

## Research Article

# PREDICTORS OF THE USE OF GASTROPROTECTIVE AGENTS IN PATIENTS USING NSAID IN YOGYAKARTA INDONESIA

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## ABSTRACT

Non Steroid Anti-Inflammatory (NSAID) is one type of Anti-Inflammatory drug that is used to treat pain in patients of osteoarthritis (OA) and rheumatoid arthritis (RA). The use of NSAIDs can cause gastrointestinal side effects. To prevent the side effects, NSAIDs are prescribed in combination with gastroprotective agent (GPA). The aim of the study is to determine the factors considered in the GPA prescription by the doctors in patients who have risk factors for gastric disorder due to NSAIDs use. This study was performed using a cross-sectional observational design. The data were collected retrospectively during a period of January to December 2010. The subjects were OA and RA patients considering the inclusion and exclusion criteria. The data included patient characteristics (gender, age, occupation, payment method, the primary diagnosis), prescription of NSAID, prescription of GPA, history of gastrointestinal disease, NSAID prescription with corticosteroids, prescription with antiplatelet. The data were processed descriptively and quantitatively, and analyzed statistically using chi-square and log. regression with 95% Confidence Interval. The results showed that there were correlation between some predictor factors with prescription of gastroprotective agent. These factors were women patient, patient age of  $\geq 65$  years, oxicam prescribing, diclofenac sodium prescribing, prescribing  $>1$  type of NSAIDs, prescription of NSAID concomitant with corticosteroids, prescription of NSAID concomitant with antiplatelet, patients with history of gastrointestinal, prescribing NSAIDs with duration of  $\geq 3$  months. Patient with a history of gastrointestinal disease was the most predictor influential factor, with OR (*odds ratio*) of 3.6 (95% CI: 2.79 - 4.66). Predictor factor of patients with a history of dyspepsia possessed the highest OR {OR=4,29 (CI 95%: 3.23–5.7)}. It means that patients with a history of dyspepsia prescribed NSAIDs would have greater risk of 4.29 times to get GPA prescription than patients without a history of dyspepsia. Prescribing NSAIDs  $> 1$  DDD (defined daily dose) had p value of 0.777, which means there was no relationship between GPA prescription with NSAIDs  $> 1$  DDD prescription.

**Key words:** Gastroprotective Agent, Non-steroid anti-inflammatory, Osteoarthritis, Rheumatoid Arthritis

## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) is one type of drug that is widely used around the world, both developed- and developing- countries. Besides being used as an anti-inflammatory and analgesic, NSAIDs also have the effect as an antipyretic. NSAIDs are often used in female and in elderly patients. Serious gastrointestinal complications increase

in elderly patients. The risk factors that can increase gastrointestinal side effects are a history of gastrointestinal diseases, long term use of NSAIDs, combination uses of several NSAIDs, the use of high doses of NSAIDs, the use of NSAIDs concomitant with corticosteroids, and concomitant use with anti-coagulant drugs. The side effects of NSAIDs start from mild, including dyspepsia with

prevalence of 20%, asymptomatic duodenal ulcer and ventricular (prevalence are 10-20% during 3 months the use of NSAIDs), until serious complications (perforation, ulceration, obstruction and bleeding of the gastrointestinal tract) (Dijk *et al.*, 2002).

The symptoms of gastrointestinal disorders (dyspepsia) can increase by 15% to 60% when the patient also uses NSAIDs concomitantly. Gastrointestinal disorder due to NSAID can increase from 2.5% to 4.5% per year, and the serious complications (severe bleeding, perforation, and obstruction) also increase about 1% to 1.5% per year (Laine, 2002). Koncz *et al.* (2008) reported that the side effects of gastrointestinal disorders due to the use of NSAIDs have occurred in 12,000 inpatients on hospital in the UK. It was also reported that there was more than 2000 deaths per year. In the United States, this incidence is increasing more than 100,000 inpatient on hospital and more than 16,000 deaths per year. In the UK the cost of treating side effects related to gastrointestinal disorders was 250 million pounds per year spent.

