Drug-Induced Nephrotoxicity and Its Biomarkers

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Abstract

Nephrotoxicity occurs when kidney-specific detoxification and excretion do not work properly due to the damage or destruction of kidney function by exogenous or endogenous toxicants. Exposure to drugs often results in toxicity in kidney which represents the major control system maintaining homeostasis of body and thus is especially susceptible to xenobiotics. Understanding the toxic mechanisms for nephrotoxicity provides useful information on the development of drugs with therapeutic benefits with reduced side effects. Mechanisms for drug-induced nephrotoxicity include changes in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy. Biomarkers have been identified for the assessment of nephrotoxicity. 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. Although some of them fail to confer specificity and sensitivity, several promising candidates of biomarkers were recently proved for assessment of nephrotoxicity. In this review, we summarize mechanisms of drug-induced nephrotoxicity and present the list of drugs that cause nephrotoxicity and biomarkers that can be used for early assessment of nephrotoxicity.

Key Words: Biomarker, Nephrotoxicity, Assessment

INTRODUCTION

The kidney is an essential organ required by the body to perform several important functions including the maintenance of homeostasis, regulation of the extracellular environment, such as detoxification, and excretion of toxic metabolites and drugs (Ferguson et al., 2008). Therefore, the kidney can be considered as a major target organ for exogenous toxicants. Nephrotoxicity is a kidney-specific feature in which excretion does not go smoothly owing to toxic chemicals or drugs (Bennett et al., 1991; Finn and Porter, 2003; Galley, 2000). Approximately 20% of nephrotoxicity is induced by drugs, but medication of the elderly increases the incidence of nephrotoxicity up to 66% as the average life span increases. Chemotherapy or anticancer medicine has been of limited use due to nephrotoxicity (Kohli et al., 2000; Naughton, 2008; Nagai and Takano, 2010).

Nephrotoxicity can be diagnosed through a simple blood test. Evaluation of nephrotoxicity through blood tests includes the measurements of blood urea nitrogen (BUN), concentration of serum creatinine, glomerular filtration rate and creatinine clearance. However, these assessments of nephrotoxicity are only possible when a majority of kidney function is damaged (Kirtane et al., 2005; Rached et al., 2008). Therefore, discovery and development of biomarkers that can detect kidney dysfunction at the early stage are needed. In this review, we summarize the mechanisms of drug-induced nephrotoxicity and highlight their involvement in diseases. We also summarize and present the list of biomarkers for assessment of nephrotoxicity.

MECHANISMS OF DRUG-INDUCED NEPHROTOXICITY

General mechanisms that cause nephrotoxicity include changes in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis, and thrombotic microangiopathy (Zager, 1997; Schnellmann and Kelly, 1999; Schetz et al., 2005; Ferguson et al., 2008).

Changes in glomerular hemodynamics

For healthy young people, glomerular filtration rate (GFR) is 120 ml per minute. Kidneys can keep a constant filtration rate as well as maintain the displacement of urine through regulation of blood flow in afferent and efferent arteries for adjustments or maintenance of intraglomerular pressure. Circulation of prostaglandin is used for expansion of afferent...
arteries (Naughton, 2008). Anti-prostaglandin drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) or drugs having anti-angiotensin activity for prevention of blood pressure elevation including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) have been shown to induce nephrotoxicity in glomerulus (Olyaei et al., 1999; Schoolwerth et al., 2001; Palmer, 2002).

**Tubular cell toxicity**

Because renal tubules, especially proximal tubule cells, are exposed to drugs in the process of concentration and reabsorption through the glomerulus, they are influenced greatly by drug toxicity (Perazella, 2005). Cytotoxicity occurs due to the damaged mitochondria in tubules, the disturbed tubular transport system, and the increase in oxidative stress by free radical generation (Zager, 1997; Markowitz and Perazella, 2005). The cytotoxicity inducing drugs include aminoglycoside antibiotics, antifungal agents such as amphotericin B, antiretroviral drugs such as adefovir, anticancer drugs such as cisplatin and foscarnet (Markowitz et al., 2003; Prezella, 2005; Markowitz and Perazella, 2005).

