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DRUG-INDUCED NEPHROPATHY

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Abstract
NSAIDs are the drugs that doctors most often prescribe for rheumatoid arthritis. The mechanism of action of NSAIDs is primarily associated with the suppression of the activity of an enzyme called cyclooxygenase. It regulates the synthesis of certain substances that control cellular activity. Due to this, NSAIDs reduce the symptoms of inflammation and pain. As a rule, NSAIDs are used in the treatment of rheumatoid arthritis. They help to cope with chronic pain, inflammation and swelling. But they do not affect the cause of the disease and do not stop the destruction of joints. For most rheumatological diseases, kidney damage portends a poor prognosis and requires aggressive immunosuppressive treatment. On the other hand, it is almost impossible to group NSAIDs by greater or lesser adverse effects on the kidneys - there are very few comparative scientific studies. Thus, it is important to diagnose and treat them at an early stage. But it can be stated that almost all NSAIDs (including selective COX-2 inhibitors) have been described to have adverse effects on the kidneys.

Keywords: Drug-induced nephropathy, rheumatoid arthritis, nephropathy, chronic kidney disease, nonsteroidal anti-inflammatory drugs.

Introduction

Drug-induced kidney injury (DIKI) is a variety of damage to kidney structures caused by drugs (DR) that varies in severity and consequences [49]. The kidneys are one of the most frequently affected organs in patients with rheumatic diseases. Kidney damage can be caused by both the direct effects of the disease and complications from the therapy used. Renal manifestations can vary from asymptomatic urinary tract disorders to serious complications leading to chronic renal failure [45]. However, rheumatological diseases complicated by kidney damage in most cases require immunosuppressive therapy and are associated with higher morbidity and mortality. A nephrologist, along with rheumatologists, plays a key role in the management of these patients not only in establishing a diagnosis and prescribing appropriate treatment in the acute phase of the disease, but also in the treatment of remote complications, such as chronic renal failure. On the other hand, patients with CKD may develop rheumatological symptoms that need to be differentiated from the primary rheumatological disease. Kidney damage is a direct consequence of the rheumatic disease. Today, it is the most common cause of kidney damage in rheumatic diseases [2].

The inflammatory process may involve different parts of the kidney. Some diseases predominantly affect the glomeruli (e.g., lupus nephritis), while others affect small (small vessel vasculitis) or large vessels (Takayasu arteritis) of the kidney, and some diseases predominantly affect the

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interstitial compartment (e.g., primary Sjögren's syndrome). Kidney damage is sometimes the result of a chronic, long-term inflammatory state caused by these diseases (e.g., secondary amyloidosis or accelerated atherosclerosis) [41, 43, 20].

The term NSAID was introduced into clinical practice in 1949 in relation to phenylbutazone, 3 years after the anti-inflammatory property of corticosteroids was demonstrated, therefore, having an anti-inflammatory effect similar to steroids, but having a different chemical structure, they were called non-steroidal anti-inflammatory drugs [29].

Risk factors for CKD

Modifiable	Non-modifiable
Alcohol, drugs, smoking	Male gender
Excess weight	Age
Pregnancy	Hereditary kidney diseases
High protein diet	Reduced number of nephrons at birth
Heart failure	Race
Arterial hypertension	
Infections	
Medicines - NSAIDs, analgesics, nephrotoxic antibiotics	
Chronic inflammation	
Stress	

The mechanism of action of these agents, associated with the blockade of prostaglandin (PG) synthesis due to the inactivation of the cyclooxygenase (COX) enzyme, was established in 1971 [38]; for this discovery, John R. Vane was awarded the Nobel Prize in Medicine in 1982.

Physiological effects of PG

NSAIDs inhibit COX, which catalyzes the process of PG synthesis. Under the influence of COX, cyclic endoperoxide PgG2 is formed from arachidonic acid, which is then converted into PgH2 by peroxidation with the simultaneous production of unstable toxic oxygen radicals. PgH2, in turn, is converted into PgE2, PgI2, PgF2 and thromboxane. PG synthesis is activated by vasoactive hormones and cytokines, as well as hypoxia, ischemia and cellular mechanical disorders [35]. The formation and localization of different PGs are determined by the features of the expression of isoenzymes - COX-1 and COX-2.

Expression of COX-1 occurs in arteriolar smooth muscle, mesangial and endothelial cells, parietal epithelial cells of the Shumlyansky-Bowman capsule, and in cells of the cortical and medullary collecting ducts. Expression of COX-2 occurs in cells of the macula densa, in epithelial cells of the ascending thick limb of the loop of Henle, as well as in podocytes and arteriolar smooth muscle, in medullary interstitial cells, and in cells of the cortical part of the collecting ducts and proximal tubules [6–22].

