

Comparative analysis of the use of non-steroidal anti-inflammatory drugs in Montenegro, Finland and Croatia in the period 2010-2019

M. ŠAHMAN-ZAIMOVIĆ^{1,2}, S. MUGOŠA^{1,2}

¹Institute for Medicines and Medical Devices of Montenegro, Podgorica, Montenegro

²Department for Pharmacology, Faculty of Medicine, University of Montenegro, Podgorica, Montenegro

Abstract. – OBJECTIVE: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used drugs. However, numerous studies have shown that non-selective cyclooxygenase (COX) inhibitors can also significantly increase the risk of cardiovascular side effects. Diclofenac has the highest risk, while naproxen has the lowest risk of developing these complications. The aim of the study was to analyze the structure and amount of NSAIDs consumed in Montenegro, Finland and Croatia in the last 10 years.

MATERIALS AND METHODS: In our study, we used 90% drug use (DU90) and ATC/DDD methodology. Drug consumption is shown in DDD/1000 inhabitants/day, and drug prices per DDD in Euros (€). Pearson's correlation test was used to examine the correlation between the number of drugs consumed and their price.

RESULTS: Diclofenac consumption is 3 to 4 times higher in Montenegro compared to Croatia, and 9 to 10 times higher than in Finland. The average price of diclofenac in Montenegro was around € 0.07 per DDD, in Finland around € 0.26 per DDD and in Croatia € 0.19 per DDD. In Montenegro, the Pearson correlation test did not show a statistically significant association between high diclofenac consumption and its DDD price but showed a positive strong correlation between DDD price growth and naproxen consumption growth.

CONCLUSIONS: The situation in Montenegro regarding the consumption of diclofenac is unfavorable and it is necessary to change the attitude and awareness of doctors and patients about the use of diclofenac. It is also necessary to replace diclofenac with naproxen, which is a slightly more expensive but safer drug.

Key Words:

Drug utilization, Diclofenac, Anti-inflammatory agents, Non-steroidal (MeSH terms).

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antipyretic, and anti-inflammatory properties. The mechanism of action of this group of drugs is based on the inhibition of the enzyme cyclooxygenase (COX)¹. There are two isoenzymes COX1 and COX2². The therapeutic effects of NSAIDs are explained by the inhibition of the enzyme COX2, which plays an important role in the production of mediators responsible for causing pain and inflammation³. The first NSAIDs synthesized inhibited both of these isoenzymes and were therefore termed non-selective COX inhibitors. The use of these drugs is related with the occurrence of side effects from the gastrointestinal tract. This is explained by the fact that these drugs strongly inhibit the isoenzyme COX1, which plays an important role in protecting the gastric mucosa⁴. On the other hand, NSAIDs that only inhibit COX2 are called selective COX inhibitors. These drugs act on COX1 to a small extent, so the occurrence of side effects from the gastrointestinal tract is very rare. Although they rarely cause gastrointestinal side effects, COX2 selective inhibitors have been shown to increase the risk of cardiovascular side effects^{5,6}. In late 2004, rofecoxib was withdrawn from the market because it was shown to increase the risk of major cardiovascular events (myocardial infarction and stroke), and in early 2005 valdecoxib was withdrawn from the market because it had an increased incidence of thrombotic events⁷⁻¹⁰. For these reasons, the use of non-selective COX inhibitors still dominated. However, numerous studies have shown that non-selective COX inhibitors can also significantly increase the risk of cardiovascular side effects. Diclofenac has

the highest risk while naproxen has the lowest risk of developing these complications¹¹. Analyses of NSAID use worldwide over the last decade, when the cardiovascular risks of this group of drugs were widely discussed in the scientific community, show that diclofenac is widespread in the structure of the NSAIDs used¹²⁻¹⁵.

The aim of the study was to analyze the structure and quantity of NSAIDs consumed in Montenegro over the past 10 years. In addition, the aim was to compare the use of NSAIDs in Montenegro with the use of the same drugs over the same period in Finland (a country with developed pharmacotherapeutic practice) and Croatia (neighboring country). Finally, the goal was to study the price of these drugs in Montenegro, Finland and Croatia.

