Vanbolnička primena nesteroidnih anti-inflamatornih lekova u Srbiji: opservaciona studija

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Kratak sadržaj

Uvod i cilj rada: Nesteroidni antiinflamatorni lekovi (NSAIL) ispoljavaju antiinflamatorno, analgetičko i antipiretičko dejstvo i primenjuju se kod akutnih bolova blagog do umerenog intenziteta, hroničnih bolnih i zapaljenskih stanja, te povišene telesne temperature. Cilj ove studije bio je da se analizira vanbolnička potrošnja NSAIL, način primene, dužina terapije i neželjene reakcije, kao i iskustva pacijenata u vezi sa efikasnošću i bezbednošću lekova. U studiju su uključeni svi pacijenti kojima je propisan NSAIL.

Metode: Istraživanje je sprovedeno u Vojnomedicinskoj akademiji u Beogradu, u periodu od juna do decembra 2008. godine. Pacijenti su, uz pomoć farmaceuta, popunjavali upitnik koji se sastojao od pitanja vezanih za pridružena oboljenja, upotrebu i neželjene efekte NSAIL. U studiju su uključeni svi pacijenti kojima je na recept bio propisan neki od NSAIL (diklofenak, ibuprofen, flurbiprofen, naproksen, piroksikam, tenoksikam, meloksikam). Odgovori su statistički obrađeni primenom χ^2-testa.

Rezultati: U studiji je učestvovalo 160 pacijenata. Većina pacijenata (59,4%) je koristila jedan NSAIL, 48,8% ispitanika je primenjivalo lek u obliku tablete. Diklofenak i ibuprofen su najčešće korišćeni lekovi. U ispitivanoj grupi pacijenata, 51,9% pacijenata je bolovalo od reumatične bolesti duže od 5 godina. Svaki drugi pacijent je istovremeno primenjivao NSAIL i gastroprotektivni lek, najčešće ranitidin (58,1%).

Zaključak: Rezultati pokazuju da se NSAIL često primenjuju duže od pet godina, u lečenju reumatičnih bolesti koje su zastupljene kod starijih pacijenata. Najčešći neželjeni efekti NSAIL su blagi gastrointestinalni problemi, nauzeja i bol u stomaku. Ovo se objašnjava time što se najviše koriste diklofenak i ibuprofen, lekovi koji imaju slab ili umeren rizik za ispoljavanje gastričnih neželjenih efekata, ali i zbog istovremene primene NSAIL i H_2-blokatora/inhibitora protonske pumpe.

Ključne reči: nesteroidni antiinflamatorni lekovi; neželjeni efekti; iskustvo pacijenata

Introduction

Non-steroidal, anti-inflammatory drugs (NSAIDs) are effective in treatment of pain and inflammation. These drugs provide symptomatic relief from pain and swelling in chronic joint disease, as well as in more acute inflammatory conditions. They are also widely used for other types of minor aches and pains. Their primary pharmacology is related to their shared ability to inhibit fatty acid COX isoenzymes, thereby inhibiting the production of prostaglandins and thromboxanes. There are two common isoforms of the enzyme, COX-1 and COX-2. Most NSAIDs inhibit both COX-1 and COX-2 but it is believed that their therapeutic effects are related to COX-2 inhibition, while their adverse effects are largely a result of COX-1 inhibition (1, 2).

NSAIDs are associated with upper and lower gastrointestinal harm, acute renal failure and congestive heart failure (3-9). The most common adverse effects are gastrointestinal (GI), ranging from mild discomfort to serious complications which usually require hospital treatment such as gastric erosions, peptic ulcer perforations, upper and lower GI hemorrhage (10-12). Particular risk factors for the development of NSAID-associated gastropathy are age (>65 years), previous history of peptic ulceration, high dose or multiple NSAID use, concomitant use of corticosteroids, antiplatelet and anticoagulant drugs, nicotine and alcohol intake (13-15).

There are several gastroprotective strategies recommended for reducing the risk of GI complications in long-term users of NSAIDs. It is recommended that gastroprotective drugs (i.e. misoprostol, proton pump inhibitors or histamine H_2 receptor antagonists) be taken concomitantly to prevent NSAID-induced GI complications (16,17). Therefore, the aim of this study was to analyse the use of NSAIDs, the occurance of adverse effects, especially NSAID-induced GI complications, as well as to investigate the extent to which NSAID users are concurrently taking gastroprotective drugs.

