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Professional paper

COMPARISON OF THE SENSITIVITY OF SEVERAL BIOMARKERS IN PATIENTS WITH MEDICATION OVERUSE HEADACHE (MOH)

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Abstract

Migraine is a common headache disorder that causes significant disabilities. Headache developed or significantly worsened during medication overuse (for simple analgesics and combination acute medications, intake must be 15 days or more per month for triptans, ergotamines, opioids, and combination analgesics; 10 days per month sufficient to get a diagnosis of Medication-overuse headache-MOH). A recent epidemiologic study on drug-induced disorders demonstrated that excessive drug use can lead to nephrotoxicity. Microalbuminuria was common in patients under the influence of nephrotoxic drugs. Subclinical renal damage cannot be identified by routine tests (serum creatinine), and microalbuminuria is a more sensitive indicator of renal dysfunction. The aim is to confirm the sensitivity of certain biomarkers when comparing patients treated with NSAIDs in combination with other drugs (analgesics, triptans and antidepressants) with patients treated with monotherapy by NSAIDs Besides conventional markers of renal functioning (serum/urine creatinine determined by Jaffe methods), enzymatic assay for urea serum and Jon selective electrode (ISE) are used for determination of electrolyte in serum. Imunoturbodimetric assay for determination of urinary albumin, microalbuminuria and β2-microglobulin will be used. In the case of combined therapy with NSAIDs and other medications (analgesics, triptans and antidepressants), a significant effect on the increase of microalbuminuria has been demonstrated, which signals us for a more sensitive indicator in compared to β2M which as specific bioindicator did not show a measured sensitivity for the detection of early changes in the tubular level. Significant glomerular damage has been reported in patients with combination therapy than patients treated with NSAID monotherapy. Following the levels of specific biomarkers, we can use them as signals for early detection of nephrotoxicity, especially in patients treated with combination therapy requiring special attention when administering them.

Keywords: Medication-overuse headache, Nephrotoxicity, Microalbuminuria

1. Introduction

Medication-overuse headache (MOH), with an increased risk of nephrotoxicity, belongs to a particular group of patients who abuse NSAIDs (Bellei et al., 2012). Medication overuse headache (MOH) is a cause of chronic daily headache, where headaches occur 15 or more days per month when a therapeutic agent is used excessively and regularly for 3 or more months (International Classification of Headache Disorders, 2004). About 40% of patients presenting to headache centers present with chronic headaches and 80% of these subjects overuse symptomatic medications that include analgesics, specific migraine medications (such as triptans), opioids, or drug combinations (Meng ID et al, 2011). Although MOH has a prevalence of 1-2% of the general population, it represents a significant health problem associated with significant long-term morbidity and disability (Diener HC, 2004). MOH manifests as increased frequency and intensity of migraine attacks and as increased sensitivity to stimuli that trigger migraine episodes (De Felice, 2011). A number of authors indicate that MOH occurs in 1-4% of the general population, with a prevalence that is similar in different countries, but with a higher incidence in women than in men, with lower socio-economic status, reduced health quality of life, increased headache-related burden (including impairments in

occupational, social, and family functioning), migraine remission during pregnancy, and psychiatric conditions (depression, anxiety, and chronic pain) and medical comorbidities (hypertension, diabetes, high cholesterol, and obesity)) (Aaseth K, et al., 2008; Buse DC, et al., 2010).

In addition, there is evidence based on the role of the genetic factor in the development of MOH and that it occurs as a continuation of chronic migraine with excessive use of symptomatic drugs (Di Lorenzo, et al., 2009, Silberstein SD, et al, 2005). The mechanism of action in medication overuse headache is unclear, but is thought to be related to dysregulation in serotonergic transmission (Paemeleire K, et al., 2006). Although the specific mechanisms leading to MOH remain unknown, several studies suggest that MOH may involve reinforcement processes, including descending facilitation and "central sensitization," and increased excitability of spinal and medullary dorsal horn neurons resulting from continuous Cfiber input. nociceptors (Dodick D, 2006; De FeliceM, 2011).

According to the International Classification of Headache Disorders, the criteria for the third beta version (ICHD-IIIß) - International Classification of Headache Disorders 3rd beta edition (ICHD-IIIβ) - divides - for headache with overuse of drugs (Headache Classification Committee of the International Headache Society, 2013) divides them into:

A. Headache present on > 15 days/month.

B. Regular overuse for > 3 months of one or more medications that may be taken for the acute and/or symptomatic treatment of headache.

