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Chapter

Nephrotoxic Effects of Drugs

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Abstract

Drug-induced nephrotoxicity is a renal dysfunction that occurs as a result of exposure to nephrotoxic drugs. It is a common problem in certain clinical situations such as underlying renal dysfunction, cardiovascular disease, diabetes, and sepsis. Drugs can cause mild to moderate nephrotoxic problems such as intrarenal obstruction, interstitial nephritis, nephrotic syndrome, acid-base and fluid-electrolyte disturbances, alteration in intraglomerular hemodynamics, inflammatory changes in renal tubular cells, tubulointerstitial disease, and renal scarring leading to acute or chronic kidney injury. Therefore, early detection of adverse effects of drugs as well as the clinical history of the patient, basic renal functions, drug-related risk factors, and nephrotoxic drug combinations must be well known in order to prevent drug-induced nephrotoxicity and progression to end-stage renal disease.

Keywords: nephrotoxicity, drugs, drug interaction, acute kidney injury, chronic kidney injury, prevention strategies, nephrotoxicity biomarkers

1. Introduction

Acute kidney injury is the deterioration of the renal function over hours or days, resulting in the accumulation of toxic wastes and the loss of internal homeostasis. It can be caused by numerous etiologies [1, 2], and medications are a relatively common cause of kidney injury among these injuries [3]. Drug-induced nephrotoxicity is a renal dysfunction that occurs as a result of direct or indirect exposure to nephrotoxic prescribed drugs, over-the-counter products, diagnostic agents, or alternative/complementary products (herbal remedies, natural products, nutritional supplements) that are widely available at most health food stores [3, 4]. Drug-induced nephrotoxicity is an extremely common condition and is responsible for a variety of pathological effects on the kidneys [4]. Nephrotoxicity most commonly affects tubulointerstitial compartment and manifests either acute tubular injury (ATI) or acute interstitial nephritis (AIN). There is a growing incidence of drug-induced glomerular disease, including direct cellular injury and immune-mediated injury [5]. However, kidney disease does not develop in all patients exposed to the various potential nephrotoxins [3]. The nephrotoxicity of medications, drugs, or other ingested substances is a complicated process that involves a combination of factors.

Potential nephrotoxic effect of the drug, comorbid diseases or conditions (underlying renal dysfunction, cardiovascular disease, diabetes, immunologic diseases, sepsis, etc.), genetic determinants of drug metabolism and transport, immune response genes, drug dose and duration of therapy, drug characteristics (solubility, structure and charge), combinations of potential nephrotoxic drugs,

urine pH, metabolic disturbances, older age (>65 year), and female sex are the common risk factors for drug-induced nephrotoxicity [1–5].

2. Preventive measures of drug-induced nephropathy

Basic renal functions should be evaluated and patient's renal functions should be considered when prescribing a new drug.

Dosage adjustments of the drugs should be done according to the patient's basic renal functions.

Risk factors for nephrotoxicity must be corrected before initiation of therapy.

Nephrotoxic drug combination should be avoided.

Adequate hydration before and during therapy must be ensured.

Whenever possible, equally effective nonnephrotoxic drugs should be used [4].

3. Biomarkers of drug-induced kidney injury

Early detection of drug-induced kidney injury is vital. Traditional biomarkers such as creatinine (Cr) and blood urea nitrogen (BUN) are insensitive for monitoring renal safety. Thus, new biomarkers have been investigated for accurate diagnosis, risk assessment, adopting therapy, and improvement of clinical outcome. [4, 6–9] Serum Cr can raise in prerenal azotemia without tubular injury, and some factors such as muscle mass, total body weight, fluid status, age, gender, race, and drugs influence serum Cr levels [8]. There are novel biomarkers that are more sensitive and can detect renal damage earlier than serum BUN and Cr levels [4, 6–9]. It is clear that which marker indicates kidney damage, but it is not yet clear when they should be measured. Also it is not clear if these biomarkers should be used for clinical decision-making or what should be done when the levels are elevated. Further studies are required for the routine clinical use of these biomarkers [8]. **Table 1** lists common novel biomarkers that are under investigation.

