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A REVIEW ON DRUG INDUCED NEPHROTOXICITY

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ABSTRACT
Drug-induced nephrotoxicity is influenced by various risk factors, such as drug overdose, drug-drug interactions, and drug-related side effects. Given the continued necessity of utilizing some nephrotoxic medications within the clinical context, it is imperative to acquire a comprehensive grasp of the pathogenic mechanisms underlying their nephrotoxic effects. This knowledge is essential in order to mitigate the occurrence of renal injury. A comprehensive understanding of risk factors linked to particular patient populations and specific drug classes, in conjunction with prompt identification, therapeutic drug monitoring with dosage modifications, and timely implementation of prospective interventions, are crucial for the prevention and improved management of these conditions. The majority of cases of drug-induced renal toxicity can be reversed if detected and treated promptly in the early stages, thereby preventing progression to end-stage renal failure. This study provides a comprehensive overview of various forms of renal failure, encompassing its diagnosis, therapy, risk factors, and preventive measures pertaining to drug-induced nephrotoxicity.

Keywords: Nephrotoxicity, Acute renal failure, Chronic renal failure, Biomarkers

INTRODUCTION
Nephrotoxicity is a term used to describe renal injury resulting from the direct or indirect effects of drugs. Common clinical manifestations of nephrotoxicity include acute renal failure, tubulopathies, and glomerulopathies. Several substances are frequently linked to the acute decrease in glomerular filtration rate. These drugs include anti-inflammatory medications, antibiotics including vancomycin and aminoglycosides, as well as chemotherapeutic agents such as cisplatin and methotrexate.[1]
Drug-induced nephrotoxicity refers to the occurrence of renal injury resulting from the direct or indirect effects of medicine. The clinical manifestation ranges from a decreased glomerular filtration rate (GFR) that can be either acute or chronic, to nephrotic syndrome and hydro electrolytic diseases (HED) that are associated with damage to the glomeruli and tubules, respectively. In the context of epidemiology, the majority of studies typically focus just on the elevation of creatinine levels, so impeding a comprehensive assessment of the actual extent of the issue.[2]
Drug-induced nephrotoxicity is one of the major pathogenic factors of acute kidney injury (AKI), chronic kidney disease (CKD), acute renal failure (ARF) and end-stage renal disease (ESRD).[3] AKI is a very common diagnosis, present in up to 60% of critical patients, and its third main cause is drug toxicity. Drug-induced renal injury may be resulted from cumulative dose-dependent toxicity or idiosyncratic dose-independent toxicity at any time during therapy.[4]

ACUTE RENAL FAILURE:
Prerenal Causes: ARF, as defined by an increase in serum creatinine of at least 0.5 mg/dL over 24 hours, can result from many medications via different mechanisms. Medications that cause

intravascular volume depletion or vasoconstriction present with a prerenal type of ARF.[5] Diuretics, alone or in combination with other antihypertensives, are frequently associated with prerenal azotemia.[6]

CHRONIC RENAL FAILURE: The extended utilization of analgesic medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and aspirin, particularly when used in combination, has the potential to result in the development of chronic interstitial nephritis, papillary necrosis, and chronic renal failure. The occurrence of end-stage renal disease in the United States is linked to analgesic-induced nephropathy in approximately 1% to 3% of patients.[7,8]

ELECTROLYTE AND ACID-BASE ABNORMALITIES: Many medications can cause subtle changes in renal function without necessarily raising the BUN and serum creatinine. These changes in renal function may present as electrolyte imbalances or as acid-base abnormalities. For instance, hypomagnesemia or hypokalemia can be seen with both aminoglycoside and cisplatin therapy. Diuretics, both of the thiazide and loop types, can also present with hypomagnesemia, hypokalemia etc.[9]

PSEUDO RENAL FAILURE: Some medications such as trimethoprim and cimetidine can mimic ARF with an increase in the serum creatinine via competitive inhibition for tubular secretion of creatinine. Other medications such as cefoxitin, levodopa, and flucytosine can interfere with laboratory creatinine determinations. The increases in serum creatinine in these instances, however, are mild, not progressive, and not associated with urinary sediment abnormalities.[10] Steroids and tetracycline are associated with a hypercatabolic response, and increase blood urea nitrogen in a manner that is disproportionate to their effect on serum creatinine.[11]

BIOMARKERS FOR DIAGNOSIS OF DRUG-INDUCED NEPHROTOXICITY

Evaluation of kidney function is crucial for a number of clinical situations. GFR is the best indicator to measure the renal function and determine the stages of kidney disease.[12] However, current approaches for assessing kidney function are time-consuming and cumbersome, therefore, delay definitive diagnosis. Serum creatinine and blood urea nitrogen are the routinely used method to measure renal function because these metabolic waste products are normally excreted by kidneys but retained in human body with injured kidney.

