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The use and safety profile of non-steroidal anti-inflammatory drugs among Turkish patients with osteoarthritis

Türkiye'deki osteoartrit hastaları arasında non-steroid antiinflamatuvar ilaçların kullanımı ve güvenlilik profili

Hürriyet YILMAZ[1], Selim GÜREL[2], Oktay ÖZDEMİR[3]

[1]*70th Year Physical Therapy and Rehabilitation Education and Research Hospital, Istanbul*

[2]*Department of Gastroenterology, Uludag University, School of Medicine, Bursa*

[3]*Omega-CRO, Istanbul*

Background/aims: *To determine the use and safety profile of non-steroidal anti-inflammatory drugs (NSAIDs) among Turkish osteoarthritis patients.* ***Methods:*** *Osteoarthritis patients were interviewed by 138 doctors from clinics in nine different cities. Doctors completed a questionnaire regarding non-steroidal anti-inflammatory drugs use and safety profile while interviewing the patients.* ***Results:*** *Totally 3,755 patients (female/male: 3/1, mean age 59.0 ± 12.2 years), 3,442 under non-steroidal anti-inflammatory drugs treatment, were included in the study. The use of meloxicam (5.5% vs. 14.4%) and specific cyclooxygenase-2 (COX-2) inhibitors (for celecoxib 3.3% vs. 12.2%; for rofecoxib 3.0% vs. 11.2%) increased more than that of other non-selective non-steroidal anti-inflammatory drugs. The most common side effects were epigastric burning (37%), other dyspeptic symptoms (25.3%), abdominal pain (17.0%), constipation (12.7%), nausea (10.6%) and diarrhea (3.0%). COX-2 selective and specific inhibitors had significantly lower incidence of dyspeptic complaints compared to non-selective non-steroidal anti-inflammatory drugs. No difference was found between the different non-steroidal anti-inflammatory drugs regarding the ratio of discontinuation of therapy due to inefficacy. The ratios of discontinuation due to side effects were lower in patients using COX-2 specific inhibitors compared to non-selective and selective non-steroidal anti-inflammatory drugs: celecoxib (7.7%), rofecoxib (10.3%), etodolac (12.4%), meloxicam (12.6%), tenoxicam (16.5%), diclofenac (16.8%), ibuprofen (19.4%), and naproxen (27.4%). Discontinuation of the non-steroidal anti-inflammatory drugs due to dyspeptic complaint was significantly less for specific COX-2 inhibitors than for non-selective and selective non-steroidal anti-inflammatory drugs: celecoxib (2.5%), rofecoxib (8.4%), meloxicam (9.5%), etodolac (13.4%), tenoxicam (14.0%), diclofenac (14.1%), ibuprofen (17.2%), and naproxen (24.4%).* ***Conclusions:*** *The use of meloxicam and specific COX-2 inhibitors seems to have increased more than that of other non-selective non-steroidal anti-inflammatory drugs, if previously used non-steroidal anti-inflammatory drugs are considered. Fewer dyspeptic complaints have been reported with specific COX-2 inhibitors.*