3.1 Neutrophil gelatinase-associated lipocalin (NGAL)

NGAL is an acute phase reactant, and it can raise in inflammatory conditions. It is expressed by tubular epithelial cells in response to injury and tubulointerstitial damage. It can be measured in both plasma and urine [8–13], but for early detection of acute kidney injury (AKI), increase in urine NGAL is more specific than increase in plasma NGAL [9]. Baseline renal functions, severity of AKI, and age influence the level of NGAL. Studies showed that plasma and urine NGAL levels rise 2 hours after the injury; thus, it is the strongest predictor of AKI [8, 9]. It is more sensitive in ischemic and toxic (tacrolimus, cisplatin, cyclosporine A, radiographic contrast agent) AKI. [9] NGAL levels can be a predictor of clinical outcomes of AKI (need for dialysis and mortality) [9, 11] and progression of chronic kidney disease (CKD) in adults [8, 10, 12, 13]. Urine excretion of NGAL may be increased by albuminuria [9].

3.2 Cystatin-C (Cys-C)

Cys-C is a protein that synthesized in all nucleated cells. It is freely filtered in the glomerulus and reabsorbed and catabolized completely in the proximal tubules without tubular secretion. It is an alternative parameter of serum Cr in the measurement of renal function [8–11, 13]. Serum Cys-C levels are not influenced

Biomarker	Source	Region specificity	Clinical application
NGAL	Plasma/urine	Proximal tubule/distal tubule	AKI/CKD
Cyclophilins	Urine	Glomerulus/proximal tubule	AKI
KIM-1	Urine	Proximal tubule	AKI/CKD
IL-18	Urine	Proximal tubule	AKI
L-FABP	Urine	Proximal tubule	AKI
H-FABP	Plasma/urine	Distal tubule	AKI
NAG	Urine	Proximal tubule	AKI
α-GST	Urine	Proximal tubule	AKI
π-GST	Urine	Distal tubule	AKI
γ-GT	Urine	Proximal tubule	AKI
Low-molecular-weight proteins			
Cystatin-C	Urine	Glomerulus/proximal tubule	AKI
α_1-Microglobulin	Urine	Proximal tubule/glomerulus	AKI/CKD
β_2-Microglobulin	Urine	Proximal tubule	AKI/CKD
RBP	Urine	Proximal tubule	AKI
Cell cycle arrest proteins			
IGFBP-7	Urine	Proximal tubule	AKI
TIMP-2	Urine	Proximal tubule	AKI
Clusterin	Urine	Proximal tubule/distal tubule	AKI/CKD
TFF-3	Urine	Proximal tubule/distal tubule	AKI/CKD

Table 1.
Summary of novel nephrotoxicity biomarkers.

by gender, age, total body weight, muscle mass, or race, but tubular reabsorption is decreased by marked albuminuria [9–11]. It is thought to be the best biomarker for early kidney injury and more reliable marker of renal function [8, 10, 11].

3.3 Cyclophilins

They are structural proteins and measured in urine and plasma. Elevated levels of cyclophilins indicate AKI [11].

3.4 Kidney injury molecule-1 (KIM-1)

KIM-1 is a transmembrane glycoprotein. After ischemic or toxic injury, its levels elevate and it helps to distinguish acute tubular nephritis (ATN) from prerenal azotemia and CKD. Elevated urine KIM-1 levels are highly specific for kidney injury, because it is only expressed in injured kidney [8–13]. Some studies suggest KIM-1 as an indicator of AKI transition to CKD, because high levels of KIM-1 are maintained during CKD progression [12].

3.5 Interleukin-18 (IL-18)

It is also known as interferon-γ (IFN-γ)-inducing factor and its urinary levels rise in ischemic and toxic AKI [9]. It predicts renal parenchymal injury [10]. Its

levels are higher in patients with ATN. Increased urinary levels of IL-18 are a predictor of poor outcome such as death and the need for short-term dialysis [8, 9]. According to some studies, urine IL-18 levels increase in contrast-induced AKI [12], 6–12 hours after administration of the radiocontrast agent [9].

