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Original Scientific Paper

Different renal effect during analgesics use in patients with headache

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Abstract

Migraine is a common headache disorder that causes significant disabilities. COX inhibitors (also referred to as NSAIDs) are frequently used as a treatment option. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most commonly used analgesics, followed by paracetamol and aspirin, as analgesic therapy that combines individual agents with different mechanisms of action. Theoretically, this approach can lead to different renal adverse effects. The purpose of the study is to compare renal function based on COX inhibition and detect early nephrotoxicity using specific bioindicators. NSAIDs are mediated via inhibition of prostaglandin synthesis by non-specific blocking cyclooxygenase, leading to vasoconstriction and reversible mild renal impairment in hypo-perfusion. Fluid and electrolyte disturbances, acute renal failure, and acute interstitial nephritis also occur predominantly with NSAIDs. Some studies have reported an association between analgesic nephropathy, as one of the most severe analgesic-related adverse renal effects. Long-term abuse of analgesic combinations or other NSAIDs, although only for some of these agents, is controversial. Besides conventional markers of renal function (serum/urine creatinine determined by Jaffe's methods of enzymatic assay for urea in serum), also Jon selective electrodes (ISE) are used for determination of electrolite in serum. Immunoturbidimetry was used to determine urinary albumin, microalbuminuria and also to monitor glomerular functioning. Patients with any history of kidney diseases were excluded from the study. In the treatment of patients with non-selective COX inhibitors (Piroxicam, Ketoprofen, Ibuprofen), related to selective COX2 inhibitors (Nimesulid / Meloxicam) when monitoring specific biomarkers (microalbuminuria), was observed a significant difference of $p < 0.01$ ** in patients treated with non-selective COX inhibitors. Following the levels of specific biomarkers in urine we can recommend constant monitoring of renal functions during usage of different groups of NSAIDs and be careful while using analgesic-anti-inflammatory drugs

Keywords: non-steroidal anti-inflammatory drugs; cyclooxygenase; migraine, adverse renal effects.

1. Introduction

Migraine is a common headache disorder that causes significant disabilities. COX inhibitors (also referred to as NSAIDs) are frequently used as a treatment option of episodic migraine. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most commonly used analgesics, followed by paracetamol and aspirin, as analgesic therapy that combines individual agents with different mechanisms of action. It is assumed that COX-2 inhibition is responsible for the therapeutic effects of NSAIDs while COX-1 inhibiting causes renal side effects. Theoretically, this approach can lead to different renal adverse effects.
But cyclo-oxygenase (COX)-2 selective NSAIDs may provide a therapeutic advantage over nonselective NSAIDs due to a reduced risk of adverse events (AEs). Up to 20% of patients who take nonselective NSAID and have more than one of these risk factors may manifest alterations in renal function. Celecoxib is a selective COX-2 inhibitor that has shown analgesic effects similar to other NSAIDs. A new COX-2 inhibitor that is effective and more rapidly absorbed than nonselective NSAIDs could provide clinical benefits in treating migraine by achieving a rapid onset of action, which patients rank among most important attributes

of acute medication. Quiralte and co-workers have confirmed that Diclofenac sodium is one of the most widely prescribed NSAIDs in the world. Meloxicam is another one that NSAIDs have been approved in recent years. Diclofenac sodium is an inhibitor of both COX1 and COX2 (Quiralte et al., 2007), but meloxicam is a selective COX2 inhibitor (Furst, 1997; Gurocak et al., 2010). According to Sagar et al., the efficacy of a new oral liquid formulation of celecoxib in adults with migraine (Sagar, 2017), compared with meloxicam, diclofenac sodium resulted in a high degree of nephrotoxicity (Swan et al., 2006). The harmful effects of diclofenac sodium and meloxicam on kidney tissue in humans and animals are well documented in the literature. COX isoenzymes, which form the basis of the mechanism of action of NSAIDs, will be described in order to understand the subject easily (Sylejman et al., 2007).