Key words: Osteoarthritis, anti-inflammatory agents, non-steroidal

Amaç: *Bu çalışma Türkiye'deki osteoartrit hastaları arasında non-steroid antiinflamatuvar ilaç (NSAİİ)'ların kullanımını ve güvenlilik profilini belirlemek amacıyla tasarlanmıştır.* ***Yöntem:*** *Türkiye'de 9 farklı şehirdeki kliniklerden 138 hekim osteoartrit hastaları ile görüşme yapmıştır. Hekimler hastalarla görüşme yaparken non-steroid antiinflamatuvar ilaçların kullanımı ve güvenlilik profili hakkında sorular içeren bir anket formunu doldurmuştur.* ***Bulgular:*** *Çalışmaya, 3442'si non-steroid antiinflamatuvar ilaçlarla tedavi görmekte olan toplam 3755 hasta (kadın/erkek: 3/1, yaş ortalaması 59.0 ± 12.2) katılmıştır. Daha önceden kullanılan non-steroid antiinflamatuvar ilaçlar göz önüne alındığında, diğer selektif olmayan non-steroid antiinflamatuvar ilaçlara göre meloksikam (%5.5 vs. %14.4) ve spesifik siklooksijenaz-2 (COX-2) inhibitörlerinin (selekoksib için %3.3 vs. %12.2; rofekoksib için %3.0 vs %11.2) kullanımının daha fazla arttığı görülmüştür. En sık rastlanan yan etkileri epigastrik yanma (%37), diğer dispeptik semptomlar (%25.3), karın ağrısı (%17.0), konstipasyon (%12.7), bulantı (%10.6) ve diyare (%3.0) idi. Selektif olmayan non-steroid antiinflamatuvar ilaçlarla karşılaştırıldığında, selektif ve spesifik COX-2 inhibitörlerini kullanan hastalarda dispeptik yakınmaların belirgin şekilde daha az olduğu bulunmuştur. Etkisizlik nedeniyle tedaviyi bırakma oranı farklı non-steroid antiinflamatuvar ilaçlar arasında farklılık göstermemektedir. Selektif olmayan ve selektif non-steroid antiinflamatuvar ilaçlarla karşılaştırıldığında, COX-2 spesifik inhibitörlerinde yan etkiler nedeniyle tedaviyi bırakma oranı daha düşük olmuştur; selekoksib (%7.7), rofekoksib (%10.3), etodolak (%12.4), meloksikam (%12.6), tenoksikam (%16.5), diklofenak (%16.8), ibuprofen (%19.4), naproksen (%27.4). Dispeptik yakınmalar nedeniyle tedaviyi bırakma oranı da spesifik COX-2 inhibitörleri ile belirgin şekilde daha düşük olarak bulunmuştur; selekoksib (%2.5), rofekoksib (%8.4), meloksikam (%9.5), etodolak (%13.4), tenoksikam (%14.0), diklofenak (%14.1), ibuprofen (%17.2), naproksen (%24.4).* ***Sonuç:*** *Daha önceden kullanılan non-steroid antiinflamatuvar ilaçlar göz önüne alındığında, diğer selektif olmayan non-steroid antiinflamatuvar ilaçlara göre meloksikam ve spesifik COX-2 inhibitörlerinin kullanımının daha fazla arttığı görülmüştür. Spesifik COX-2 inhibitörleri ile bildirilen dispeptik yakınmalar da daha azdır.*

Anahtar kelimeler: Osteoartrit, anti-inflamatuvar ilaçlar, non-steroid

Address for correspondence: Hürriyet YILMAZ
FORMED, İstasyon Caddesi Leyla Apt. No: 10/1-2, 34800 Yeşilyurt, İstanbul, Turkey
Phone: +90 212 662 86 19 • Fax: +90 212 662 15 25
E-mail: hurriyety@superonline.com

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INTRODUCTION

The most common chronic joint disease throughout the world is osteoarthritis, which is associated with degeneration of the joints. The prevalence of osteoarthritis of the knee is between 0.1%-44% and is dependent on increasing age and female gender (1, 2).

Current guidelines for the treatment of osteoarthritis recommend pharmacological therapy, including acetaminophen for mild-to-moderate pain and non-steroidal anti-inflammatory drugs (NSAIDs) for moderate-to-severe osteoarthritis symptoms, if non-pharmacological interventions fail (3).

NSAIDs are among the most widely prescribed and used classes of drugs worldwide. Despite their clinical benefits in the management of osteoarthritis and rheumatoid arthritis, NSAIDs have considerable side effects, mostly affecting the upper gastrointestinal system, which limit their use (4, 5). Selective and specific cyclooxygenase-2 (COX-2) inhibitors, which have a better gastrointestinal risk profile, have been shown to be comparably effective, safer and cost-effective alternatives to conventional NSAIDs, which are mostly non-selective cyclooxygenase inhibitors (6, 7).

This hospital-based epidemiological surveillance study was designed to determine the use and safety profile of NSAIDs among a large population of Turkish patients with osteoarthritis.

MATERIALS AND METHODS

This study was designed as an epidemiological surveillance study. Between May 2002 and January 2003, a total of 250 doctors (primary care physicians, physical therapy and rehabilitation specialists, orthopedic surgeons, internists and rheumatologists) from nine different cities in Turkey were invited to the study, and 138 of them interviewed the osteoarthritis patients who were under NSAIDs treatment and had provided informed consent. Participating doctors were located in cities scattered widely enough geographically as to be representative of the whole country. The specialty distribution of the doctors showed a similar profile; therefore, the study was considered to include a representative sample of osteoarthritis patients.

A questionnaire regarding previous and current NSAIDs usage, reasons for discontinuation of NSAIDs and the side effects of NSAIDs was completed for each patient during the interview in one visit. The questionnaire is given in Figure 1.

Date: ..... / ..... / .....

