AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 01, Issue 05, 2023 ISSN (E): 2993-2149

DRUG NEPHROPATHY

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Annotation: In recent years, the number of drug-induced kidney lesions in the practice of doctors of all specialties has significantly increased. The reason is the continuous expansion of the arsenal of medicines. In some European countries, complications of drug therapy occur in 30% of patients who are in the hospital. Of these, 25% of these complications are the cause of death.

Key words: toxic effect of drugs, analgesic nephropathy, acute renal failure.

Renal drug-induced injury is much less common than liver or bone marrow injury. However, recent studies conducted by a large group of scientists have shown that 30% of cases of non-oliguric acute renal failure (ARF) are associated with medication [8].

The vulnerability of the kidneys to the toxic effects of drugs is due to four main factors:

1) high intensity of renal blood flow (25% of cardiac output compared to other organs);

2) the presence in the epithelial cells of the proximal tubules of the nephron of numerous enzyme systems that provide a high rate of metabolic and transport processes;

3) removal of most drugs from the body through glomerular filtration and tubular secretion;

4) nephrotoxicity of many drugs, aggravated by a decrease in kidney function for any reason.

In addition to the toxic effect, the most important mechanism of drug nephropathies is allergy, within which immune inflammation of the glomeruli is triggered, vessels and interstitium are affected, renal hemodynamics and endocrine function of the kidneys suffer.

MECHANISM OF DRUG NEPHROPATHY

When taking therapeutic doses of drugs, the cause of the development of acute renal failure is the direct toxic effect of the drug on the epithelium of the proximal tubule with the development of tubular necrosis. Less commonly, hypersensitivity is noted with the onset of acute interstitial nephritis, in the pathogenesis of which cellular immune mechanisms play a role.

Acute drug-induced kidney injury includes:

1) papillary necrosis (with prolonged use of analgesics);

2) intrarenal blockade with crystals of sulfonamides or urates (with cytostatic or radiation therapy of tumors);

3) violation of central hemodynamics due to hypovolemia (during treatment with diuretics, antihypertensive drugs);

4) violations of local intrarenal hemodynamics.

The occurrence of drug nephropathies does not mean that many drugs are unconditionally damaging agents. For the development of a disease under the influence of a particular drug, certain prerequisites are necessary: biological, biochemical, biophysical, morphological, genetic, etc. The concentration of many drugs in the kidneys and urine is higher than in the blood. Drugs and their metabolites are most often eliminated by glomerular filtration and, less commonly, by tubular secretion with the participation of enzymatic transport systems, the mechanisms of which are not well understood.

In this case, the highest concentration of the drug is found in the renal lymph, consisting of blood plasma and primary reabsorbed urine. The rate of excretion of drugs and their metabolites depends on the glomerular filtration rate, the concentration of the substance in the blood and the pH of the urine. With changes in these parameters, the concentration of medicinal substances increases, which can be unfavorable for the kidneys and the whole body. In the kidneys, biotransformation of many drugs occurs through oxidation, reduction, hydrolysis and binding reactions. Drug metabolites are often more active than the drugs themselves, and their effects are sometimes unpredictable.

Among the drugs leading to the development of chronic tubulointerstitial nephritis, one of the first places is occupied by non-steroidal anti-inflammatory drugs. For the occurrence of tubulointerstitial nephritis, it is not so much the dose of the drug that matters, but the duration of administration and sensitivity to it. Ya.N. Zalkalis and N.N. Zhuravleva [6], who conducted a screening examination, revealed a pathological urinary syndrome in 1262 people. 20.08% of them took non-steroid drugs and analgesics. The urinary syndrome in chronic drug-induced kidney damage was characterized by a decrease in the relative density of urine, proteinuria, leukocyturia and erythrocyturia.

Among those taking these drugs, the most common (19.6%) was a decrease in the relative density of urine. 71.34% of patients with identified proteinuria systematically took analgesics. Analgesic nephropathy is characterized as a chronic disease, the morphological basis of which is chronic interstitial nephritis, papillary necrosis, cortical atrophy and capillary sclerosis. Sometimes clearly visible brown staining of the renal parenchyma and urinary tract mucosa. Such a morphological picture is usually observed when taking combinations of analgesics: "phenacetin + paracetamol + salicylates + pyrazolone preparations" and "caffeine + codeine or caffeine + barbiturates". 12 years after the description of analgesic nephropathy, Haltengren in 1965 described an increased incidence of urinary tract tumors in patients systematically taking analgesics.

And after 9 years, the so-called "analgesic syndrome" was described, which includes 9 components:

1) analgesic nephropathy,

2) stomach ulcers,

3) psychiatric disorders,

4) cardiovascular complications,

5) hematological disorders,

6) discoloration of the skin,

7) premature aging,

8) tumors of the urinary system,

9) the prevalence of pathology in women.