3.6 Cell cycle arrest biomarkers

Insulin-like growth factor-binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinase-2 (TIMP-2) are the two biomarkers included in this group. They are measured in urine and can be used for risk stratification of AKI [8, 9]. According to some studies, the most important advantage of these biomarkers is that their levels are not affected by comorbid diseases such as CKD, diabetes, and sepsis [8].

3.7 Liver-type fatty acid-binding protein (L-FABP)

FABP is a cytoplasmic protein found in all tissues with fatty acid metabolism. In kidneys, liver-type (in proximal tubule) and heart-type (in distal tubule) FABP present. Studies showed that urinary L-FABP is a useful biomarker in ischemic and toxic (especially cisplatin toxicity and contrast-induced nephropathy) AKI [9, 10, 12]. Elevated urinary and plasma H-FABP levels are indicator of distal tubular injury [10].

3.8 N-acetyl-beta-D glucosaminidase (NAG)

It is an enzyme produced by the proximal tubular cells. It can be found in the urine in very small amounts in healthy people. It cannot be filtered by glomerulus; thus, elevated levels of urine NAG indicate tubular damage [9, 10, 12]. Studies showed that NAG is a useful, sensitive, and early biomarker of contrast-induced AKI and high urinary levels correlate with poor outcome [9]. Also, high urinary NAG levels have been showed to be an indicator of clinical and subclinical tubular damage after chemotherapy [10] and are a sensitive biomarker of acute oxidative stress [11].

3.9 Midkine

It is a heparin-binding growth factor. Although not studied well, it may increase in contrast-induced AKI [9].

3.10 α- and π-glutathione S-transferase (α-GST, π-GST)

They are cytosolic, microsomal, and membrane-bound enzymes. They are detoxification enzymes that present in kidney and many other organs. Some studies showed elevation in urine α-GST indicating epithelial necrosis in the proximal tubules and π-GST indicating epithelial necrosis in the distal tubules [9–11]. α-GST is thought to be a biomarker of proximal tubular necrosis of cisplatin-induced injury. α-GST and KIM-1 are sensitive biomarkers for predicting polymyxin-induced nephrotoxicity [10].

3.11 γ-Glutamil transpeptidase (γGT) and alkaline phosphatase (AP)

They are two enzymes that may increase in urine in proximal tubular epithelial damage [9–11]. Some studies showed increased levels of γGT, 24 hours after

contrast administration [9], and some showed that it may be a sensitive biomarker of acute paracetamol nephrotoxicity [11].

Alanine amino peptidase (AAP), lactate dehydrogenase (LDH), β-galactosidase, β-glucuronidase, and leucine aminopeptidase are the other enzymes that are used for nephrotoxicity biomarkers [10, 11].

3.12 β-2-Microglobulin

It is a low-molecular-weight protein. It is normally found in urine but increases in tubular injury secondary to antibiotic, analgesic, solvent, heavy metal, or pesticide poisoning. In these conditions, it has been proved to be a sensitive biomarker of renal tubular damage [9–13]. But it rapidly degrades in room temperature and urine pH < 6; therefore, its utility as a urinary biomarker is limited [12].

3.13 α-1-Microglobulin

It is a low-molecular-weight protein, and elevated urinary levels can be used as a biomarker of tubular injury [10–12]. It is resistant to pH changes; thus, it is a sensitive biomarker of proximal tubular dysfunction [12].

3.14 Retinol-binding protein (RBP)

It is a low-molecular-weight protein that functions in vitamin A transportation from the liver to other tissues. It is a sensitive biomarker in proximal tubular damage [9–11].

3.15 MicroRNA (miRNA)

Although not demonstrated well, some subgroups of miRNA (miRNA-30a, -30c, and -30e) may rise in serum and urine in the states of contrast-induced AKI [9].

3.16 Clusterin

It is a glycoprotein and may be used as a biomarker for cisplatin-induced nephrotoxicity [10]. Urinary clusterin levels may increase following drug-induced nephrotoxicity [13].

