MIGRAINE AND THE EFFECTS OF NSAIDS ON RENAL FUNCTION

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ABSTRACT

Trigeminovascular system (TGV) activation is a basic mechanism for generating pain during a migraine attack. Many experimental results highlight the importance of the cyclooxygenase system in the peripheral arm of TGV and suggest that NSAIDs may be effective in migraine therapy through the action of these peripheral nociceptors. Inhibition of NSAID-mediated prostaglandin synthesis prevents neurogenically mediated inflammation of the trigeminal system and reduces pain, but at the same time inhibition of prostaglandin in the kidney may reduce renal blood flow,speed glomerular filtration retention. and water. The purpose of the study is to follow the renal function, in patients with cefalea-migraine that has been treated for a long period, treated with Diclofenac and Paracetamol.We used Jaffe's method for the determination of serum/urine creatinine and enzymatic assays for urea and uric acid in serum and $_{\gamma}$ glutamyl transferase ($_{\gamma}$-GT) in serum and jon selective electrode (ISE) are used for determination of electrolite in serum. We used nephelometry by β2 microglobulin (β2M) and photoelectric colorimetry for microalbuminuria in urine, to monitor glomerular and tubular functioning. Any history of kidney diseases was exclusion criteria to enter the study. In chronic treatment of patients with headache with Diclofenac and Paracetamol in symptomatic headaches, they have been confirmed as renoprotective in their use.

Keywords: non-steroidal anti-inflammatory drugs, migraine, renal function, trigeminovascular system

Migraine and the effects of NSAIDs on renal function

1. Introduction

Trigeminovascular system (TGV) activation is a basic mechanism for generating pain during a migraine attack. Triggers that trigger TGV remain controversial and can be multiple. Activated nociceptors release neuropeptides including calcitonin gene-related peptide (CGRP), supstanca P (SP), and neurokinin A (Ebersberger et al, 1999). Elevated CGRP and SP levels in peripheral blood and saliva have been observed in patients and in experimental animal models of migraine attacks. Released neuropeptides cause sterile neurogenic inflammation in the dura mater, in which blood vessels continue to dilate.plasma protein extravasation (PPE) occurs, fat cells degranulate to release histamine and polymorphonuclear leucocytes (Williamson D. J., et al., 2001). Released inflammatory substances stimulate trigeminal nociceptors and induce peripheral sensitization (Strassman A. M., et al., 1996). This is thought to correlate during a migraine attack with a disturbing headache and its worsening with Valsalva maneuvers, including exercise, bending, coughing or sneezing (Blau J. N., et al., 1986). Many experimental results support the role of cyclooxygenases in the peripheral activation of the trigeminal vascular system.

Both COX-1 and COX-2 isoforms are present in dura mater. COX-1 is found in dural mast cells and small and medium-sized blood vessels, while COX-2 can be found in dural macrophages and some acronyms containing CGRP. Release of prostaglandin E2 (PGE2) from dura mater in experimental

animals has been observed by chemical or electrical stimulation. As with ASA treatment it may reduce meningeal nociception. Naproxen also reduces dura nociceptor activation and decreased peripheral nociceptive sensitization (Pardutz, et al., 2010) ASA or Indomethacin reduce PPE in dura mater after electrical stimulation of the gastric ganglion, Schuh et al, (2006) reported that the selective parecoxib selective COX-2 inhibitor is also effective in similar experimental conditions (Schuh et al., 2006).These results emphasize the importance of the cyclooxygenase system in the peripheral arm of TGV and suggest that NSAIDs may be effective in migraine therapy through the action of these peripheral nociceptors (Pardutz, 2010; Yang G.Y. et al., 2009). In contrast, William et al showed that inhibition of NSAID-mediated prostaglandin synthesis has been shown to prevent inflammation of the trigeminal vascular system and reduce pain, but inhibition of renal prostaglandin may reduce renal blood flow and rapid renal flow filtration, which promotes sodium and water retention. Clinically, this may lead to the development of edema. Patients with heart failure (HF), hepatic cirrhosis with ascites, or those with chronic renal disease are at the highest risk of developing acute renal failure due to NSAIDs due to the effects of NSAIDs on renal haemodynamics. This risk is present even when cyclooxygenase-2 selective NSAIDs are used. For these reasons, the use of NSAIDs may be considered as a relative contraindication in patients with hepatic cirrhosis with ascites, chronic renal failure, and hypertension . Hassan, K., et al. reported 11 adult patients who developed AKI after ingestion of Metamizole sodium (Hassan, K., et al., 2011). On the other hand, recent studies by Weng S-C et al. (2017) confirmed that migraine may be an independent risk factor for CKI, especially in younger patients with long-term use of non-steroidal anti-inflammatory drugs without medical supervision (Weng S-C, et al., 2017). NSAIDs are still the most widely used effective agents in the treatment of mild to moderate migraine attacks, especially given the fact that the use of COX-2 inhibitors minimizes serious gastrointestinal adverse effects. However, their nephrotoxicity is still a concern and remains a major subject of research and scientific research in their use (Brater, 2002; D.Uzeiri.Havziu, 2014).

