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RENAL EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS: A LITERATURE REVIEW

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Abstract: Kidney diseases are currently one of the greatest morbidities in the world, and their development is sometimes associated with the administration of non-steroidal anti-inflammatory drugs, which can cause nephrotoxicity and compromise the physiological function of the kidneys, leading to glomerulopathies and acute kidney injuries. Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used drugs worldwide to inhibit COX activity in the treatment of pain and inflammation. Its nephrotoxicity has been well documented. Thus, the objective of this work is to clarify the relationship between the repercussion in patients with chronic kidney diseases and the use of NSAIDs, as well as an approach to nephrotic syndrome. A free literature review will be carried out on digital platforms such as Google Scholar, Scielo, Pubmed, Embase and Lilacs, selecting articles published between 2010 and 2020 for analysis. The results showed that renal side effects vary with the extent of COX-2-COX-1 selectivity and the administered dose of these compounds. While young healthy individuals rarely experience adverse renal effects from NSAID use, elderly patients and patients with chronic comorbidities taking drug combinations (eg, ACE inhibitors or ARBs, diuretics plus NSAIDs) may develop acute renal failure. This review summarizes our current knowledge of how traditional NSAIDs and selective COX-2 inhibitors can affect the kidney in various experimental and clinical conditions, and how these drugs can influence renal inflammation, organ dysfunction and may result in renovascular hypertension.
Keywords: Anti-inflammatory, nephro-toxicity, Glomerulopathy, kidney injury.

INTRODUCTION

Chronic kidney disease has had an increased incidence over the years, being

considered a serious public health problem and one of the main causes of morbidity worldwide, leading, in more advanced cases, to end-stage renal disease. expensive renal replacement therapy required 1.

Some drugs have been associated with the development of chronic kidney diseases, such as non-steroidal anti-inflammatory drugs, which are inhibitors of vasodilating prostaglandins that interfere with renal hemodynamics and that can lead to complications that lead to acute renal failure in patients due to ischemia. or the induction of cytokine production that induce glomerular injury 2.

Non-steroidal anti-inflammatory drugs (NSAIDs) are currently the most prescribed class of drugs in the world, as they have numerous analgesic and anti-inflammatory effects, in addition to the ease of access, but these drugs can have a number of side effects, especially in patients who have reduced renal perfusion, compromising the functioning of the kidneys 3.

NSAIDs represent one of the most common classes of drugs used worldwide, with an estimated use of over 30 million per day. NSAIDs exert anti-inflammatory, analgesic and antipyretic effects through suppression of prostaglandin (PG) synthesis, inhibiting the enzyme cyclooxygenase (COX). It is known that there are two isoforms of this enzyme COX-1 and COX-2. The gastrointestinal tract and kidneys are important targets for undesirable clinical events associated with the use of NSAIDs. Approximately 2.5 million Americans experience NSAID-mediated kidney effects annually 7.

Non-selective NSAIDs inhibit COX-1 (constitutively expressed in the kidney) and COX-2 (inducible in most tissues in response to injury or inflammation, but also present at detectable levels in the normal kidneys of adult mammals), which are blood-limiting enzymes. rate of production of PGs and thromboxane (TX). COX-2 is regulated in response to intravascular volume. COX-1 functions primarily in controlling renal hemodynamics and glomerular filtration rate (GFR), while COX-2 primarily affects salt and water excretion. Blocking one or both enzymes can therefore have different effects on kidney function 7.

Nephrotoxicity caused by the use of non-steroidal anti-inflammatory drugs includes acute tubular necrosis, nephritis interstitial tissue, membranous glomerulonephritis, renal papilla necrosis, hyperkalemia, necrotic lesion, among others, being a risk factor especially for patients with kidney, heart and elderly diseases, so that, in the presence of any symptom, the use must be discontinued. 3. Thus, the objective of this study is to clarify the relationship between patients with chronic kidney disease and the use of NSAIDs, as well as nephrotic syndrome as the focus of renal involvement.

MATERIAL AND METHODS

The main objective of the study methodology is based on a descriptive and qualitative analysis, it is to gather and synthesize knowledge about the proposed theme, about the relationship between the repercussion in patients with chronic kidney diseases and the use of non-steroidal anti-inflammatory drugs, as well as an approach on nephrotic syndrome, this approach was chosen for this study. According to GIL (2007) descriptive analysis helps the researcher to verify, examine, record and explain situations without directly intervening in them, detailing characteristics of an event in which the researcher must have a domain and knowledge about the subjects and the doubts to be investigated followed by for the interpretation and comparison between analyzes and case studies that make

up each study.

For this, in the data research, scientific studies published in recent years were analyzed that evaluate information about opinions and values, unlike statistical data, creating a framework to respond to the problem, the choice was to collect information on the relationship between the repercussion in patients with chronic kidney diseases in a first part, on some main points such as the forms and limitations as concepts are articulated in practice. The second part is about the interpretation and comparison between other studies, finding information and significant evidence on the topic in question, the collection databases were through GOOGLE ACADÉMICO, SCIELO, PUB, EMBASE and LILACS published in recent years with the following topics: Anti-inflammatory. nephrotoxicity. Glomerulopathy. Kidney injury.

It was also hoped that this study could contribute to making the development and implementation as successful as possible. Therefore, the objective of this study was to use the action research methodology to introduce, study and clarify the relationship between the repercussion in patients with chronic kidney diseases and the use of non-steroidal anti-inflammatory drugs in different contexts, in order to meet to the local needs of specific patients.