3.17 Trefoil factor 3 (TFF3)

It is another new biomarker of nephrotoxicity that is mainly expressed in kidneys. Studies showed marked decrease in urinary TFF3 after nephrotoxic AKI [13].

4. Common nephrotoxic drugs

4.1 Antibiotics

4.1.1 β-Lactam antibiotics

β-Lactam antibiotics include penicillins, cephalosporins, cephamycins, carbapenems, monobactams, and β-lactamase inhibitors, and these are among the most commonly prescribed antibiotics [14]. β-Lactam antibiotics, especially penicillins and cephalosporins, frequently cause hypersensitivity reactions. Methicillin

and nafcillin are the prototypical drugs for hypersensitivity reactions associated with AIN. It is generally characterized by acute and severe renal failure. Hematuria, proteinuria, leucocyturia, and pyuria are seen in urinary sediment of affected patients. Hypersensitivity reactions such as fever, rush, and peripheral eosinophilia are commonly seen [5, 14].

Piperacillin-tazobactam and vancomycin must not be used concurrently; they may cause AKI. Cephalosporins may exacerbate the renal toxicity of aminoglycosides [14].

4.1.2 Non-β-lactam antibiotics

They can cause AIN. Rifampicin-induced AIN is dose dependent and is commonly associated with oliguric acute renal failure, hemolytic anemia, thrombocytopenia, and hepatitis. Approximately two-thirds of patients affected by rifampin-induced AIN require renal transplantation [5].

4.1.3 Aminoglycosides

Aminoglycosides are antibiotics used in the treatment of Gram-negative and *Staphylococcus aureus* infections [1]. Aminoglycosides commonly cause acute kidney injury during therapy. It typically manifests after 5–7 days of therapy. It is described as a rise in the plasma creatinine concentration of more than 0.5–1 mg/dL or 50% increase in plasma creatinine concentration from baseline [15].

Tubular uptake of aminoglycosides is a saturable process; thus, a single daily high dose is preferable to divided low doses. Administration of aminoglycosides by this way will cause less nephrotoxic effect [4, 15, 16].

Aminoglycosides primarily affect proximal tubules [1, 16], and patients present with acute tubular necrosis, showing features such as nonoliguric acute renal failure [4]. Proximal dysfunction leads to loss of enzymes, proteins, glucose, calcium, potassium, and magnesium [1]. In some patients, distal tubular segments can be affected and this manifests as polyuria and hypomagnesemia. Most patients may recover but some progress to irreversible kidney damage, especially if the patient is hypovolemic, septic, or catabolic. Aminoglycoside nephrotoxicity risk factors are nearly the same as other nephrotoxic agents. In addition to common factors, higher creatinine clearances and hypoalbuminemia are also independent risk factors for aminoglycoside nephrotoxicity [9].

4.1.4 Polymyxins/colistin

Polymyxins are a group of antibiotics that are used for pan-resistant nosocomial infections, especially for *Pseudomonas* and *Acinetobacter* spp. They may cause nephrotoxicity by IV injection. The nephrotoxicity mechanism is ATN leading to acute renal failure (ARF) with hematuria, proteinuria, and oliguria.

According to data, colistin appears more nephrotoxic than polymyxin B. Colistin-induced nephrotoxicity may exacerbate by older age, preexisting renal insufficiency, hypoalbuminemia, and concomitant use of NSAIDs. There are limited data on the risk factors for polymyxin-B associated nephrotoxicity. Methoxyflurane and cefazedone may enhance the nephrotoxic effect of polymyxin-B. Methoxyflurane-polymyxin-B combination should be avoided, but polymyxin-B-cefazedone combination may be used by close monitoring renal functions. Also, polymyxin-B may enhance the nephrotoxic effect of bacitracin [17, 18].

4.2 Analgesics

Analgesic nephropathy is a CKD characterized by papillary necrosis and chronic interstitial nephritis. It is caused by prolonged consumption of analgesic agents. Hypertension is a common clinical finding. The major laboratory manifestations are hematuria, sterile pyuria, elevation in serum Cr levels, and anemia [19, 20].