2. Materials and Methods

The study included a total of 24 patients with chronic headaches who were divided according to the duration of the headache: a group of patients with symptomatic headaches of which 12 patients were treated for 10 years with Diclofenac duo 75 mg capsules, and 12 patients with Paracetamol 500 tablets mg, treated for more than 5 years with occasional headaches (symptomatic). Average age of patients is 42.047±7.41 years, with a range of 35-65 years with mean follow-up of up to 120±12.6, all patients regardless the duration of therapy are compared with a control group of subjects (different in relation to the study region) with normal renal function. Patients included in the examination were informed about the method of implementation and the purpose of the research before giving their written consent. They were also asked not to use any other medicines before taking the examinations. Patients with prior renal disease were excluded from the study. The examination was conducted according to the designed protocol, respecting 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 "GoceDelcev" – Stip , (WMO, 2001).

The results represent the average value of the three measurements, made under identical conditions. In purpose of analysis sample was used 5 ml of blood, collected in special tubes, without anticoagulants. All materials for analysis are measured in the laboratories of Clinical Hospital in Tetovo (Yzeiri Havziu, et al, 2020).

To determine of creatinine and specific biomarkers (β2M and microalbuminuria), the first morning urine was used. The samples were processed according to the protocol described by Havziu et al. (2020) and subsequently used for further biochemical characterization.

For testing the creatinine serum/urine, we 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 change of absorbance at a time interval of 510 nm (Dimension Rxl) (Yzeiri Havziu, et al, 2020).

Urea serum, the enzymatic-urea hydrolysis under the influence of the urease enzyme, the formed ammonia (NH_3) 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 NH_3, measured at a value of 340 and 383 nm (Dimension Rxl) (Yzeiri Havziu, et al, 2020).

Ureic acid is based on the methods of Bulger and Jons. Ureic acid is oxidized to allantoin by uricase (Flex reagent cartridge) to release hydrogen peroxide (H2O2). Ureic acid absorbs light at 293 nm, while allantoin does not absorb light at 293 nm. The absorption difference at 293 nm due to the disappearance of ureic acid is directly proportional to the concentration of ureic acid in the sample and is measured using a bichromatic (293,700 nm) technique (Uzeiri Havziu, 2014).

$_{\gamma}$-glutamyl transferase (γ-GT) in urine / serum is determined using a standardized method by the IFCC (Uzeiri Havziu, 2014).

For the determination of urinary albumin, microalbuminuria, we used visual Reading urine tape test in Combilyzer 13 - a test is based on the "protein error" principle of the indicator, which is caused by the presence of albumin. Sulfanephthalein has a high sensitivity to albumin. The color fields correspond to following values: 10, 30, 80 and 150 mg/L urinary albumin.

For β2M determination imunonephelometry by BN II/BN ProSpec^{R} System was used (Yzeiri Havziu, et al, 2020).

3. Statistical data processing

Statistical data processing was performed in SPSS for Windows 23.0 statistical software.Shapiro-Wilks tests, as well as skewness and kurtosis measures were used to test the normality of the data distribution. Nonparametric and parametric tests for independent samples (H Kruskal-Wallis test) and post - hoc (Mann-Whitney test), were used to compare the analyzed groups. The data of interest are shown in tables and graphs. P values <0.05 were considered statistically significant.