Headache developed or significantly worsened during medication overuse (for simple analgesics and combination acute medications, intake must be 15 days or more per month for triptans, ergotamines, opioids, and combination analgesics; 10 days per month sufficient to get a diagnosis of MOH). A recent epidemiologic study on drug-induced disorders demonstrated that excessive drug use can lead to nephrotoxicity and the potential for kidney damage (Davies P et al 2012; Negro A, et al 2011). In particular, drug-related nephrotoxicity accounts for 18-27% of all acute kidney injury in the US and drugs can affect all aspects and every part of the kidney structure by various mechanisms of renal dysfunction (Taber SS, et al., 2008). According to Rahman A, et al., (1993) the pattern of analgesic use, abuse and frequency of analgesic-related nephropathy in 79 patients with chronic headache was studied. Sixty-eight of these patients had migraine. A large number of patients were users of a combination of analgesics (81%), while 19% were users of monotherapy analgesics for headache, with 96.2% of patients being users of non-steroidal anti-inflammatory drugs followed by Paracetamol (70.9%) and compounds of Aspirin, Phenacetin and Caffeine (5.1%). Of the 65 patients, 45 were those who abused analgesics, performed an intravenous urogram or ultrasound, where renal papillary necrosis was documented in only one patient. In three patients (4.6%) a slight elevation of the serum creatinine level was observed. Mild proteinuria of less than 1 g/L was observed in 27.7% of patients. They concluded that the use and abuse of analgesics is common in patients with chronic headache and demonstrated a low short-term incidence of analgesic-related nephropathy of 2.2% and renal damage of 4.6% (Rahman A, et al., 1993). Various epidemiological studies have shown that different types of analgesics can cause nephrotoxicity, especially in chronic patients, associated with overuse of analgesics, triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, or combinations of drugs.

Microalbuminuria was often detected in patients under the influence of nephrotoxic drugs. Subclinical renal impairment cannot be identified by routine tests (serum creatinine), and microalbuminuria is a more sensitive indicator of renal dysfunction.

Although new biomarkers are used in practice, for the diagnosis of AKI and CKD it is still set with surrogate markers such as glomerular filtration rate (GFR), serum creatinine (SCr), urine excretion, and creatinine-based SCr scaling is limited as a marker of both renal dysfunction and settings and may be inaccurate in several situations. In some cases, serum Cr may increase in prerenal azotemia without tubular damage, as in patients with low muscle mass or with fluid and drug overload affecting serum Cr levels (Havziu, Drita Yzeiri et al 2021).

New biomarkers have the potential to identify previous patients with Acute Kidney Injury (AKI) and Chronic kidney disease (CKD) and potentially intervene in the future to modify results (Havziu, Drita Yzeiri et al 2021).

1.1. Microalbuminuria: Microalbuminuria defined as the pathological excretion of urinary albumin below the detection threshold (from 30 to 300 mg/L) with a conventional urine control sample, has long been established as a useful marker for the development and progression of kidney diseases, especially in nephropathy. Approximately 30% of urine protein belongs to albumin, and this is a good indicator for assessing changes in glomerular permeability. Historically, microalbuminuria was thought to arise from alterations in glomerular filtration and secondarily from changes in intraglomerular pressure or structural changes in the glomerular basement membrane. Intermediary proteins, which are usually filtered in small amounts in glomeruli, but larger amounts are reabsorbed in tubules (D.Uzeiri.Havziu. 2020).

1.2. β2-microglobulin : (β2-microglobulin) (β2M) is an 11.8-kDa protein that is the light chain of the major histocompatibility complex (MHC) class I, a molecule present on the cell surface of all nucleated cells. β2M is cleaved from the heavy chain during cellular turnover and enters the circulation as a monomer (Tolkoff-Rubin et al., 1988). β2M is filtered by the glomeruli and almost completely reabsorbed and catabolized by the proximal tubular cells, a process that may be hindered by AKI. Increased urinary excretion of β2M has already been observed as an early marker of tubular damage under several conditions, including exposure to nephrotoxic substances (Vaidya et al., 2008) prior to elevation of serum creatinine within 4 to 5 days (D.Uzeiri.Havziu. 2020).
According to Azade (2019), low molecular weight protein is normally found in urine, but increases in tubular damage, secondary poisoning with antibiotics, analgesics, solvents, heavy metals or pesticides. Under these conditions, it has been shown to be a sensitive biomarker of renal tubular damage, but it is rapidly degraded at room temperature and urine pH <6; therefore, its utility as a urinary biomarker is limited (Azade, 2019; D.Uzeiri.Havziu. 2020).
The aim is to confirm the sensitivity of certain biomarkers when comparing patients treated with NSAIDs in combination with other drugs (analgesics, triptans and antidepressants) with patients treated with monotherapy by NSAIDs and which group of patients shows increased expression of the protein profile

