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THE EFFECT OF SELECTIVITY AND HALF-LIFE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS FOR THE DEVELOPMENT OF SUBCLINICAL KIDNEY DAMAGE

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Sh.A.Mustafayeva.
Bukhara State Medical Institute

Resume

The article presents data on the incidence of chronic kidney disease in rheumatoid arthritis. Kidney damage is a common occurrence in patients with rheumatological diseases, and can also develop either because of the disease itself or secondary to the drugs used in the treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to relieve pain in patients with rheumatoid arthritis. In rheumatoid arthritis, the occurrence of chronic kidney disease depends primarily on the duration of the disease and the nature of the inflammatory process. These data are fully confirmed at the moment. The problem of kidney damage in rheumatoid arthritis has been little studied and requires further research.

Keywords

rheumatoid arthritis; nonsteroidal anti-inflammatory drugs; a1-microglobulin; kidney damage.

In the scientific community, rheumatoid arthritis (RA) is positioned as a central, key problem of modern rheumatology, since advances in the study of the etiology, pathogenesis and treatment of this disease have a great impact on the development of not only rheumatology, but also medicine in general [E.D. Harris, 1997; Ya.A. Sigidin, G.V. Lukina, 2001; E.L. Nasonov, V.A. Nasonova, 2008].

RA has a potentially unfavorable prognosis, since there are no methods to achieve its complete cure [A.I. Vyalkov et al., 2001; E.L. Nasonov, 2002]. Nevertheless, modern multicomponent and aggressive pathogenetic pharmacotherapy allows to induce and consolidate remission, but its use requires solving complex problems of early reliable diagnosis, prognosis of the course of the disease and anticipation of possible adverse drug reactions.

Rheumatoid arthritis (RA) is the most frequent autoimmune human disease [Sigidin Ya.A. et al., 2004] and occupies one of the leading places among diseases of the musculoskeletal system and connective tissue in terms of its medical and social significance. A feature of RA is the progressive course, which leads to the

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generalization of the pathological process involving new joints and extra-articular structures, the formation of irreversible changes leading to rapid disability of patients, and a decrease in susceptibility to therapy is also characteristic [Olyunin Yu.A., 2010].

Renal manifestations can range from asymptomatic lesions to the development of terminal renal failure requiring renal replacement therapy; they have enormous prognostic significance, require a specific therapeutic strategy, and cause higher mortality. The nephrologist and rheumatologist play a key role in the introduction of such patients: in early verification of the diagnosis, determining the treatment strategy, prescribing appropriate treatment methods in the acute stage of the disease and long-term management of such patients.

Kidney damage can either be caused by direct exposure to systemic autoimmune disease, or be the result of complications or side effects of the therapy used [4].

One of the most severe visceral manifestations of RA is nephropathy, which occupies a special place, since it remains a factor determining not only the severity of the course and prognosis of the disease, but also its outcome. The causes of nephropathy in RA are diverse: kidney damage can be one of the manifestations or complications of the disease (secondary amyloidosis), as well as be the result of drug therapy [Shulutko B.I., 1993; Bacon P.A., 1997; Batyushin M.M. et al., 2009].

The term nonsteroidal anti–inflammatory drugs was introduced into clinical practice in 1949 after receiving evidence of the anti-inflammatory properties of the steroid phenylbutazone. Drugs that had a different chemical structure and the ability to have an anti-inflammatory effect similar to steroids were called nonsteroidal [20].

The mechanism of action of drugs of the NSAID class is based on the ability to block the synthesis of prostaglandins (PG) due to the inactivation of the cyclooxygenase enzyme (COX), which allows to specifically influence the development of inflammation and pain syndrome [42]. For this discovery, J.R. Vane was awarded the Nobel Prize in Medicine in 1982. [29].

There are three types of COX inhibitors.

The first group includes acetylsalicylic acid, which inhibits the enzyme irreversibly by covalent modification of the acetylation reaction. COX inactivation in non-nuclear platelets is actively used in cardiology in patients with coronary heart disease.

The second group is non–specific (non-selective) NSAID – interacts with the application point of COX and inactivates both its isoforms (COX-1 and COX-2).

Inhibition of the latter is the basis for the effects: antipyretic, anti-inflammatory, and analgesic. Inactivation of COX-1 can affect vascular hemostasis and reduce the ability of afferent and efferent arterioles to direct and cAMP-mediated vasodilation, which can significantly disrupt kidney function [19].

The third group of NSAIDs – specific (selective) COX-2 inhibitors (coxibs), were developed to replace non-selective drugs in order to reduce side effects [33].

Clinically nonspecific renal pathology is diagnosed in the case of pronounced changes in urine and blood, although pathological studies can detect kidney damage in more than half of cases.

