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Original scientific paper

RENAL TOXICITY COMPARISON BY NSAIDS DEPENDING ON THE MECHANISM OF ACTION IN PATIENTS WITH HEADACHES

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Abstract

Non-selective COX inhibitors are the most widely prescribed NSAID treatment for headaches. Celecoxib is another NSAID therapy that has been approved in the last several years, with different mechanisms of action. Nonsteroidal anti-inflammatory drugs (NSAIDs) cause renal toxicity following the inhibition of cyclooxygenases. Relatively little is known about the comparative nephrotoxicity of NSAIDs in patients with a chronic headache based on COX inhibition. Therefore, this study was designed to compare the nephrotoxic effects of nonselective COX inhibitors, relatively selective inhibitors, and selective inhibitors based on the mechanism of action. Besides conventional markers of renal function (serum/urine creatinine determined by Jaffe's methods of enzymatic assay for urea in serum, uric acid in serum, and glutamyl transferase [γ-GT] in serum). We used nephelometry by β2 microglobulin (β2M) and photoelectric colorimetry for microalbuminuria in urine, as well as ion selective electrode (ISE) for electrolyte detection in serum, to evaluate glomerular and tubular functioning. Kidney disease history was a requirement to be excluded from the study.
The results showed increased values of microalbuminuria in patients treated with NSAIDs as non-selective COX inhibitors compared with patients treated with NSAIDs as relatively selective and highly selective COX-2 inhibitors - 52.8% (19), 16.7% (2), 16.7% (4), consequently and in β2 microglobulin 97.2% (35), 91.7% (11), 54.2% (13), consequently. The renoprotective properties of highly selective COX-2 inhibitors have been confirmed with non-selective COX inhibitors that are less nephrotoxic agents.

Keywords: Nephrotoxicity, Nonsteroidal anti-inflammatory drugs, COX inhibitors, Headaches.

1. Introduction

Non-selective COX inhibitors are the most widely prescribed NSAIDs treatment of headaches The main effect of conventional NSAIDs is the non-selective inhibition of both isoforms, unlike NSAIDs which are specific only for COX-2 inhibition, which is also effective in migraine. The new COX-2 inhibitors (coxibi) are highly effective and rapidly absorbed by non-selective inhibitors, can provide clinical benefits in migraine by achieving a rapid mechanism of action for acute treatment, and prevent the development of central sensitization, which reduces the likelihood of a successful outcome. Meloxicam is another NSAID that has 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). *Quiralte* and co-workers have confirmed that diclofenac sodium is one of the most widely prescribed NSAIDs in the world. According to *Sagar et al.,* (2017), the efficacy of a new oral liquid formulation of celecoxib has been demonstrated in adults with migraine episodes. Many authors have shown the effectiveness of aspirin, diclofenac potassium, ketoprofen, and naproxen sodium in acute migraine headaches (*John F. Rothrock, MD,* 2011).

Based on the selective COX inhibition in accordance with COX-1/COX-2 - IC50 coefficient NSAIDs are divided into:

- Selective COX-1 inhibitors such as aspirin with COX-1/COX-2 coefficient IC50 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 - IC50 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-inhibitors (Havziu, 2014; Sylejmanet al., 2007; Yzeiri Havziu, 2020). According to Fackovcava et al. (2000), indomethacin is a more effective inhibitor of both COX-1 and COX-2 isoenzymes, naproxen primarily inhibits COX-1, and to a lesser extent COX-2, ibuprofen is a weaker inhibitor of COX-1 and COX-2, with no apparent selectivity to COX-2, with excellent analgesic effect at low doses.

