

Cost-Efficiency of Nonsteroidal Anti-Inflammatory Drug Prescribing in Zagreb, Croatia

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ABSTRACT

The utilization and prescribing quality of non-steroidal anti-inflammatory drugs (NSAIDs) in Zagreb were assessed by calculating the number of defined daily doses (DDDs) from the number and size of packages of each prescription NSAID dispensed at 31 and 32 pharmacies during the years 2001 and 2002. NSAIDs accounting for 95% of overall NSAID utilization (DU95% segment) were analyzed. The proportion of NSAIDs associated with high (piroxicam), medium (diclofenac, naproxen, indometacin and ketoprofen) and low (ibuprofen) risk of gastrointestinal side effects, cost for each NSAID in DU95% segment, and cost per DDD were calculated. Four NSAIDs fell within DU95% segment: ibuprofen, diclofenac, ketoprofen and piroxicam. The cost for NSAIDs per DDD was by half lower within than beyond DU95% segment. Piroxicam was most expensive, and diclofenac and ketoprofen least expensive NSAIDs within DU95% in 2001 and 2002, respectively. The NSAID prescribing pattern was found to be in discrepancy with their relative gastrointestinal toxicity.

Key words: nonsteroidal anti-inflammatory drugs, drug utilization, cost-efficiency

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of drugs that are most commonly used as analgesics, anti-inflammatory agents or antipyretics. The wide use of these drugs results in gastrointestinal (GI) complications, which are the main cause of morbidity and mortality associated with this type of therapy^{1,2}. The risk of GI complications shows several-fold variation and dose dependence among NSAIDs^{3,4}. In addition to patient risk, these drugs also rank high according to the rate of hospitalization^{1,5,6}, thus causing high total costs for both NSAIDs and treatment of GI complications^{7–9}. In order to reduce the morbidity and costs associated with the use of NSAIDs, the utilization and quality of prescribing these drugs should first be evaluated. With this objective in mind, we embarked upon this study in the City of Zagreb, the capital of Croatia, with some 25% of the population of Croatia living in and around Zagreb, and 43% of the national health resources being located in the area. Study results were evaluated in comparison with those reported from other capitals in Europe.

Materials and Methods

Data on the number and size of packages of each individual NSAID dispensed at 32 and 31 pharmacies evenly distributed all over the City of Zagreb were obtained from the Zagreb Municipal Pharmacy owned by the state. These pharmacies represented a sample (16% in 2001 and 15% in 2002, respectively) of the total number of pharmacies registered in the City of Zagreb. The data were exclusively collected for prescription drugs in oral dosage form and referred to the years 2001 and 2002.

The number of defined daily doses (DDDs) for each NSAID was calculated from the collected data classified according to the Anatomical Therapeutic Chemical System (ATC) of the World Health Organization (WHO) and DDDs for NSAIDs listed in the ATC Index with DDDs 2002. Then, each NSAID (ATC: M01A) was ranked according to DDD number to restrict our studies to those NSAIDs which accounted for 95% of total NSAID utilization, i.e. to the drug utilization 95% segment. This method is identical to that of Bergman et al¹⁰, which has recently been introduced for assessing the quality of drug prescribing and usage. Within the drug utilization (DU95%) segment, we determined the pro-

portion of high risk (piroxicam), medium risk (diclofenac, naproxen, indometacin and ketoprofen) and low risk (ibuprofen) NSAIDs with respect to the risk of upper GI bleeding/perforation (UGIB)⁴. The remaining drugs were categorized as unclassified due to the lack of epidemiologic GI safety data (meloxicam, nabumetone, tenoxicam) and ambiguities about the safety profile (rofecoxib)¹¹.

DU95% segment was determined for the years 2001 and 2002 according to DDD number for each NSAID and overall DDD number for all NSAIDs in DU95%. Costs for each individual NSAID in DU95% were calculated. In addition, the cost *per* DDD for each NSAID in DU95% segment, mean total cost *per* DDD for all NSAIDs within and beyond DU95% segment, and mean cost *per* DDD for all NSAIDs dispensed at Zagreb Municipal Pharmacy units during 2001 and 2002 were also calculated. The price of NSAIDs was uniform in all pharmacies.