**Inflammation**

Nephrotoxic drugs often induce inflammation in glomerulus, proximal tubules, and surrounding cellular matrix, and then fiberize the kidney tissue. Inflammation that disturb normal kidney functions and induce toxicity includes glomerulonephritis, acute and chronic interstitial nephritis. Glomerulonephritis has been shown to be closely related to proteinuria (Perazella, 2005). Acute interstitial nephritis, a type of drug-induced immune response, is induced by NSAIDs and antibiotic drugs such as rifampicin (Rossert, 2001). Chronic interstitial nephritis occurs frequently by long-term use of calcineurin inhibitors, lithium, some anticancer drugs or analgesics (Perneger et al., 1994; Fored et al., 2001; Isnaard Bagnis, et al., 2004; Rodríguez-Iurbe and García García, 2012). In case of chronic interstitial nephritis, early detection is especially important because it is difficult to diagnose until most of the functionality of the kidney is destroyed.

**Crystal nephropathy**

Disorder in renal function is also affected by medications that make insoluble crystals in human urine (Perazella, 1999). The formation of insoluble crystals depends on the acidity of urine and drug concentration. Drugs that can cause crystal nephropathy are antibiotics such as ampicillin and antiviral agents such as acyclovir (Markowitz and Perazella, 2005; Perazella, 2005).

**Rhabdomyolysis**

Rhabdomyolysis is a condition in which muscle fiber contents are released into the bloodstream when skeletal muscle is destroyed due to some injury. As renal muscle cells disintegrate due to damage in muscle tissue, myoglobin and serum creatine kinase are released into the blood. Released myoglobin degrades and depresses the function of filtration in kidney resulting the acute tubular necrosis or renal failure (Coco and Klasner, 2004). Major causes of rhabdomyolysis are drug abuses from heroin, methadone, methamphetamine, and statin as well as alcoholism (Coco and Klasner, 2004; Huerta-Alardin et al., 2005).

**Thrombotic microangiopathy**

Drug-induced thrombotic microangiopathy results from organ damage through inflammation or direct toxicity in renal epithelial cells (Pisoni et al., 2001). Antiplatelet agents including cyclosporin, mitomycin-C and quinine have been shown to cause thrombotic microangiopathy (Pisoni et al., 2001; Manor et al., 2004).

**Biomarkers for Assessment of Nephrotoxicity**

Many pathophysiological mechanisms mentioned above are directly related to the induction of nephrotoxicity. Because traditional standard markers such as BUN and serum creatinine have low sensitivity and specificity, the timing of the diagnosis and treatment are often delayed. Therefore, development of new biomarkers is needed for the specific diagnosis of nephrotoxicity at earlier stages (Ferguson et al., 2008).

Biomarkers designate the biomolecules showing the relationship between exogenous toxic substances and diseases. Generally, biomarkers enable us to determine early damage to health caused by exposure to exogenous toxic substances, and provide an insight into the mechanism of the onset of these toxicants to adversely affect certain groups or individuals (Finn and Porter, 2003). The identification of biomarkers that can be determined from blood or urine resulted from exposure to a nephrotoxicant is a promising approach (Shao et al., 2011). Especially, urine is regarded as attractive and efficient sample because it is non-invasive and easy to be obtained in considerable amounts (Wu et al., 2010).

Biomarker candidates have been identified for the assessment of nephrotoxicity. Although some of them fail to confer specificity and sensitivity of biomarkers, several promising candidates have been proved for diagnosis of nephrotoxicity (Ferguson et al., 2008; Bonventure et al., 2010). List of biomarkers for nephrotoxicity assessment and drugs in different nephron segments is presented in Table 1.

**Urinary proteins with enzymatic activity**

If there is acute or chronic kidney damage due to exposure to nephrotoxic substances, diabetic kidney disease, hypertension, renal ischemia, transplant, or glomerular diseases, the enzymes present in tubular epithelial cells are spilled into the urine and can be detected as nephrotoxic biomarkers. Biomarkers related with urinary proteins with enzymatic activity include alanine aminopeptidase, alkaline phosphatase, α-glutathione-S-transferase, γ-glutamyl transpeptidase, α-glutathione-S-transferase, and N-acetyl-D-glucosaminidase (Ferguson et al., 2008).

**Proteinuria**

In normal conditions, the glomerulus restricts the migration of high molecular weight proteins from blood to nephron lumens by filtration (Finn and Porter, 2003). In some pathological states, however, high molecular weight proteins can be detected in the urine because the selective penetration through glomerulus is not functioning properly (Guder and Hoffman, 1992). High molecular weight proteins that can reveal kidney damage include albumin which can be used for early diagnosis of changed glomerular filtration and diabetes (Morgensen, 1971), transferrin which transports iron and represents glo-