4.2.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs lead to AIN, chronic interstitial nephritis and finally CKD [20, 21]. Risk factors that may increase the nephrotoxic effect of NSAIDs are congestive heart failure, age > 65 years, and preexisting renal disease [4, 21].

4.2.2 Acetylsalicylic acid (ASA)

When used alone, even if prolonged, acetylsalicylic acid is not thought to cause kidney damage. It aggravates the nephrotoxic effects of both phenacetin and acetaminophen; thus, it should not be used simultaneously with these drugs. Acetylsalicylic acid and acetaminophen combination leads to papillary necrosis and calcification. Acetylsalicylic acid and NSAID combination leads to ischemic injury [20].

4.2.3 Acetaminophen (paracetamol)

Oral and rectal forms of acetaminophen may cause nephrotoxicity with chronic overdose [12]. The incidence of renal dysfunction is related to the severity of the acetaminophen ingestion [22]. IV forms may cause oliguria in neonates, infants, children, and adults [23]. AKI, which is primarily ATN, is manifested by elevations of BUN and Cr along with proteinuria, hematuria, and granular and epithelial cell casts on urine analyses. Also vascular endothelial damage can occur. It may be used in severe renal impairment with caution and dosing must be adjusted. Renal functions spontaneously return to baseline within 1–4 weeks. Rarely dialysis may be required. There is no evidence that N-acetylcysteine has any protective effect on nephrotoxicity [22, 23].

4.3 5-Aminosalicylates (5-ASAs)

5-ASAs are used to treat inflammatory bowel diseases. They lead hypersensitivity reactions in multiple organs, especially in kidneys, leading to acute interstitial nephritis [5, 24, 25]. During 5-ASA therapy, regular monitoring of renal functions is recommended [24]. AIN occurs most commonly during the initial year of therapy and it is non-dose-dependent. But in some patients with inflammatory bowel disease, AIN may occur as a complication of the disease [5].

4.4 Proton pump inhibitors (PPIs)

Proton pump inhibitors are used to treat acid-related gastrointestinal disorders. According to recent studies, many side effects of proton pump inhibitors have been reported. One of the side effects of the drug is nephrotoxicity, especially acute interstitial nephritis. PPI is thought to be associated with increased chronic kidney disease and its progression [5].

Recently, more concerns have been raised for proton pump inhibitors about the risks of acute interstitial nephritis, chronic kidney disease, and end-stage renal disease, and similar adverse kidney effects, such as interstitial nephritis and acute

renal failure, have been attributed to histamine-2 receptor antagonists [26]. But according to a newly published review, these potential adverse effects of PPIs must be proven by demonstrable evidence [27].

4.5 Interferon (IFN)

Interferons are cytokines that protect body against viral infections. Exogenous interferons are used to treat hepatitis B, hepatitis C and various malignancies (IFN-α), multiple sclerosis (IFN-β), and chronic granulomatous disease and malignant osteoporosis (IFN-γ). They may cause nephrotic syndrome with histological finding of minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS) [5, 28, 29], and renal vascular injury [28].

4.6 Bisphosphonates

Bisphosphonates are used to prevent bone absorption. The oral forms are used to treat osteoporosis and are thought to be nonnephrotoxic. But IV forms (pamidronate and zoledronic acid) can cause nephrotoxicity. Some reports reveal MCD and FSGS—not otherwise specified (FSGS-NOS) after pamidronate therapy and some reveal collapsing—FSGS (C-FSGS) after IV zoledronate therapy [5, 30]. According to some reports, zoledronic acid mainly leads to ATN [29]. The severity of nephrotoxicity depends on dosing, infusion time, and total number of infusion. Ibandronate is thought to be safe for kidneys [30].

4.7 Lithium

Lithium carbonate is generally used to treat bipolar disorder. It causes multiple renal side effects, most commonly nephrogenic diabetes insipidus. Acute lithium toxicity causes ATN. Chronic lithium toxicity occurs after more than 10 years of therapy and most commonly causes chronic tubulointerstitial nephritis with distal tubular cysts and sometimes secondary glomerulosclerosis. Lithium also causes nephrotic syndrome and histological findings of MCD or FSGS. Rarely it leads to end-stage renal disease secondary to lithium-associated chronic tubulointerstitial nephropathy. Lithium may also lead to renal tubular acidosis and hypercalcemia [5, 29, 31].