Materials and Methods

NSAID use in Montenegro was compared to use of the same drugs in Finland and Croatia. Finland was selected as a country with a developed pharmacotherapy practice. Montenegro was part of a common state together with Croatia for more than half a century. Today, these two countries border each other, with Croatia being a member of the European Union (EU) and Montenegro being an EU candidate country.

Data on the consumption and price of medicines in Montenegro were obtained from the Institute of Medicines and Medical Devices (CInMED). Data on the consumption and price of medicines in the Republic of Croatia were taken from the official website of the Croatian Medicines and Medical Devices Agency (HALMED)¹⁶. Data on prices and drug use in the Republic of Finland were taken from the official website of the Medicines Agency of Finland (FIMEA)¹⁷.

The analysis covered a period of 10 years (from 2010 to 2019). The analyzed data included the total consumption of pharmaceuticals in all three countries.

The classification system Anatomical Therapeutic Chemical (ATC) and the Defined Daily Dose (DDD) as a unit of measurement are recommended by the WHO for monitoring and research of drug consumption¹⁸. In our investigation, we used the ATC/DDD methodology.

The DDD is the assumed average daily dose for a medicinal product used for its main indication in adults. Drug use is shown in units of DDD/1000 inhabitants/day (DDDs/TID). The drug consumption shown in DDDs/TID indicates how many

patients out of a total of 1000 inhabitants were treated with the DDD in one day. The presentation of drug use in this unit does allow us to compare drug use in different regions and in different years¹⁸.

In the ATC classification system, group M (medicines for the musculoskeletal system) is divided into 6 subgroups. Within the first subgroup (M01 – anti-inflammatory and anti-rheumatic products) are drugs whose consumption was analyzed in our study (M01A – anti-inflammatory and anti-rheumatic products, non-steroids)¹⁸.

Drug prices per DDD are given in Euros (€). The 90% drug utilization (DU90%) methodology was also used. This methodology offers us the possibility of a precise analysis of drug use. The DU90% segment includes drugs that account for 90% (or slightly more) of the total use of the analyzed drug group. Based on this assumption, we can see which drugs are most involved in the overall use¹⁹.

Pearson's correlation test was used to examine the correlation between the number of drugs consumed and their price.

Statistical Analysis

The statistical analysis was performed using the SPSS version 23.0 (SPSS Inc., IBM Corp., Armonk, NY, USA) package. Results were presented as absolute values and percentages. All reported probability values were two-tailed, and a 0.05 level ($p < 0.05$) of significance was considered to be appropriate.

Results

A comparison of all subgroups of group M shows that drugs of subgroup M01A have the highest consumption in all three countries considered in the analyzed period. The M01A subgroup in Montenegro shows consumption in the period 2010-2019 from about 94% (84.41 DDDs/TID) to about 91% (75.54 DDDs/TID) of all group M drugs, with slight fluctuations. In Finland these drug subgroups are used about 81% (74.20 DDDs/TID) to 79% (78.74 DDDs/TID) of all group M drugs over the same period, also with slight variations. This subgroup of drugs shows in Croatia in the same period constant increases in consumption, ranging from about 80% (42.35 DDDs/TID) to 83% (65.11 DDDs/TID) of all group M drugs.

The number of drugs from M01A group available to patients in Montenegro was 15 (2010),

Use of non-steroidal anti-inflammatory drugs

18 (2011), 17 (2012-2014), 16 (2015-2017) and 15 (2018-2019). The number of drugs within the DU90% segment was only 5 in 2010 and 2011. In all subsequent years (2012-2019), the number of drugs within the DU90% segment was only 4 (Table I). During the observation period in Montenegro, diclofenac (M01AB05) ranked first and ibuprofen (M01AE01) second. In Montenegro in

the same period within the DU90% segment was also naproxen (M01AE02). However, the consumption of naproxen was very low (Figures 1-3).