Piroxicam is an effective inhibitor of COX-1. The nephrotoxicity of the above NSAIDs has been confirmed in patients with compromised renal function. Indomethacin, naproxen and ibuprofen are prominent. Sulindac is again mentioned as a renoprotective agent (*D. Uzeiri Havziu,* 2014*; Yzeiri Havziu, 2020).* According to Burkhard Hinz and colleagues, their ongoing research on COX isoforms has shown that paracetamol has a stronger effect on COX preparations in the brain than on COX preparations in the spleen. It has been suggested that a third isoform of the enzyme, COX-3, may be present in the brain (*Sasan et al.,* 2011). Attempts to explain its effect by inhibiting central cyclooxygenase (COX) -3 have since been rejected. The fact that acetaminophen acts functionally as a selective inhibitor of COX-2 has led us to test the hypothesis that it works through preferential COX-2 blockade. *Burkhard*

Hinz (2007), confirmed coagulation induced by thromboxane B2 and prostaglandin E2-induced lipopolysaccharide measured ex vivo and in vitro in whole human blood as COX-1 and COX-2 activity coefficients. Ex vivo COX inhibition and pharmacokinetics of acetaminophen in 5 volunteers receiving single 1000 mg oral doses In vitro, acetaminophen-induced 4.4-fold selectivity for COX-2 inhibition (IC50 = 113.7 μmol / L for COX-1; IC50 = 25.8 μmol / L for COX-2). Following oral administration, maximal ex vivo inhibitions were 56% (COX-1) and 83% (COX-2). Unlike previous concepts, acetaminophen inhibits COX-2 by more than 80%, to a degree similar to nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors *(Burkhard Hinz,* 2008). Paracetamol is the analgesic of choice for elderly patients or those with impaired renal function. At therapeutic doses, renal toxicity is rare *(Schug SA,* 2005). No dose adjustment is required in renal failure, but some authors recommend increasing dose intervals of 6 to 8 hours when GFR is below 10 ml.min-1 (*Mazer M, et al,* 2008). According to *Sejoong Kim M.D.,* (2007) NSAIDs can cause hyponatremia by reducing renal free water clearance. Hyperkaliemia may occur to some extent to cause cardiac arrhythmias. Renal function may be reduced sufficiently to cause acute renal failure The association of electrolyte and acid-base disorders with NSAIDs is not uncommon in some clinical situations. The renal side effects of NSAIDs are usually associated with prostaglandin-dependent conditions, such as conditions that tend to impair renal perfusion. On the other hand, other studies have not shown significant differences in renal risk between COX-2-selective inhibitors (celecoxib / Celebrex) Perkins *S.,* (2002) and non-selective NSAIDs *(Swan et al.,* 2000*; Whelton et al.,* 2000*).* According to Weir et al., (2000), clinical trials comparing renal changes between nonselective NSAIDs and coxibs indicate only subtle changes in renal haemodynamics. They found that the renal effects of celecoxib were like those of nonselective NSAIDs. And because of the role of COX-2 in regulating electrolyte and water excretion, the COX-2-selective inhibitors, rofecoxib, celecoxib, and valdecoxib, were expected to have similar effects. Therefore, when applying the standard precautions that apply to the use of non-selective NSAIDs, they also apply to the use of coxibes (*Weir et al,* 2002*).* While *Lucas et al,* (2019) that specific COX-2 inhibitors fail to offer advantages in terms of renal toxicity over traditional NSAIDs. COX-2 is a critical enzyme for sodium excretion and renin release, its inhibition contributes to sodium retention, hyperkaliemia, and water intoxication. Some studies also suggest lower nephrotoxic potential in low-dose non-selective COX drugs,

such as ASA and ibuprofen, compared to selective COX-2 agents.

According to Kim et al. (1999), patients at risk for treatment with nonselective and selective COX-2 inhibitors were monitored, with both groups of NSAIDs causing changes in electrolyte status with hyponatremia and hyperkalemia. The highest incidence of AKI has been reported with the use of indomethacin with ibuprofen and piroxicam (Griffin et al., 2000). Celecoxib (selective COX-2 inhibitor - has a lower risk of developing AKI compared to other non-selective NSAIDs (Winkelmayer et al., 2008; Schneider, et al., 2006, D. Uzeiri.Havziu, 2014).