NSAID classification based on selective COX inhibition:

Based on the selective inhibition of COX determined according to the COX-1 / COX-2- IC 50 coefficient (Sylejman et al., 2007), NSAIDs are divided into:

- Selective COX-1 inhibitors such as Aspirin with COX-1 / COX-2 coefficient IC 50 of 0.01.
- Non-selective COX inhibitors (the drug equally inactivates the two cyclooxygenase isoforms): with COX-1 / COX-2 IC50 coefficient between 0.5 and 3;
- Relatively selective COX-2 inhibitors - are characterized by a lower inactivation of the COX-1 enzyme: such as Meloxicam, Nimesulide, Diclofenac, with COX-1 / COX-2 IC 50 coefficient between 10 and 20;
- Highly selective COX-2 inhibitors, a celecoxib prototype with COX-1 / COX-2 IC50 coefficients between 140 and 250, placebo-controlled COX-2 only, are known as coxibs and referred to as selective COX-2 inhibitors (Sylejman et al., 2007).

The main effect of conventional NSAIDs is the nonselective inhibition of both isoforms, unlike Coxibs, a class of non-steroidal anti-inflammatory drugs (NSAIDs) that performs selective inhibition only COX-2. According to Raz et al. (2002) and Parezela et al. (2001), the paradox is that most NSAIDs also block COX-1 and not only COX-2, which means that they block the synthesis of all prostaglandis, effecting the normal physiological renal function. William et al. (2000) have confirmed that concomitant prostaglandin inhibition in the kidney can reduce renal blood flow and glomerular filtration rate (GFR). Thereby, promoting sodium and water retention, where renal hypoperfusion may result in acute kidney injury (AKI). This risk is present even when COX-2 selective NSAIDs are used (Raymond et al., 2006; Drita Yzeiri Havziu, 2020).

According to the study of Weir et al. (2002), based on clinical trials on comparing renal changes between non-selective NSAIDs and coxibi, the results indicate only subtle changes in renal hemodynamics. They found that the renal effects of celecoxib are similar to non-selective NSAIDs. The highest incidence of AKI (Acute kidney injury) is reported during usage od Indomethacin in combination with ibuprofen and piroxicam (Griffin et al., 2000). Celecoxib, a selective COX-2 inhibitor, has a lower risk of developing AKI, compared to other non-selective NSAIDs (Schneider et al., 2006; Winkelmayer et al., 2008). According to Swan et al. (2006), diclofenac sodium, compared to meloxicam resulted in a higher degree of nephrotoxicity. So they suggested that diclofenac sodium can be replaced with meloxicam. The damaging effects of diclofenac sodium and meloxicam on kidney tissue in animals are well documented in the literature (D. Uzeiri. Havziu, 2014).

Many nephrologists report that NSAIDs have been classified into the second group due to causing nephrotoxicity, after aminoglycosides as the cause of AKI (Schrier et al., 1984). Nephrotoxicity caused by NSAID includes the following stages of renal impairment: tubular necrosis, acute tubular nephritis, glomerulonephritis, renal papillary necrosis, chronic renal impairment, electrolyte and water retention, hypertension, hyperkalaemia, and hypoaldosteronism. However, more recent studies have summarized these enumerated phases in the following conditions: acute renal impairment, chronic renal impairment, interstitial nephritis, and subclinical nephrotoxicity (Ejaz et al., 2004, D. Uzeiri. Havziu, 2014).

It is clear that NSAIDs are associated with all forms of renal impairment, but, however, if they are detected early, acute syndromes have a good prognosis. However, this assumption does not apply to chronic renal impairment (Clive et al., 1984; Ejaz et al., 2004; Drita Yzeiri Havziu, 2020).

Subclinical renal impairment cannot be identified by routine analysis (urea, creatinine in serum and urine) and microalbuminuria is a more sensitive indicator of renal dysfunction as a marker of glomerular function (Spasovski et al., 2007). In conclusion, they confirmed that the majority of patients treated with various nephrotoxic drugs showed reversible microalbuminuria that is rarely developed to end-stage renal disease (Pedersen et al., 1995). The presence of subclinical increases in urinary albumin excretion is associated with impaired endothelial vasodilation and is believed to reflect endothelial dysfunction in migraine patients (Malik A, 2007).
There is relatively little data to compare the nephrototoxicity of different types of NSAIDs based on COX inhibition in patients with cephalea-migraines, treated for a long period of time with an analgesic. The purpose of the study is to compare renal functions based on COX inhibition and to detect early nephrotoxicity using specific bioindicators.