Renal colic caused by necrotic changes may be the first manifestations of analgesic nephropathy, but more often papillary necrosis is asymptomatic or with a picture of pyelonephritis. The diagnosis is established only with the help of retrograde pyelography. Obstruction of the ureters by necrotic masses in combination with infection can cause a clinic of pyonephrosis and acute renal failure. In milder cases, hematuria, mild abacterial pyuria, and proteinuria rarely exceeding 1 g per day may be detected, in combination with slight increases in plasma creatinine and urea.

Less common is gross hematuria due to rupture of the calcified pelvicalyceal system or fresh acute necrosis. Much more often as the first manifestation of a tumor of the uroepithelium, hematuria occurs. Early symptoms of the disease are polyuria and nocturia as a result of destruction of the papillary layer. A feature of analgesic nephropathy is acidosis and renal tubular acidosis. Arterial hypertension occurs in the majority of patients with analgesic nephropathy (up to 80%), but usually proceeds mildly, not reaching such figures as in glomerulopathies [1].

High hypertension is observed less frequently and is explained by the combination of nephropathy with atherosclerosis of the renal arteries or nephroangiosclerosis. The course of analgesic nephropathy is often benign, if patients stop taking analgesics, kidney function improves. As with other nephropathies, the prognosis greatly benefits from the absence of hypertension. The terms "malignant" and "irreversible" do not characterize the course of analgesic nephropathy.

In Switzerland, most patients with analgesic nephropathy undergoing kidney transplantation survived the age of 60. The concept of drug nephropathy was formulated by B.I. Shulutko. The pathological process is based on a significant sensitization of the body to various medicinal substances, which develops against the background of congenital or acquired hemodynamic disorders of the kidneys. Sensitization is manifested by increased production of immunoglobulins, which leads to the formation of drug-protein complexes and activates the release of anaphylaxis mediators. Further, prostaglandins are involved, leading to edema and damage to the interstitium and the formation of interstitial nephritis.

CLASSIFICATION OF DRUG NEPHROPATHY

I.E. Tareeva [5] identified the following forms of drug-induced kidney damage:

1. Acute tubular necrosis. It manifests itself as a clinical picture of acute renal failure, develops during treatment with kanamycin, gentamicin, tobramycin, cephalosporins, ampicillin, quinine;

2. Acute ischemic necrosis of the cortex with acute renal failure. It develops as part of anaphylactic shock, more often during vaccinations without taking into account contraindications;

3. Acute interstitial nephritis. Complicates the course of treatment with penicillin, rifampicin, sulfonamides;

4. Chronic interstitial nephritis. It occurs against the background of long-term use of analgesics - analgesic nephropathy. It occurs more often in women over 40 who suffer from migraines or lumbodynia. Morphologically, a pathognomonic sign is the detection of brown pigmentation of the renal papillae and the mucous membrane of the urinary tract. There is an increase in the volume of interstitial connective tissue in the medulla, atrophy of the tubular epithelium, necrosis of the papillae. Clinically, nephropathy can be asymptomatic, or hypostenuria, polyuria, anemia are detected. In 50% of cases, nephropathy is detected at the stage of chronic renal failure;

5. Acute nephritis as part of a drug disease. It manifests itself against the background of treatment with gold preparations, cuprenil, anticonvulsants. Morphologically, under the mask of acute glomerulonephritis, membranous glomerulonephritis is revealed;

6. Chronic glomerulonephritis as an outcome of "acute nephritis". It develops in the form of a nephrotic form during treatment with mercury salts, hydralazine, novocaine and other medicines. Perhaps the course of the disease in the form of an isolated urinary syndrome; 7. Electrolyte-hemodynamic disorders. Occur during treatment with indomethacin and other non-steroidal anti-inflammatory drugs that inhibit prostaglandins in the medulla and reduce intrarenal hemodynamics. Changes in hemodynamics develop when taking diuretics, antihypertensives, ganglionic blockers, peripheral vasodilators.

ENZYMES AND METABOLISM

In the 1970s, the study of induction and inhibition of kidney enzymes was started. It has been established that the kidney, which has active enzyme systems, is capable, like the liver, of activating the metabolism of drugs and other chemicals, sometimes to its own detriment. Most of the work in this direction is devoted to acetaminophen, a drug chosen by English suicides, a drug known to us as paracetamol. This drug is similar in structure and effect to phenacetin. Experimental studies have shown that taking a non-lethal dose of acetaminophen once causes acute necrosis of the proximal convoluted tubules of the nephron in the inner layer of the cortex under conditions of high concentrations of cytochrome P-450 in the kidneys.