Fujihara C.K et al., (2003) confirmed the renoprotection of a specific COX-2 inhibitor in an 8-week treatment of experimental animals with celecoxib. Studies by *Whelton A, et al.,* (2001) also confirmed renal safety in the use of at-risk patients using the subsequent efficacy and safety of celecoxib-Successive Celecoxib Efficacy and Safety Studies (SUCCESS) VI and VII. On the other hand, *Zhang et al.,* (2017) proved that the elderly who were users of a group of NSAIDs of selective COX-2 inhibitors have somewhere twice the risk of developing AKI, but did not confirm strong evidence of association with a lower risk of AKI with selective COX-2 inhibitors. NSAIDs with high selectivity of COX-2 (≥5 times) had a lower association with AKI than NSAIDs with the selectivity of COX-2 <5-fold, and heterogeneity in the subgroups was reduced compared to the overall results according to part of the heterogeneity due to differences in the age of the population in studies and the type of NSAIDs examined. Compared with meloxicam, diclofenac sodium has resulted in a high degree of nephrotoxicity *(Swan et al.,* 2006). The detrimental effects of diclofenac sodium and meloxicam on renal tissue in animals have been well documented in the literature. Relatively little is known about the comparative nephrotoxicity of NSAIDs, especially in human renal *tissue* (*Andalib Sasan,* 2011) based on COX inhibition. Therefore, this study is designed to compare the side effects of nonselective COX inhibitors, relatively selective inhibitors, and selective inhibitors on renal tissue, especially in patients with chronic headaches for which literature is lacking.

The purpose of the study is to follow the renal function and comparisons of nephrotoxicity of different types of NSAID based on COX inhibition, in patients with cefalea-migraine treated for a long period.

2. Materials and methods

To accomplish the goal of this study we used urine and venous blood from randomly selected patients of Clinical Center-Neurology-Tetovo (Polog Region of R.N.M), with a chronic headache--migraine, with normal renal function. The study included a total of 72 patients with an average age of 42.047±7.41 years, with a range of 35-65 years with a mean follow-up of up to 120±12.6 months treated with different 3 groups of NSAIDs:

Group 1- non-selective COX inhibitors (piroxicam, ketoprofen and ibuprofen)

Group 2 relatively selective COX2 inhibitors (diclofenac)

Group 3 selective COX-2 inhibitors (celecoxib, paracetamol).

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 Ethics Committee of the Faculty of Medical Sciences at the University "Goce Delcev" – Stip (WMA, 2000). The results represent the average value of the three measurements, made under identical conditions. For purpose of analysis, the sample was used 5 ml of blood, collected in special tubes, without anticoagulants. All materials for analysis are measured in the laboratories of the Clinical Hospital in Tetovo (*Yzeiri Havziu,* 2020).

To determine creatinine and specific biomarkers (β2M and microalbuminuria), was used the first-morning

urine. The samples were processed according to the protocol described by Havziu et al. (2016) and subsequently used for further biochemical characterization. For β2M determination imunonephelometry by BN II/BN ProSpecR System was used *(Yzeiri Havziu,* 2020).

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,* 2020).

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) (*Yzeiri Havziu,* 2020).

$_{\gamma}$-glutamyl transferase ($_{\gamma}$ -GT) in urine/serum is determined using a standardized method by the IFCC. In a buffer substrate containing TRIS HCL buffer in which $_{\gamma}$-glutamyl-3 carboxy-4-nitroanilide (Flex reagent cartridge) and glycyl glycine (Flex reagent cartridge) are dissolved. The reaction is started by adding 0.2 ml of sample and monitoring the increase in absorbance to 405 nm using a program applied to a biochemical analyzer (Cobas Integra 400 Roche Diagnostics and Dimension EXL 200). Mean values of extension differences (deltae/min) were used to calculate $_{\gamma}$ -GT activity (*D.Uzeiri Havziu,* 2014).