In Finland, there were 19 (2010 and 2016), 20 (2011-2015), and 18 (2017-2019) drugs available to patients from the M01A group. The number of drugs within the DU90% segment was 5 in every ten years (Table I). Ibuprofen took first place

Table I. Overview of the consumption of NSAIDs (subgroup M01A) within the DU90% segment, in Montenegro, Finland and Croatia in the year 2010, 2015 and 2019, presented as the number DDDs/TID and as the percentage of total consumption in the M01A subgroup.

Montenegro					
2010		2015		2019	
INN (DDD _s /TID)	%	INN (DDD _s /TID)	%	INN (DDD _s /TID)	%
M01A (84.41)	100.00	M01A (72.09)	100.00	M01A (75.54)	100.00
diclofenac (47.93)	54.83	diclofenac (43.57)	60.44	diclofenac (43.92)	58.14
ibuprofen (13.62)	15.58	ibuprofen (14.98)	20.78	ibuprofen (15.67)	20.74
dexketoprofen (10.67)	12.21	naproxen (5.39)	7.48	naproxen (6.72)	8.90
naproxen (3.55)	4.06	nimesulide (2.67)	3.70	aceclofenac (4.12)	5.45
nimesulide (3.78)	4.32				
DU90% - 15*/5**	91.01	DU90% - 16*/4**	92.40	DU90% - 15*/4**	93.24
Finland					
2010		2015		2019	
INN (DDD _s /TID)	%	INN (DDD _s /TID)	%	INN (DDD _s /TID)	%
M01A (74.20)	100.00	M01A (78.49)	100.00	M01A (78.74)	100.00
ibuprofen (42.68)	57.52	ibuprofen (49.19)	62.67	ibuprofen (51.05)	64.83
glucosamine (8.57)	11.55	etoricoxib (6.48)	8.26	etoricoxib (10.07)	12.79
naproxen (5.64)	7.60	naproxen (6.21)	7.91	naproxen (5.95)	7.56
etoricoxib (5.02)	6.77	glucosamine (5.84)	7.44	diclofenac (3.68)	4.67
diclofenac (4.99)	6.73	diclofenac (4.29)	5.47	glucosamine (2.98)	3.78
DU90% - 19*/5**	90.16	DU90% - 20*/5**	91.74	DU90% - 18*/5**	93.64
Croatia					
2010		2015		2019	
INN (DDD _s /TID)	%	INN (DDD _s /TID)	%	INN (DDD _s /TID)	%
M01A (42.35)	100.00	M01A (48.33)	100.00	M01A (65.11)	100.00
diclofenac (14.01)	33.08	ibuprofen (22.67)	46.91	ibuprofen (31.96)	49.09
ibuprofen (12.71)	30.01	diclofenac (12.26)	25.37	diclofenac (11.38)	17.48
ketoprofen (8.06)	19.03	ketoprofen (7.58)	15.68	ketoprofen (10.01)	15.37
piroxicam (3.11)	7.34	meloxicam (1.75)	3.62	naproxen (6.34)	9.74
meloxicam (2.52)	5.95				
DU90% - 12*/5**	95.42	DU90% - 18*/4**	91.58	DU90% - 20*/4**	91.68

INN - international name of drug. M01A - anti-inflammatory and antirheumatic products, non-steroids. DU90% - drug utilization 90% segment. *Number of drugs used. **number of drugs within the DU90% segment

Table II. Overview of the price for DDD of NSAIDs (subgroup M01A) within the DU90% segment in Montenegro, Finland and Croatia in the period 2010–2019, presented in Euros (€).