Methods

In order to get reliable data we used a questionnaire for all outpatients who were using NSAIDs, regardless of the disease they suffered from. Patients were asked about their age, sex, level of education, smoking habit, the presence of a rheumatic disease, concomitant diseases, use of NSAIDs (which drug and which formulation, the reason why, length of use, efficacy and adverse effects, concomitant use of gastroprotective agents, antiplatelet and anticoagulation drugs, etc). The interview was performed by a pharmacist who filled in the questionnaire with the patient in the pharmacy. The research was conducted in the Military Medical Academy (MMA), Belgrade, Serbia from June to December 2008. The study was performed in accordance with the recuirements of the MMA Institutional Review Board/Human Subjects Research Commitee.

All results were shown as mean value ± standard deviation (SD) or in the form of absolute values with the corresponding percentage. Statistical significance between and within groups was investigated using the χ^2-test or Goodness of fit test. Due to low frequencies, we used χ^2-test and the correction factor. A prevalence of 0.05 and less was considered statistically significant. For statistical analysis we used the Stat Plus 2007 Programme.

Results

160 were asked and consented to participate in the study. Their average age was 61 years, (46-78 years) 53% were men; 20% were smokers; the majority (71%) had rheumatic disorders such as osteoarthritis and rheumatoid arthritis. Patient characteristics, comorbidities, NSAID use and adverse effects are presented in Table I.

Diclofenac had the highest prescription rate (46.2%), followed by ibuprofen (23.2%). At the time of survey, diclofenac, ibuprofen, naproxen and flurbiprofen accounted for 96.3% of the total consumption of NSAIDs whereas oxicams (tenoxicam, piroxicam, meloxicam) were present less than 5%. No coxibs were prescribed. Concomitant to the administration of NSAIDs, 58.1% patients used ranitidine, whereas 21.2% used a proton pump inhibitor (PPI) or another H_2 receptor antagonist.

Table I Patient characteristics, NSAID use and adverse effects

Characteristic	n (%) or mean ± SD; χ^2
Age	61.1±15.1
Gender (male)	85 (53.1)
Educational background	
primary school	19 (11.9)
secondary school	81 (50.6); χ^2-test = 113,0 p < 0,001
college	19 (11.9)
faculty	38 (23.8)
no education	3 (1.9)
Smokers	32 (20)
Allergy	60 (37.5)
Concomitant diseases	
high blood pressure	97 (60.7)) χ^2-test=304,3 p < 0,001
diabetes	18 (11.2)
asthma	14 (8.7)
gastric ulcer	30 (18.7)
duodenal ulcer	9 (5.6)
kidney disease	14 (8.7)
no disease	38 (23.7)

Characteristic	n (%) or mean ± SD; χ^2
Use of NSAIDs	
ibuprofen	37 (23.2)
flurbiprofen	20 (12.3)
naproxen	23 (14.6)
diclofenac	74 (46.2)
piroxicam	2 (1.0)
tenoxicam	4 (2.3)
meloxicam	1 (0.4)
Use of gastroprotective drugs	
ranitidine	93 (58.1); χ^2-test=226,47 p <0,001
famotidine	8 (5.0)
omeprazole	10 (6.2)
lansoprazole	1 (0.6)
Al-Mg hydrate	14 (8.7)
other	34 (21.2)
Reasons for NSAID use	
treatment of rheumatic diseases	114 (71.2); χ^2-test=348,00 p < 0,001
treatment of headaches (migraine)	60 (37.5)
treatment of toothaches	25 (15.6)
treatment of neurological diseases (back pain)	15 (9.4)
treatment of menstrual cramps	8 (5.0)
other conditions (posttraumatic conditions, postoperative pain)	20 (12.5)
Length of treatment	
less than 6 months	16 (10)
less than a year	17 (10.6)
from one to five years	44 (27.5)
more than five years	83 (51.9); χ^2-test = 74,25 p < 0,001
Form of NSAIDs currently used	
tablets (all NSAID)	78 (48.9); χ^2-test = 116,60 p < 0,001
suppositories (diclofenac)	14 (8.9)
cream (gel) (diclofenac, ibuprofen)	36 (22.2)
injection (diclofenac)	32 (20)
Patient adherence to NSAID use	65 (40.6)
Use of anticoagulation/antipletelet drugs	
aspirin	57 (35.6)
ticlopidine	2 (1.3)
acenocoumarol	2 (1.3)
warfarin	4 (2.5)