Serum electrolytes - Ion Selective Electrodes (ISE) - determine the difference in the electrochemical potential between the glass or liquid membrane electrode (Flex Reagent Cartridges) and the reference electrode (Flex Reagent Cartridges) that is proportional to the concentration of electrolytes in the serum (*Yzeiri Havziu,* 2020)

For the determination of urinary albumin, and microalbuminuria, we used a visual Reading urine tape test in Combilyzer 13 - a test 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 the following values: 10, 30, 80, and 150 mg/L urinary albumins (*Yzeiri Havziu,* 2020).

3. Statistical data processing

Statistical data processing was performed in SPSS for Windows 23.0 statistical software. Nonparametric and parametric tests for independent samples F (Analysis of Variance), (H Kruskal-Wallis test), post - hoc (Mann-Whitney test), and post –hoc Bonferroni, 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

And at the same time comparing the average and mean values of the analyzed parameters to confirm which group is more nephrotoxic or renoprotective, are shown in the results in Table 1.

The results of the study shown in Table 1 showed that the mechanism of action of non-steroidal anti-inflammatory drugs had a significant effect on creatinine values. For p = 0.026, a significant difference in urine creatinine values was confirmed between the groups of non-selective COX inhibitors, relatively selective, and highly selective COX-2 inhibitors. This significance was due to significantly higher urinary creatinine values measured in patients treated with NSAIDs for non-selective COX inhibitors than for highly selective COX-2 inhibitors (median 8.8 vs 4.4; p = 0.029). The results have no clinical significance because other parameters according to the nephrological protocol do not show statistically significant changes, and knowing the fact that creatinine is not a real-time biomarker, and its levels may not increase until renal function is compromised, which may result in a missed therapeutic outcome, although urinary excretion is a very sensitive and early marker of renal dysfunction, is not a widely used criterion for diagnosing AKI (*Mahrukh S. et al.,* 2017). However, given the results obtained that correspond to several

studies suggesting that COX-2-selective inhibitors cause fewer renal side effects including decreased glomerular filtration rate (GFR), elevated serum creatinine (SCr), and hypertension, compared with nonselective NSAIDs (*Silverstein et al*, 2000; *Whelton et al*, 2000).

Table 1. Comparison of median and mean values of analysed parameters depending on the mechanism of action

Variable	*median (IQR)*	*p-level*			
		group 1/2/3	*Group*		
				2	*3*
Urea (serum)	*4.65(4.125 – 5.2)*	*H=2.84*	*Group 1*		
	5.2(4.6 – 6.6)	*p=0.24 ns*	*Group 2*		
	5.6(4.1 – 6.4)		*Group 3*		
Creatinine (serum)	*67(56 – 82)*	*H=0.68*	*Group 1*		
	65.5(59 – 75)	*p=0.71 ns*	*Group 2*		
	68(59 – 82)		*Group 3*		
Acid ureic (serum)	*240(232 – 289)*	*H=1.84*	*Group 1*		
	279.5(234 – 330)	*p=0.4 ns*	*Group 2*		
	235(233 – 355.5)		*Group 3*		
Creatinine (urine)	*8.8(8.8 – 17.7)*	*H=7.26*	*Group 1*	*Ns*	*0.029 sig*
	7.6(4.4 – 13.25)	*p=0.026 sig*	*Group 2*		*Ns*
	4.4(4.4 – 8.8)		*Group 3*		
Sodium	*139(138 – 140.5)*	*F=0.89*	*Group 1*		
(serum)	*139(137.5 – 140)*	*p=0.64 ns*	*Group 2*		
	139(137 – 140)		*Group 3*		
Potasium (serum)	*4.(4.2 – 4.7)*	*F=2.89*	*Group 1*		
	4.35(4.25 – 4.75)	*p=0.23 ns*	*Group 2*		
	4.3(4.2 – 4.5)		*Group 3*		
Chlorides (serum)	*98(98 – 101)*	*H=1.28*	*Group 1*		
	97(96.5 – 99)	*p=0.46 ns*	*Group 2*		
	100(99 – 102)		*Group 3*		
Microalbuminuria	*30 (10 – 30)*	*H=10.59*	*Group 1*	*0.047sig*	*0.047sig*
	10 (10 – 10)	*p=0.005 sig*	*Group 2*		*Ns*
	10 (10 – 10)		*Group 3*		
β2 M	*0.206(0.206-0.206)*	*H=16.2*	*Group 1*	*Ns*	*0.001 sig*

