Acute Renal Failure and Nephrotoxic Drugs

Acute renal failure (ARF) is a common clinical syndrome. It is defined as a rapid decline in renal function resulting in abnormal retention of blood nitrogen and serum creatinine which must be excreted. The clinical manifestations of ARF are the decline in glomerular filtration rate (GFR) and the inability of the kidney to excrete the toxic metabolic substances produced in the body.

Some of the drugs administered by physicians possess nephrotoxicities and occasionally induce ARF. Therefore, physicians must have vast knowledge in relation to the nephrotoxicities of therapeutic agents in order to avoid iatrogenic ARF.

In this article, I would like to briefly review some of the drugs which possess such nephrotoxicity and occasionally induce ARF and the mechanisms of their nephrotoxicities.

Antibiotics, antineoplastic agents, heavy metals such as gold and platinum, and contrast media are well known to be nephrotoxic drugs. In addition, drugs such as vitamin C and Naftidrofuryl oxalate praxilene are precursors of oxalate which possess severe nephrotoxic effects. Antibiotics are the most common drugs acting through a variety of mechanisms including direct cellular injury, immunologic or hypersensitivity reactions, and intratubular obstruction resulting from precipitation of the drug. Especially, aminoglycoside and Amphotericin B, are well known to possess severe nephrotoxicity. Aminoglycoside is still widely used in outpatients as well as inpatients, because of its superior effectiveness in gram-negative infections. As aminoglycoside accumulates in the proximal renal tubular cells, alterations in membrane integrity and intracellular organelle function begins to occur (1). Risk factors such as dose and duration of antibiotics, increased age, preexisting renal insufficiency, hepatic failure, volume depletion, potassium and magnesium depletion should be carefully avoided.

Amphotericin B is an effective drug in the treatment of systemic fungal infections. Renal insufficiency is generally dose related and develops as a result of renal vasoconstriction, and tubular injury. Vancomycin is widely used nowadays for the patient with MRSA infection. Although nephrotoxicity of vancomycin seems to be low, the risk of nephrotoxicity increases when aminoglycoside is also used together. Antineoplastic agents are becoming common nephrotoxic drugs, since a progressively increasing number of cancer patients receive antineoplastic agents (2). For example, Azathioprine, 6-Mercaptopurine, Bleomycin, Cisplatin, Cyclophosphamide, and Mitomycin C are well known nephrotoxic agents. Cyclophosphamide has a broad antineoplastic spectrum and is used widely. The mechanism of nephrotoxicity may be the potentiation of the action of antidiuretic hormone on the kidney.

The nephrotoxicity of mitomycin C is frequently caused by hemolytic uremic syndrome due to endothelial cell injury.

Nonsteroidal antiinflammatory agents (NSAIDs) inhibit a principal enzyme in prostaglandin biosynthesis, cyclooxygenase, which metabolizes arachidonic acid to various prostaglandins and structurally related compounds. An upward effect of NSAIDs hemodynamically mediates reversible acute renal failure; this seems to be one of the more common causes of drug-induced renal failure (3). Since the number of elderly patients who readily suffer renal deterioration is markedly increasing, physicians should be well aware of the risk factors of NSAIDs.

Risk factors such as congestive heart failure, cirrhosis with ascites, hypotensive hemorrhage and severe burns need to be avoided. The administered NSAIDs result in an increase in renovascular resistance due to inhibition of renal prostaglandins, leading to reduction of both renal blood flow and glomerular filtration in rates, and occasionally ARF.

Heavy metals are used as the therapeutic agents: Gold sodium thiomalate for rheumatoid arthritis, and cisplatinum and carboplatinum for various kinds of the cancer. Both heavy metals injury the proximal tubular cells of the kidney, resulting in ARF (4). In fact, a large volume of saline solution must be administered with diuretics, when cisplatinum is used for patients with cancer.

Contrast media such as iodinated radiocontrast agents also induce ARF (5).

Regional hypoperfusion, intrarenal vasoconstriction, and the direct toxic effect might induce outer medulla hypoxia which leads to ARF accompanied by renal insufficiency. Congestive heart failure, dehydration, and aging, and especially, both diabetes mellitus and renal insufficiency or atherosclerosis are higher risk factors of ARF due to contract media.

Oxalate, an end-product of several metabolic pathways in mammals, also causes ARF, particularly when the plasma oxalate concentration is increased, owing either to the increased rates of intestinal oxalate absorption or to increased biosynthesis. Oral administration of large doses of vitamin C and Naftidrofuryl oxalate praxilene which is a vasodilator, and Methoxyflurrate, which is used for anesthesia, increase the serum oxalic acid concentration (6, 7), since these drugs are a precursor of oxalate.

High serum oxalic acid concentration produces not only rapid deterioration of renal function, but also occasionally ARF due to massive precipitation of calcium oxalate in the lumen and epithelial cells of the proximal tubules in the kidney.

When ethylene glycol (EG) which is used as an antifreeze is ingested, large amounts of various kinds of metabolites of
ethylene glycol which are nephrotoxic as well as oxalic acid are increased (8). Therefore, EG intoxication frequently causes ARF. Although it is speculated that some of these metabolic substances as well as oxalate have a nephrotoxic effect, it was demonstrated by Konta et al in this issue (9) that oxalate causes proximal tubular dysfunction due to massive precipitation of calcium oxalate crystals.

See also p 762.

Numerous new drugs are coming out every year, and are used for the patients. It is impossible, however, to find out all of the adverse effects of these drugs in patients with different pathological conditions. In the terms of a nephrologist, I would like all physicians to pay much attention to avoid renal deterioration and ARF due to such new drugs. In addition, we must bear in mind that we know little about nephrotoxicities due to interactions of several kinds of drugs.

It is important for physicians, therefore, to keep careful and continuous observation of each patient whether nephrotoxicity appears or not.

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References