Characteristic	n (%) or mean ± SD; χ^2
NSAID adverse effects (not related to GI tract)	
dizziness	15 (9.4)
rash	6 (3.8)
urine symptoms	8 (5.0)
changes in blood analysis	4 (2.5)
no adverse effect	127 (79.4)
GI adverse effects of NSAIDs	
nausea	25 (15.6)
pain in stomach	21 (13.1)
diarrhea	6 (3.8)
melaena	10 (6.3)
gastric ulcer	7 (4.4)
duodenal ulcer	1 (0.6)
bleeding	4 (2.5)
no adverse effects	86 (53.8)

n- number of patients; SD- standard deviation; χ^2- Chi square test

The survey showed that the majority of patients (71.2%) used NSAIDs in treating rheumatic diseases (rheumatoid arthritis and osteoarthritis) and 51.9% were treated longer than 5 years. There were additional 27.5% patients who were treated from one to five years. Therefore, the results from the survey showed that 79.4% of patients involved in the therapy of rheumatic disease used NSAIDs longer than one year. At the interview time most patients used NSAIDs as tablets (48.9%), only 8.7% used diclofenac suppositories.

Patients were asked to describe their use of NSAIDs, which dosage, dosing interval. The results showed that only 40.6% used NSAIDs regularly, according to prescription. The usual daily doses for NSAIDs were their defined daily doses. Most patients used NSAIDs occasionally or in longer dosing intervals than prescribed.

Having in mind that we were dealing predominantly with older patients, we asked them about the administration of drugs for concomitant diseases, which are known to interact with NSAIDs. Especially important are interactions between NSAIDs and oral anticoagulant/antiplatelet drugs. Out of the total number of patients, 40.7% regulary used either anticoagulant or antiplatelet treatment. In order to reduce the risk of cardiovascular events, 35.6% of patients used low-dose aspirin (100 mg) together with NSAIDs.

Out of the total number of the interviewed patients, 46.3% had some GI adverse effects. Most important adverse effects were nausea and pain in the stomach, and the least frequent adverse effects were symptoms of ulcer in the duodenum. Serious GI adverse effects (melaena, gastric ulcer and duodenal ulcer) were present in 13.8% of

patients. Other adverse effects were dizziness, rush, urinary problems and haematological changes in 20.6% of patients.

Patients were asked to give a personal evaluation of efficacy and safety of NSAIDs, results are shown in Table II. The patients were asked which drug had helped them most in the past. The most common answer was diclofenac (45.6%), whereas, 15.7% of the interviewed stated it was nimesulide or meloxicam, which they had used at some point in the past. The majority of the patients stated that they had taken tablets (65.0%) in the therapy, which they tolerated well. On the other hand, 43.7% of the interviewed patients were administered injections, which they tolerated poorly.

The majority (61.2%) were satisfied with the efficacy of NSAID and did not want to change the prescribed NSAID with other drugs from the same group. Adverse effects associated with the use of diclofenac were reported by 18.1% of the interviewees. The same number had adverse effects associated with the use of ibuprofen. Adverse effects for nimesulide and meloxicam were not mentioned, whereas 5% patients had some adverse effects after taking naproxen.

Table II Patient's experience about efficacy and safety of NSAIDs

Question	n (%); χ^2
Which drug helped you the most?	
ibuprofen	45 (28.1)
naproxen	6 (3.7)
diclofenac	73 (45.6) χ^2-test = 213,13 p < 0,001
nimesulide	14 (8.8)
meloxicam	11 (6.9)
none	11 (7.5)
Which forms did you tolerate well?	
syrup	4 (2.5)
tablets	104 (65.0) χ^2-test = 344,80 p < 0,001
dragee	19 (11.9)
capsule	11 (6.9)
suppositories	5 (3.1)
cream (gel)	9 (5.6)
injection	8 (5.0)
Which forms did you not tolerate well?	
syrup	10 (6.2)
tablets	31 (19.4)
dragee	8 (5.0)
capsule	26 (16.2)
suppositories	12 (7.5)
cream (gel)	3 (1.9)
injection	70 (43.7) χ^2-test = 142,12 p < 0,001