	0.206(0.205-0.2095)	*p=0.0003 sig*	*Group 2*	*0.033 sig*
	0.202(0.186-0.206)		*Group 3*	
GGT serum	*23 (17 – 29)*	*H=1.33*	*Group 1*	
	24.5 (18 – 35.5)	*p=0.51 ns*	*Group 2*	
	21.5 (12.5 – 29.5)		*Group 3*	

F (Analysis of Variance), H (Kruskal-Wallis test); post –hoc Bonferroni, Mann-Whitney test
group 1 non selective mechanism COX inhibitors
group 2 relatively selective COX-2 inhibitors
group 3 highly selective COX-2 inhibitors

The results of the study shown in Table 1 showed total statistical significance in the concentration of excreted albumin in the urine depending on the mechanism of action (p = 0.005). Post-hoc analysis for intergroup comparisons showed that this significance was due to significantly higher values of microalbuminuria in the NSAID group than nonselective COX inhibitors relative to relatively selective and highly selective COX-2 inhibitors (median p = 0.047); the results suggest that nonselective COX inhibitors affect glomerular changes. The results correspond to the claims of *Huerto et al.,* (2005), who concluded that out of 103 patients with AKI, 29% were current users of non-selective COX1 inhibitors - ibuprofen. A statistically significant difference between the three groups was also confirmed in the values of β2 microglobulin (p = 0.0003). Significantly higher values of this parameter were presented in the NSAID groups of non-selective COX inhibitors and relatively selective COX-2 inhibitors compared to highly selective COX-2 inhibitors (p = 0.001, p = 0.033 consistently). Mean median β2 microglobulin values were 0.206 in the NSAID group of nonselective COX inhibitors and relatively selective COX-2 inhibitors and 0.201 in the group of highly selective COX-2 inhibitors. From a clinical-biochemical point of view, this fact reaffirms that COX1 inhibitors significantly affect changes in the epithelium of the proximal tubules, which is reflected by increased urinary excretion of β 2M (an early marker of tubular dysfunction). The results are consistent with studies by *Whelton A, et al.,* (2001) that confirmed renal safety in the use of at-risk patients using the subsequent efficacy and safety of celecoxib-Successive Celecoxib Efficacy and Safety Studies (SUCCESS) VI and VII (*Whelton A, et al.,* 2001). On the other hand, other studies have not shown significant differences in renal risk between COX-2-selective inhibitors (celecoxib/celebrex) (*Perkins, S.,* 2002) and non-selective NSAIDs (*Swan et al.,* 2000; *Whelton et al*., 2000). According to *Weir et al.,* (2000), clinical trials comparing renal changes between nonselective NSAIDs and coxibs indicate only subtle changes in renal hemodynamics. They found that the renal effects of celecoxib were similar to those of nonselective NSAIDs (*Weir et al,* 2000).

To confirm the renal safety or nephrotoxicity of the groups of drugs with a different mechanism of action, the results will be compared to normal and increased or decreased values of the analyzed parameters shown in Table 2.