Inclusion Criteria

❑ Has diagnosis of osteoarthritis ❑ Under NSAIDs treatment for osteoarthritis

❑ Signed informed consent form ❑ In suitable condition to give medical history

Age: ..... **Gender:** ❑ Male ❑ Female

NSAIDs

	Name of drug	Form	Daily dose	Duration (month)	Regularly used?
Currently being used					Yes No
Previously used					**Reason for discontinuation**

SIDE EFFECTS THOUGHT TO BE RELATED TO NSAIDs

Symptom	None	Mild	Moderate	Severe	Very severe	Starting date	Name of related drug
Epigastric burning	❑	❑	❑	❑	❑	..../..../.....	.....
Abdominal pain	❑	❑	❑	❑	❑	..../..../.....	.....
Nausea	❑	❑	❑	❑	❑	..../..../.....	.....
Diarrhea	❑	❑	❑	❑	❑	..../..../.....	.....
Constipation	❑	❑	❑	❑	❑	..../..../.....	.....
Other dyspeptic symptoms*	❑	❑	❑	❑	❑	..../..../.....	.....

*Abdominal discomfort, bloating, fullness, indigestion

Figure 1. The questionnaire used in the study

Statistical Method

The data were expressed using descriptive statistics such as number and percentage of patients. The frequencies and ratios were compared using χ^2 test. The statistically significant level of P was regarded as 0.05. The total number of patients in the different tables may differ because of some missing information in the questionnaires.

RESULTS

NSAIDs Usage

A total of 3, 755 patients (female/male: 3/1, mean age 59.0 ± 12.2 years), 3, 442 of whom were under NSAIDs treatment, were included in the study. Most of the patients (87.2%) were using only one NSAID, while others were using two or three NSAIDs (Table 1). Forty-nine percent of the patients had used NSAIDs previously.

Table 1. Distribution of patients according to the number of NSAIDs used

Number of NSAIDs used	N	%
1	3003	87.2
2	424	12.3
3	15	0.4
Total	3442	100.0

Table 2. Distribution of patients according to current and previously used NSAIDs agents

	Currently used	Previously used	Difference
NSAIDs agents	**N (%)**	**N (%)**	**%**
Diclofenac	632 (18.4)	511 (14.2)	4.2
Meloxicam	495 (14.4)	199 (5.5)	8.9
Naproxen	486 (14.1)	446 (12.4)	1.7
Celecoxib	421 (12.2)	117 (3.3)	8.9
Rofecoxib	384 (11.2)	107 (3.0)	8.2
Ibuprofen	256 (7.4)	186 (5.2)	2.2
Tenoxicam	219 (6.4)	164 (4.6)	1.8
Etodolac	189 (5.5)	89 (2.5)	3.0
Others	802 (23.3)	607 (17.0)	6.3
Total	3884 (100.0)	2426 (100.0)	

The most common currently used NSAIDs were diclofenac, meloxicam, naproxen, celecoxib and rofecoxib, while the most commonly previously used NSAIDs were diclofenac, naproxen, meloxicam, ibuprofen and tenoxicam (Table 2).

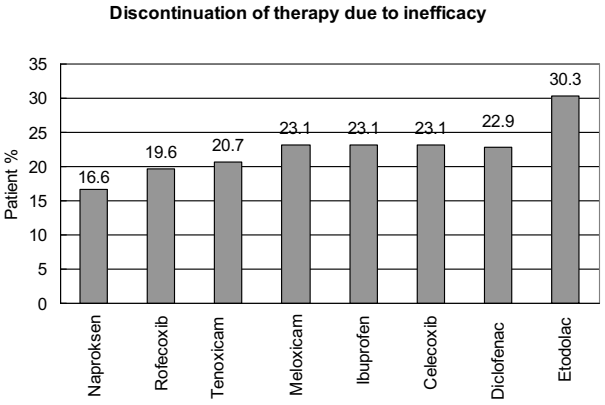

Figure 2. The percentages of discontinuation of therapy due to inefficacy for the most frequently used NSAIDs

Table 3. Distribution of patients according to the reasons for discontinuation of previously used NSAIDs (n=1749)

Reasons for discontinuation of previously used NSAIDs	N	%
Inefficacy	494	28.2
Side effects	428	24.5
Doctor's decision	346	19.8
Completion of the drug	134	7.7
Recovery of the patient	128	7.3
Others	216	12.4

The most common reasons for the discontinuation of previously used NSAIDs were inefficacy, side effects, and doctor's decision, in order of frequency (Table 3). The difference in the percentage of patients who discontinued NSAIDs therapy due to inefficacy was statistically insignificant (P=0.10) for the different NSAIDs (Figure 2). On the other hand, the ratio of discontinuation due to side effects was significantly lower (P<0.001) in patients using COX-2 specific inhibitors (celecoxib and rofecoxib) compared to non-selective NSAIDs (Figure 3). This difference was more remarkable (P<0.001) regarding discontinuation of therapy due to dyspeptic complaints (Figure 4).