MANAGEMENT OF DRUG-INDUCED NEPHROTOXICITY

The management of drug-induced nephrotoxicity often involves hospitalization of the patients.[13] The overall goal is renal perfusion to ensure an adequate supply of blood/oxygen to the kidneys and restoration of its normal function in a timely manner. Failure to implement appropriate measures at an early stage may eventually lead to ESRD. Some of the steps that are taken to ensure an adequate supply of oxygen/blood and careful management of nephrotoxicity are described below[14,15]

- Maintain Blood Volume and Hemodynamic Stability
- Nutrition and Glycemic Control
- Discontinuation of Nephrotoxic Drugs and Use of Diuretics or Vasodilators
- Renal Replacement Therapy

PREVENTION STRATEGIES OF DRUG-INDUCED NEPHROTOXICITY IN PRE-CLINIC AND CLINIC

In order to minimize the potential harm of drug-induced nephrotoxicity, various practical measures have been explored within clinical settings. These include refraining from the use of drugs known to be nephrotoxic, closely monitoring for signs of nephrotoxicity, administering the lowest effective dosage whenever feasible, identifying potential risk factors, and implementing personalized medicine approaches tailored to specific populations. Nevertheless, certain over-the-counter (OTC) medications and other pharmaceuticals administered to patients outside of healthcare facilities pose challenges in terms of monitoring and regulation. Hence, it is imperative to closely monitor the nephrotoxic effects of drugs in the preclinical phase.[16]

Clinical Monitor of Nephrotoxicity: Intensive clinical monitor of drug-induced nephrotoxicity is crucial in clinical practice. Firstly, old patients (>60 age), infants and other high-risk patients must be identified and extensive monitor of kidney function should be conducted. Secondly the drug dosage and drug combinational treatment should be carefully considered for different individuals.[17]
Adequate attention should be also devoted to ensure valid hydration before and during therapy with potential nephrotoxins, use equally effective non-nephrotoxic drugs whenever possible, monitoring drug levels to use the correct dose.[18] Improving overall quality of prescriptions may also contribute to reducing risks. In a study of hospitalized patients with at least 0.5 mg/dl increase in serum creatinine receiving a nephrotoxic or kidney cleared medication, failure to adjust dosing for kidney function and persistent use of potentially nephrotoxic agents during AKI accounted for 63% and 28% of all recorded adverse drug events.[19]
Prediction of the potential nephrotoxicity during drug development is the first step to decrease the risk of toxic effects. In vitro models such as human cells culture-based models, three dimensional (3D) models and microfluidic models as well as in vivo animal models provide valuable tools for pre-clinical screening during drug nephrotoxicity studies.[16]

RISK FACTORS

Patient Related: Nonmodifiable patient characteristics are important factors in developing renal injuries. Underlying risk factors common to all nephrotoxic drugs, such as old age (>60 years) or renal insufficiency in certain disease states, which can lead to changes in total body water and/or body mass, can contribute to adverse drug reactions including nephrotoxicity. Also, such populations are more prone to have a lower glomerular filtration rate (GFR) and hypoalbuminemia, leading to higher free drug concentrations and overexposure to potentially renal toxins.[20] Structural as well as functional changes in the kidney and its surrounding vasculature in the elderly make them more vulnerable to developing nephrotoxicity. There are conflicting reports about the influence of race and genetic variation, as well as whether men are at greater risk of developing acute renal failure compared with women.[21] The risk of acute renal failure increases with the presence of each additional risk factor.[22,23]
Drug related: The first stage in the development of drug-induced kidney injury involves being exposed to potential nephrotoxic substances. A significant portion of these substances are accessible to the general populace in the form of prescribed medications or non-prescription agents. Nephrotoxicity can be induced by various medication classes, such as anti-inflammatory, antibacterial, antiretroviral, and chemotherapeutic drugs, among others. Various mechanisms can lead to kidney harm caused by medications. However, the primary factors influencing drug toxicity are likely the dosage and length of treatment. This is evident in drugs that contribute to the formation of crystals or deposits inside the renal tubules, as well as in cases of interstitial nephritis.[24,25]

DISCUSSION

Drug-induced nephrotoxicity is one of the major pathogenic factors of acute kidney injury (AKI), chronic kidney disease (CKD), acute renal failure (ARF) and end-stage renal disease (ESRD). It can be influenced by various risk factors, such as drug overdose, drug-drug interactions, and drug-related side effects.[4] In recent times, there has been the identification of some biomarkers that have the potential to offer valuable insights for the early detection of nephrotoxicity. Biomarkers play a crucial role in the advancement of novel drug development due to their ability to facilitate the early detection of drug-induced nephrotoxicity based on previous studies.[12] This early diagnosis is helpful as it can help mitigate the economic costs incurred during the safety evaluation of new medications. In order to minimize the potential harm of drug-induced nephrotoxicity, various practical measures have been explored within clinical settings. These include refraining from the use of drugs known to be nephrotoxic, closely monitoring for signs of nephrotoxicity, administering the lowest effective dosage whenever feasible, identifying potential risk factors, and implementing personalized medicine approaches tailored to specific populations.[16]

CONCLUSION

The occurrence of drug-induced nephrotoxicity is strongly linked to the development of acute kidney injury (AKI) and chronic kidney disease (CKD). While there is a wide range of medicines that can cause nephrotoxicity, it is not feasible to provide an exhaustive list due to the large number of drugs now in circulation. Biomarkers play a crucial role in the advancement of new drug development, as their utilisation in the early detection of drug-induced nephrotoxicity offers considerable benefits in terms of minimising economic losses incurred during the safety evaluation of novel pharmaceuticals. Hence, there is an imminent requirement for the advancement of highly sensitive and specific biomarkers to assess nephrotoxicity, as well as the development of more efficient and user-friendly techniques for biomarker detection in the future. In addition, it is imperative to develop more efficient biomimetic models, such as in vitro and in vivo models, in order to anticipate and mitigate potential nephrotoxicity during the process of drug development. These models will aid in the evaluation and reduction of drug-induced toxicity at an early stage. Prior knowledge of risk factors, early diagnosis, and treatments in a timely manner are essential to better manage drug-induced kidney injury. Most episodes are thought to be reversible only if diagnosed at an early stage and treated promptly; hence, early diagnosis is the need of the hour.

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