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Use of gastroprotective agents in recommended doses in hospitalized patients receiving NSAIDs: a drug utilization study

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ABSTRACT

Objective: In recent years studies have been conducted with the aim to investigate the extent to which recommendations for co-prescribing gastroprotective agents in prevention of NSAID-induced gastrointestinal complications are followed in clinical practice. However, only a few studies have also taken into consideration the recommended dose of gastroprotectives prescribed in NSAID-induced ulcer prophylaxis. The aim of our study was to evaluate the prevalence of concomitant use of gastroprotectives with NSAIDs in hospitalized patients, with emphasis on the recommended dose of gastroprotectives for ulcer prophylaxis.

Method: This observational, cross-sectional, drug utilization study included all adult patients receiving NSAIDs hospitalized in the Clinical Hospital Center Zagreb on the day of the study. Data on age, sex, comorbidities, indications for NSAID use, type/dose of NSAIDs and gastroprotectives, history of gastrointestinal events, active gastrointestinal symptoms and risk factors were evaluated.

Main outcome measure: Study outcomes were: (1) prevalence of prescription of gastroprotectives among NSAID-users at risk; (2) prevalence of prescription of gastroprotective in recommended dose; (3) association between risk factors and prescription of GPAs.

Results: The rates of gastroprotectives prescription were significantly higher in NSAID-users with concomitant risk factors as compared to patients without risk factors [47/70 (67,1%) and 8/22 (36,4%), respectively; p=0,01072]. However,

gastroprotection in recommended ulcer-preventive dose was low in both groups [8/70 (11,4%) and 9/92 (9,8%), respectively]. The number of concomitant risk factors did not increase the odds of receiving anti-ulcer therapy (odds ratio 0,7279). Thirty-three percent of patients with concomitant risk factors were not prescribed gastroprotectives. Ibuprofen, NSAID with the lowest risk of inducing gastrointestinal complications, was prescribed in only 2 patients.

Conclusion: The results indicate high awareness among hospital physicians about possible NSAID- induced gastrointestinal complications, but insufficient knowledge about risk factors related to NSAID-induced gastrointestinal toxicity, recommended dose of gastroprotectives in NSAID-induced ulcer prophylaxis and gastrointestinal toxicity of different types of NSAIDs.

KEY WORDS: non-steroidal anti-inflammatory agents, anti-ulcer agents, drug utilization, risk factors, gastroprotection, prevention, Croatia, secondary care

STATEMENTS

- NSAID prescribing patterns and implementation of recommended preventive strategies in hospitals are considered important due to the more vulnerable patient population and their influence on prescribing habits among general medicine physicians.
- The prevalence of gastroprotection in our study was relatively high, but when recommended daily dose of gastroprotective agents taken into consideration, the actual prevalence of gastroprotection was unacceptably low.
- The evaluation of NSAID and gastroprotective agents prescription patterns, which were similar across all risk groups, could be contributed to insufficient knowledge about the gastrointestinal toxicity of different types of NSAIDs, as well as about the most effective gastroprotection strategy.
- Further studies with the aim to assess the use of gastroprotective agents with NSAIDs in secondary care are needed.

Use of gastroprotective agents in recommended doses in hospitalized patients receiving NSAIDs: a drug utilization study

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications[1]. A major factor limiting their use is gastrointestinal (GI) toxicity, ranging from dyspepsia to life-threatening events [2 3]. It is estimated that up to 15-30 % of patients taking NSAIDs develop GI adverse effects[4 5], and that significant GI events occur in 2-4% patients taking NSAIDs[6].

NSAIDs are exhibiting their effect by inhibition of cyclooxygenase (COX-1 and COX-2) enzymes. Non-selective NSAIDs inhibit both COX-1 and COX-2 to varying degrees, where the anti-inflammatory effect is derived from inhibition of COX-2, while the adverse effects arise from inhibition of COX-1 activity. Selective COX-2 inhibitors are therefore associated with less GI morbidity[7 8 9]. However, the recent safety concerns surrounding the entire class of COX-A inhibitors[10], are resulting in the reestablishment of conventional, nonselective NSAIDs as a mainstay of clinical care for patients with musculoskeletal disorders.

Factors associated with increased risk of NSAID-associated serious complications are history of ulcer complications, concomitant anticoagulant therapy, advanced age (>65 years), concomitant corticosteroid use, chronic major organ impairment, the use of high dose or multiple NSAIDs and severe rheumatoid arthritis[11 12 13]. Strategies in prevention of NSAID-induced GI events are: (1) acetaminophen as the first-line therapy in musculosceletal disorders[14];

(2) use of less GI toxic NSAIDs; (3) use of the lowest effective dose of NSAID; (4) concomitant use of gastroprotective agents (GPAs) in patients with increased risk.

