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ACUTE KIDNEY INJURY CAUSED BY THE USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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Abstract: Non-Steroidal Anti-Inflammatory Drugs are frequently prescribed in medical practice, are one of the most widely used drug classes in the world and carry a low but tangible risk of causing Acute Kidney Injury, electrolyte imbalances and increased blood pressure. However, studies showing the long-term effects of NSAID use on the development of CKD are still minimal, as such studies routinely exclude people with CKD and rarely report renal outcomes. The present study aimed to report the importance of using this pharmacological class with caution. A descriptive, qualitative study of current Literature Review was carried out to prepare the work. Was the risk of ARI associated with the use of NSAIDs in patients with CKD evaluated? The Medline database (via PubMed) was used, with preference given to the most current full-text articles, such as from 2014 to 2021. Only articles in English were selected. The results of the literature review showed that current exposure to NSAIDs was associated with an approximately 1.5-fold increase in the odds of developing Acute Kidney Injury in the general population and in people with Chronic Kidney Disease. This study found that the chances of developing ARI increased by more than 50% in people who were exposed to NSAIDs in the general population and in people with CKD, and in older people the chance of developing ARI doubled. Future research must quantify the level of high-dose use in patients with CKD and explore the effects of comorbidities and co-prescription.

Keywords: Acute kidney injury; Non-steroidal anti-inflammatory drugs; Risk factors; Chronic kidney disease, Kidney disease, NSAIDs.

INTRODUCTION

Since the isolation of salicylate from willow bark around 1830, followed by the discovery of aspirin (acetyl salicylate) by Felix Hoffman of the Bayer industry, Germany in 1897, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have enjoyed glorious status in the industry. pharmaceutical (MONTINARI et al. 2019; MÉRIDA et al. 2019). Around 500 BC, even before the conceptualization of clinical trials and scientific knowledge, Hippocrates wrote about the potential of willow bark and leaves in curing pain and fever. Subsequently, generations of scientists, chemists and science enthusiasts worked extensively and led to the development of these "wonder drugs". Currently, NSAIDs are among the most popular over-the-counter drugs worldwide, constituting 5% of all prescription drugs (BINDU et al. 2020; OSTERMANN et al. 2020; OKORO et al. 2019).

Acute Kidney Injury (AKI) is one of the fastest growing conditions affecting the kidney and a risk factor for accelerated loss of kidney function and cardiovascular disease (CVD) (LEFEBVRE et al. 2020; ADAMS et al. 2011). Improving outcomes among the growing population of ARI survivors requires identifying modifiable risk factors to reduce these events. NSAIDs are the most commonly used analgesics worldwide and an established risk factor for ARI. The current definition of Chronic Kidney Disease (CKD) by Kidney Disease Improving Global Outcomes (KDIGO et al. 2012) addresses structural and functional abnormalities of the kidneys present for more than three months (KIRSZTAJN et al. 2014; OSTERMANN et al. 2020). One of the changes from previous guidelines was to emphasize that there may be a variety of abnormalities in kidney structure and function; however, not all of them have clinical implications for the individual's health. According to KDIGO, the diagnosis, classification and monitoring of CKD must be based on estimating the Glomerular Filtration Rate (GFR), using the CKD-EPI tool. The probability of an individual having chronic kidney disease is assessed by the cause, by GFR (<60 ml/min/1.73m² or markers of kidney damage) and by A1 albuminuria (normal or slightly increased if <30mg/g); A2 (moderately increased, in the range of 30-300mg/g) and A3 (markedly increased, if >300mg/g) (KDIGO et al. 2012).

ARI has already been classified by several protocols, the most currently used is the KDIGO, which classifies ARI in three stages. Stage I: increase in serum creatinine by 1.5-1.9 times baseline in seven days or increase by 0.3mg/dl in 48 hours or urine output <0.5ml/kg/h for 6-12 hours. Stage II: increase in serum creatinine by 2.0 -2.9 times baseline or urine output <0.5 ml/kg/h for more than 12 hours. Stage III: increase in serum creatinine to 3.0 times baseline or increase in baseline creatinine to > 4.0mg/dl or initiation of renal replacement therapy (RRT) or GFR<35ml/min/1.73m² in children under 18 years of age and urine output <0.3ml/kg/h for more than 24 hours or anuria for more than 12 hours (KDIGO et al. 2012). In fact, the incidence of ARI increases year after year all over the world. The incidence of ARI in the population varies from 2,147 to 4,085 cases per million inhabitants per year in developed countries. Patient mortality associated with ARI is inversely proportional to income in developing countries (KDIGO et al. 2012; LI et al. 2013). According to different reports, the disease is present between 5 and 57% in critical units (ONG et al. 2007; ABD ELHAFEEZ et al. 2019).

