The Journal Of The International Federation Of Clinical Chemistry And Laboratory Medicine

How to Cite this article: Drug-Induced Kidney Injury - eJIFCC 20/01 2009 http://www.ifcc.org

7. DRUG-INDUCED KIDNEY INJURY

Mladen Knotek

7.1 Introduction

Acute kidney injury is an independent risk factor for patient mortality, even with small decrements in kidney function. In addition, it increases length of stay in the hospital and increases cost of treatment. Renal injury is often multifactorial, with drugs being only one of the factors in its pathogenesis. Hence, it is often difficult to estimate involvement of drugs as a cause of acute kidney injury. However, some data shows that in almost one quarter of cases of severe acute kidney injury nephrotoxic drugs are signifficant contributors. Renal handling of drugs involves glomerular filtration, excretion through transcellular transport into tubular fluid and reabsorbtion from the tubular fluid. High renal blood flow and process of concentration of drugs and their metabolites during formation of urine predisposes kidneys to toxic drug injury. From the pathogenic (pathophysiologic) perspective drug-induced kidney injury can be devided into hemodynamic, intrinsic (injury to renal tissue) and intrarenal obstruction (obstruction of tubule fluid flow). From didactical point of view kidney histology can be divided into four compartments: glomeruli, tubules, interstitium and vasculature. Each of these compartments can be target of drug-induced injury, with clinical and laboratory manifestations being dependent on which of them is predominantly involved. It is important to appreciate that a single drug renal toxicity can involve multiple pathophysiologic pathways and that predisposing factors are common to virtually all causative agents mediating kidney injury. Dehydration, hypotension, preexisting kidney disease, advanced age, diabetes and simultaneous use of multiple nephrotoxic drugs all greatly increase risk for any nephrotoxic drug to exert its nephrotoxic effect. At an increased risk are particularly patients in intensive care units.

7.2 Hemodynamic kidney injury

7.2.1 Non-steroidal antiinflammatory drugs and drugs that inhibit renin-angiotensin system

Renal blood flow and glomerular filtration normaly depend on renal perfusion pressure (determined by the mean arterial pressure) and on tonus of the afferent and efferent arteriole. In the setting of decreased perfusion pressure glomerular filtration is maintained by the afferent arteriole dilatation, mediated in part by vasodilatory prostaglandins and by the efferent arteriole vasoconstriction mediated partly by

angiotensin II. Therefore, it is not surprising that inhibition of prostaglandin synthesis by the non-steroidal antiinflammatory drugs (NSAID) may precipitate kidney dysfunction. Renal microvasculature expresses both isoforms of cyclooxygenase (COX), COX-1 and COX-2. In conditions where renal blood flow is impaired, such as congestive heart failure, liver cirrhosis, dehydration and chronic kidney disease vasodilatory prostaglandins help to maintain renal blood flow and glomerular filtration. Both, selective (COX-2) and non-selective COX inhibitors impair synthesis of vasodilatory prostaglandins in the kidney and are associated with development of intrarenal vasoconstriction and renal function impairment. Other forms of kidney injury by the NSAID are acute tubulointerstitial nephritis, chronic interstitial nephritis and glomerulopathy (usually minimal change disease).
Similarly, in the setting of effective blood volume depletion (decompensated heart failure, decompenstaed cirrhosis, systemic hypotension), or renal hypoperfusion due to bilateral renal artery stenosis, administration of drugs that block synthesis of angiotensin II (angiotensin-converting enzyme inhibitors), or its binding to type I receptors (AT1 receptor antagonists) reverses efferent arteriole vasoconstriction and decreases intraglomerular pressure, which reduces glomerular filtration rate.

Both NSAID-induced or anti-angiotensin drug-induced kidney injury is functional and quickly resolves upon withdrawal of a causative drug. Diagnosis relies on clinical judgement. Urinalysis reveals blank sediment. Hemodynamic kidney injury is treated by withdrawal of causative drug. Renal replacement therapy is rarely needed.

Other drugs that may cause kidney injury by intrarenal vasoconstriction are vasopressors, calcineurin inhibitors (cyclosporine and tacrolimus) and amphotericin B.