RESULTS

PATHOPHYSIOLOGICAL APPROACH

The kidneys are essential for excretion and receive about 25% of all cardiac output, where any drug that enters the bloodstream passes through these organs, so if in high concentrations, drugs can trigger inflammatory responses and compromise their function, glomerular filtration function 3.

Non-steroidal anti-inflammatory drugs have three different main actions, the anti-inflammatory, analgesic and antipyretic 4, where their use inhibits the arachidonic acid cascade, affecting the formation of prostaglandins, which act as vasodilators and increase renal perfusion, which may so the use of the drug causes vasoconstriction, spinal cord ischemia and acute kidney injury, in addition to inhibiting the transport of sodium and chloride in the loop of Henle and collecting ducts, resulting in natriuresis, diuresis and sometimes edema formation 5.

GLOMERULOPATHIES

Glomerulopathies are a set of diseases that affect the glomeruli, responsible for blood filtration and urine production, and some studies suggest that the use of large amounts of non-steroidal anti-inflammatory drugs can lead to nephrotic syndrome in this structure, due to the changes deleterious effects that this drug causes by blocking prostaglandins 6.

Most patients who develop glomerulopathy make special use of the anti-inflammatory drug diclofenac, but any drug of this class can cause this nephropathy 2.

NEPHROTIC SYNDROME

Nephrotic syndrome (NS) is a clinical syndrome defined by massive proteinuria (greater than 40 mg/m2 per hour) responsible for hypoalbuminemia (less than 30 g/L), with hyperlipidemia, edema and various resulting complications. It is caused by increased permeability through the damaged basement membrane in the renal glomerulus, especially infectious or thromboembolic. It is the result of an abnormality of glomerular permeability that can be primary with a specific disease of the kidneys or secondary to congenital infections, diabetes, systemic lupus erythematosus, neoplasia or use of certain medications 8,9,10.

The disorder can affect people of all ages. In most children, the first sign of nephrotic

syndrome is facial swelling. Adults usually have dependent edema. Nephrotic syndrome is an important chronic disease in children. The estimated annual incidence of nephrotic syndrome in healthy children is two to seven new cases per 100,000 children under 18 years of age. More common in boys than girls in younger age groups, but once reached adolescence, there is no significant difference between the sexes. Higher incidence and more severe disease seen in African American and Hispanic populations 11.

DISCUSSION

Overall, nephrotic syndrome is more common in men. The glomerular capillaries are lined by a fenestrated endothelium that lies on the glomerular basement membrane, which in turn is covered by glomerular epithelium, or podocytes, which surround the capillaries with cell extensions called foot processes (pedicelles), these processes interdigitate with junctions cells called the slit diaphragm filtration that together form the glomerular filter. Normally, larger proteins (greater than 69 kD) are excluded from filtration. Destruction of podocytes above a critical mass also leads to irreversible glomerular damage 12,13,14.

NSAIDs can cause a variety of kidney problems, which include acute kidney failure, abnormalities in sodium, water, and potassium homeostasis, acute interstitial nephritis (AIN), chronic kidney injury, and nephrotic syndrome. The two main mechanisms for its renal toxicity are hemodynamically and immunologically mediated. Most of the renal effects of NSAIDs are hemodynamically mediated. Interstitial nephritis and nephrotic syndrome are closely associated and their pathogenesis is considered to be immunologically mediated. The incidence of NSAID-related AIN has been reviewed 15,22.

It was diagnosed in only 1% of the 460 patients with renal impairment. Biopsies reviewed by Abraham and Keane on 0.4% of 1,500 kidney biopsies and 200 autopsy samples in a 10-year survey. However, AIN was present in 18.6% of kidney injuries associated with the use of NSAIDs 16,17,18.

Several NSAIDs have been reported to cause AIN 19. Nephrotic proteinuria occurs in 80% of NSAID-related AIN cases. The clinical manifestations of AIN with NSAID-induced heavy proteinuria are nonspecific. Patients are usually elderly and may have been using the drug for months. Symptoms and signs of hypersensitivity are usually absent. Urine on microscopy may show red blood cells and leukocytes with a low excretion sodium fraction. However, proteinuria may improve within days or weeks after discontinuing the responsible drug. Complete remissions are often seen. However, some patients may have permanent damage, resulting in chronic kidney failure or even progression to end-stage disease. The classic renal biopsy findings are interstitial nephritis with only mild mesangial proliferation. Electron microscopy usually shows a fusion of epithelial deposits similar to minimal lesion with occasional mesangial nephropathy and electron dense deposition. In immunofluorescence studies, they are generally normal 20,21.

FINAL CONSIDERATIONS

NSAID-induced nephrotic syndrome can also occur without interstitial nephritis. About 10% to 12% of patients develop kidney damage, while some drug users have nephrotic syndrome in which kidney biopsy shows only minimal changes in the disease. They usually go into complete remission within a few weeks but can relapse with proteinuria even when they are not being re-exposed to the drug. Some cases of membranous nephropathy have also been

reported, but proteinuria may persist for a period of 3 months to 3 years after withdrawal of the responsible drug. Treatment is favorable. Usually, kidney function improves gradually unless the patient has already suffered permanent damage. The use of steroid therapy that are controversial, although there have been reports showing some improvement in patients with drug-induced AIN and epithelioid cell granulomas. A detailed drug history is important to make the correct diagnosis, as in these patients presenting with nephrotic syndrome without significant renal failure. The patient must avoid any further exposure to NSAIDs, such as cutaneous application of NSAIDs that have been reported to be capable of inducing nephrotic syndrome.

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