Prevention of NSAID-induced GI morbidity by co-prescription of GPAs has been validated in many clinical studies[15] [16] [17]. The use of GPAs has focused on two approaches: prostaglandin replacement (misoprostol) and inhibition of acid secretion (proton pump inhibitors and histamine2-receptor antagonists). Misoprostol was of no relevance for our study since it is not approved in Croatia. Histamine2-receptor antagonists (H2RA) heal almost all NSAID ulcers when the patient discontinues NSAID use. However, in patients who continue NSAID use, H2RA in traditional doses are more effective in healing duodenal ulcers than gastric ulcers[18] [19]. It appears that larger than traditional doses of H2RAs are more effective at NSAID-associated ulcer prevention[20]. Several studies have confirmed the superior efficacy of proton pump inhibitors (PPIs) in the short and longer-term prevention of NSAID-induced ulcers as compared to H2RA [17] [21]. However, prophylactic use of PPIs in all patients is unnecessary and cost-prohibitive[22].

Two recent systematic reviews have assessed the effectiveness of various GPAs against GI complications induced by NSAIDs use. A Cochrane review by Rostom et al. assessed the effectiveness of H2RAs, PPIs and misoprostol against endoscopic ulcers, ulcer complications, symptoms and dropouts[23]. The results showed that all GPAs included prevented endoscopic ulcers. A systematic review by Hooper et al. assessed the effectiveness of H2RAs, PPIs and misoprostol plus non-selective NSAIDs, and COX-2 selective NSAIDs in

reducing serious GI complications, symptomatic ulcers, serious cardiovascular/renal disease, death, and improving quality of life. They found that misoprostol, COX-2 specific NSAIDs and probably PPIs significantly reduce the risk of symptomatic ulcers, and misoprostol and probably COX-2 selective NSAIDs significantly reduce the risk of serious GI complications. Data were insufficient to draw conclusions on effect of H2RAs compared with placebo on any primary outcomes. Endoscopic ulcers were significantly reduced in participants taking H2RAs compared to placebo. In half of the 15 studies included the dose of H2RAs was higher than the traditional dose[24]. These reviews and previous studies [5] **Error! Bookmark not defined.** [17] support the consensus that PPIs and high dises of H2RAs offer significant protection in patients receiving NSAIDs.

The prevalence of co-prescription of GPAs with NSAIDs is estimated to be 20-40%[25] [26]. According to recommendations from professional societies such as The American College of Rheumatology[27] [38], patients with at least one gastrointestinal risk factor should receive NSAID plus a coprescribed protective agent. Several countries have established relevant clinical guidelines. However, the extent to which such guidelines are implemented in clinical practice is not known. There are only a few studies that have also taken into consideration the recommended dose of H2RAs when used in NSAID-ulcer prophylaxis[20] [28].

Rational and evidence based drug prescribing is one of the main goals in pharmaceutical care. Underutilization, as well as inappropriate use of GPAs, can contribute to increased health costs[29] [30]. Only by optimal prescribing it is possible to control the rising share of these drugs in national drug budgets. It is

estimated that anti-ulcer drug prescriptions consume around 10% of the national drug budgets in Australia and England[31 32 33].

The purpose of this study was to evaluate not only the prevalence of concomitant use of GPAs with NSAIDs, but also the extent to which NSAID users receive therapy that really provides gastroprotection. Previous studies assessed the utilization of gastroprotective measures in primary care. The aim of our study was to assess the use of GPAs with NSAIDs in secondary care. The fact that most GI complications induced by NSAID therapy are occurring during the start of NSAID therapy makes the secondary care prescribing even more important. Although most prescribing takes place in general practice, the influence of secondary care prescribing on primary care prescribing is well recognized [34 35 36 37].

METHODS

Study design

We conducted an observational, cross-sectional study on November 11th, 2003. The study included all adult patients (aged >18 years) hospitalized in the Clinical Hospital Center Zagreb on the day of the study who received NSAIDs. An exclusion criterion was an indication for which gastroprotective drugs were indicated other than NSAID ulcer prophylaxis. A structured questionnaire was developed at the Division of Clinical Pharmacology with the aim to collect information on age, sex, reason for hospitalization, concomitant diseases, indications for use of NSAIDs or/and GPAs, type and dose of NSAIDs and GPAs prescribed, history of GI disease, presence of active GI symptoms and concomitant risk factors. On the day of the study, ten clinical pharmacologists and residents in clinical pharmacology visited all departments and collected data on all patients prescribed NSAIDs according to the prepared questionnaire. Informed oral consent was obtained from all patients prior to inclusion. The data collection was anonymous. Included were patients prescribed gastroprotectives as NSAID ulcer prophylaxis, which was determined by interview and/or reviewing clinical charts. Use of recommended gastroprotective strategy was defined as the co-prescription of PPIs in standard dose or H2RAs in double dose of the NSAID prescription. The co-prescription of an antacid or H2RA in standard dose was considered as less than recommended in NSAID ulcer prophylaxis.