7.2.2 Contrast-induced nephropathy

Contrast-induced nephropathy (CIN) is a form of acute kidney injury that occurs after intravenous administration of iodine-based radiocontrast agents for radiologic examinations. At particular risk for CIN are diabetics, volume-depleted patients, older patients and patients with preexistant kidney injury. Acute worsening of glomerular filtration occurs within several days of radiologic procedure (usually after 48-72 hrs). Decrease in glomerular filtration is usually small or moderate and renal function returns to baseline level within several days. However, sometimes hemodialysis is needed to bridge period to recovery. Even small decrements in kidney function have been linked to increased mortality in patients with CIN, although it is not clear whether CIN is an independent risk factor for mortality. Because of this potential effect on patient survival, and increased costs of care for patients with CIN, great effort should be put to prevention of CIN in patients at risk. Preventive measures include adequate hydration of patients prior to and after procedure, use of low-osmolar or iso-osmolar contrast agents and limiting ammount of agent used. Role of particular agents such as bicarbonate and N-acetyl cystein, as well as continuous venovenous hemofiltration in prevention of CIN is not clearly established.

7.3 Intrinsic kidney injury

7.3.1 Tubulointerstitial injury

Acute tubulointerstitial injury can be caused by two mechanisms: by the hypersensitive idiosyncratic reaction that is dose-independent and is reffered to as acute hypersensitive tubulointerstitial nephritis and by the toxic acute kidney injury characterized by acute tubular necrosis. Acute tubular necrosis is dose-dependent. Chronic form of tubulointerstitial nephritis is seen with long-term use of NSAID, usually in combination and is reffered to as analgesic nephropathy.

7.3.2 Acute hypersensitive interstitial nephritis

It is an idiosyncratic fenomenon, caused by the allergic reaction to variety of drugs. Characteristically, reexposure to the same drug causes recidive of the disease. Many drugs have been implicated in inducing tubulointerstitial nephritis (TIN). Among them are beta-lactam antibiotics (penicillins and cephalosporins), quinolone antibiotics (ciprofloxacin), NSAID, proton pump inhibitors (e.g. omeprazole), sulfonamides, allopurinol, etc. Histologicaly, interstitial inflammatory infiltrate consisting of T and B lymphocytes, with frequently prominent eosinophils is found in renal tissue obtained by biopsy. Accordingly, sterile leucocyturia with eosinophyluria is found on urinalysis. Acute interstitial nephritis causes acute kidney injury, characterized by an increase in serum creatinine levels, which is reversible upon discontinuation of the offending drug. Corticosteroids may foster resolution of kidney inflammation and recovery of renal function.

7.3.3 Acute tubular necrosis

Prototype class of agents that induces acute tubular necrosis (ATN) are aminoglycoside antibiotics. These drugs are freely filtrable by the glomerulus. Their nephrotoxic potential is dependent on the number of cationic groups on the molecule. Aminoglycosides bind to acidic phospholipids and megalin on the apical membrane of proximal tubule cells, and after uptake into the cells by endocytosis they accumulate in lysosomes causing their rupture. They are also thought to interfere with cellular functions such as protein synthesis and mitochondrial function. Ultimately, proximal tubule cell apoptosis and necrosis occurs, leading to acute kidney injury. In addition, there is some evidence that aminoglycosides may potentiate nephrotoxicity of gramm-negative bacterial endotoxin. Acute kidney injury caused by aminoglycosides is frequently non-oliguric, with increases in serum urea and creatinine within days of initiation of antibiotic therapy. Kidney injury may be severe enough to require renal replacement therapy. Urinalysis shows mild proteinuria with hyaline and granular casts in the sediment. After stopping the drug renal function returns to baseline values usually within weeks. To prevent aminoglycoside-induced acute kidney injury it is important to identify patients at risk, as stipulated in the introduction section. In patients with reduced kidney function, it is of paramount importance to adjust the dose according to glomerular filtration rate. Also, it seems that once-daily dosing of aminoglycosides decreases incidence of acute kidney injury (although this is a metter of some controversy). The role of therapeutic drug monitoring, usually by measuring trough plasma concentration is helpful in determination of appropriate dose, but its role in preventing kidney injury is not clearly established.