		2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Montenegro	M01AB05 (diclofenac)	0.07	0.07	0.07	0.07	0.07	0.08	0.07	0.07	0.10	0.07
	M01AE01 (ibuprofen)	0.16	0.20	0.27	0.26	0.27	0.28	0.27	0.27	0.27	0.27
	M01AE02 (naproxen)	0.08	0.08	0.09	0.10	0.10	0.10	0.10	0.10	0.10	0.09
	M01AE17 (dexketoprofen)	0.72	0.72								
	M01AB16 (aceclofenac)										0.31
	M01AX17 (nimesulide)	0.18	0.16	0.17	0.19	0.25	0.22	0.23	0.23	0.18	
Finland	M01AB05 (diclofenac)	0.31	0.28	0.27	0.25	0.26	0.27	0.27	0.27	0.26	0.20
	M01AE01 (ibuprofen)	0.31	0.28	0.29	0.25	0.27	0.29	0.29	0.29	0.29	0.29
	M01AE02 (naproxen)	0.19	0.16	0.16	0.14	0.17	0.19	0.18	0.17	0.16	0.14
	M01AH05 (etoricoxib)	0.87	0.74	0.74	0.57	0.63	0.68	0.60	0.43	0.21	0.17
	M01AX05 (glucosamine)	0.30	0.28	0.28	0.24	0.25	0.27	0.27	0.27	0.28	0.30
Croatia	M01AB05 (diclofenac)	0.23	0.23	0.22	0.21	0.23	0.18	0.17	0.16	0.15	0.15
	M01AE01 (ibuprofen)	0.30	0.31	0.31	0.30	0.31	0.30	0.30	0.29	0.28	0.29
	M01AE02 (naproxen)								0.17	0.15	0.14
	M01AE03 (ketoprofen)	0.14	0.13	0.13	0.13	0.12	0.12	0.12	0.12	0.12	0.13
	M01AC01 (piroxicam)	0.13	0.12	0.12	0.12	0.12					
	M01AC06 (meloxicam)	0.19					0.15	0.15			

during the analyzed period in Finland. In the second place, in Finland, there was glucosamine in 2010-2014 and etoricoxib in 2015-2019. Naproxen ranked fourth in 2012-2014, while it ranked third in other observed years. Diclofenac was also present in Finland in the DU90% segment, most frequently in fifth position with very low consumption (Figures 1-3).

The number of medicines from the M01A group available to patients from Croatia was constantly growing. Therefore, we have 12 (2010), 13 (2011 and 2012), 15 (2013), 16 (2014), 18 (2015), 19 (2016 and 2017), 21 (2018) and 20 (2019) drugs that were available for patients from the M01A group. The number of drugs within the DU90% segment in the last nine years (2011-2019) in Cro-

atia was 4. In 2010 alone there were 5 drugs (Table I). Diclofenac ranked first in Croatia only in 2010, while it ranked second in the following nine years. With ibuprofen, the situation is reversed. He was second only in 2010 and then first for the next nine years. Ketoprofen ranked third in Croatia during the observation period. In the last three years considered, naproxen ranked fourth and, interestingly, we observed a constant increase in consumption both in absolute and relative terms (Figures 1-3).

Drug prices per DDD are shown in Table II. We can see that diclofenac has the lowest price in Montenegro. The price for 1 DDD diclofenac in Montenegro is around € 0.07. Compared to Finland the price is about 3-4 times lower and com-