The urinary proteome is a potential source of information for kidney diseases [26]. According to proteomic analysis, from 900 to 2500 different proteins and polypeptides may be present in a urine sample [30]. In laboratory practice, it is customary to evaluate the total excretion of all proteins in the urine – proteinuria. The total concentration of proteins in urine is an important diagnostic indicator that is included in routine urine analysis, at the same time, the assessment of proteinuria does not answer some questions, for example, about the localization of nephron damage. In this work, we supplemented the analysis of proteinuria with the identification of high-molecular [transferrin (Trf), immunoglobulin G (IgG)] and low-molecular [α1-microglobulin (α1-MG), β2-microglobulin (β2-MG)] proteins whose urinary excretion may reflect two main variants of proteinuria – a violation of the permeability of the glomerular filter and a decrease in reabsorption in the tubules [43,7].

An increase in urinary excretion of albumin, alpha – 1 microglobulin and beta-2 microblobulin makes it possible to detect renal pathology at the early stages of its development [32,37,44]. It should be noted that the reliability of the results of this method, according to the literature, is comparable with such complex instrumental and laboratory techniques as dynamic renal scintigraphy and the study of glomerular filtration rate and renal blood flow [40,5,6]. On the other hand, the determination of the excretion levels of low molecular weight proteins is a non–invasive method, practically independent of the gender, age and condition of the patient, and therefore it is easy to use it as a screening test for early diagnosis of nephropathies.

To identify renal pathology at the preclinical stage and clarify its nature, methods for determining the excretion of low-molecular-weight proteins with urine should be used.

Albumin is a non-glycosylated protein with a molecular weight of 66,000 D (66 kD), and the diameter of its molecules is significantly smaller than the diameter of

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the pores of the basement membrane of the renal glomerulus (3.6 and 7.0 nm), however, their charges of the same name lead to mutual repulsion and prevent protein loss. A decrease in the charge of the renal filter during its destruction leads to an increase in albuminuria. Urinary albumin excretion in the range of 30-300 mg/day is called microalbuminuria (MAU) and is currently considered as an available and early marker of pathological changes in the basement membrane. The method is based on the reaction between polyclonal antialbumin antibodies and the antigen of the test sample with the formation of an antigen-antibody complex. The daily urine is examined, which is centrifuged for 10 minutes at a speed of 800 or more rpm. With a high albumin content, urine is diluted with 0.9% sodium chloride solution. Urinary albumin excretion should normally not exceed 30 mg/day [31,2].

Currently, medicine knows a huge number of conditions manifested by the development of pain and requiring the use of painkillers. Thus, the systematic use of nonsteroidal anti-inflammatory drugs (NSAIDs) can not only slow down the diagnosis of a disease accompanied by pain syndrome, but also lead to the development of other, more serious diseases. One of the serious side effects of prolonged and uncontrolled administration of nonsteroidal anti-inflammatory drugs is, along with damage to the gastrointestinal tract, kidney damage.

According to the literature, pronounced side effects from the kidneys were registered with the use of cyclosporine, gold salts and D-penicillamine, while methotrexate (MT, in immunosuppressive doses), azathioprine, antimolarial drugs, sulfasalazine, leflunomide, etanercept and infliximab did not have significant nephrotoxicity [27].

Of course, the largest number of studies are devoted to the development of medicinal nephropathy with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), the use of which is unlikely to be abandoned in the near future. Toxicity of NSAIDs

it is determined primarily by their selectivity. It was previously assumed that cyclooxygenase isoforms (COX) regulate the physiological effects of prostaglandins.

While an increase in the level of type 2 COX in tissues occurs during inflammatory processes. All this served as the basis for the creation of a new generation of selective NSAIDs (c-NSAIDs), which have all the positive aspects of non-selective NSAIDs (n-NSAIDs), but less toxicity.

However, it was later shown that COX2 is constantly synthesized in various parts of the nephron and its metabolites play an essential role in the functioning of both the glomerulus and the tubular apparatus of the kidney [17,14], and the main

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cause of nephrotoxicity is a decrease in the tissue concentration of prostaglandins, which are synthesized by both isoforms of COX [15, 41]. Thus, in animal experiments and in studies in healthy volunteers, it was revealed that in conditions of reduced sodium intake, COX2 inhibitors increase blood pressure, reduce renal blood flow and glomerular filtration rate (GFR), thereby creating prerequisites for the development of both acute and chronic nephrotoxicity [24, 25].

It is known that the glomerular filtration rate decreases with age. Thus, according to R.C. Harries, the incidence of NSAID nephropathy increases 10-fold in people over 65 years of age [8].

Other researchers believe that kidney damage in elderly patients in the absence of risk factors such as hypovolemia, previous renal failure and others is rare [28].

First of all, the pharmacokinetic features affecting the toxicity of NSAIDs include their half-life (T1/2). Depending on this, all NSAIDs are divided into "short-lived" (T1/2<6 h) and "long-lived" (T1/2>6 h). It is noted that longer circulation of the drug in the blood is associated with prolongation of the therapeutic effect (which is undoubtedly a big plus in the treatment of chronic pain), however, the same property creates prerequisites for enhancing the toxic effects of NSAIDs [9]. Special care should be taken when prescribing "long-living" drugs in patients with an existing functional kidney defect. This feature is reflected in the recommendations for the management of patients with chronic pain and chronic kidney disease [3].