TABLE 1
UTILIZATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IN ZAGREB EXPRESSED AS NUMBER OF DEFINED DAILY DOSES (DDDS)

Drug name	DDDs		Share (%)		
	2001	2001	2001	2002	
Diclofenac	2126602	2004742	53.3	52.3	
Piroxicam	714240	617800	17.9	16.1	
Ketoprofen	583491	698560	14.6	18.2	
Ibuprofen	567978	515475	14.2	13.4	
DU95%*	1–4	3992311	3836577	100.0	100.0
	5–10	266666	193039		
Total	1–10	4258977	4029616		

* The number of NSAIDs that accounts for 95% of NSAID use

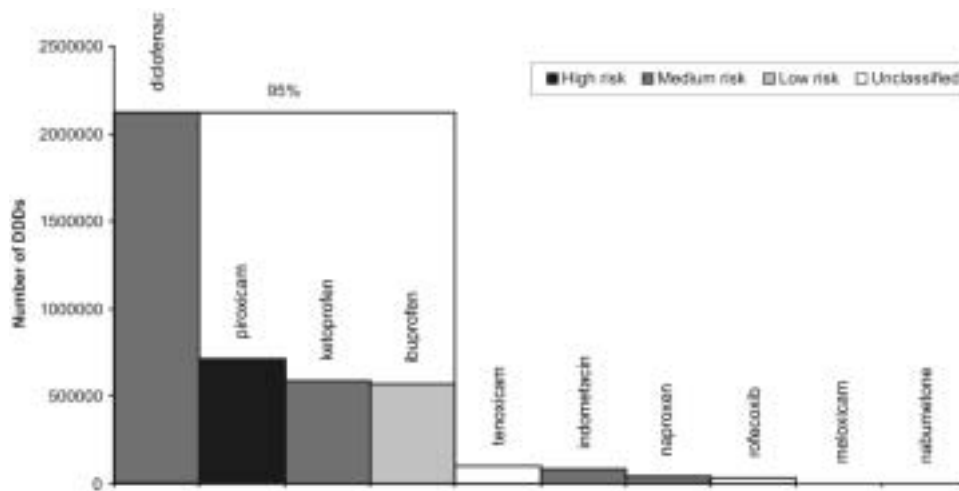


Fig. 1. NSAID prescribing pattern in Zagreb according to number of defined daily doses (DDDs) based on dispensing data from 32 Zagreb pharmacies in 2001.

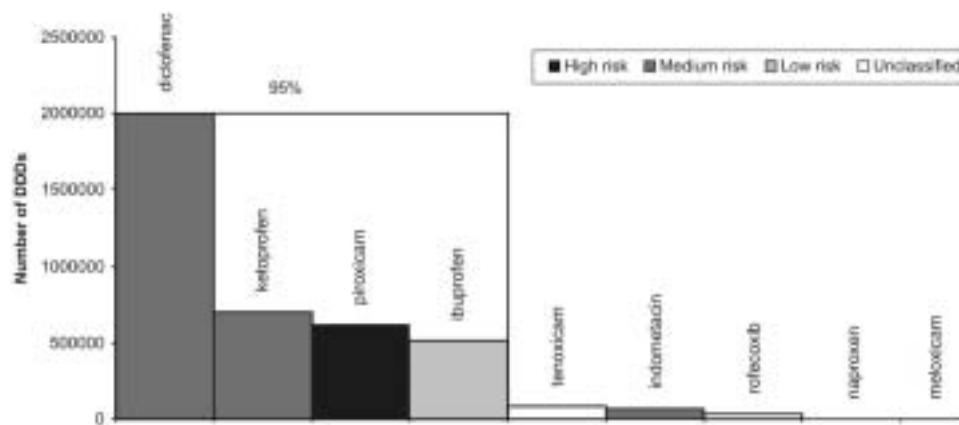


Fig. 2. NSAID prescribing pattern in Zagreb according to number of defined daily doses (DDDs) based on dispensing data from 31 Zagreb pharmacies in 2002.