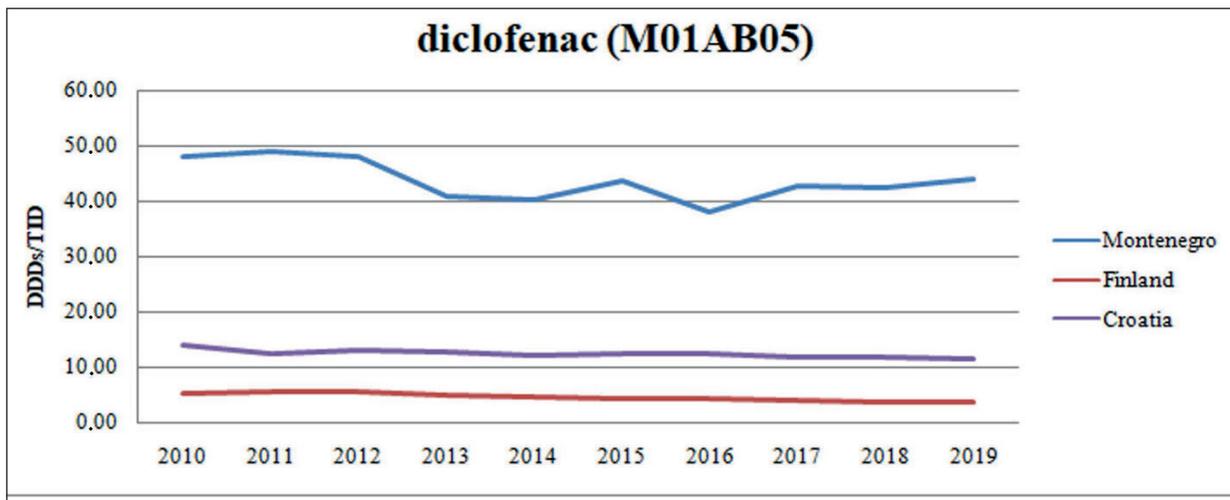


Figure 1. Comparison of diclofenac consumption (M01AB05) between Montenegro, Finland and Croatia over a 10-year period (2010-2019), presented as number DDDs/TID.

pared to Croatia about 3 times lower. The price of ibuprofen in Montenegro is significantly higher than the price of diclofenac. Depending on the year of observation, ibuprofen is 2-4 times more expensive than diclofenac. In the analyzed period the price of ibuprofen in Montenegro is similar than the price of the same drug in Finland and Croatia. If we compare prices of diclofenac and ibuprofen in Finland, we see that diclofenac is a bit cheaper compared to ibuprofen. The biggest difference is noticeable in the last year. In Croatia we can see that diclofenac has been twice as cheap as ibuprofen in recent years.

In Montenegro, the Pearson's correlation test showed no statistically significant associa-

tion between high diclofenac use and its DDD price (Table III). Diclofenac consumption has decreased by about 8%, but the price has remained about the same over the 10 years. Ibuprofen consumption increased by about 15% over the same period, while the price increased by almost 70%. Here we find a positive very weak correlation, but without statistical significance. The consumption of naproxen has increased by almost 90% in 10 years, but the price of this drug has also increased by 25%. In the case of naproxen in Montenegro, we find a positive strong correlation between the growth in the price per DDD and the growth in consumption.

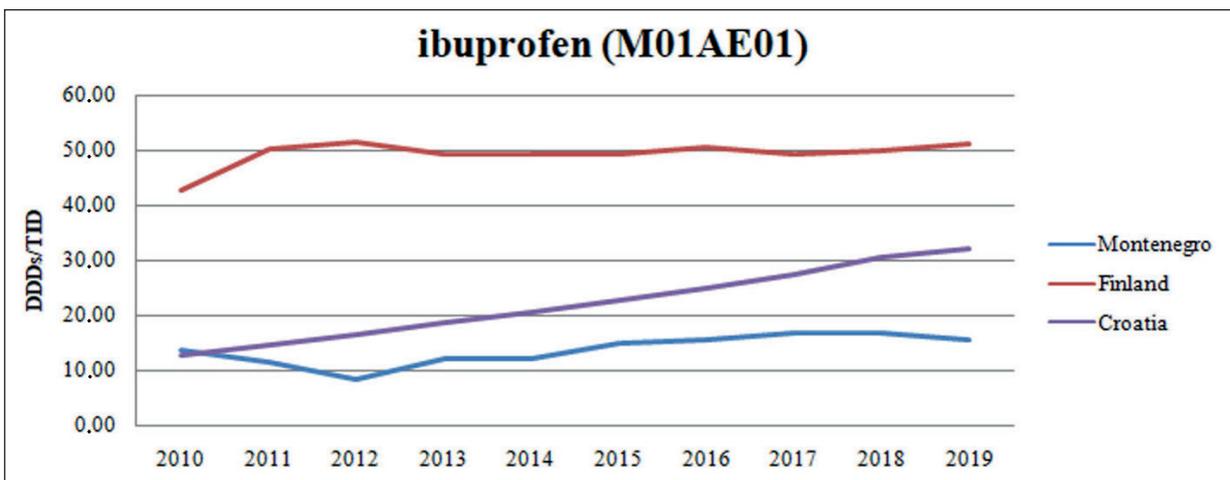


Figure 2. Comparison of ibuprofen (M01AE01) consumption between Montenegro, Finland and Croatia over a 10-year period (2010-2019), presented as number DDDs/TID.