NSAIDs are commonly prescribed in primary care for their analgesic, antipyretic, and anti-inflammatory effects. One in fifteen US adults is actively prescribed NSAIDs at any given time, and low-dose preparations

are also available in many countries (ZHANG et al. 2017). In part due to their widespread use, NSAIDs account for 25% of adverse drug events (ADEs) reported in the UK (UK) and 21% in the United States (US). NSAIDs are also commonly implicated in hospital admissions due to ADEs, including those that are fatal, but gastrointestinal and cardiac toxicity are better quantified than renal toxicity.

NSAIDs can reduce renal blood flow, cause tubular obstruction through crystal deposition, and induce direct cytotoxicity and cell-mediated immune injury mechanisms leading to the occurrence of Acute Kidney Injury (AKI). Another symptom that is commonly caused by NSAIDs is interstitial nephritis (AIN), which requires specialist review, kidney biopsy, high-dose corticosteroids, and/or immunosuppressive treatments and will typically be progression into CKD (CHOUDHURY et al. 2016). Advanced age and underlying CKD are also related to the onset of AKI while using NSAIDs, with early studies showing that the risk of renal function deterioration increases 3-4 times in patients with abnormal baseline renal function compared to those with renal function. normal (BROWN et al. 2012). Notably, NSAIDs are commonly prescribed to people with CKD despite guidance to avoid them in this population. In US veterans in 2005, 15.4% of people with CKD received traditional NSAIDs or COX-2 inhibitors, compared to 11.1% of people with CKD in the UK in 2012, and 15.9% of people with CKD in Australia in 2004–2006 (ZHANG et al. 2017). Better quantification of risk in people with CKD is therefore of particular clinical interest, as is whether NSAID risk varies with age and COX-2 selectivity. In terms of COX-2 selectivity, early studies suggested that selective COX-2 inhibitors caused fewer renal adverse effects, including reduced GFR, increased serum creatinine, and hypertension. Other studies have not shown significant differences in renal risk between selective COX-2 inhibitors and non-selective NSAIDs.

NSAIDs, frequently prescribed in medical practice, are one of the most widely used drug classes in the world. The pharmacological action of NSAIDs depends on the dose and time used, which predisposes to involvement of specific organs. NSAIDs inhibit the cyclooxygenase (COX) enzyme, both centrally and peripherally, thus interfering with the conversion of arachidonic acid to prostaglandins E2 (PGE-2), prostacyclins, and thromboxanes. Nephrotoxicity occurs through reduced GFR and renal blood flow, resulting in acute vasoconstriction and spinal cord ischemia, which can lead to AKI. Some factors, such as advanced age and comorbidities, which in themselves already lead to a decrease in GFR, increase the risk of NSAID nephrotoxicity (ZHANG et al. 2017; SRIPERUMBUDURI et al. 2019).

The ARI theme caused by the use of NSAIDs has been widespread in the current scientific literature. However, studies showing the long-term effects of NSAID use on the development of CKD are still minimal, as such studies routinely exclude people with CKD and rarely report renal outcomes. Therefore, if the nephrotoxic effects of NSAIDs and specific management strategies for ARI are studied, there will be greater treatment. Thus, the relevance and need for knowledge of kidney disease caused by the use of NSAIDs is reiterated for the development of studies that give visibility to medical practice, expanding and deepening the scientific knowledge related to this issue. Based on the possible nephrotoxic effects of NSAIDs, the present study aimed to report the importance of using this pharmacological class with caution.

MATERIAL AND METHOD

This is a descriptive, qualitative study, in which a Review of the current Literature was carried out to prepare the work. As a primary hypothesis, the following question was asked as a guiding question: What is the risk of ARI associated with the use of NSAIDs in people with CKD? Then, the study will move towards a theoretical analysis of the material available for consultation related to the subject worked, thus verifying the most relevant and the most recent aspects directly linked to the theme.