PGs are biologically active lipids, derivatives of fatty acids, and participate in a wide range of physiological and pathophysiological processes.

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They regulate numerous renal functions: vascular tone, salt and water balance, and renin release [18].

The kidneys generate mainly PgE2 and PgI2 and, to a lesser extent, PgF2. The vasodilator effect of PgI2 and PgE2 plays a leading role in the regulation of renal blood flow and glomerular filtration rate (GFR), concentration processes, renin release, and excretion of sodium, water, and potassium [14, 9].

In euvolemic conditions, the physiological role of PG in maintaining renal blood flow and SCF is insignificant. With activation of vasoconstrictor hormones (angiotensin II, norepinephrine, endothelin and vasopressin), cytokines and a decrease in sodium consumption, local renal vasodilator PgE2 and PgI2 prevent their vasoconstrictor effect [50, 12].

In subsequent years, as molecular biology developed, the existence of several cyclooxygenase isoenzymes was established – COX-1, COX-2 and COX-3 (the role of the latter is being clarified), encoded by different genes [25, 7]. Synthesis of COX-1 in different organs and tissues, in particular the kidneys, is carried out independently of inflammatory processes, and prostanoids formed under the influence of the enzyme are of great importance in maintaining hemostasis and cytoprotection.

COX-2 synthesis is usually induced by inflammatory cytokines and chemokines, so it was believed that COX-1 inhibition leads to the development of side effects, while COX-2 inhibition has a therapeutic effect. The identified differences allowed the development of a new class of drugs - coxibs, which selectively inhibit COX-2 activity, thereby reducing the severity of the inflammatory reaction, while the analgesic effect is not reduced compared to non-selective drugs. However, the results of experimental and clinical studies showed that COX-2 formation can occur regardless of inflammation processes and both isoenzymes are present in different organs, including the kidneys. The resulting PGs participate not only in the pathogenesis of some diseases, but also in maintaining the normal function of many organs [31]. For example, PGI2 in the brain prevents damage and death of neurons [34], which may be important in the treatment and prevention of strokes [5], reduces pressure in the pulmonary circulation in pulmonary hypertension [26, 27], and participates in the regulation of embryo implantation. In addition, experimental studies have shown the role of NSAIDs in slowing the development of atherosclerosis in the postmenopausal period [10].

Non-steroidal anti-inflammatory drugs (NSAIDs), due to their unique analgesic, antipyretic and anti-inflammatory activity, are widely and successfully used in various areas of internal medicine, traumatology, otolaryngology, urology, ophthalmology and pediatrics.

The high frequency (often unjustified) of prescribing NSAIDs and a wide range of side effects (including life-threatening ones), including complications from the gastrointestinal tract (dyspepsia, ulcers, bleeding and perforation of the upper and lower gastrointestinal tract), cardiovascular system (destabilization of blood pressure and heart failure, increased risk of cardiovascular catastrophes), liver and kidneys, confirm the complexity and importance of studying this problem.

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Side effects of various drugs have become a serious medical and social problem today, which can be explained by [6–7]:

• their often-unjustified prescription, inadequate dosages, and unjustified duration of use;
• interactions between different classes of drugs;
• insufficient understanding of the pharmacodynamic and pharmacokinetic characteristics of drugs;
• insufficient knowledge of the specifics of side effects of different classes of drugs;
• lack of proper monitoring of patients during drug therapy;
• late diagnosis of side effects that have developed, which makes it difficult to eliminate them and increases the unfavorable prognosis;
• an increase in the frequency of hospitalizations and deaths caused by side effects of drugs;
• high financial costs aimed at eliminating side effects.

NSAIDs and Chronic Kidney Disease

Data on the effect of NSAIDs on the development and progression of CKD are quite contradictory. Some studies and meta-analyses have not found any adverse effect of NSAIDs on the course of CKD or its development. Thus, P. Nderitu et al. [32] did not reveal any significant effect of regular use of NSAIDs on the progression of CKD (odds ratio - OR 0.96, 95% CI 0.86-1.07). Only at their high doses was an increase in the rate of progression (decrease in SCF ≥15 ml/min per 1.73 m2 over a 2-year period) of renal function decline by 26% (OR 1.26, 95% CI 1.06-1.50) observed. The authors of this study believe that at stages III-IV CKD, the use of low doses of NSAIDs is acceptable.

