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CLINICAL STUDY

Comparison of NSAID consumption in Slovakia, Finland and Norway

Hudec R[1], Kriska M[1], Bozekova L[1], Foltan V[2]

Department of Pharmacology, Faculty of Medicine, Comenius University, Bratislava, Slovakia.
dr.hudec@gmail.com

Abstract: *Background:* Non-steroidal anti-inflammatory drugs (NSAIDs) belong to most frequently used drugs worldwide. NSAIDs belong to the family of drugs that represent the biggest drug risk as to the number of adverse drug reactions (ADRs), as well as to the number of deregistered drugs.
Methods: We analysed the whole consumption of NSAIDs from ATC class M01 in Slovakia during 1996–2007.
Results: Most frequently used NSAIDs in Slovakia were ibuprofen and diclofenac. There was a marked increasing trend in piroxicam, meloxicam, ibuprofen and especially nimesulide medicines. Conclusion: Prescription habits of doctors in Slovakia reflect the drug risk only partially, nevertheless the total consumption of dangerous medicines is decreasing and substances with safer profile remain being more used. In the prescribing process the patients• risk factors together with the differences in drug characteristics should be considered. Nevertheless some of these drugs are OTC, and their consumption is strongly influenced by pharmacists and advertisement *(Tab. 2, Fig. 1, Ref. 18).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: NSAID consumption, piroxicam, nimesulide, ibuprofen, diclofenac, statistic.

Non-steroidal anti-inflammatory drugs (NSAIDs) belong to the most frequently used drugs worldwide. NSAIDs belong to the family of drugs that represent the biggest drug risk as to the number of adverse drug reactions (ADRs) as well as to the number of deregistered drugs.

Their chemical structure varies but their acting point and mechanism of action are the same, i.e. the inhibition of enzyme called cyclooxygenase (COX-1, COX-2) (1). This enzyme is responsible for the production of prostaglandins, prostacycline and thromboxane. Especially prostaglandin PGE2 is responsible for inflammatory reactions and sensible nociception.

Activity of COX-1 (constitutive isoenzyme) is necessary for many physiological functions (like production of protective agent in gastric mucosa). COX-2 is produced during inflammation and is called inducible. It has also normal physiological localisation too (e.g. in kidneys). NSAIDs are used as drugs of first choice in the treatment of arthritis and related inflammatory diseases of the locomotor system (2–4).

The most common ADR is gastrotoxicity (gastric ulcer and its possible complications) as a result of blockage of genesis of protective PGE2 (5). Following the impairment of microcirculation in gastric mucosa, the patients' complications vary from discomfort symptoms to serious events like ulcer perforation and GIT haemorrhage. Pain and pressure in epigastrium are the most common warning signs (6). Haemorrhage is very often a complication of therapy or self-treatment. Statistics show lethal consequences in 1–10 %, especially in older patients.

Decreased prostaglandin synthesis could also result in nephrotoxic acute renal failure (7). Functional renal insufficiency can manifest after short-term therapy (days) while interstitial nephritis after weeks and analgesic nephropathy after several years.

Hepatotoxicity is another reversible ADR, which is usually dose-dependent and appears especially after diclofenac and naproxen. Contemporary administration of other hepatotoxic substances and excessive alcohol intake increases the risk of hepatic disorder (8).

Several NSAIDs with high risk are currently being revaluated by European Medicines Agency (EMEA). The key role in the evaluation process is plaid by drug risk perception. The risk/ /benefit perception in the medical community and in the public remains a positive factor that justifies such a broad usage. For example EMEA dissuades from administration of coxibs in patients with ischemic heart disease (9).

Consistent monitoring of analgesic consumption can be helpful in the explanation of various pain treatment approaches. Drug consumption data are an integral part in evaluation of health quality level (10).

Methods

We analysed the whole consumption of non-steroidal anti-inflammatory drugs from ATC class M01 in Slovakia during

[1]Department of Pharmacology, Faculty of Medicine, Comenius University, Bratislava, and [2]Department of Organization and Management of Pharmacy, School of Pharmacy, Comenius University, Bratislava, Slovakia

Address for correspondence: R. Hudec, MD, PhD, Dept of Pharmacology, Faculty of Medicine, Comenius University, Sasinkova 4, SK-813 72 Bratislava, Slovakia.
Phone: +421.2.59357229, Fax: +421.2.59357508

Tab. 1. Comparison of consumption of five most consumpted NSAIDs in Slovakia with Norway and Finland (in DDD/1000 inhabitans/day).