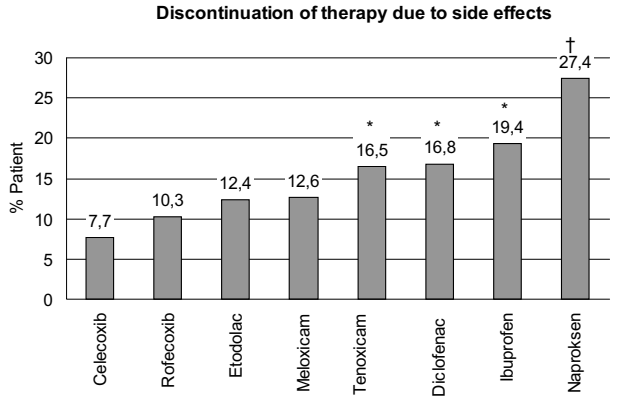

Figure 3. The percentages of discontinuation of therapy due to side effects for the most frequently used NSAIDs. **P*<0.05, †*P*≤0.001 versus celecoxib, χ^2 test

Table 4. Distribution of patients according to type of dyspeptic complaints (n=3436)

Dyspeptic complaints	N	%
Epigastric burning	1270	37.0
Abdominal pain	583	17.0
Constipation	437	12.7
Nausea	365	10.6
Diarrhea	104	3.0
Other dyspeptic symptoms	869	25.3

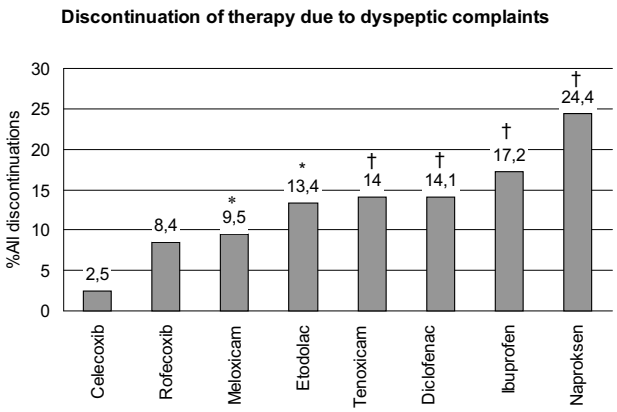

Figure 4. The percentages of discontinuation of therapy due to dyspeptic complaints for the most frequently used NSAIDs. **P*<0.05, †*P*≤0.001 versus celecoxib, χ^2 test

Table 5. The number and percentage of patients with different dyspeptic complaints for the most frequently used NSAIDs

	Celecoxib N (%)	Rofecoxib N (%)	Etodolac N (%)	Meloxicam N (%)	Tenoxicam N (%)	Diclofenac N (%)	Naproxen N (%)	Ibuprofen N (%)
Epigastric burning	19 (4.5)	17 (4.4)	12 (6.3)	34 (6.8)	33 (15.0)†	142 (22.4)†	153 (31.4)†	40 (15.6)†
Other dyspeptic symptoms	7 (1.6)	9 (2.3)	4 (2.1)	19 (3.8)*	12 (5.4)*	57 (9.0)†	61 (12.5)†	17 (6.6)†
Abdominal pain	6 (1.4)	4 (1.0)	3 (1.5)	11 (2.2)	7 (3.1)	54 (8.5)†	52 (10.7)†	20 (7.8)†
Constipation	3 (0.7)	2 (0.5)	1 (0.5)	2 (0.4)	4 (2.4)	11 (1.7)	5 (1.0)	1 (0.3)
Nausea	6 (1.4)	6 (1.5)	-	8 (1.6)	8 (3.6)	26 (4.1)	26 (5.3)	8 (3.1)

*P<0.05, †$P \leq 0.001$ versus celecoxib, χ^2 test

Dyspeptic Complaints

Epigastric burning, other dyspeptic complaints (bloating, postprandial fullness, abdominal fullness, indigestion), abdominal pain, constipation and nausea were the five most commonly seen dyspeptic complaints of NSAIDs in the studied patient population (Table 4). The patients using COX-2 specific inhibitors (celecoxib and rofecoxib) were found to have a significantly lower incidence of dyspeptic complaints compared to non-selective NSAIDs (P<0.001) (Table 5).

DISCUSSION

This hospital-based non-interventional epidemiological study is the first to be performed on a large number of patients representing a population of Turkish patients with osteoarthritis under NSAIDs therapy.