2. Materials and methods

We used venous blood and urine sample from randomly selected patients with cephalea-migraine of University Clinic of Neurology – Skopje (wider region of R.N.M), who has had a headache less than 15 days a month and migraine attacks with frequencies less than 15 days a month.
The study included a total of 16 female patients with an average age of 36.2 ± 9.2, with an age range from 21 to 51 years, with a mean follow-up of up to 120±12.6 months, treated with two groups of NSAIDs: nonselective COX inhibitors (8 patients with Ibuprofen with a total dose of up to 600 mg per day, and 3 patients with caps Piroxicam or Ketoprofen) and relatively selective COX2 inhibitors (5 patients with Nimesulide or Meloxicam 100 mg). After 12 months of therapy, we have compared the experimental (treated) group with a control group of healthy individuals with normal kidney function with an average age range of 47.02 ± 5.58 (35 - 60 years). Patients included in the examination were informed about the method of implementation and the purpose of the research before giving their written consent. The examination was conducted according to the designed protocol, in accordance with the ethical principles of the Helsinki Declaration on Medical Research on People and Licenses from the Ethic Committee of the Faculty of Medical Sciences at the University "Goce Delcev" - Stip (WMA, 2000). The presented results represent the average value of the three measurements, under identical conditions. As a sample for analysis, 5 ml of blood collected in special tubes was used without anticoagulants. All the material for analysis were measured in the Clinical Biochemistry in Skopje. For the determination of creatinine, and specific biomarkers microalbuminuria, the first morning urine sample was used. After proper processing the pure supernatate is used for further processing (Yzeiri Havziu et al., 2016).

2.1 Method of work

For creatine serum / urine, is used the Jaffe method - during the reaction of the creatinine with the basic reagents (Flex reagent cartridge) a complex of red color is formed which is followed by measuring the changes in absorbance at a time interval of 510 nm (Dimension Rxl) (Yzeiri Havziu et al., 2019).
Urea serum, the enzymatic-urea hydrolysis under the influence of the urease enzyme, the formed ammonia (NH3) reacts with the catalytic effect of the GLDH (Flex Reagent Cartridge), α-KG (Flex Reagent Cartridge) and NADH (Flex Reagent Cartridge). As a result of the reaction, glutanamic acid and NAD are formed. The decrease in absorbance due to the reduced NADH oxidation is proportional to the release of the urea NH3 (Flex Reagent Cartridge). As a result of the reaction, glutanamic acid and NAD are formed. The decrease in absorbance due to the reduced NADH oxidation is proportional to the release of the urea. Measured at a value of 340 to 383nm (Dimension Rxl) (Yzeiri Havziu et al., 2019)
Serum electrolytes - Ion Selective Electrodes (ISE) - determines the difference in the electrochemical potential between the glass or liquid membrane electrode (Roche Diagnostics) and the reference electrode (Roche Diagnostics) that is proportional to the concentration of electrolytes in the serum.

For the determination of urinary albumin, microalbuminuria was used immunoturbodymetric method (Cobas Mira Plus) (Yzeiri Havziu et al., 2019).

2.2 Statistical data processing

Statistical data processing is performed in Microsoft Excel, calculating the average value (M) and the standard deviation (standard deviation, SD). Differences between variance of patients during the course of therapy are recorded by variance analysis (ANOVA) and Student T-test.

3. Results and discussion

Follow-up in patients with cefalea-migren who had headaches less than 15 days per month of which 8 patients treated with Ibuprofen with a total dose of up to 600 mg per day, 5 patients with Nimesulide or Meloxicam 100 mg and 3 patients with caps Piroxicam or Ketoprofen. After 12 months of therapy treated patients were compared to the control group of healthy individuals according to the protocol, which includes the parameters that are presented in Table1.