SR	ATC	2002	2003	2004	2005	2006
Diclofenac	M01AB05	19.654	17.892	15.101	12.040	10.263
Piroxicam	M01AC01	0.875	1.861	1.978	2.583	1.928
Meloxicam	M01AC06	2.084	2.004	1.540	1.953	5.030
Ibuprofen	M01AE01	16.075	16.562	18.220	19.303	19.973
Nimesulid	M01AX17	0.902	1.149	1.152	4.843	6.256
Finland	ATC	2002	2003	2004	2005	2006
Diclofenac	M01AB05	5.070	5.050	4.850	5.550	5.500
Piroxicam	M01AC01	0.500	0.380	0.330	0.310	0.270
Meloxicam	M01AC06	2.680	3.280	3.380	3.870	3.500
Ibuprofen	M01AE01	30.760	32.980	33.930	40.850	32.910
Nimesulid	M01AX17	–	–	–	–	–
Norway	ATC	2002	2003	2004	2005	2006
Diclofenac	M01AB05	5.150	5.300	5.430	7.680	8.690
Piroxicam	M01AC01	4.200	3.800	3.680	4.520	4.740
Meloxicam	M01AC06	0.830	0.780	0.860	1.770	1.800
Ibuprofen	M01AE01	10.400	10.900	12.740	13.990	15.200
Nimesulid	M01AX17	–	–	–	–	–

Tab. 2. Drugs that accounted for 90 % of the total volume of DDDs in the year 2006.

SR	Year 2006		Finland	Year 2006		Norway	Year 2006	
Ibuprofen	19.973	42.05	Ibuprofen	32.910	55.53	Ibuprofen	15.200	39.33
Diclofenac	10.263	21.61	Naproxen	6.260	10.56	Diclofenac	8.690	22.48
Nimesulid	6.256	13.17	Diclofenac	5.500	9.28	Piroxicam	4.740	12.26
Meloxicam	5.030	10.59	Etorikoxib	4.190	7.07	Naproxen	4.500	11.64
Piroxicam	1.928	4.06	Meloxicam	3.500	5.91	Meloxicam	1.800	4.66
			Ketoprofen	3.170	5.35			
		91.48			93.69			90.38

1996–2007. The data were obtained from the State Institute for Drug Control in SR. The analysis was based on Defined Daily Doses (DDD) methodology according to ATC classification. The expression of data as DDD per 1000 inhabitants per day enables the comparison of active substance in different drug products.

Results obtained from 2002 till 2006 were compared with the data based on annual health statistics in Finland and Norway. We have chosen these countries as representatives of countries with high standard of pain therapy and pharmacovigilance.

We then calculated drugs that accounted for 90 % of the total volume of DDDs in the year 2006. We used the methodology described by Bergman et al (11).

The statistical analysis of obtained data was done using Statgraphics Plus 5.1. For statistical comparison between Slovakia, Norway and Finland, Student's t-test was used. Differences were tested using an level of 0.05.

Results

Trends in consumption of NSAIDs in SR reflect the situation in pain and inflammation management and help us to estimate the prescription habits of Slovak doctors. Some medicines containing diclofenac and ibuprofen are OTC drugs and our wholesale data include these remedies too. Table 1 shows the consumption of five most consumed non-steroidal anti-inflammatory drugs in observed years in selected countries.

The analysis of Slovak consumption showed that most frequently used NSAIDs were ibuprofen and diclofenac, which represented almost 70 % of the total group consumption. There is a marked increasing trend in piroxicam, meloxicam, ibuprofen and especially nimesulide medicines. After a strong decrease in the first years we have noted a slightly increasing consumption of indometacin in the past two years.

We compared the consumption data related to each particular year. Figure 1 shows a marked increasing trend in consumption of piroxicam, meloxicam and nimesulide as well as a constant increase in the consumption of ibuprofen.