Gastroprotective agents

Prescribed GPAs included antacids (Al-hydroxide-Mg-carbonate gel), H2RA ranitidine and PPIs (omeprazole, pantoprazole, lansoprazole). The recommended daily doses of GPAs were defined as ranitidine 600 mg, omeprazole 20 mg, pantoprazole 40 mg and lansoprazole 30 mg. Lower doses of these drugs were classified as “less than recommended”. Antacids were considered inappropriate gastroprotective strategy in prevention of NSAID-induced GI adverse effects. Misoprostol was not approved in Croatia at the time of the study.

Identification of patients at high risk for NSAID-associated GI complications

Factors that identified patients at high risk of developing NSAID associated complications were defined as age > 65 years, history of GI events, present GI symptoms (dyspepsia, gastritis), concomitant use of corticosteroids, anticoagulant therapy or of aspirin, serious co-morbidities, ≥2 prescribed NSAID, higher than recommended daily doses of NSAIDs. In patients with 1≥ risk factors the co-prescription of GPAs was considered recommended. Standard daily doses of NSAIDs were defined as ketoprofen 300 mg, diclofenac 100 mg, indomethacin 50 mg, ibuprofen 1200 mg and piroxicam 20 mg.

Outcomes

Study outcomes were: (1) prevalence of GPAs prescription among patients at risk for NSAID-induced GI complications vs. patients not at risk; (2) prevalence of GPAs prescription in recommended doses; (3) estimation of the association between risk factors and prescription of GPAs.

Statistical analysis

Standard descriptive statistics were used to describe the study population and their utilization of NSAIDs and GPAs. Means and Standard Deviations (SD) were calculated for age. The proportions of NSAID users with and without gastroprotective therapy in relation to concomitant risk factors and type of GPAs prescribed were calculated and compared using the chi-squared test. The relationship between co-prescription of GPAs and number of concomitant risk factors by estimation of odds ratio, was performed using the logistic regression model. All tabulations and statistical analysis were done using Statistica for Windows, Version 5.5, StatSoft, Inc. (2000).

RESULTS

Out of 770 patients hospitalized on the day of the study 93 patients received NSAIDs. One patient with rheumatoid arthritis was prescribed a COX-2 selective NSAID (rofecoxib). This patient was excluded being the only one receiving a selective COX-2 inhibitor.

The mean age of patients receiving NSAIDs was 59 years, more than a half of the patients were aged over 65 (54,3%), and half of the patients were female (51,1%). In approximately two thirds of patients NSAIDs and GPAs were prescribed during hospitalization (72,7% and 80,0%, respectively). Seventy of 92 patients had one or more concomitant risk factors (76,1%), which identified them as patients at high risk of developing NSAID associated complications, and almost half of them (45,7%) had ≥ 2 concomitant risk factors (Table 1). *Insert Table 1*. The most frequent indication for prescription of NSAIDs was analgesia [(postoperative pain, malignant pain, neurologic disorders, musculosceletal disorders, abdominal pain); 87,0%] and rheumatic disease (13,0%).

The most frequently prescribed NSAID was ketoprofen (78,3%), followed by diclofenac, indomethacin, ibuprofen and piroxicam. Three patients were concomitantly prescribed 2 NSAID. All patients received NSAIDs in standard doses (except 3 patients taking concomitantly 2 NSAIDs). The distribution of NSAIDs by type was similar across risk groups (Table 2). *Insert Table 2.*

Overall, GPAs were prescribed in 59,7% patients. The prevalence of GPA prescription was significantly higher in the subset of 70 NSAID users with concomitant risk factors, as compared to the subset of patients without risk

factors [47/70 (67,1%) and 8/22 (36,4%), respectively; p=0,01072]. However, only 9 NSAID users overall and 8 NSAID users with concomitant risk factors, received GPAs in the recommended ulcer-preventive dose [9/92 (9,8%) and 8/70 (11,4%), respectively]. The number of concomitant risk factors did not increase the odds of receiving anti-ulcer therapy (odds ratio 0,7279; 95% CI: 0,24-2,19). Thirty-three percent of patients with any risk factor present, and 31 percent of patients with more than 2 concomitant risk factors, did not receive GPAs. Thirty-six percent of patients (8/22) without risk factors were receiving gastroprotectives. Individual risk factors identified in the study were age ≥65 years, positive history of GI events, concomitant therapy with corticosteroids, present GI symptoms (including ulcer in one patient), therapy with ≥2 NSAID and concomitant use of aspirin. There was no significant difference in the prevalence of GPAs prescription between patients with a specific risk factor versus patients without the risk factor (Table 3). *Insert Table 3.*