4.8 Antiangiogenesis drugs (AADs)

AADs are used for treatment of cancers and neovascular eye disorders such as diabetic retinopathy, macular degeneration, and retinal vein occlusion. They cause nephrotoxicity by endothelial cell injury and thrombotic microangiopathy (TMA) [5, 29]. Clinical manifestations of AAD-associated TMA are proteinuria and hypertension [29].

4.8.1 Chemotherapeutic agents

4.8.1.1 Mitomycin-C

Mitomycin-C is an alkylating agent used for treatment of malignancies. It can lead to TMA and AKI. AKI is dose-dependent, and the risk of TMA significantly increases with the cumulative doses of >60 mg [5, 29]. While TMA can occur during therapy, it usually occurs several week, average 75 days, after last dosage [29].

4.8.1.2 Gemcitabine

Gemcitabine is a pyrimidine antagonist that is used to treat a variety of malignancies. AKI is dose-dependent. Higher cumulative dose and prior exposure to other chemotherapeutic drugs increase the risk of TMA [5, 29]. AKI occurs almost in all patients treated with gemcitabine. TMA most commonly occurs weeks to months after initiation of therapy [29].

4.9 Oxymorphone-hydrochloride

Oral-extended release formulation of oxymorphone-hydrochloride is a long-acting opioid that is used to treat moderate to severe pain. Some data reveal AKI and TMA secondary to IV abuse of the drug [5, 32].

4.10 Levamisole

Levamisole has been used in treatment of pediatric nephrotic syndrome, colon cancer, inflammatory bowel disease, and rheumatoid arthritis. It was removed from the market due to agranulocytosis side effect. But it is still available in illegal form mixed with cocaine. Levamisole may cause antineutrophil cytoplasmic autoantibodies (ANCAs)-associated vasculitis (AAV) [5]. It may also rarely lead to hyponatremia, Wegener's granulomatosis, and renal failure [33].

Also antithyroid drugs such as propylthiouracil, carbimazole, and methimazole, and an antihypertensive drug hydralazine may lead to AAV [5].

4.11 Angiotensin-converting enzyme inhibitors (ACE-Is)

Captopril is an ACE inhibitor that is used for treatment of hypertension and proteinuria. Kaptopril may be the only ACE-I leading to nephrotic syndrome [5].

4.12 Anabolic androgenic steroids

Anabolic androgenic steroids like testosterone and illicitly used forms may lead to CKD [34].

4.13 TNF-α inhibitors

TNF-α inhibitors are biologic agents. Based on renal biopsy and clinical findings, glomerulonephritis associated with systemic vasculitis (GNSV), glomerulonephritis in lupus-like syndrome, and isolated autoimmune renal disorder are the subgroups of autoimmune renal diseases that may be caused by TNF-α inhibitors [5].

4.14 Gold salts

Gold compounds have been used for treatment of rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis. Because of side effects, low efficacy, and high cost, newer medications take place of gold salts. Parenteral use 0f gold leads to proteinuria, and gold-induced proteinuria is an indication of gold discontinuation. With oral gold therapy, proteinuria is rare. Renal pathology shows membranous glomerulonephritis. This may progress to nephrotic syndrome in patients continuing gold therapy [5, 35, 36].

4.15 Amphotericin-B

Amphotericin-B is an antifungal agent that is the choice in immunocompromised patients. It causes AKI via the tubular cell toxicity [1].

Amphotericin-B damages membrane integrity by causing pores and increases membrane permeability, and this leads to distal renal tubular acidosis [16]. Risk factors for nephrotoxicity are similar as any toxic nephropathy, but sodium deficiency is important especially in patients taking diuretic therapy [4]. Preventive procedures of amphotericin-B nephrotoxicity include saline hydration before and after drug administration, use of liposomal formulations, limiting the duration of therapy, and considering a continuous low-dose infusion over a 24 hours' period [1].