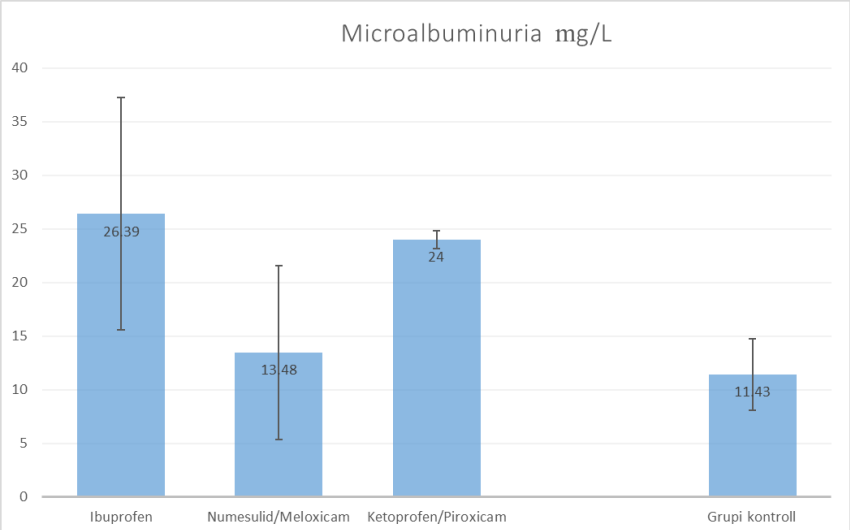
Table 1. Concentration of biochemical parameters by nephrological protocol: urea, creatinine in (serum / urine), and serum electrolyte status in the studied patient groups compared to the control group of subjects.

Biochemical analyzes covered by the standard nephrological protocol	**M±SD**	**P values**	Control Group **n=80** **M±SD**	Referential values
Urea (serum) mmol/L				
After 24 months of therapi				
Ibuprofen N=8	3,48±0,94	p<0.01		
Numesulid/Meloxicam N=5	4.46±1.01	p<0.01	5.65±1.3	2,7– 7,8
Ketoprofen /Piroxicam N=3	3,67±0.66	p<0.05		
Creatinin (serum) µ mol/L				
After 24 months of therapi				
Ibuprofen N=8	78±17,67	NS	82.9±14.3	45 – 109
Numesulid/Meloxicam N=5	67,16±17.31	p<0.05		
Ketoprofen /Piroxicam N=3	66±7,35	p<0.05		
Creatinin (urina) mmol/D				
After 24 months of therapi				
Ibuprofen N=8	12,98±10.3	p<0.01	7.5± 4.2	7-17
Numesulid/Meloxicam N=5	9.34±0.97	NS		
Ketoprofen /Piroxicam N=3	9,73±0.19	NS		
Natrium mmol/1				
After 24 months of therapi				
Ibuprofen N=7	140,14±0,90	NS		
Numesulid/Meloxicam N=5	140±0,71	NS	140±1.2	137 – 145
Ketoprofen /Piroxicam N=3	140,33±1,25	NS		
Kalium mmol/1				
After 24 months of therapi		p<0.01		
Ibuprofen N=8	4,33±0,43	p<0.01	4±0.5	3,8 – 5,5
Numesulid/Meloxicam N=5	4,4±0,26	NS		
Ketoprofen /Piroxicam N=3	4,1±0,14			

*p <0.01 ** represents a very high statistical difference at values with a 99% confidence interval*
*p <0.05 * statistically significant difference in values with a safety interval of 95 %.*