2. Materials and Methods

For realization of the set goals will use urine and venous blood from patients with chronic headache and migraine pains from Clinic of Neurology – Tetovo (Polog Region of R.N.M), patients with normal renal function. special group of 24 patients with overdose headache (Medication-overuse headache (MOH) treated more than 15 days a month with combination therapy of NSAIDs + triptans + antidepressants Compassion with patients treated with monotherapy by NSAIDs .12 patients treated for 5 years with Ibuprofen 600 mg, 12 patients were treated for 10 years with Diclofenac duo 75 mg capsules,12 patients with Ketoprofen 100 mg tablets for up to 10 years and 12 patients with Celecoxib 200 mg. - treated for 12 months. 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.
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 "Goce Delchev" – Shtip (WMA, 2000). 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 (Drita Yzeiri Havziu, et al 2022).
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. (2016) and subsequently used for further biochemical characterization (D.Yzeiri Havziu, et al. 2016).
For testing the creatinine serum/urine, we used the Jaffe method - during the reaction of the creatinine withthe 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) (Havziu, Drita Yzeiri et al, 2021).
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, measured at a value of 340 and 383 nm (Dimension Rxl) (Havziu, Drita Yzeiri et al 2021).
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 ProSpecR System was used (Drita Yzeiri Havziu et al 2022).

3. Statistical data processing

Statistical data processing was performed in SPSS for Windows 23.0 statistical software. We used p (Chi-square test) 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

In order to confirm the degree of nephrotoxicity of the combined therapy and at the same time to once again confirm the sensitivity of certain biomarkers, the following text shows the comparison - patients with MOH -NSAID in combination with other drugs (analgesics, triptans and antidepressants) with all other experimental groups, in relation to the analyzed parameters (normal values and values deviating from the reference) are presented in “Tables 1, 2.3”

Table 1. Comparison – of patients treated with combined therapy* and groups of patients treated with Diclofenac in comparison with the analysed parameters (normal values and values that differ from referent)

Variable		Group			p-level
		N	Diclofenac n (%)	Combined therapy*	
Urea (serum)	Increase	9	4 (33.33)	5 (26.32)	p=0.98 ns
Creatinin (serum)	Decrease	1	1 (8.33)	0	p=0.81 ns
Creatinin (urine)	Decrease	17	9 (75)	8 (42.11)	p=0.15 ns

Natrium (serum)	Decrease	4	0	4 (21.05)	p=0.25 ns
Chlorides (serum)	Decrease	12	7 (58.33)	5 (26.32)	p=0.16 ns
Microalbuminuria	Increase	18	2 (16.67)	16 (84.21)	p=0.0008 sig
β2 M	Increase	25	11 (91.67)	14 (73.68)	p=0.44 ns

p (Chi-square test)
** NSAIDs in combination with other drugs (analgesics, triptans and antidepressants)*

Based on the obtained data from Table 1, the comparison of the * NSAID group in combination with other drugs (analgesics, triptans and antidepressants), versus the Diclofenac group in terms of the analyzed parameters, showed that these two groups have significantly different frequencies of increased risk of withdrawal albumin in urine (p=0.0008). The increased risk of microalbuminuria was significantly more often registered in patients treated with combined therapy* compared to patients treated with Diclofenac - 84.2% (16) vs 16.7% (2). From the biochemical and clinical point of view, this indicates that the combined therapy significantly affects changes in the glomerular level, which is directly related to the increased urinary excretion of microalbuminuria. Based on the monitoring of microalbuminuria (as a marker for early identification of renal damage at the glomerular level), changes are detected at the glomerular level, which may occur as a complication of the disease itself or under the effect of combined therapy with *NSAIDs in combination with other drugs (analgesics, triptans and antidepressants).The results correspond according to Rahman A., et al., (1993) who showed nephropathy in 79 patients with chronic headache that was closely correlated with the high use of analgesics and their abuse, where 68 patients had migraines. A large number of patients were users of combination analgesics (81%), while 19% were users of monotherapy of analgesics for headache.