Diclofenac and piroxicam tended to have higher consumption ($p=0.006165$ and $p=0.00857$ respectively), ibuprofen and meloxicam had lower consumption when compared to Finland ($p=0.000356$ and $p=0.265246$ respectively). The comparison with Norway showed that diclofenac, meloxicam and ibuprofen

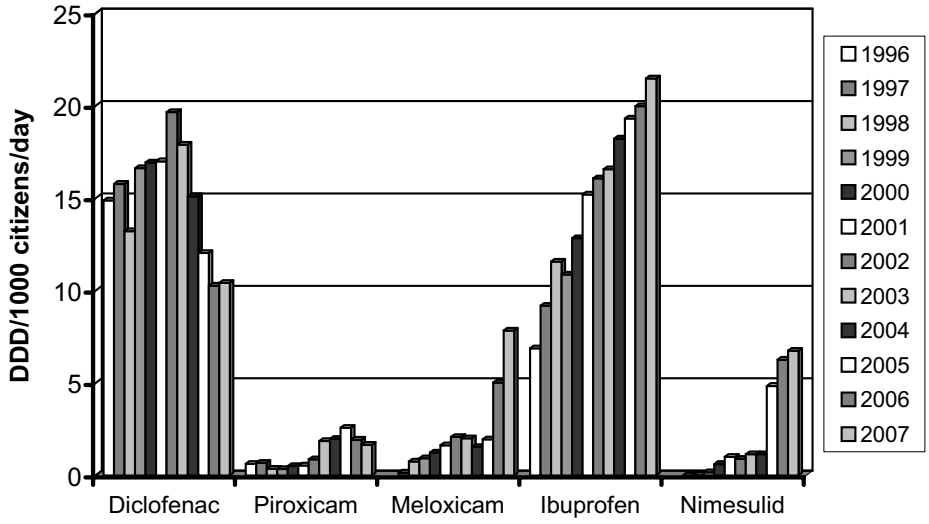

Fig. 1. Trends in consumption of 5 top nonsteroidal antiinflammatory drugs in Slovakia during 1996–2007. Wholesale data expressed as defined daily doses per 1000 inhabitans per day.

had higher consumption in Slovakia (p=0.024965, p=0.064139 and p=5.37 x 10^{-6} respectively). Piroxicam was significantly more used in Norway (p=0.001644).

Tables 1 and 2 indicate varying decision making between doctors in Slovakia, Norway and Finland. Among drugs that accounted 90% of the total consumption we found ibuprofen, diclofenac and meloxicam in all countries, but nimesulide only in Slovakia, whereas naproxen and etoricoxib are more used in Finland. The highest consumption of piroxicam was surprisingly in Norway. A similar high consumption is in Slovakia, but the 2007 data showed a decrease in its consumption.

Discussion

There are some liminations in the presented study. Our analysis is based on wholesale data only, thus we had no access to patient-oriented data. Therefore a more detailed risk factor stratification of NSAID users was not possible.

Our analysis of consumed NSAIDs showed that ibuprofen was mostly used in 2006 followed by diclofenac in all of the three countries. At the same time these two substances represent fast two thirds of whole NSAID consumption in three European regions (Bologna, Italy; Funen, Denmark and Stockholm, Sweden) (14).

Ibuprofen is regarded as the safest classic non-steroidal antiinflammatory drug from the point of gastric bleeding risk (15). The biggest relative change in consumption was in nimesulid, the preferential COX-2 inhibitor with better gastrointestinal tolerance in comparison to classic non-selective NSAID.

The increasing consumption of nimesulid in Finland, as well as in Norway was followed by a rapid decrease in 2002 and it could be related to the fact that information on severe hepatotoxic adverse reaction with fatal consequences had been published (16, 17). However in Slovakia, nimesulide is the third most frequently used NSAID.

Meloxicam as another preferential COX-2 inhibitor was registered in 1995 in more than 100 countries worldwide and its effect and safety was verified in several studies. More than 30 million of patients take this drug worldwide. The analgesic effect is equal to other NSAIDs but the number of gastrointestinal adverse reactions is lower (18).

Consumption of piroxikam in Slovakia is higher than in Finland, but surprisingly lower than in Norway. It could be related to the usage of cyclodextrine derivate of piroxicam with lower risk of adverse drug reaction (9).

NSAIDs have been used for more than a century. Prescription habits of doctors in Slovakia reflect the drug risk only partially, nevertheless the total consumption of dangerous medicines is decreasing, and substances with a safer profile remain being used more. In the prescribing process, the patients risk factors together with differences in drug characteristics should be considered. Nevertheless some of these drugs are OTC and their consumption is strongly influenced by pharmacists and advertisement.

"Conditio sine qua non!" (Ultimative request) is to continue in decreasing the consumption of drugs with higher risk. It is important to assert the principles of EBM in therapy of pain and emphasize the acceptation of pharmacotherapeutical risks.

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