Question	n (%); χ^2
How often have you changed one NSAID with another because of inefficiency?	
once a month	16 (10)
once in six months	18 (11.3)
once a year	28 (17.5)
no changes	98 (61.2) χ^2-test=114,20 $p < 0,001$
Which NSAIDs have caused adverse effects in the past?	
ibuprofen	29 (18.1)
naproxen	8 (5.0)
diclofenac	29 (18.1)
nimesulide	0
meloxicam	1 (0.6)

Discussion

The aim of our survey was to obtain data about the administration of NSAIDs among outpatients with different diagnosis. The statistic data processing of the obtained answers from the questionnaire helped us to get the insight into the consumption patterns of NSAID use and their adverse effects. Moreover, we investigated patient`s attitudes about efficacy and tolerability of NSAIDs.

A pilot study preceeded this study, in which patients filled in the questionnaire. Only 30% answered questions fully (18). The results of the pilot study showed that it was essential for the questionnaire to be clear, simple and comprehensible. The results also revealed that supervision by a trained person is necessary in order to obtain reliable data.

Non-selective NSAIDs diclofenac and ibuprofen were prescribed most frequently in our population. We found no significant consumption of selective NSAIDs and coxibs. Possible explanation for such result is that those drugs, except meloxicam, were not on the reimbursement price list so the doctors rarely prescribed them.

Hypertension, gastric ulcer, diabetes, asthma, renal insufficiency and duodenal ulcer were most frequent concomitant diseases in our cohort. Such results are in accordance with other pharmacoepidemiological studies which studied the administration of NSAIDs (19-21).

A substantial number of patients in our survey (35.6%) were taking aspirin in their therapy. Such results set up a serious question: how can we administer certain antiplatelet drugs in patients suffering from associated cardiovascular diseases and not increase the risk of adverse effects from NSAIDs? The aim of administering clopidogrel was to decrease the frequency of adverse effects. Its efficacy is slightly better, but the price of the drug was much higher. At present, in the majority of cases, a low dose aspirin (100 mg) in combination with the proton pump inhibitors was administered

more often (22). Moreover, it was suggested that because of the absence of pharmacodynamic interactions with aspirin, the use of COX-2 inhibitors was preferable to the use of non-selective NSAIDs in patients on low-dose aspirin (23). Nevertheless, the use of COX-2 inhibitors should be regarded with caution in patients with high cardiovascular risk.

The long-term treatment of rheumatic diseases and the results obtained showed that as many as 79.4% of patients used NSAIDs longer than one year. While examining the data about administered types of NSAIDs and the way the doses are taken, we had to find out whether patients respected the usual and recommended intervals of dosing as well as their dosage. NSAIDs can be divided into two groups: drugs which are eliminated faster and drugs which are eliminated more slowly. The first group (diclofenac, ibuprofen, ketoprofen, flurbiprofen and indomethacin) require administration several times a day, whereas oxicams are eliminated slowlier and require administration once or twice daily. The NSAIDs with short term duration could not offer any therapeutic response if not taken regularly (20). Unfortunately, patients who were administered this group of drugs had poor adherence. The results showed that only 40.6% patients respected the recommended regimen of drug administration.

On the basis of GI intrisic toxity NSAIDs are divided into three groups: NSAIDs with low risk (ibuprofen, diclofenac), drugs with medium risk (naproxen and indomethacin) and drugs with high risk (piroxicam, ketoprofen) (24). Results obtained from our study, showed that there was higher consumption of drugs with low risk.