From this approach mentioned above, it is possible to reach the final result, structured in this work in a presentation to publicize the work performed. All data and information will be collected through searches of bibliographic references of texts and articles on the internet, through the scientific information base Medline (via PubMed), as well as in books and periodicals of national circulation conducted independently.

In addition, there was no restriction on the year of publications to obtain the answer. However, the most current ones, such as from 2014 to 2020, were preferred. Only articles in the English language were selected. The main inclusion and exclusion criterion was to answer the structured question. Only works whose full texts were available were considered for critical evaluation.

Finally, this study was prepared through a relevant medical question in nephrology in order to gather scientific information from medicine and the field of diseases to evidence the best conduct at the time of the event.

RESULTS

In all included studies, eligible ARI cases were chosen from articles over a defined period of time, exposure verification was through secure electronic records, and the same verification method was used among control cases. Eighty percent of the included studies had independent case validation, while the remaining 20% relied only on record linkage (CID codes in the database) without reference to the primary record. In the aligned case-control study using the UK's General Practice Research Database, participants were 386,916 patients aged 50 to 84 years with no known cancer, kidney disorder, cirrhosis or systemic connective tissue disease (HUERTA et al. 2005). After validation of the cases identified in this cohort, 103 patients were confirmed as idiopathic cases of AKI and compared with the frequency of 5,000 age- and sex-matched controls. From this, current NSAID users had a relative risk for ARI of 3.2 (95% confidence interval), and the risk decreased after treatment was stopped. The increased risk was present with both short-term and long-term therapy and was slightly higher among high-dose users. History of heart failure (HF), hypertension, diabetes, and hospitalizations and office visits in the previous year were all associated with an increased risk of AKI. There was a suggestion of modifying the effect of NSAIDs in patients with hypertension and those with HF. Use of selected cardiovascular drugs was associated with a 5-fold increase in the risk of AKI. Diuretics carry the greatest risk. The risk increased with the concomitant use of NSAIDs and diuretics and NSAIDs and calcium channel blockers (HUERTA et al. 2005).

In addition, a cross-sectional study was performed among 350 adult patients with CKD presented to at the institution: Hospital Principal da Universidade de Alexandria. Those with end-stage kidney disease and diagnosed with acute kidney injury and pregnant women were excluded. Among enrolled patients, 57.1% were hypertensive, 46% were diabetic, 28% had osteoarthritis, and 18.3% had cardiovascular disease. CKD stages were 3.7%, 40.3% and 56% in stages 2, 3 and 4, respectively. Almost two-thirds

(65.7%) were NSAID users. Of these, 82.6% were regular users. Headache was the most reported reason for use (68.7%). The use of drugs that may interact with NSAIDs (such as diuretics or inhibitors of the renin-angiotensin-aldosterone system) was reported in 36%. In multiple logistic regression, the odds of NSAID use decreased by 4% for each year increase in patient age and decreased by 3% for each 1 ml/min/1.73 m2 increase in glomerular filtration rate (ABD ELHAFEEZ et al. 2019). Thus, it is recommended that NSAIDs be used with caution among patients with CKD and patients be warned about their adverse health consequences.

In contrast, little is known about the comparative risk of individual NSAIDs, including specific COX-2 inhibitors. From this, we analyzed a systematic review and meta-analysis of cohort studies that reported relative risk, hazard ratio, or standardized incidence ratio with 95% confidence comparing the risk of ARI in NSAID users versus non-users. Pooled hazard ratios were calculated for seven traditional NSAIDs and two specific COX-2 inhibitors, including indomethacin, piroxicam, ibuprofen, naproxen, sulindac, diclofenac, meloxicam, rofecoxib, and celecoxib that were evaluated in at least two studies. The present study was able to demonstrate a statistically significant elevated risk of ARI among most of the traditional NSAIDs included. Pooled hazard ratios were quite consistent across individual traditional NSAIDs, ranging from 1.58 to 2.11. Elevated risk of ARI was also observed in users of diclofenac, meloxicam, rofecoxib and celecoxib, although it did not reach statistical significance (UNGPRASERT et al. 2015). In addition, the review found no significant association between aspirin use and decline in renal function (BOZIMOWSK et al. 2015). Likewise, most studies found no significant association between aspirin use and renal dysfunction (CURHAN et al. 2013; KURTH et al. 2003). Regular use of NSAIDs, especially phenacetin-containing drugs, is prevalent in China. And long-term intake of NSAIDs (≥ 48 months) was independently associated with reduced renal function (PAN et al. 2014).