The most frequently prescribed GPA was ranitidine, prescribed in 81,8 % of patients receiving a GPA, followed by PPIs and antacids (14,5 % and 3,6%. respectively). However, in all but one patient ranitidine was prescribed in lower dose than recommended for ulcer prophylaxis. PPIs were prescribed in recommended dose in all patients. They typically were prescribed in NSAID users at risk for developing NSAID-induced GI complications (7/8 patients). Three patients were prescribed antacids as gastroprotective measure in ulcer prophylaxis, one patient in combination with ranitidine (Table 4). *Insert Table 4.*

DISCUSSION

Although the prevalence of prescribing GPAs overall and in NSAID users at high risk was relatively high (59,8 and 67,1%) compared to similar studies [38] [39] [40] [41] [42], when recommended daily doses of GPAs were taken into consideration, the actual prevalence of gastroprotection was unacceptably low (9,8% and 11,4%, respectively). High prevalence of GPA utilization with NSAIDs may be contributed to the high prevalence of concomitant risk factors and higher awareness of possible NSAID-induced GI effects among hospital physicians[43] [44]. Higher prevalence of individual risk factors as compared to other studies could be contributed to the more vulnerable hospital population (more co-morbidities, older age, concomitant therapy). Furthermore, the hospitalization itself could be considered a risk factor, but was not taken into account as a separate risk factor in this study. Although the presence of any risk factor among NSAID users resulted in significantly higher prevalence of GPA prescription, the prescription rates of GPAs were similar across all risk groups. The number of concomitant risk factors did not increase the odds of GPA prescription. The high prevalence of GPA prescription without significant difference in prescription rates between different risk groups could be explained by awareness of possible NSAID-induced GI complications, but insufficient knowledge about individual risk factors related to increased risk.

The most prescribed NSAID was ketoprofen, which is one of the NSAIDs with highest relative risk of inducing GI events. Ibuprofen, the NSAID with the lowest relative risk of inducing GI events[12], was prescribed in only 2 patients. One patient with present duodenal ulcer (confirmed by endoscopy) was receiving

ketoprofen with co-prescription of a PPI. The prescription patterns of NSAIDs demonstrate lack of knowledge about differences in GI toxicity of various types of NSAIDs.

All patients receiving PPIs were appropriately protected, since PPIs are effective in ulcer prophylaxis in their standard dose. H2RAs have to be taken in double dose to be effective in ulcer prophylaxis[23]. Although PPIs are considered the appropriate gastroprotective drug in patients with high risk for NSAID-induced GI toxicity, due to their lower cost, in our hospital H2RAs are still the most prescribed GPAs (45/55; 81,8%). Only one patient received H2RAs in ulcer preventive dose. This indicates insufficient knowledge about dose recommendations of H2RAs when used in NSAID-ulcer prophylaxis. Antacids are not considered appropriate therapy in NSAID-induced ulcer prophylaxis. However, three patients received antacids in ulcer prevention, one patient in combination with ranitidine.

Monitoring of GPA prescription strategies in NSAID users in hospitals is important due to their influence on prescribing habits in general practice [34 35 36 37], where the GPA prescription rate is low, ranging from 7,9-41,6%[45 46]. The risk for serious gastrointestinal complications seems to be related to the beginning of NSAID use[47], and according to our results more then two thirds of patients were prescribed NSAIDs and GPAs during hospitalization.

The methodological weaknesses of our study include lack of data on duration on NSAID therapy, long/short term prescription, concomitant drug therapy, as well as no categorization by indications for NSAID use (analgesia or rheumatic disease), no assessment of appropriateness of the NSAID prescription in the

individual patient, as well as no data on the extent of repeat prescribing of NSAIDs and GPAs in primary care. However, we believe that our study offers useful information on GPAs prescription strategies in NSAID users in the hospital setting, with the emphasis on the extent to which NSAID users receive recommended therapy that really provides gastroprotection. More studies assessing the use of H2RAs as ulcer-preventive drugs are needed, as well as studies dealing with the evaluation of GPAs use with NSAIDs in secondary care.