TABLE 2
COST OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IN ZAGREB EXPRESSED IN EUR, PERCENTAGE IN 2001 AND 2002, AND COST *PER* DEFINED DAILY DOSE (DDD)

Drug name	Cost (Euro)		Share (%)		Cost/DDD (Euro)	
	2001	2002	2001	2002	2001	2002
Diclofenac	320507	323047	43.1	46.1	0.15	0.16
Piroxicam	190217	162783	25.6	23.3	0.27	0.26
Ketoprofen	106470	100008	14.3	14.3	0.18	0.14
Ibuprofen	126028	114195	17.0	16.3	0.22	0.22
DU95%* 1–4	743224	700035	100.0	100.0	0.19	0.18
5–10	98352	78128			0.37	0.40
Total 1–10	841576	778163			0.20	0.19

*The number of NSAIDs that accounts for 95% of NSAID use

Results

Four of the ten NSAIDs fell within DU95% segment according to their utilization in 2001 and 2002, respectively (Figures 1 and 2). The absence of nabumetone from the market was the only change recorded in 2002 as compared with 2001. Ibuprofen accounted for only 14.2% and 13.4% whereas diclofenac and ketoprofen accounted for 67.9% and 70.5% in 2001 and 2002 respectively. The respective figures for the high risk piroxicam as the fourth drug in DU95% segment were 17.9% and 16.1% (Table 1). The leading drug in DU95% segment was diclofenac accounting for 53.3% and 52.3% of DU95% segment in 2001 and 2002, respectively.

Table 2 shows costs for each individual NSAID in DU95% segment, overall costs for NSAIDs within and beyond DU95% segment, and total costs for all NSAIDs. In addition to absolute amounts, the proportion for each drug within DU95% and cost *per* DDD for each drug in DU95% segment, mean cost *per* DDD for drugs within and beyond DU95% segment, and mean cost *per* DDD for all NSAIDs on the market are presented for 2001 and 2002. The respective costs for NSAIDs in DU95% segment accounted for 88.3% and 90.0% of total cost for all NSAIDs on the market. The medium risk drugs in DU95% segment accounted for 57.4% and 60.4%, the low risk ibuprofen for 17.0% and 16.3%, and the high risk piroxicam for 25.6% and 23.3% of the cost in DU95%

segment in 2001 and 2002, respectively. The mean cost *per* DDD for NSAIDs in DU95% was half those beyond DU95% segment. Piroxicam was the most expensive NSAID in DU95% (0.27 and 0.26 EUR/DDD in 2001 and 2002, respectively), whereas least expensive ones were diclofenac and ketoprofen (0.15 and 0.16 EUR/DDD, and 0.18 and 0.14 EUR/DDD in 2001 and 2002, respectively). Ketoprofen was the only drug showing a considerable decline in the cost *per* DDD (from 0.18 EUR in 2001 to 0.14 EUR in 2002).

Discussion

Cost-efficiency of prescribing NSAIDs in the City of Zagreb in 2001 and 2002 were assessed by identifying the type and number of NSAIDs accounting for 95% of total NSAID utilization, and ranking them according to GI complications based on the systematic review of case-control and cohort studies of serious GI complications and nonaspirin NSAIDs published between 1990 and 1999⁴ although it seems difficult to sort them according to their GI toxicity^{3,12,13}. However the pertinence of the cost-analysis remain. Comparison of the prescribing pattern in Zagreb with that reported from other European cities and from Rijeka in Croatia^{14,15} revealed a similar pattern with Rijeka but considerable differences from other European cities or area (Table 3).

TABLE 3
PRESCRIBING PROFILE FOR NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) IN EUROPEAN CITIES AND FUNEN, DENMARK, RANKED BY NUMBER OF DEFINED DAILY DOSES (DDD)

City or area	Rank of NSAID					
	Ibuprofen	Diclofenac	Naproxen	Indometacin	Ketoprofen	Piroxicam
Zagreb ^a	4	1	8	6	2	3
Rijeka ^b	3	1	–	5	6	2
Stockholm ^b	6	1	2	9	4	11
Bologna ^c	6	4	5	–	3	2
Funen ^c	1	3	2	6	7	4

^aIn 2002 year; ^bData from Vlahović-Palčevski et al¹⁵; ^cData from Bergman et al¹⁴

