluria suggest the diagnosis, but this group of findings is notconsistently reliable since one or more are frequently absent. [41]Anaemia, leucocytosis,and elevated IgE concentrations may be present. Tubular dysfunction may bemanifested by acidosis, hyperkalaemia, salt wasting, and concentrating defects. Given that lymphocytes, monocytes, and eosinophils make up the majority of the interstitial infiltrate, B-lactam-induced AIN is most likely an immunological T cell-mediated reaction. [42]

Chronic Interstitial Nephritis

Lithium

Only a small number of medications, including lithium, have been linked to chronic interstitial nephritis, a gradual and permanent damage. There have been several renal tubular lesions linked to lithium medication. Historically, the most important question regarding lithiumuse was whether long-term therapy, with lithium concentrations maintained in the therapeutic range, caused chronic Tubulointerstitial nephritis with kidney disease. It is now known that long-term lithium therapy is associated with nephrotoxicity in the absence of episodes of acute intoxication, and

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that the duration of therapy and the cumulative dose are the major determinants of toxicity. Lithium induced AKI occurs predominantly during episodes of acute lithium intoxication. Moderate proteinuria, a few red and white blood cells, and granular casts may all be visible on a urine analysis. After lithium concentrations are brought down to the therapeutic range, renal function often returns to the pre-treatment levels. The most typical biopsy results for chronic tubulointerstitial nephritis linked to lithium include interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Since the length of medication shows a positive correlation with the decline in GFR, the aetiology may include cumulative direct lithium toxicity. Elevated lithium concentrations, particularly when coupled with dehydration, are the main risk factor for AKI. [41, 44]

Cyclosporine

The endoplasmic reticulum is stressed by Cyclosporine, which also increases the formation of reactive oxygen species in the mitochondria. This changes the redox equilibrium, which leads to lipid peroxidation and, ultimately, nephrotoxicity. Delayed chronic interstitial nephritis has been reported after 6–12 months of therapy and can result in irreversible kidney disease. [21] Typical biopsy findings include arteriolar hyalinosis, glomerular sclerosis, and a striped pattern of tubulointerstitial fibrosis. The pathogenesis appears to involve sustained renal arteriolar endothelial cell injury which ultimately results in chronic renal ischemia because of increased release of endothelin-1, decreased production of nitric acid, and increased expression of transforming growth factor-β. Nephrotoxicity occurs even during low-dosage therapy and has been shown to be dose dependent in certain analyses, but not all. [22, 23]

Nephrocalcinosis

Oral Sodium Phosphate Solution

Nephrocalcinosis is a clinical-pathologic disorder characterised by significant calcium phosphate deposition and tubular calcification as a result of substantial renal tubular precipitation. However, in recent years, a number of recorded occurrences of nephrocalcinosis in patients without hypercalcemia have implicated the bowel-cleansing medication oral sodium phosphate solution (OSPS) as the underlying cause. [45] Since the pathophysiology of OSPS-induced nephrocalcinosis is due to increased phosphate intake rather than hypercalcemia, the term "acute phosphate nephropathy" has been created expressly to describe the condition. Acute kidney injury frequently develops in patient's days to months following OSPS exposure. The telltale sign of OSPS-induced nephrocalcinosis is calcium phosphate in the distal tubules and collecting ducts without glomerular or vascular damage. [46]

Papillary Necrosis

Analgesics

A kind of chronic tubulointerstitial nephritis called papillary necrosis is characterised by the necrosis of the renal papillae. [41] A third of all cases of papillary necrosis are caused by the use of analgesics. The development of analgesic nephropathy has also been linked to the use of recent analgesics, particularly aspirin, acetaminophen, and NSAIDs, despite the fact that chronic excessive use of combination analgesics containing phenacetin was initially thought to be the primary cause. [43]9% of dialysis patients have stated that analgesic nephropathy is the main cause of ESRD. Uncertain mechanisms because analgesic nephropathy. Due to accumulating toxic metabolites, limited blood flow, and compromised cellular energy production, the renal lesion starts in the papillary tip. The initial factor that produces toxicity through methods similar to acetaminophen hepatotoxicity appears to be the conversion of phenacetin to acetaminophen, which is then oxidised to harmful free radicals that are concentrated in the papilla. The availability of reduced glutathione prevents toxicity. Salicylates, however, reduce renal glutathione, which facilitates acetaminophen and phenacetin toxicity. [47, 48]

Glomerulus Disease

Drug-induced minimal change glomerular damage, which most typically occurs during NSAID therapy, is frequently accompanied by interstitial nephritis and nephrotic range proteinuria (i.e. > 3.5 g/day). Lithium, phenytoin, ampicillin, and rifampin have also been linked to focal segmental glomerulosclerosis (FSGS), which is marked by patchy glomerular sclerosis along with interstitial inflammation and fibrosis. HIV-related glomerulosclerosis can be separated from heroin nephropathy by tubuloreticular features in endothelial cells, a more rapid progression, and a worse prognosis. [49, 50]Pamidronate, a bisphosphonate often used to treat hypercalcemia caused on by cancer, has also been linked to the emergence of collapsing FSGS. Patients at the biggest risk are those receiving either large doses or

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prolonged therapy. Although uncommon, Membranous Nephropathy is characterised by immune complex formation along glomerular capillary loops and has traditionally been linked to the use of NSAIDs, penicillamine, and gold therapy. Damage to the proximal tubule epithelium may result in the release of antigens, the production of antibodies, and the deposition of glomerular immune complexes. [51]

Renal Vasculitis & Thrombosis

Numerous drugs have been associated with the development of vasculitis. For example: propylthiouracil and hydralazine is associated with cutaneous, renal, and pulmonary vascultis; allopurinol is associated with cutaneous, renal, and hepatic vasculitis; and isotretinoin is associated with cutaneous, renal, pulmonary and gastrointestinal vascultis.[52] Systemic polyarteritis nodosa, a vasculitis with involvement of small and medium sized renal arteries, has been described following minocycline use. Patients may present with haematuria, proteinuria, reduced renal function, and hypertension. [53]Hydralazine, propylthiouracil, allopurinol, and penicillamine have been implicated in the development of antineutrophil cytoplasmic antibody (ANCA)-positive Vasculitis. Numerous medications, including mitomycin C, oral contraceptive agents,cyclosporine, tacrolimus, muromonab-CD3, antineoplastic agents, interferon, ticlopidine,clopidogrel, and quinine can cause a thrombotic microangiopathy (haemolyticuremic syndrome or thrombotic thrombocytopenic purpurea) manifested byendothelial proliferation and thrombus formation in the renal and central nervoussystem vasculature. Systemicendothelial damage with multisystem organ failure has occurred. [54] Kidney injury can be severe and irreversible, although corticosteroids, antiplatelet agents, vincristine, plasma exchange, plasmapheresis, and high-dose intravenous IgG have each induced clinical improvement. [55, 56]

II. CONCLUSION

Nowadays, vast amount of drugs are being used globally. The administration of some drugs is an absolute necessity for Health related reasons, but others are being overused. These medications may induce Nephrotoxicity. Kidney are frequently exposed to drugs or toxic metabolites and also this is a common site for Drug toxicity. These Drugs induced toxicity is closely associated with Acute Kidney injury and chronic kidney Disease. In this review, various types of Nephrotoxicity and their associated drugs have been mentioned with their mechanisms which is provide us relevant information to newer pharmacotherapies and similar drug classes. Also it can be useful to study the development of nephrotoxicity and may helpful to overcome side effects of toxicity.

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