CONCLUSION

Although we did not directly measure the knowledge of hospital physicians on the studied topic, the results of our study nevertheless indicate high awareness of possible NSAID induced GI complications among hospital physicians (high GPA prescription rate), but also insufficient knowledge about specific risk factors related to NSAID-induced toxicity, recommended dose of H2RAs in ulcer prophylaxis and GI toxicity of different types of NSAIDs. Although the prevalence of GPAs among NSAID users overall and in patients at high risk was relatively high, when recommended daily doses of GPAs were taken into consideration, the actual prevalence of gastroprotection was unacceptably low.

More than 2/3 of patients receiving NSAIDs were prescribed NSAIDs and GPAs for the first time during hospitalization. Since secondary care prescribing has considerable influence on general practicioners' prescribing, studies aimed at evaluation of the use of GPAs with NSAIDs in secondary care are needed.

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Table 1 Basic characteristics.

Baseline characteristics	N (%)
patients taking NSAIDs *	93/770 (12,1)
patients included	92
Age, Mean±SD	58,9±13,5

	N (%)
females	47 (51,1)
age >65	50 (54,3)
NSAIDs prescribed during hospitalization**	67/92 (72,8)
GPAs prescribed during hospitalization†	44/55(80,0)

no risk factor	22/92 (23,9)
1 risk factor	38/92 (41,3)
2 risk factors	20/92 (21,7)
3 risk factors	8/92 (8,7)
4 risk factors	4/92 (4,3)

* including a patient who was prescribed rofecoxib; excluded from further evaluation

** missing data for 15 patients

† missing data for 3 patients

Table 2. NSAIDs prescription by risk factors.

	≥ 2 risk factors, N (%)	1 risk factor, N (%)	no risk factors, N (%)	Total
ketoprofen	22 (31)	30 (43)	18 (26)	70
diclofenac	3 (25)	5 (42)	4 (33)	12
indomethacin	2 (67)	1 (33)	0 (0)	3
ibuprofen	0 (0)	2 (100)	0 (0)	2
piroxicam	2 (100)	0 (0)	0 (0)	2
diclofenac+indomethacin	1 (100)	0 (0)	0 (0)	1
ketoprofen+indomethacin	1 (100)	0 (0)	0 (0)	1
diclofenac+ketoprofen	1 (100)	0 (0)	0 (0)	1

Table 3. GPAs prescription by risk factors

	Number of patients	Absent of GPA [N (%)]	Less than recommended dose [N (%)]	Recommended dose [N (%)]	p-value*
Total	92	37 (40)	46 (50)	9 (10)	
No risk factors	22	14 (64)	7 (32)	1 (4)	
Specific risk factors					
age >65 years	50	17 (34)	27 (54)	6 (12)	n.s.
history of GI disorders	23	8 (35)	11 (48)	4 (17)	n.s.
history of peptic ulcers	5	0 (0)	4 (80)	1 (20)	n.s.
presence of GI symptoms	14	4 (29)	8 (57)	2 (14)	n.s.
concomitant corticosteroids therapy	16	5 (31)	9 (56)	2 (12)	n.s.
concomitant aspirin therapy	2	1(50)	1 (50)	-	n.s.

≥2 NSAIDs	3	0 (0)	3 (100)	0 (0)	n.s.
concomitant aspirin therapy	2	1 (50)	1 (50)	0 (0)	n.s.
Any risk factor	70	23 (33)	39 (56)	8 (11)	p=0,01072
≥2 risk factors	32	10 (31)	17 (53)	5 (16)	n.s.**
1 risk factor	38	13 (34)	22 (58)	3 (8)	
2 risk factors	20	7 (35)	10 (50)	3 (15)	
3 risk factors	8	3 (37)	4 (50)	1 (13)	
4 risk factors	4	0 (0)	3 (75)	1 (25)	

* p values were calculated for difference in GPAs presription versus those without the specific risk factors

** compared to NSAID users with 1 risk factor

Table 4. Prescription of gastroprotective agents by tipe and dose recommendation

	Number of patients	No GPAs [N (%)]	Less than recommended dose [N (%)]	Recommended dose [N (%)]
Total anti-ulcer therapy	92	37 (40)	46 (50)	9 (10)
H2RAs	45		44 (98)	1 (2)
PPIs	8		0 (0)	8 (100)
antacids	3		3 (100)	0 (0)
Anti-ulcer therapy in patients at risk	70	23 (33)	39 (56)	8 (11)
H2RAs	38		37 (97)	1 (3)
PPIs	7		0	7 (100)
antacids*	2		1 (100)	0 (0)

* 3 patients were receiving antacids, 1 patient in combination with H2RA and this patient is included in the H2RA group

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