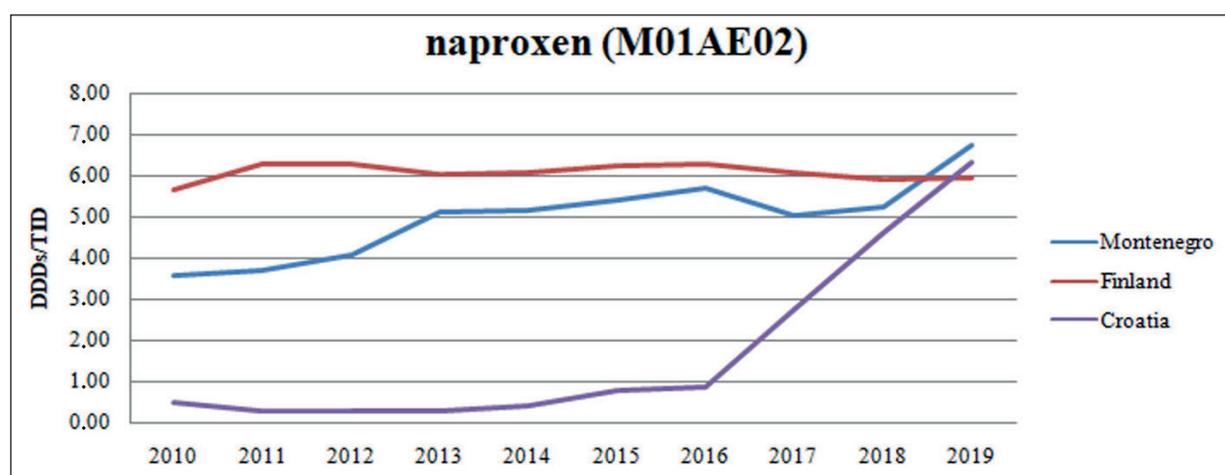


Figure 3. Comparison of naproxen (M01AE02) consumption between Montenegro, Finland and Croatia over a 10-year period (2010-2019), presented as number DDD_s/TID.

Table III. Changes in utilization (DDD_s/TID) and prices (€) of individual drugs between 2010 and 2019 and results of Pearson's correlation test between utilization and prices of drugs.

	2010	2019	Change	2010	2019	Change	beta	Significance
	DDD _s /TID	DDD _s /TID	%	€	€	%		
M01AB01 (indometacin)	0.10	0.07	-30.00	0.12	0.15	25.00	0.110	0.763
M01AB05 (diclofenac)	47.93	43.92	-8.37	0.07	0.07	0.00	-0.135	0.711
M01AB08 (etodolac)	0.10*	1.18	1080.00	0.25*	0.23	-8.00	-0.447	0.227
M01AB11 (acemetacin)	0.07	0.02	-71.43	0.35	0.34	-2.86	-0.072	0.854
M01AB15 (ketorolac)	0.23	0.46	100.00	0.83	1.03	24.10	-0.109	0.765
M01AB16 (aceclofenac)	0.02*	4.12	20500.00	0.28*	0.31	10.71	-0.012	0.976
M01AC01 (piroxicam)	1.94	0.54	-72.16	0.03	0.05	66.67	-0.787	<i>p</i> < 0.007
M01AC05 (lornoxicam)	0.46	0.17	-63.04	0.17	0.43	152.94	-0.547	0.102
M01AC06 (meloxicam)	0.76	0.39	-48.68	0.17	0.20	17.65	-0.910	<i>p</i> < 0.001
M01AE01 (ibuprofen)	13.62	15.67	15.05	0.16	0.27	68.75	0.208	0.565
M01AE02 (naproxen)	3.55	6.72	89.30	0.08	0.10	25.00	0.849	<i>p</i> < 0.002
M01AE03 (ketoprofen)	0.47	1.36	189.36	0.19	0.20	5.26	-0.173	0.633
M01AE17 (dexketoprofen)	10.67	0.10**	-99.06	0.72	0.7**	-2.78	-0.043	0.912
M01AH05 (etoricoxib)	0.05*	0.26	420.00	0.59*	0.50	-15.25	-0.636	0.066
M01AX05 (glucozamine)	0.03	0.15	400.00	0.73	0.62	-15.07	0.061	0.867
M01AX17 (nimesulide)	3.78	0.52	-86.24	0.18	0.20	11.11	-0.045	0.901