In all cities and Funen area (Denmark), the mentioned drugs were within the DU90% segment, with the exception of indometacin in Zagreb, Rijeka and Stockholm, piroxicam in Stockholm, and ketoprofen in Rijeka. The best NSAID profiles were found in Funen, Denmark and Stockholm, Sweden, whereas Bologna, Italy had the worst profile, with Zagreb and Rijeka, Croatia lying in between. The pattern recorded in Rijeka and Zagreb was highly comparable for a small number of drugs falling within DU95% segment (only three and four drugs, respectively). In the present study, DU95% instead of DU90% segment was used because in the City of Zagreb three drugs accounted for a considerably less than 90%, and four drugs for about 95% of the overall NSAID utilization. Furthermore, Zagreb and Rijeka were comparable by the predominance of diclofenac relative to other drugs according to DU95% and DU90% proportion; high proportion of the high risk piroxicam; and low proportion of the low risk ibuprofen in both cities. The high proportion of piroxicam and lowest proportion of ibuprofen in DU95% segment appear to suggest that evidence based medicine was not the leading impact factor in prescribing these drugs. We stressed that ibuprofen was only prescription drug during 2001 and 2002. Zagreb and Rijeka also showed similar patterns in the cost for particular NSAIDs *per* DDD in DU95% and DU90% segment, however, the mean costs for NSAIDs *per* DDD beyond DU95% and DU90% differed significantly. The introduction of rofecoxib to the Croatian market contributed to the higher cost *per* DDD beyond DU95% in Zagreb. The significant difference recorded for both Zagreb and Rijeka as compared with other European cities implied that in the latter, DU90% included between six and eight drugs, along with a considerably greater number of drugs being available on the market^{14,15}. In Zagreb, the COX-2 selective inhibitor rofecoxib was not included in DU95% segment, which is quite conceivable due to its high price, thus being not included in the List of Drugs approved by the Croatian In-

stitute of Health Insurance (CIHI) as well as because of the controversy about the safety profile of COX-2 inhibitors, reported in the studies published until May 2002¹⁰. In spite of the limitations related to DDD *versus* prescribing daily dose (PDD), our cost analysis yielded quite interesting information. Thus, the DDD cost for NSAIDs was by half lower within than beyond DU95% segment, suggesting that less expensive drugs tended to be prescribed in Zagreb. However, it was not low risk ibuprofen that appeared as the least expensive drug but diclofenac in 2001 and ketoprofen in 2002.

Even considering all the limitations of DU methodology (PDD may be higher or lower than DDD in particular settings, reimbursement systems, education, marketing, pricing, demography, socioeconomic, morbidity etc. differ among different countries), the results of the present study indicate Zagreb to be one of the European cities where the prescribing patterns of NSAIDs do not follow their relative GI toxicity. Our results suggest that other factors rather than evidence based medicine must have predominantly influenced the prescribing of NSAIDs in Zagreb during the past two years. This also holds for other European cities, as reported by other investigators^{14,15}. Target education from independent sources in the prescribing, dispensing and use of drugs poses itself as a necessary measure to improve the quality of prescribing NSAIDs. The higher use of ibuprofen and reduced use of piroxicam will improve the NSAID profile in Zagreb.

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RAZINA EKONOMIČNOSTI PROPISIVANJA NESTEROIDNIH PROTUUPALNIH LIJEKOVA U ZAGREBU

S A Ž E T A K

Cilj istraživanja bio je ustanoviti potrošnju i kvalitetu propisivanja nesteroidnih protuupalnih lijekova (NSAIDs) u Zagrebu. Iz podataka o broju i veličini pakovanja svakog NSAID s režimom izdavanja na recept izdanih u 31 odnosno 32 javne ljekarne tijekom 2001. odnosno 2002. godine izračunat je broj definiranih dnevnih doza (DDD). Istraživani su oni NSAID koji čine 95% ukupne potrošnje svih NSAID, tzv. segment DU95%. Utvrđen je udio NSAID s visokim (piroksikam), srednjim (diklofenak, naproksen, indometacin i ketoprofen) i niskim (ibuprofen) rizikom za nastanak gastrointestinalnih nuspojava, troškovi za svaki NSAID unutar segmenta DU95% te troškovi po DDD. Četiri NSAID čine segment DU95%: ibuprofen, diklofenak, ketoprofen i piroksikam. Troškovi po DDD su dvostruko niži unutar segmenta DU95% u odnosu na NSAIDs izvan segmenta DU95%. Najskuplji NSAID unutar segmenta DU95% je piroksikam, dok su najjeftiniji diklofenak u 2001. odnosno ketoprofen u 2002. godini. Propisivanje NSAID u Zagrebu ne slijedi njihovu relativnu gastrointestinalnu toksičnost.