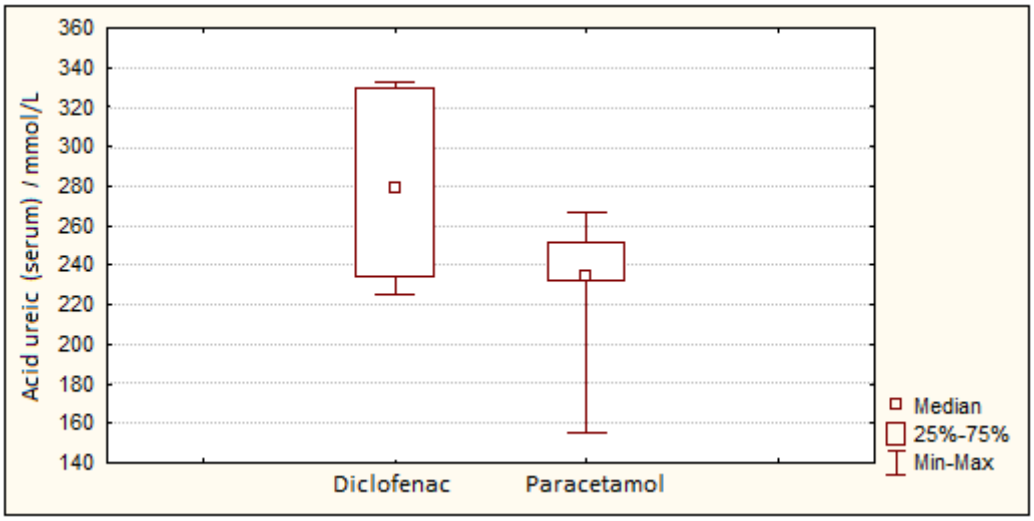
4. Results and discussion

Based on follow-up of patients treated only for symptomatic headaches treated with caps. Diclofenac 75 mg and tab. Paracetamol 500 mg relative to the mean or median values of the analyzed parameters compared to the normal and increased or decreased values of the analyzed parameters are shown in more detail in Tables 1 - 2 and Figures 1 and 2.

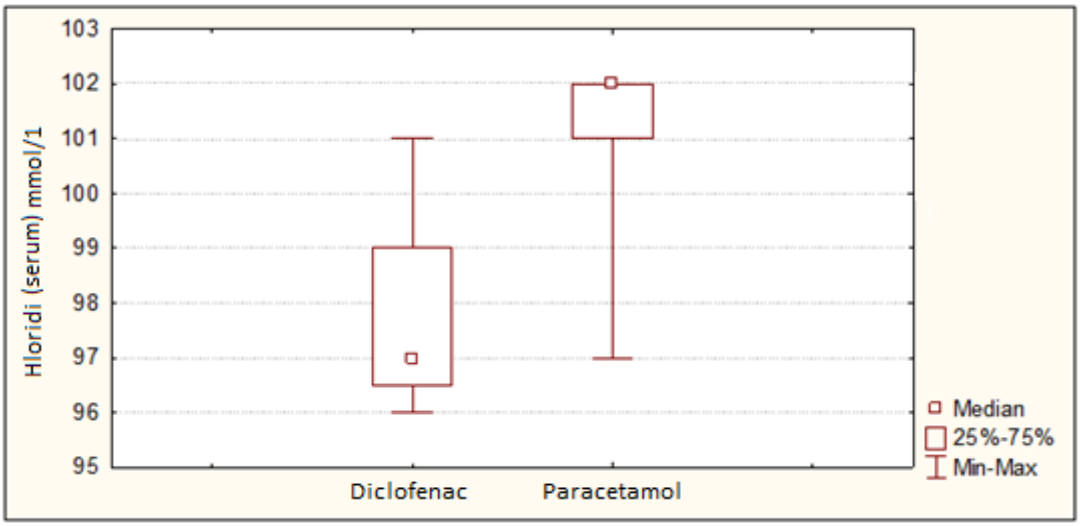
Table 1. Comparation – group of patients treated for symptomatic headaches with Diclofenac and Paracetamol, in comparison with mean and median values of the analysed parameters