4.16 Calcineurin inhibitors

Cyclosporine and tacrolimus cause reversible AKI by inducing afferent and efferent arteriolar vasoconstrictions. Persistent injury can lead to interstitial fibrosis and glomerulosclerosis, and this leads to irreversible chronic nephrotoxicity. Tacrolimus may cause TMA [16, 37].

4.17 Cisplatin

Cisplatin may affect glomeruli and distal tubule, but it primarily affects proximal tubules. It leads to tubular necrosis or tubulointerstitial disease. It may increase serum creatinine and decrease GFR and lead to hypomagnesaemia, hyponatremia, hypocalcemia, and hypokalemia. When administered with hypertonic saline, cisplatin is better tolerated [1, 4, 16].

4.18 Cyclosporin-A

Cyclosporin-A leads to acute reversible and chronic irreversible nephrotoxicity. Acute reversible form is seen most commonly in renal transplant recipients and manifests as acute renal failure. Chronic form typically manifests after 1-year therapy. Clinical features are marked decline in glomerular filtration rate (GFR), hypertension, mild proteinuria, and rarely hematuria [4].

4.19 Ifosfamide

Ifosfamide is an analog of cyclophosphamide [16] and is used in the treatment of solid tumors in both children and adults [1] Cyclophosphamide is not nephrotoxic, but ifosfamide is toxic to the tubular cell. It prefers proximal tubular toxicity and leads to Fanconi's syndrome [1, 16]. It may also affect glomerulus and decreases GFR. These impairments may lead to clinical manifestations including hypophosphatemic rickets, proximal and distal renal tubular acidosis, diabetes insipidus, and hypokalemia [1].

4.20 Foscarnet

Foscarnet is used for treatment of resistant cytomegalovirus (CMV) infections. It causes acute interstitial nephritis and intratubular crystal formation. Foscarnet may chelate with calcium and cause hypocalcemia [16].

4.21 Methotrexate (MTX)

Methotrexate is an antiproliferative and immunomodulating agent that is widely used. Its high-dose regimen leads to AKI. It may cause cellular damage or crystal nephropathy. Hydration therapy and urine alkalinization can prevent the concentration of MTX to become too high in the tubules. Also toxic systemic concentrations caused by AKI can be prevented by leucovorin administered 24–48 hours after MTX [1].

4.22 mTOR inhibitors

mTOR inhibitors such as sirolimus or everolimus can worsen any significant underlying proteinuria in liver recipients with preexisting chronic renal disease [1].

4.23 Vancomycin

Vancomycin is an antimicrobial agent used in the treatment of Gram-positive infections. Vancomycin use is associated with nephrotoxicity. Nephrotoxicity range was as high as 50% in the past, but now it ranges about 1.0–42.6% by newer formulations. In addition to common nephrotoxicity risk factors, patients weight exceeding 101.4 kg, daily vancomycin dose over 4 g are also risk factors for vancomycin nephrotoxicity [38].

4.24 BRAF inhibitors

The selective BRAF inhibitors vemurafenib and dabrafenib are used to treat metastatic melanomas. There are no data reported dabrafenib use causing acute kidney injury, but there are a few case series with vemurafenib. The Food and Drug Administration Adverse Event Reporting System (FAERS) reports renal toxic effect of both agents. Vemurafenib appears more nephrotoxic than dabrafenib. Although not clear, they are thought to cause tubular interstitial injury with hypokalemia and hyponatremia [39].

4.25 Dekstran

Dekstrans are used for volume replacement therapy and may cause acute kidney injury. Therefore, fluid status and urine output should be monitored closely [39].

4.26 EDTA

It is a chelating agent used to get rid of iron from the body. It may produce toxic effect that may be fatal. Genitourinary effects of EDTA are nephrosis, nephrotoxicity, occult blood in urine, and proteinuria [40].