Frequency and severity of GI adverse effects varied and the prediction is that 10-25% of all patients, who regularly take NSAIDs will develop ulcer. The mortality rate, in patients with upper GI bleeding is 5-10% (25). Our results showed that 46.3% of interviewees had some GI adverse effects. The majority of GI adverse effects was mild, such as pain in the stomach, nausea and/or vomiting. Serious adverse effects such as melaena, gastric ulcer and duodenal ulcer were reported in 13.8% of patients. According to some authors (26) the administration of H_2 receptor antagonists decreased dyspepsia, which represented the most frequent adverse effect in the use of NSAIDs, but did not prevent occurence of ulcer. Omeprazole administered in the dose of 20 mg once a day was more efficient than ranitidine administered in the dose of 150 mg twice a day, as well as the drug of choice in the therapy of gastropathies which were provoked with the administration of the NSAIDs (27). The results of our survey showed that patients used H_2 receptor antagonists ten times more often than PPIs. This discrepancy could be explained by the difference in price between H_2 receptor antagonists which were cheaper and more prescribed in our hospital than PPIs. Relatively low intensity and frequency of GI adverse effects could be explained due to the simultaneous administration of PPIs and/or H_2 receptor antagonists with NSAIDs as well as the use of drugs with low or moderate ulcerogenic potentials such as diclofenac and ibuprofen.

We investigated patient`s experience with different NSAIDs. The results indicate that patients were satisfied with the efficacy of diclofenac, ibuprofen, nimesulide and meloxicam. The results for diclofenac and ibuprofen were expected due to the fact that they were most prescribed NSAIDs. Interestingly, nimesulid was not prescribed to any patient (because it was not on the reimbursement list) but was listed as the most helpful NSAID in patient's opinion. It is possible that patients may have obtained this and other NSAIDs, by purchase in the pharmacy or otherwise. However, this result is very important because if a drug is perceived as helpful patients may prefer to use it instead of, or additionally to the prescribed NSAID which further may have implications on adherence and safety of NSAID use. According to patient's opinion, naproxen was associated with poorest efficacy/adverse effect ratio whereas diclofenac scored better than ibuprofen, which is in accordance with Nicolescu et al. (28).

Our survey gives an insight into the patterns of NSAID consumption in outpatients. The main shortcoming of our study is the lack of insight in OTC use of NSAIDs. Further investigation should evaluate prescription and OTC NSAID consumption using DDD/1000 inh/day.

Conclusion

The survey showed that non-selective NSAIDs diclofenac and ibuprofen were the most frequently prescribed drugs in our outpatient cohort. They were used predominantly for treating rheumatic diseases in the elderly population and the treatment lasted longer than five years. NSAIDs were mostly administered as tablets, but patient adherence was poor. The majority of adverse effects were GI adverse effects. NSAIDs caused nausea as well as the pain of low grade intensity. This is most probably the consequence of the use low GI toxicity drugs such as diclofenac and ibuprofen as well as the use of H_2 receptor antagonists and PPIs simultaneously with NSAIDs. Patients may associate diclofenac and ibuprofen with better efficacy whereas naproxen had the least favourable efficacy/adverse effects ratio.

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Use of non-steroidal anti-inflammatory drugs in outpatients in Serbia: observational study

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Summary

Introduction and objectives: Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with anti-inflammatory, analgetic and antipyretic properties and are used in the treatment of acute mild to moderate pain, chronic pain and inflammatory conditions and fever. The aim of the study was to analyze the consumption of NSAIDs, purpose of use, length of therapy, adverse effects and patient's perception about efficacy and safety of the drugs. All patients, who had a NSAID prescribed, were included in the study.

Method: The research was done in the Military Medical Academy, Belgrade, Serbia from june to december 2008. A questionnaire filled with the assistance of a pharmacist, contained questions about co morbidities, use and adverse effects of NSAIDs. All patients with at least one NSAID prespription (diclofenac, ibuprofen, flurbiprofen, naproxen, piroxicam, tenoxicam, meloxicam) were included in the study. The responses were statistically processed using the χ^2-test.

Results: 160 patients were included in the study. The majority of the patients (59.4%) used one NSAID in tablet form (48.8%). The most frequent used were diclofenac and ibuprofen. 51.9% suffered from rheumatic diseases for more than 5 years. Every other patient used both NSAIDs and gastroprotective drugs, most often ranitidine (58.1%).

Conclusion: The results show that rheumatic diseases are often present in older patients and that treatment with NSAIDs lasts longer than five years. Mild gastric problems have been recorded as adverse effects of NSAIDs, most often nausea and pain in the stomach. This is probably due to the frequent use of diclofenac and ibuprofen, drugs with low or moderate risk for gastric toxicity as well as the concomitant use of H_2-antagonists and proton pump inhibitors.

Keywords: Non-steroidal anti-inflammatory drugs; Adverse effects; Patient's experience.