Parameters		Group		p-level
		Diclofenac	Paracetamol	
Urea (serum)	mean ± SD	5.4 ± 1.6	4.28 ± 1.1	[a]p=0.065 ns
Natrium (serum)	mean ± SD	138.92 ± 2.1	139.92 ± 0.9	[a]p=0.13 ns
Creatinin (serum)	median (IQR)	65.5 (59 - 75)	61.5 (59 - 67)	[b]p=0.73 ns
Acid ureic (serum)	median (IQR)	279.5 (234 - 330)	234 (232 – 251.5)	[b]p=0.03 sig
Creatinin (urine)	median (IQR)	4.4 (4.4 - 13.25)	4.4 (2.65 - 8.8)	[b]p=0.28 ns
Kalium (serum)	median (IQR)	4.3 (4.25 - 4.75)	4.3 (4.3 - 4.5)	[b]p=0.45 ns
Hloridi (serum)	median (IQR)	97 (96.5 - 99)	102 (101 - 102)	[b]p=0.0009 sig
Mikroalbuminuria	median (IQR)	10 (10 - 10)	10 (10 - 10)	
β2 M	median (IQR)	0.206(0.205-0.209)	0.204(0.186-0.206)	[b]p=0.065 ns
GGT	median (IQR)	24.5 (18 - 35.5)	18.5 (12 - 25.5)	[b]p=0.12 ns

[a](t – test) [b](Mann-Whitney test)



Picture 1. Values of Acid ureic in patients treated with Naklofen 75 mg and Paracetamol for symptomatic headaches compared with the control group of examinees



Picture 2. Values of chlorides in patiens treated with Diclofenac 75 mg and Paracetamol during symptomatic headaches in comparison with the control group of examiees

Based on the results obtained from Table 1 and Figures 1-2, the statistical analysis showed that these two groups of patients differed significantly in terms of serum uric acid and chloride levels (p = 0.03, p = 0.0009, respectively). Uric acid had significantly higher serum values in patients on chronic Diclofenac therapy - median 279.5 vs 234. Serum chloride levels were significantly higher in patients receiving Paracetamol for more than 10 years - median 102 vs 97, but values were not clinical.

However, based on elevated uric acid levels in patients treated with Diclofenac compared with patients treated with Paracetamol also used for symptomatic headaches, the results are of clinical significance, indicating once again that Diclofenac, acted in cellular changes, but because the comparison with other biochemical parameters showed no changes in values and due to the fact that it remains unclear whether uric acid levels can be used as an indicator of reduced renal function, because it is associated with a number of cases such as cardiovascular surgery, radiocontrast administration, rhabdomyolysis and heat stress, and other pathologies (J. Johnson, 2011), can not be taken as a competent indicator of the mentioned renal cell changes. More serious organ damage is required in order to assess the damage with the above biochemical parameters. On the other hand, Paracetamol (acetaminophen) inhibits COX-2 by more than 80%, to a similar degree to the highly selective COX-2 inhibitors of nonsteroidal anti-inflammatory drugs (NSAIDs) (Burkhard Hinz, 2008), wherein at therapeutic doses renal toxicity is rare (Schug SA, 2005).

Table 2. Comparation- group Diclofenac and Paracetamol, compared according analysed parameters (normal values and values that differ from referent values)

Analysed parameters	Values	**Group**			**p-level**
		N	**Diclofenac**	**Paracetamol**	
Urea (serum)	Increased	4	4(33.33)	0	p=0.1 ns
Creatinin (serum)	Decreased	1	1 (8.33)	0	p=0.1 ns
Creatinin (urine)	Decreased	19	9 (75)	10 (83.33)	p=0.1 ns
Hloridi (serum)	Decreased	9	7 (58.33)	2 (16.67)	p=0.09 ns
MA	Increased	4	2(16.67)	2 (16.67)	p=0.58 ns
β2 M	Increased	18	11(91.67)	7 (58.33)	p=0.16 ns

p (Yates Chi-square test)

Based on the results obtained from Table 2 when comparing the groups of patients treated with Diclofenac and Paracetamol, in terms of normal and increased or decreased values of the analyzed parameters, showed that serum concentrations of urea and β2 microglobulin were more frequently increased in patients in the Diclofenac group, and serum creatinine and urine as well as serum chlorides were more frequently decreased in this group of patients compared with the paracetamol group.

There was no statistically significant difference between the two groups of patients, in terms of normal values and values that deviate from the reference for any parameter, which is a very important key data for the renoprotectiveness of chronic use of Diclofenac and Paracetamol, in symptomatic headaches.

5. Conclusion

- In chronic treatment of patients with headache with Diclofenac and Paracetamol in symptomatic headaches, they have been confirmed as renoprotective in their use.

6. References

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