In Table 1 when monitoring the values of biochemical parameters according to the nephrological protocol the results are showing that: urea and kalium in serum of the studied groups of patients treated with non-selective COX inhibitors (Ibuprofen) and relatively selective COX2 inhibitors Numesulid/Meloxicam was observed a statistically significant difference in the confidence interval of 99% CI for p <0.01 **, while creatinine serum in patients treated with (Meloxicam/Nimesulid) and Ketoprofen/ Piroxicam showed statistically significant differences in CI 95% confidence interval for p <0.05 *. Serum natrium values in all examined groups of patients did not show a statistically significant difference also in the follow-up of creatinine in urine in patients treated with relatively selective COX2 inhibitors (Meloxicam / Nimesulide) and Ketoprofen / Piroxicam, except in the group of patients treated with nonselective COX inhibitors Ibuprofen observed statistically significant differences for a CI 99% confidence interval of p <0.01 **. All the above values do not deviate from the interval of normal reference values, which is important from a clinical biochemical point of view, because it indicates that when using cyclooxygenase inhibitors (NSAIDs) no pathological changes in the values of degradation products were detected. In particular no changes in tubular electrolyte reabsorption were observed. The findings correlate with the study results of Hegazy et al. where during the comparison of selective COX2 inhibitors and Ibuprofen have been confirmed that the group of patients treated with Ibuprofen have shown elevated serum creatinine levels than patients treated with COX2 inhibitors. The results obtained correspond to the data of other authors, confirming the NSAID status of electrolyte serum and urine during usage, remain within normal reference values (Kim.H et al., 1999). Non-significant changes were found for the values of serum electrolytes in both groups of patients (Hegazy et al., 2011). Conversely, According to Kim and co-workers (Kim H et al., 1999), patients at risk for treatment with non-selective and selective COX-2 inhibitors were followed, with both NSAIDs causing changes in electrolyte status with hyponatraemia and hyperkalaemia. The highest incidence of AKI is indicated by the use of Indomethacin with Ibuprofen and Piroxicam (Griffin et al., 2000).

The effects of NSAIDs on glomerular and tubular functions are of great clinical-pathological significance and should therefore be monitored by the more sensitive methods and biomarkers, which are presented in Figures 1.



*p <0.01 ** represents a very high statistical difference at values with a 99% confidence interval*
*p <0.05 * statistically significant difference in values with a safety interval of 95 %.*

Figure 1. Tested after 12 months with specific biomarkers, low molecular weight proteins microalbuminuria.

From the results presented in Figure 1 it can be observed that after 12 months of treatment with non-selective COX inhibitors and relative selective COX2, comparing to the control group, there is a statistically significant difference of p <0.01 **, at values with a safety interval of 99% in the specific biomarker

microalbuminuria in patients using non-selective COX inhibitors Ibuprofen and Ketoprofen / Piroxicam. No statistically significant differences were found in patients treated with relative selective COX2 inhibitors Nimesulid / Meloxicam compared to the control group. This is clinically and biochemically importance, because it indicates nephrotoxicity in a group of patients treated with nonselective COX inhibitors Ibuprofen and Ketoprofen or Piroxicam compared with patients treated with relative selective COX2 inhibitors Nimesulid or Meloxicam. In patients, based on the monitoring of microalbuminuria (as a marker for early identification of renal impairment at the glomerular level), early changes at the glomerular level were identified as early as the 12th month of therapy. This fact is crucial, as it once again confirms the high sensitivity of microlabuminuria to the identification of small changes in GFR caused by nephrotoxic agents. Our results correlate with the results of other authors where it is confirmed that the relative selective inhibitors of COX2 - Meloxicam are more renoprotective compared to COX1 inhibitors that have resulted in a high degree of nephrotoxicity (Swan et al., 2006; Schneider et al., 2006; Winkelmayer et al., 2008). Also according to the study of Griffin et al. (2000) the highest incidence of AKI is observed with the use of Indomethacin with Ibuprofen and Piroxicam.

4. Conclusion:

In the chronic treatment of cephalea patients with headaches less than 15 days a month with: non-selective COX inhibitors (Piroxicam, Ketoprofen, Ibuprofen) and relative selective COX2 inhibitors Nimesulid / Meloxicam. The renoprotective properties of Nimesulid / Meloxicam with non-selective COX inhibitors have been demonstrated to be less nephrotoxic agents. This fact suggests that non-selective COX inhibitors significantly affect glomerular changes.

-The great sensitivity of microalbuminuria (marker for identification of early damage to glomeruli) has been confirmed.

- Individualized and rational use of NSAIDs is recommended, especially for the group of non-selective COX inhibitors, due to the risk of the increased potential of nephrotoxicity, as well as continuous monitoring of renal function in patients included in the study.

Nomenclature

COX-1 Cyclooxygenase1
COX-2 Cyclooxygenase 2
GLDH Glutamate dehydrogenase
α-KG α-ketoglutarate
NADH Nicotinamide adenine dinucleotide

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