Table 2. Comparison of the results in accordance with the normal and increased and decreased levels of the analysed parameters

Variable	*Values*	*Group*				*p-level*
		N	*Group 1*	*Group 2*	*Group 3*	
Urea (serum)	*Increased*	*14*	*5 (13.89)*	*4 (33.33)*	*5 (20.83)*	*[a]p=0.33 ns*
Creatinine (serum)	*Decreased*	*5*	*3 (8.33)*	*1 (8.33)*	*1 (4.17)*	*[b]p=0.83 ns*
Acid ureic (serum)	*Increased*	*4*	*1 (2.78)*	*0*	*3 (12.5)*	*[b]p=0.29 ns*

Creatinine (urine)	*Decreased*	*50*	*22 (61.11)*	*9 (75)*	*19 (79.17)*	*[a]p=0.3 ns*
Sodium (serum)	*Decreased*	*2*	*1 (2.78)*	*0*	*1 (4.17)*	
Chlorides (serum)	*Decreased*	*18*	*8 (22.22)*	*7 (58.33)*	*3 (12.5)*	*[a]p=0.01 sig*
Microalbuminuria	*Increased*	*25*	*19 (52.78)*	*2 (16.67)*	*4 (16.67)*	*[a]p=0.006 sig*
β2 M	*Increased*	*59*	*35 (97.22)*	*11 (91.67)*	*13 (54.17)*	*p<0.001 sig*

ap (Chi-square test), bp (Fisher exact test)
group 1 non selective mechanism COX inhibitors
group 2 relatively selective COX-2 inhibitors
group 3 highly selective COX-2 inhibitors

The results shown in Table 2 showed a statistically significant difference between chlorides (p = 0.01), microalbuminuria (p = 0.006), and β2 microglobulin (p <0.001). Decreased serum chloride levels were significantly more common in patients treated with NSAIDs than relatively selective COX-2 inhibitors compared with patients treated with NSAIDs as non-selective COX inhibitors and NSAIDs as highly selective COX-2 inhibitors - 58.2% (7.2%). 8), 12.5% (3), consequently.
Patients treated with NSAID non-selective COX inhibitors were significantly more likely to have microalbuminuria than those treated with NSAIDs with relatively selective and highly selective COX-2 inhibitors - 52.8% (19), 16.7% (2), 16.7% (4), consequently.
Elevated levels of β2 microglobulin were significantly more common in patients treated with NSAIDs as non-selective COX inhibitors and NSAIDs as relatively selective COX-2 inhibitors than in patients treated with highly selective COX-2 inhibitors - 97.2% (35), 91.7% (35), 91.7%, 54.2% (13), consequently. The results are of great clinical importance because the obtained data again indicate the renoprotective properties of highly selective COX-2 inhibitors - celecoxib. The data obtained correspond to *Fujihara C.K et al*., (2003) who confirmed the renoprotective specificity of a specific COX-2 inhibitor during the 8-week treatment of experimental animals with celecoxib. The highest incidence of AKI has been reported with the use of indomethacin with ibuprofen and piroxicam (*Griffin et al.,* 2000). Celecoxib (selective COX-2 inhibitor - has a lower risk of developing AKI compared to other non-selective NSAIDs (*Winkelmayer et al.*, 2008; *Schneider, et al.,* 2006, *D. Uzeiri. Havziu,* 2014*).*

5. Conclusion

- This fact suggests that non-selective COX inhibitors significantly affect changes in the glomeruli and tubules.
- During the chronic treatment of patients with cephalea with: non-selective COX inhibitors (piroxicam, ketoprofen, ibuprofen), relative selective COX2 inhibitors (diclofenac), and selective COX2 inhibitors (celecoxib, paracetamol), confirmed renoprotection of selective COX2 inhibitors with non-selective COX inhibitors that have proven to be more nephrotoxic agents.
- Individualized and rational use of NSAIDs is recommended especially in the group of non-selective COX inhibitors, due to the danger of increasing the potential for nephrotoxicity throughout therapy as well as constant monitoring of renal function in patients.

Nomenclature

COX-1 Cyclooxygenase1
COX-2 Cyclooxygenase 2
COX-3 Cyclooxygenase3
GLDH Glutamate dehydrogenase
α-KG α-ketoglutarate
NADH Nicotinamide adenine dinucleotide

Reference

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