*Calculated from the first available year (2011). **Calculated in relation to the last available year (2018).

Discussion

Based on the obtained results, we can see that the consumption of NSAIDs in Montenegro is slightly lower compared to Finland, but significantly higher compared to Croatia. Of particular concern is the extremely high consumption of diclofenac in Montenegro. Of all the NSAIDs marketed in Montenegro for all ten years, diclofenac took first place convincingly. Consumption in Montenegro is 3-4 times higher than in Croatia and 9-10 times higher than in Finland. When choosing NSAIDs, drugs such as ibuprofen and naproxen are preferred according to current opinion, while the use of diclofenac should be reduced²⁰. By analyzing the consumption of these drugs in Croatia, we noted that according to these recommendations, the situation changed from year to year (decrease in consumption of diclofenac; increase in consumption of ibuprofen; the appearance of naproxen in DU90% and the growth of its consumption in the last 3 years). We do not find changes for the better in Montenegro that we see in Croatia.

In September 2004, the first selective COX inhibitor was withdrawn from the market in the United States⁷. The VIGOR study showed that rofecoxib has lower gastroduodenal toxicity but a significantly higher risk of all thromboembolic complications, including myocardial infarction⁸. For similar reasons, valdecoxib was withdrawn from the market shortly after this event^{7,9,10}.

Numerous studies soon followed, establishing a clear association between nonselective COX inhibitors and increased cardiovascular morbidity and mortality. Many of these studies²¹⁻²³ have shown that the use of diclofenac carries one of the greatest risks of developing CVD side effects. According to many authors, diclofenac had a risk similar to rofecoxib, a drug that was withdrawn from the market^{24,25}. For these reasons, current attitudes are to reduce the use of diclofenac and other NSAIDs.

As a result of these studies, the use of NSAIDs has decreased in many countries around the world and the use of alternative analgesics has increased. The main alternatives to NSAIDs are opioids and paracetamol. For some specific pain indications, antiepileptic drugs and antidepressants can be helpful. Comparing the use of NSAIDs and alternative analgesics in 2005 and 2017, we find a decrease in the use of NSAIDs and an increase in the use of alternative analgesics in Finland, Portugal, Czech Republic, Denmark, Luxembourg, Spain, Belgium, United Kingdom and the Netherlands²⁰.

However, as we can see, Montenegro has not kept up with these countries. NSAID use is at a fairly high level with no tendency to decrease.

Despite all the information that could be heard in the international scientific community, the consumption of diclofenac in Montenegro remained at an extremely high level. In 2013, CInMED was forced to send an open letter to healthcare workers on recommendations for the safe use of medicines containing diclofenac. However, this measure only had a short-term effect. This was reflected in a decrease in diclofenac use of approximately 8 DDDs/TID in 2013 compared to 2012. In 2014, diclofenac consumption remained at the same level as in 2013. However, it already increased in 2015. CInMED published an open letter again in 2015 and again in 2016 there was a slight decrease in the consumption of diclofenac by about 5 DDDs/TID compared to 2015. But already in 2017, the situation returned to the old with increased consumption of diclofenac. We can assume that a more aggressive CInMED campaign and stricter conditions for the issuance of diclofenac by the Republican Health Insurance Fund could achieve better results in reducing the consumption of this drug in Montenegro.