Significant risk of renal failure was assessed in an older study, with a mean age of admission of 15.2 ± 2.3 years (ten women and five men) (DIXIT et al. 2010). In a study of more than 10,000 community-dwelling elderly (> 65 years), an increased risk of rapid progression of ARD [defined as a decrease in GFR > 15 ml/min/1.73 m 2 during the study period] was observed in users of NSAID. However, the increased risk was on the order of 25-30% higher risk, and observed only in those with TGF 60-89, not those with GFR less than 60. Furthermore, this risk was isolated to those with high exposure to NSAIDs. (eg, 700 mg daily for ibuprofen for more than 3 years without interruption) (GOOCH et al. 2007). In addition, a systematic review and meta-analysis of general observational practice or population studies with patients aged 45 years and older estimated the association between NSAID use and accelerated progression of CKD (estimated drop in TGF ≥ 15 ml / min / 1.73 m2). From a possible 768 articles, after screening and selection, seven studies were identified (5 cohort, 1 case-control and 1 cross-sectional) and three were included in the meta-analysis. Regular-dose NSAID use did not significantly affect the risk of accelerated CKD progression, but high-dose NSAID use significantly increased the risk of accelerated CKD progression (NDERITU et al. 2013).

One study used a representative sample of 47,204 adults in China. The prevalence of regular use of NSAIDs has been reported. A total of 1,129 participants reported regular use of NSAIDs, with an adjusted prevalence of

3.6%, and 76.9% of them (n = 868) had taken phenacetin-containing analgesics, with an adjusted prevalence of 3.2%. After adjusting for possible confounders, long-term (≥ 48 months) NSAID intake was associated with and GFR < 60 mL/min per 1.73 m^2) (PAN et al. 2014).

A recent cohort study studied the association between prescribed dosages of NSAIDs and later incidence of kidney disease in active young and middle-aged adults. This retrospective longitudinal cohort study used unidentified medical and administrative data on 764,228 active-duty US Army soldiers serving over 4 years. Among the 764,228 participants, 85.8% men, were not dispensed with NSAIDs prescribed in the previous 6 months, 137,108 (17.9%) were dispensed from 1 to 7 average total daily doses per month, and 124,594 (16.3%) received more than 7 defined daily doses per month. There were 2356 AKI outcomes (0.3% of participants) and 1634 CKD outcomes (0.2%) observed. Compared with participants who did not receive medication, the higher exposure level was associated with significantly higher adjusted hazard ratios for AKI and CKD, with annual outcome excesses per 100,000 exposed individuals totaling 17 (NELSON et al. 2019). We found 15% of AKI cases associated with NSAID use, with a 25% greater propensity for contraction in patients over 65 years of age. Overall, even a systematic review of the literature around this topic concludes that avoiding NSAIDs is unnecessary in moderate to severe CKD (NDERITU et al. 2013).

DISCUSSION

The results of the literature review showed that current exposure to NSAIDs was associated with an approximately 1.5-fold increase in the odds of developing ARI in the general population and in people with CKD (ZHANG et al. 2017; HILL et al. 2016). There was considerable heterogeneity across studies, particularly in the general population group surveyed, and therefore pooled estimates must be interpreted with caution. The limited number of studies eligible for inclusion precluded meta-regression, so subgroup analyzes were performed in an attempt to explore and explain heterogeneity. After analyzing the scientific bases, ARI caused by the careless and long-term use of NSAIDs was reported. The systematic review performed by UNGPRASERT et al. revealed a statistically significant elevated risk of ARI among traditional NSAID users. Pooled hazard ratios between individual traditional NSAIDs were not significantly different. The combined hazard ratios of specific COX-2 inhibitors and the two traditional NSAIDs with the highest COX-2 selectivity (diclofenac and meloxicam) were also comparable to other traditional NSAIDs, although they did not reach statistical significance.