The latter is the terminal oxygenase that regulates the oxidation in the kidneys of most drugs. It is believed that the cause of kidney damage is the formation and exposure of the acetomifen metabolite. This hypothesis has received experimental confirmation. The fact is that under normal conditions, glutathione is formed in the kidney, which protects the kidney from necrosis. Only with the depletion of glutathione reserves in the cells of the proximal tubules, the toxic effect of the acetaminophen metabolite is realized. Kidney damage is of a different nature with the abuse of analgesic mixtures, which include salicylates, paracetamol and phenacetin. In these cases, papillary necrosis and interstitial fibrosis occur in both the cortical and medulla of the kidneys. At the same time, salicylates and paracetamol tend to accumulate in the medulla, which was not detected in relation to phenacetin.

Therapeutic doses of salicylates reduce glomerular filtration of certain substances (3-acetyl-β-glucosomidinases) by inhibiting prostaglandins. Due to the toxic effect on the epithelium of the proximal tubules, tubular functions are also inhibited. In the experiment, the introduction of cobalt chloride, an inhibitor of microsomal enzymes, reduces the degree of damage to the epithelium. Morphological processes in the kidneys of persons systematically taking phenacetin are represented by a picture of chronic pyelonephritis with symptoms of papillary necrosis. Analysis of cases of phenacetin nephropathy often makes the involvement of phenacetin

doubtful in some patients. Nevertheless, clinical and epidemiological studies establish clinically obvious kidney damage in 70% of patients treated with phenacetin.

A clear dependence of the severity of renal lesions on the duration of administration and the total dose of phenacetin was noted. According to modern views, with the toxic effect of the drug, papillary necrosis primarily develops, followed by cortical atrophy and sclerosis. Later accession of chronic pyelonephritis is possible. The development of cortical sclerosis is associated with the formation of para-aminophenol metabolite in the papillary zone. Allergy is discussed as one of the mechanisms of phenacetin damage. In this regard, the increase in the occurrence of pyelonephritis is regarded as a layering of infectious pathology on an allergic reaction in the kidneys. In addition, exposure to the metabolites phenacetin and 2-hydroxyphenacetin sulfate allegedly causes an increase in the development of tumors of the pelvis.

In any case, there is no doubt that long-term use of analgesics, especially phenacetin, in large doses increases the susceptibility of the kidney to infection, including tuberculosis. Comparing different groups of drugs, we see that most often nephropathy complicates treatment with antibiotics: aminoglycosides, rifampicin, semi-synthetic penicillins. Of the group of aminoglycosides, neomycin has the greatest nephrotoxicity, and streptomycin is the "softest" drug in this group. The target of the toxic action of these drugs are the cells of the proximal tubules. Treatment with drugs of this group is best done as monotherapy with constant monitoring of kidney function. In second place in the frequency of development of drug nephropathy are non-steroidal anti-inflammatory drugs.

According to O.A. Androsova, in 20% of patients treated with indomethacin, there was a decrease in glomerular filtration and a moderate increase in the level of creatinine and potassium in the blood. A decrease in glomerular filtration occurred 1-2 days after the start of indomethacin. In immunohistochemical studies, non-steroidal anti-inflammatory drugs are found as part of immune complexes on the basement membrane. Interestingly, the decrease in renal function is more pronounced if indomethacin treatment is carried out against the background of hyperreninemia or renal artery stenosis.

In third place in terms of the frequency of complications are radiopaque agents. More often, kidney damage occurs against an unfavorable background. The development of acute renal failure with the introduction of a radiopaque substance is typical for those suffering from multiple myeloma. The fourth place in the frequency of development of drug nephropathy belongs to diuretics, the fifth - to lithium salts.

TREATMENT OF DRUG NEPHROPATHY

Treatment of patients, taking into account immune pathogenesis, is carried out in accordance with the clinical and morphological forms in which they manifest themselves. Corticosteroid therapy can be considered pathogenetic, which has to be carried out in medium and high therapeutic doses. In cases of development of acute renal failure, which is based on cortical necrosis, acute interstitial nephritis, tubular necrosis, emergency hemodialysis has to be used. Pathogenetic therapy of drug-derived glomerulonephritis is supplemented by carbohemoperfusion and plasmapheresis. The least favorable prognostic factor is analgesic nephropathy. Thus, due to a significant increase in the drug arsenal in clinical practice and, consequently, an increase in the frequency of drug reactions, including renal ones, the participation of a clinical pharmacologist in the treatment process becomes necessary. To prevent

the development of drug-induced kidney damage, it is necessary to remember the factors of nephrotoxicity: the presence of diabetes mellitus, gout, nephroangiosclerosis, anomalies in the development of the kidneys, previous chronic kidney diseases, chronic heart failure, liver cirrhosis.

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