The main effects of NSAIDs on the human body include analgesic, anti-inflammatory and antipyretic effects.

The unfavorable prognostic value of kidney damage in rheumatoid arthritis (RA) has been actively attracting the attention of researchers in recent years [11]. Certain clinical variants of involvement of the kidneys in the pathological process in rheumatoid arthritis are noted in most patients [38]. Various variants of kidney damage in rheumatoid arthritis are described, in particular, glomerulonephritis, amyloidosis, vasculitis, as well as iatrogenic forms (analgesic tubulopathy, membranous nephropathy, etc.) [39, 36].

The term NSAID was introduced into clinical practice in 1949 after receiving evidence of the presence of anti-inflammatory properties of the steroid phenylbutazone. Drugs that had a different chemical structure and the ability to have an anti-inflammatory effect similar to steroids were called nonsteroidal [35].

The outcome of rheumatoid nephropathy is the development of nephrosclerosis, a decrease in the number of functions!nephrons with the formation

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of chronic renal failure [Sihvonen S. et al., 2004; Shilov E.M., 2008], which determines the importance of timely diagnosis of kidney damage in RA and the initiation of therapy.

An early sign of kidney damage is microalbuminuria

(MAU), has been well studied in patients with diabetes mellitus and is considered as a diagnostic criterion for initial diabetic nephropathy [Poulsen P.L. et al., 1999; Gross J.L. et al., 2005], as well as in cardiovascular pathology [Klausen K.P. et al., 2006; Trie F. et al.., 2006; Mukhin H.A. et al. 2009; Sorokin E.V., 2010]. Studies of urinary albumin excretion in RA and developing amyloidosis are isolated, their results are contradictory, which determines the relevance of the problem of studying early markers of damaging kidneys in this pathology.

Renal complications, in patients regularly taking NSAIDs, are common [10, 12]. Renal manifestations when using NSAIDs can vary widely. The development of the disease of minimal changes, membranous nephropathy, tubulointerstitial nephritis with nephrotic syndrome, acute tubular necrosis is described. Less dangerous, however, are more frequent side effects from the kidneys – fluid retention, increased blood pressure, the development of edema and hyperkalemia [23]. Data on the effect of NSAIDs on the progression and development of chronic kidney disease are contradictory. Thus, in a long-term cohort study, there were no functional changes in patients taking NSAIDs compared to the control group [16]. According to meta-analysis, only the use of high doses of NSAIDs was accompanied by an increase in the risk of progression of renal failure [18].

According to a number of authors, the ability to regulate the local hemodynamics of the nephron and the water-electrolyte balance at the level of its tubules is due to the paracrine role of PG, the synthesis of which is influenced by this group of drugs [21]. Since NSAIDs are a heterogeneous group of drugs, various effects, including side effects, may occur within the same class and even doses of one drug [13]. Thus, low doses of aspirin are manifested at the level of portal circulation platelets and have a higher selectivity for the COX-1 enzyme, high doses of aspirin block both isoforms.

The question of the time required for the development of nephrotoxic effects remains relevant. Some authors believe that NSAID nephropathy should be understood only as those changes that develop with the abuse of analgesics, i.e. the use of analgesic should be daily for at least 5 years at a total dose of 3000 conventional units, where one unit is one tablet [34].

Others consider as kidney damage all possible clinical manifestations of NSAID nephropathy by the time of occurrence: acute renal failure (ARF), which

develops within a few hours from the start of taking NSAIDs, acute tubulointerstitial nephritis - after 2-18 months in combination with papillary necrosis and chronic interstitial nephritis – after taking NSAIDs for several years [22].

Conclusions:

Increased urinary excretion of albumin, alpha 1 – microglobulin and beta 2-microglobulin makes it possible to identify renal pathology in the early stages of its development. Urinary albumin excretion in the range of 30-300 mg/day, called microalbuminuria (MAU), is considered as an accessible and early marker of pathological changes in the basement membrane. Increased excretion of microglobulins in the urine with preserved functional ability of the kidneys and their normal level in the blood indicates a violation of the tubular functions of the nephron.

Kidney damage is a common occurrence in patients with rheumatological diseases, and can also develop either because of the disease itself or secondary to the drugs used in the treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to relieve pain in patients with rheumatoid arthritis. In rheumatoid arthritis, the occurrence of chronic kidney disease depends primarily on the duration of the disease and the nature of the inflammatory process.

Thus, even a short intake of high doses of NSAIDs can lead to acute kidney injury. The picture of CRF develops with prolonged use of analgesics, and the pathogenesis of this nephropathy is associated with slowly progressive necrosis of the renal papillae. The problem of kidney damage in rheumatoid arthritis has been little studied and requires further research.

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