In another perspective, the results of the present study were compared with the full-text studies identified reporting the use of NSAIDs and CKD which, although not meeting our inclusion criteria, closely corresponded to the included studies. Findings on NSAID use and CKD progression are consistent with Curhan et al. and Kurth et al. who found no significant association between NSAID use and decline in renal function in women or men, respectively. However, neither found a significant association between high-dose NSAID use and worsening renal function (CURHAN et al. 2013; KURTH et al. 2003). This contradiction with our own findings may be due to differences in the age and sex of study participants, as both factors affect levels of NSAID use and the prognosis of CKD (HILL et al. 2016; COUSER et al. 2011; CHRISCHILLES et al. 1992). The mean age in the studies by Gooch et al. was 74 and 76 compared to 57 and 49 in the studies

by Curhan et al. and Kurth et al. on health, respectively. Although the review shows that high-dose NSAID use may lead to an increased risk of CKD progression, the absolute risk attributable to high-dose NSAID use is likely small. In the study by Yarger et al, high-dose NSAID users represented only 4.2% of the total sample population and only 13.4% of these patients had accelerated progression of CKD (YARGER et al. 2011; KARATEEV et al. 2018).).

As with all literature reviews, the results depend on the quality of the included studies. We chose to review observational studies because an initial literature search identified that NSAID trials rarely report renal outcomes (the focus of this study) and exclude people with CKD (a topic of primary interest) and other comorbidities, as well as elderly people and minority groups. Indeed, evidence suggests that the cumulative consumption of NSAIDs is capable of causing chronic kidney injury with manifestations similar to those seen in classical analgesic nephropathy, including chronic interstitial nephritis and papillary necrosis. CKD caused by NSAIDs is likely to be rare and patients with CKD must be closely monitored while taking NSAIDs (CLIVE et al. 2015).

One example is confusing by indication, which in this context is likely to occur if prescribers avoid NSAIDs in people who they perceive to be at increased risk for NSAID toxicity, including ARI, which would lead to an underestimation of the risk of ARI if gift. There were also large differences between studies in the population examined and in the way ARI was measured, both of which likely contributed to the moderate to large heterogeneity observed between the studies. It is also important to recognize that the estimate of the risk of NSAIDs in the general population is adjusted for possible confounders, but the estimate in people with CKD is not because only one study reported an adjusted estimate. Other limitations include that we only included studies published in English, that there were a relatively small number of studies suitable for inclusion, which made meta-regression to explore heterogeneity unfeasible, and that the rate of concomitant use of OTC NSAIDs could not be assessed in the populations studied.

No studies reported baseline risk of ARI in different populations, meaning that absolute risks could not be estimated, but baseline risk and therefore absolute risk of exposure to NSAIDs are likely to be higher in people with CKD and the elderly (ZHANG et al. al. 2017). Large population-based studies measuring ARI using current definitions and estimating the absolute risk of harm are needed to better inform clinical decision making.

CONCLUSION

NSAIDs are associated with 30% of hospital admissions for preventable adverse drug reactions (DAVIS et al. 2016). However, the present study does not aim to project NSAIDs in a negative light; rather, it presents a comprehensive view of the susceptibility of some important organs to an almost unavoidable drug widely used in everyday life. This raises awareness of the prudent use of these drugs. Therefore, AKI is an increasingly common global problem, causing significant morbidity and mortality and with large resource implications. Exposure to NSAIDs and other nephrotoxic drugs is an important cause of ARI, but the risk of these exposures is modified by susceptibilities such as increasing age and the presence of CKD. This study found that the chances of developing ARI increased by more than 50% in people who were exposed to NSAIDs in the general population and in people with CKD, and in older people the chance of developing ARI doubled. However, the absolute risk of

developing AKI also depends on the baseline risk of AKI in the exposed population, which none of the included studies reported. Future studies must use internationally accepted definitions of AKI and estimate the absolute risk of AKI in different populations, including the elderly and people with CKD, to better inform clinical decision making. As the definition of high-dose use is unclear and the fact that NSAIDs have other detrimental effects on kidney function, such as AKI, they must always be used with caution and given at the lowest effective dose. Annual screening is recommended in CKD patients with continued NSAID use. Future research must quantify the level of high-dose use in patients with CKD and explore the effects of comorbidity and co-prescription.

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