As expected from previous epidemiological studies on rheumatological diseases, most of the patients included in the study were female and over 50 years of age (8).

In this study, diclofenac was found to be the most commonly used NSAIDs among Turkish patients. Regarding the NSAIDs usage, the most remarkable finding of the study was the increased preference of patients and doctors towards meloxicam and specific COX-2 inhibitors (celecoxib and rofecoxib). This preference is similar to that observed in the other countries in which selective and specific COX-2 inhibitors have been introduced into the market (9, 10).

It has been demonstrated in many previous large scale studies that selective (meloxicam, nimesulide and etodolac) and specific (celecoxib and rofecoxib) COX-2 inhibitors have an efficacy that is comparable to non-selective, conventional NSAIDs (i.e. naproxen, ibuprofen, diclofenac), but with a significantly lower incidence of gastrointestinal complications (11-16).

In this study, patients under NSAIDs therapy reported mostly dyspeptic complaints, and the incidence of dyspeptic complaints in patients using non-selective conventional NSAIDs was significantly higher than that in patients under selective or specific COX-2 inhibitor therapy. Also, the percentage of discontinuation of previous NSAIDs due to side effects was higher in the conventional NSAIDs therapy group. Regarding the discontinuation of therapy for dyspeptic complaints, specific COX-2 inhibitors seem superior to both conventional and selective COX-2 inhibitors. This indicates that specific COX-2 inhibitors (celecoxib and rofecoxib) have a better dyspeptic complaint profile than both conventional and selective COX-2 inhibitors. On the other hand, no difference was found in the percentage of discontinuation of therapy due to inefficacy between patients using non-selective, selective or specific COX-2 inhibitors.

This study is important due to its naturalistic, hospital-based epidemiological design in a large osteoarthritis population in Turkey. The findings of the study are consistent with the previous studies and add further daily practice data to the outcome of large clinical trials.

In conclusion, the use of meloxicam and specific COX-2 inhibitors seems to have increased more than that of other non-selective NSAIDs, when previously used NSAIDs are considered. Fewer overall side effects have been reported with selective and specific COX-2 inhibitors. Furthermore, the percentage of patients who discontinued the NSAIDs due to dyspeptic complaints was significantly less in the specific COX-2 inhibitor therapy patient group.

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REFERENCES

1. Davis M, Ettinger W, Neuhaus J, et al. Knee osteoarthritis and physical functioning: evidence from the NHANES I Epidemiologic Follow up Study. J Rheumatol 1991; 18: 591-8.
2. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1987; 30(8): 914-8.
3. McColl GJ. Pharmacological therapies for the treatment of osteoarthritis. Med J Aust 2001; 175: S108-11.
4. Goldstein JL. Significant upper gastrointestinal events associated with conventional NSAIDs versus celecoxib. J Rheumatol Suppl 2000; 60: 25-8.
5. MacDonald TM. Epidemiology and pharmacoeconomic implications of non-steroidal anti-inflammatory drug-associated gastrointestinal toxicity. Rheumatology 2000; 39 (Suppl): 13-20.
6. Schwappach DL, Koeck CM. Selective COX-2 inhibitors: a health economic perspective. Wien Med Wochenschr 2003; 153(5-6): 116-22.
7. Kivitz AJ, Moskowitz RW, Woods E, et al. Comparative efficacy and safety of celecoxib and naproxen in the treatment of osteoarthritis of the hip. J Int Med Res 2001; 29(6): 467-79.
8. Shanga O. Epidemiology of rheumatic diseases. Rheumatol 2000; 39 (Suppl): 3-12.
9. Green A. Understanding NSAIDs: from aspirin to COX-2. Clin Cornerstone 2001; 3(5): 50-60.
10. Landsberg PG, Pillans PI, Radford JM. Evaluation of cyclooxygenase-2 inhibitor use in patients admitted to a large teaching hospital. Intern Med J 2003; 33(5-6): 225-8.
11. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies (SELECT) trial in osteoarthritis. Br J Rheumatol 1998; 37(9): 946-51.
12. Hawkey C, Kahan A, Steinbruck K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. International MELISSA Study Group. Meloxicam Large-scale International Study Safety Assessment. Br J Rheumatol 1998; 37(9): 937-45.
13. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999; 282(20): 1929-33.
14. Benseng WG, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. Mayo Clin Proc 1999; 74(11): 1095-105.
15. Benseng WG, Zhao SZ, Burke TA, et al. Upper gastrointestinal tolerability of celecoxib, a COX-2 specific inhibitor, compared to naproxen and placebo. J Rheumatol 2000; 27(8): 1876-83.
16. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000; 284(10): 1247-55.