J. Kohlhagen et al. [21] compared the prevalence of CKD in rheumatological patients who regularly took NSAIDs and a control group. CKD occurred in 1 out of 5 rheumatological patients who had been taking NSAIDs for a long time, but did not exceed that in the compared patients who did not take NSAIDs. L. Agodoa et al. [1] also did not reveal a clear association between regular use of NSAIDs and an increased risk of developing CKD.

J. Yaxley, T. Litfin [39] analyzed the results of 9 studies (12,418 patients) devoted to the study of the effect of NSAIDs on the development of CKD, and noted the absence of evidence of the risk of developing "analgesic" nephropathy, i.e. CKD that develops with long-term use of analgesics. However, the authors note that the end point of most studies included in the meta-analysis was end-stage renal failure (ESRD), and not "analgesic" nephropathy or any other stage of CKD. Any results based on such data will be questionable, since "analgesic" nephropathy develops into ESRD relatively infrequently.

Results of other studies indicate nephrotoxicity of NSAIDs, manifested by deterioration of renal function. Yu-Kang Chang et al. [3] demonstrated a progressive decrease in SCF in patients with ESRD.

The authors of this study concluded that the use of NSAIDs may be the ≪last straw≫, worsening ESRD, requiring hemodialysis. In their opinion, even short-term use of NSAIDs in patients with ESRD is unacceptable (OR 2.73, 95% CI 2.62-2.84 for non-selective NSAIDs and OR 2.17, 95% CI 1.83-2.57 for celecoxib). Compared with oral forms, a significantly higher risk was observed with parenteral use of NSAIDs (OR 8.66, 95% CI 6.12-20.19), especially when used for 2 weeks.

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Results of the study by Yu-Kang Chang et al. [3] also indicated an increase in NSAID nephrotoxicity in patients who underwent excretory urography using a contrast agent (OR 5.89).

In a retrospective study by A. Schwarz et al. [4] of morphologically confirmed cases of ATIN (1068 renal biopsies from 1968 to 1997), it was found that analgesics, especially NSAIDs, are risk factors for the development of CKD. Renal dysfunction was reversible in 69% and irreversible in 31% of cases, with NSAIDs causing the development of CKD in 56% of cases.

Data from Y. Ingrasciotta et al. [17] indicate a statistically significant increase in the risk of CKD with the use of NSAIDs. A significant increase in the risk of CKD was found with short-term use of ketorolac (OR 2.54, 95% CI 1.45–4.44), meloxicam (OR 1.98, 95% CI 1.01–3.87) and piroxicam (OR 1.95, 95% CI 1.19–3.21). The authors suggest that the use of NSAIDs with a long half-life, such as oxicams, is associated with an increased risk of CKD.

Currently, the leading pathogenetic mechanism for the development of glomerulo- and tubointerstitial changes in the kidneys is chronic inflammation. In particular, elevated levels of C-reactive protein (CRP) in the blood of patients with RA cause dysfunction of the glomerular vascular endothelium and trigger the synthesis of proinflammatory cytokines. [20,36]. Previously published studies have shown that in patients with RA treated with cytokine inhibitors, renal function remained stable for a long time [23]. According to other data, in RA and renal amyloidosis, therapy with tumor necrosis factor alpha inhibitors led to a simultaneous decrease in proteinuria [11].

The study of the pathogenesis of glomerulonephritis continues, since existing methods of therapy do not have the desired effectiveness [13]. The connection of glomerulonephritis with a change in the balance of cytokine synthesis associated with the mechanisms of the immune response has been proven [42,16]. It has been established that cytokines participate in the regulation of proliferative processes, differentiation, growth, and cell activity [24,15]. The quantitative content of cytokines and their ratio reflect the dynamics of the pathological process, correlate with the activity of the disease, which allows us to judge the effectiveness of the therapy and predict the outcome of the disease [37].

Patients with RA may have various kidney diseases: secondary renal amyloidosis, glomerulonephritis, interstitial nephritis, renal vasculitis, nephrosclerosis, and in some cases, their combinations [48,40]. Etiologically, kidney damage in patients with RA can be conditionally divided into 2 groups: firstly, nephropathy as one of the extra-articular manifestations or complications of RA itself, for example, renal vasculitis, chronic glomerulonephritis, secondary amyloidosis, and secondly, as a complication of drug therapy for RA: analgesic nephropathy (AN), drug-induced glomerulonephritis. The pathogenesis of such different kidney diseases cannot be the same. A certain contribution to the progression of chronic kidney disease is made by disorders in the hemostasis system, endothelial dysfunction [44,46], the frequency of exacerbations of the disease, the presence of crescents and the severity of tubulointerstitial changes in the nephrobiopsy [33,19,50].

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