Other agents that may cause acute tubular necrosis are chemotherapeutics such as platinum derivatives, amphotericin B, foscarnet, cidofovir and statins (by causing rhabdomyolysis and myoglobinuria).

7.3.4 Osmotic nephrosis

Osmotic nephrosis is a form of acute kidney injury caused by a high-dose intravenous immunoglobuline, or osmotic diuretics such as mannitol and plasma expanders, such as hydroxiethylstarch. Histologicaly, it is characterized by isometric vacuolization of proximal tubules. It is thought that proximal tubule cell injury occurs after uptake of either osmotic agent itself, or its vehicle (such as sucrose in case of intravenous immunoglobuline) with consequent tubule cell swelling and injury.

7.3.5 Analgesic nephropathy

Analgesic nephropathy was a relatively frequent cause of chronic kidney disease in the past. It is characterised by the chronic interstitial nephritis, often with papillary necrosis. First manifestation is mildly decreased glomerular filtration and decreased urinary concentration capability. Later, interstitial fibrosis, especially in the medulla, with papillary necrosis occurs. Unless analgesic abuse is stopped, renal injury is progressive and leads to end-stage kidney disease. Responsible agents are analgesics in combinations. The most important causative drug was phenacetin, often in mixtures with acethylsalicilic acid, codeine or caffeine. A metabolite of phenacetin, acetaminophen, which is a very frequently used analgesic may be also associated with nephrotoxicity, although the risk is lower compared to phenacetin. Similarly, consummation of other NSAID may be related to development of chronic kidney disease. However, large quantities of these drugs is required over many years to induce chronic kidney disease. Mechanisms by which these drugs induce kidney damage include oxidative stress and chronic inhibition of synthesis of vasodilatory prostaglandins with consequent chronic renal ischemic injury. Diagnosis relies on careful history taking, urinalysis showing sterile leucocyturia and mild or moderate (usually subnephrotic) proteinuria, with or without erythrocyturia. Urinary infections are frequent in patients with analgesic nephropathy. Hallmark of analgesic nephropathy, papillary necrosis can be diagnosed by intravenous urography, CT scan, or by the ultrasound. Other suggestive features on imaging procedures are shrunken kidneys, nephrocalcinosis and kidneys with bumpy contours.

7.4 Intrarenal obstruction

Drug-induced intrarenal obstruction is mainly due to antiviral drug precipitation. It is observed sometimes with use of acyclovir. Risk factors are rapid bolus administration in a volume-depleted patient. Crystaline nephropathy has also been a complication of antiretroviral drugs such as indinavir or tenofovir, especially in patients with high urinary pH values (pH >6). Toxicity of these drugs is potentiated by concomitant use of sulfometoxazole. Another drug which may precipitate in kidney tubules is methotrexate used in high doses, in the setting of dehydration and/or low urine pH (pH < 7). Crystal-induced tubule obstruction is accompanied with crystaluria, which helps establishing diagnosis. Kidney injury caused by drug precipitation may be

severe and hemodialysis is frequently needed to treat renal failure and decrease drug burden.

7.5 Conclusion

Drug-induced kidney injury is a frequent, and probably underappreciated causative or contributory event in pathogenesis of acute or chronic kidney injury. At the same time, it is often preventable and easily treatable if diagnosed early. Diagnosis of drug-induced kidney injury requires vigilance and knowledge of drug pharmacokinetics and pharmacodynamics. It is a multidisciplinary task involving clinicians, pharmacists and clinical chemists.

Recommended literature:

1. Pannu N, Nadim M. An Overview of Drug-Induced Acute Kidney Injury. Crit Care Med 2008;36(Suppl.):S216.
2. Markowitz G S, Perazella M.A. Drug-Induced Renal Failure: A Focus on Tubulointerstitial Disease. Clin Chim Acta 2005;351:31.
3. Perazella M.A. Crystal-Induced Acute Renal Failure. Am J Med 1999;106:459.
4. Launay-Vacher V, Izzedine H, Karie S, Hulot J S, Baumelou A, Deray G. Renal Tubular Drug Transporters. Nephron Physiol 2006;103:97.