Table 2. Comparison – of patients treated with combined therapy* and groups of patients treated with Ibuprofen in comparision with the analysed parameters (normal values and values that differ from referent)

Variable		Group			p-level
		N	Ibuprofen n (%)	Combined therapy* n (%)	
Urea (serum)	Increase	5	0	5 (26.32)	p=0.15 ns
Creatinin (urine)	Decrease	16	8 (66.67)	8 (42.11)	p=0.34 ns
Natrium (serum)	Decrease	5	1 (8.33)	4 (21.05)	p=0.66 ns
Chlorides (serum)	Decrease	11	6 (50)	5 (26.32)	p=0.34 ns
Microalbuminuria	Increase	20	4 (33.33)	16 (84.21)	p=0.012 sig
β2 M	Increase	25	11 (91.6	14 (73.68)	p=0.44 ns

p (Chi-square test)
** NSAIDs in combination with other drugs (analgesics, triptans and antidepressants)*

Based on the data obtained from Table 2, the comparison of the group with * NSAID in combination with other drugs (analgesics, triptans and antidepressants), versus the Ibuprofen group in terms of the analyzed parameters, showed that these two groups have significantly different frequency of increased risk of withdrawal albumin in urine (p=0.012 sig).The increased risk of microalbuminuria was significantly more often registered in patients treated with combined therapy* compared to patients treated with Ibuprofen - 84.2% (16) vs 4 (33.33)% (4). From the biochemical and clinical point of view, this indicates that the combined therapy significantly affects changes in the glomerular level, which is directly related to the increased urinary excretion of microalbuminuria. The results have clinical significance, because they confirm again that the combined therapy significantly affects the increase in microalbuminuria, as in previous results. The obtained data are in contrast to the national health and nutrition survey conducted by non-institutional residents aged at least 20 years through the analysis of common long-term use of > 5 years. The subjects used an analgesic every day for at least one month as a monotherapy with Ibuprofen or combined analgesic therapy, and the increased frequency of albuminuria was not found in them (Agodoa, Lawrence Y. et al., 2007).

Table 3. Comparison – of patients treated with combined therapy* and groups of patients treated with Celecoxib in comparision with the analysed parameters (normal values and values that differ from referent)

Variable		Group			p-level
		N	Celecoxib n (%)	Combined therapy* n (%)	
Urea (serum)	Increase	10	5 (41.67)	5 (26.32)	p=0.62 ns
Creatinin ((serum)	Decrease	1	1 (8.33)	0	p=0.81 ns
Creatinin (urine)	Decrease	17	9 (75)	8 (42.11)	p=0.15 ns
Natrium ((serum)	Decrease	5	1 (8.33)	4 (21.05)	p=0.66 ns
Chlorides ((serum)	Decrease	6	1 (8.33)	5 (26.32)	p=0.44 ns
Microalbuminuria	Increase	18	2 (16.67)	16 (84.21)	p=0.0008 sig
β2 M	Increase	20	6 (50)	14 (73.68)	p=0.34 ns

p (Chi-square test)
** NSAIDs in combination with other drugs (analgesics, triptans and antidepressants)*

From the values of Table 3, a statistically significant difference is confirmed between the group with combined therapy* and the group with Celecoxib, regarding the frequency of increased microalbuminuria (p=0.0008). Increased excretion of albumin in urine was significantly more often registered in patients treated with combined therapy with NSAIDs and other drugs (analgesics, triptans and antidepressants – 84.2% (16) versus 16.7% (2). The results have great clinical significance, because they indicate early changes at the glomerular level in patients treated with combined therapy* compared to patients treated with the selective COX2 inhibitor Celecoxib. This fact is a key piece of data, as it once again confirms the high sensitivity of microalbuminuria for identifying small changes in GFR caused by nephrotoxic agents, i.e. combined therapy*. These results correspond to the claims of Pedersen et al., that the biomarker microalbuminuria is a more sensitive indicator for the identification of renal dysfunction, as opposed to

monitoring others parameters (Pedersen et al., 1995), where at the same time it confirms the verifications of Azade (2019), thanβ 2M has been shown to degrade rapidly at room temperature and urine pH <6; therefore, its utility as a urinary biomarker is limited (Azade, 2019).

5. Conclusion

In chronic monotherapy with different groups of NSAIDs and in combined therapy :

- β2M as a specific bioindicator did not show a measured sensitivity for the detection of early changes in the tubular level in relation to microalbuminuria, which signals us for a more sensitive indicator.
- in patients placed on combined therapy with NSAIDs and other medications (analgesics, triptans and antidepressants) were confirmed nephrotoxic changes compared to patients treated with chronic monotherapy of different groups of NSAIDs.

Nomenclature

MOH-Medication-overuse headache
GLDH Glutamate dehydrogenase
α-KG α-ketoglutarate
NADH Nicotinamide adenine dinucleotide

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