Diclofenac and similar medicines can only be obtained or bought in pharmacies in Montenegro with a doctor's prescription. This means that patients use any pack of these drugs with a doctor's permission. This study did not look at OTC (over-the-counter) preparations and this can certainly be a limiting factor of this study. There are OTC preparations containing some of the NSAIDs on the Montenegrin market. The question remains whether the consumption of OTC preparations containing diclofenac would increase if the restrictive measures for the sale of diclofenac were tightened and the consumption of this drug was reduced as a result.

According to the data available to the CInMED, in 2019, 27 DDDs/TIDs of diclofenac were issued to the account of the Republic Health Insurance Fund. This accounts for about 61% of total diclofenac consumed this year (43.92 DDDs/TID). The situation was similar in 2018. About 26 DDDs/TID of diclofenac were issued to the account of the Republic Health Insurance Fund, which also makes for about 61% of the total diclofenac consumed in 2018 (42.29 DDDs/TID). As a consequence, we can conclude that about 40% of patients buy diclofenac in pharmacies with a prescription issued by a doctor. The question is whether patients insist on diclofenac or whether

doctors prescribe this drug on their own initiative.

Such a high consumption of diclofenac can be partially explained by the low price of this drug per DDD. The average price of diclofenac was around € 0.07 per DDD in Montenegro, around € 0.26 per DDD in Finland and € 0.19 per DDD in Croatia. In our study, we found no statistically significant correlation between the change in diclofenac consumption and the change in its price per DDDs. On the other hand, the average price of ibuprofen in Montenegro was € 0.27 per DDD. The average price of this medicine was € 0.29 per DDD in Finland and € 0.30 in Croatia. For naproxen, its price was around € 0.10 per DDD in Montenegro, € 0.17 per DDD in Finland, and around € 0.15 per DDD in Croatia. Naproxen consumption and its price are increasing in Montenegro. Here we find a positive strong correlation that is statistically significant. We can only assume that if the price was lower, consumption of naproxen would be even higher, and naproxen would replace diclofenac to a greater extent. Diclofenac's low price is likely to influence patients to choose this drug from several NSAIDs on offer. This attitude of the patient can be changed by educating the patient about alternative drugs in pain management. In Montenegro, the doctors, who mainly prescribe diclofenac for their patients, bear a great deal of responsibility for this situation. This shows the need for continued education of physicians about NSAIDs and their good and bad properties. We were able to determine twice that the situation had improved slightly after CInMED addressed the healthcare workers in an open letter. The question is, what would have happened if such campaigns had been more common?

Finally, something needs to be done because this situation in Montenegro is not acceptable. It is necessary to reduce the consumption of NSAIDs in general. It is necessary to replace diclofenac with naproxen, which is a slightly more expensive, but safer drug. It is certainly necessary to try to reduce the price of naproxen and ibuprofen in Montenegro.

Conclusions

From all of the above, we can conclude that the consumption of NSAIDs in Montenegro is very high. The high consumption of diclofenac is particularly noteworthy. Some steps need to be taken to improve the situation. It is necessary to establish stricter restrictions on the issuance of this drug on account of the Republican Health

Insurance Fund. It is necessary to change the attitude and awareness of doctors towards the use of diclofenac. They must be aware that the use of diclofenac, especially in higher doses, carries a high risk of cardiovascular side effects. It is also necessary to change the attitude and awareness of patients towards the use of diclofenac. It is necessary to enlighten them through the media that diclofenac is not an absolutely safe drug, i.e., its use carries a high risk of cardiovascular side effects. Patients should be made aware that the cheapest drug is not the best drug in this case. Finally, it should be explained to them that there are adequate substitutes for diclofenac that are not significantly more expensive but have a better side effect profile, such as naproxen. All these steps take a long time to see the results.

Conflicts of Interest

The authors declare no conflicts of interest.

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