5. Contrast-induced nephropathy

Contrast-induced nephropathy is defined as an increase in serum Cr level of greater than 0.5 mg/dL or 25% over baseline during a period of 12–48 hours after contrast administration and the exclusion of other causes of AKI [2, 41].

Contrast agents generally lead to reversible AKI. Histopathologic evidence generally shows ATN. Compared with other types of ATN, contrast nephropathy is

usually characterized by relatively rapid recovery of renal function. Most patients are nonoliguric. If occurs, oliguria occurs immediately after the procedure. Other manifestations of acute kidney injury, such as hyperkalemia, acidosis, and hyperphosphatemia, may be present. The urinary sediment may show classical findings of ATN. Proteinuria is absent or mild [41].

Underlying chronic renal disease, diabetes, and nephrotoxic medications predispose patients to renal injury from contrast. If IV contrast is necessary, patients can be pretreated with N-acetylcysteine (600 mg twice daily for two doses before study and after study) and alkalinized IV hydration (three ampules of 50 mEq sodium bicarbonate in 1000 mL D_5W solution). In most cases, Cr usually starts to decline within 3–7 days. Dialysis is rarely required for contrast-induced AKI [37].

6. Crystal-induced nephropathy

Crystal nephropathies cause mechanical obstruction, local intrarenal inflammation, and tissue injury. There are three subgroups of crystal nephropathies: renal ischemic, tubular injury, and obstructive nephropathy [42].

Crystal-induced acute kidney injury commonly occurs following the administration of drugs or toxins that are poorly soluble or have metabolites that are poorly soluble in the urine [3, 43]. Especially in volume depletion status, glomerular ultrafiltrate can be enriched with minerals, proteins, or drug metabolites. Acute accumulation can induce a sudden onset of crystal formation leading to AKI, and long-term accumulation can lead to CKD [3, 42].

Patiens with drug- related crystal- induced AKI are usually asymptomatic. Kidney injury usually manifests with increased serum Cr, accompanying with hematuria, pyuria, and crystalluria. Crystal-induced AKI is generally reversible by discontinuation of the drug. It may rarely progress to CKD and dialysis may be required.

Risk factors for crystal-induced nephropathies are intravascular volume depletion, underlying kidney or liver disease, and metabolic disturbances that change urinary pH [3, 43].

6.1 Sulfonamide antibiotics

Sulfadiazine and sulfamethoxazole are relatively insoluble in acid urine. Alkalinization of urine to a pH > 7.15 increases sulfadiazine solubility.

6.2 Methotrexate

High-dose methotrexate can both precipitate in the tubules and cause direct tubular injury. Alkalinization of urine to a pH > 7 increases methotrexate solubility. Methotrexate-induced acute kidney injury is typically nonoliguric and often reversible.

6.3 Indinavir

It is a protease inhibitor used in the treatment of human immunodeficiency virus infection. Acidic urine pH (<6) increases indinavir solubility, but acidification of urine may be harmful; thus, it is not recommended.

6.4 Ciprofloxacin

It is a fluoroquinolone antibiotic and causes acute interstitial nephritis and crystal-induced nephropathy. Crystals precipitate in alkaline pH [43].

The other drugs that may lead to crystal-induced nephropathy are acyclovir; protease inhibitors such as indinavir, atazanavir; foskarnet; megadose vitamin C; orlistat; oral sodium phosphate; purgatives; triamterene; and high-dose amoxicillin [2, 3, 16, 43].

6.5 Acyclovir

It is used in the treatment of herpes infections and sepsis in neonates. It can most commonly lead to crystal-induced nephrotoxicity and also to nephrotoxicity by direct tubular injury [21].

7. Conclusion

Many drugs both prescribed or over-the counter have potential to cause kidney damage. Therefore, some basic items such as past medical history, age and weight of the patient, drug-related risk factors, and nephrotoxic drug combinations should be taken into consideration before starting the treatment. If a nephrotoxic drug use is mandatory, patients should be followed up closely and frequently with appropriate biomarkers. Basic renal functions should be evaluated before treatment. The early detection of drug-induced nephropathies and application of the appropriate treatment methods are critical, because many patients recover when the drug is discontinued.

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