One risk factor of gastrointestinal complications of NSAIDs is the long-term use of the drug in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) diseases. At a hospital in Yogyakarta Indonesia, patients with these diagnoses would have long-term use of NSAIDs. Reportedly, based on data from Poly Geriatrics in this hospital, the number cases of OA in the elderly patient reached 1171 cases (22.39%) of all cases that went to the hospital in 2006. In Indonesia is not yet known urgency doctors prescribing gastroprotective GPA in patients taking NSAIDs. There are two factors considered by doctors in prescribing GPA co-treatment for the NSAIDs, namely: 1). the presence of risk factors that the patient uses NSAIDs especially during long term use and 2). the appropriate selection of therapeutic strategies to prevent the occurrence of gastrointestinal complications due to NSAIDs use (Anonim, 2007).

Based on that background described above, the study aimed to provide informations of the relationship of several risk factors with prescription of gastroprotective agent in a hospital in Yogyakarta Indonesia, and the most

influential risk factors that are considered by the doctor in the prescription of gastroprotective agents.

## METHODOLOGY

This study included an observational study with cross sectional method using secondary data through patient medical record data. The study was performed by analyzing the prescriptions of patients (diagnosis of RA and/or OA) receiving NSAIDs at a hospital in Yogyakarta. The subject of this study were outpatients who had primary diagnosis of OA and or RA with NSAIDs prescription in this hospital between January until December in 2010.

Predictors of the use of GPAs were analyzed using bivariate analysis methods. Bivariate analyzes in this study is a descriptive analysis carried out statistically by chi-square method ( $\chi^2$ )(significance level of  $p < 0.05$ ). The another analysis was bivariate log regression with confidence interval (CI) of 95%. Log regression conducted as a follow-up of the bivariate test was to include a variable that was statistically significant ( $p < 0.05$ ). Statistical analysis was performed to determine the relationship and influence of independent variables on the dependent variable, so it can be estimated magnitude of risk (Odds Ratio) of independent variables to the variable bound. In the study, statistical software was SPSS 13.0 for windows.

## RESULT AND DISCUSSION

### Osteoarthritis dan rheumatoid arthritis patient characteristic

The result of research data was done by observing medical records of osteoarthritis (OA) and rheumatoid arthritis (RA) outpatient who got a NSAID prescription in the hospital during January until December 2010. The amount of patients that could be collected by medical record during the period of this study were 525 arthritis patients. In the study, majority of OA and RA patients were female as many as 348 patients (66.3%). We observed that the average of patients age in the study were 59 ( $\pm 12$ ) year old, and the amount of patients older than 65 years is about 144 (27.4%) patients.

Patients with a diagnosis of primary OA, primary RA, and patients with OA and RA were 429 (81.7%), 69 (13.1%), and 27 (5.1%), respectively. In the study, among 525 patients, a patient received 4 ( $\pm$  3) prescription per year. The average of NSAIDs were prescribed in each patient were 4 ( $\pm$  3) drugs. The total of concomitant use of NSAIDs with GPA was 318 cases (60.6%). The total of concomitant use of NSAIDs with corticosteroids was 118 cases (22.5%), and concomitant use of NSAIDs with antiplatelet was 41 cases (7.8%).

### **Characteristics of NSAIDs Prescribing**

Prescribing characteristics of OA and RA patients who received NSAIDs at a hospital in Yogyakarta in 2010 is showed in Table I. Total prescriptions of NSAIDs in the study were 1871. The average of NSAIDs each prescription was 2 ( $\pm$  1) drugs. As many as 577 (30.8%) NSAID users were  $\geq$  65 years old, and 1228 (69.2%) NSAID users were females. The most NSAIDs was oxicam group (1135 prescriptions or 60.7%).

Patients with gastrointestinal disorders who use NSAIDs was as many as 318 (17%). As many as 254 (13,6%) prescriptions were prescribed more than 1 type in 1 prescription, and 93 (5,1%) prescriptions were prescribed with NSAIDs more than 1 defined daily dosage (DDD). The amount of concomitant use of NSAIDs with other drugs were 324 (17.3%) prescriptions with corticosteroid, and 100 (5.3%) prescriptions with antiplatelet. The duration of NSAIDs use for less than three months was found in 483 (92.0%) cases, and the NSAIDs use for more than three months was found 42 (8.0%) cases.

### **Predictors of Gastroprotective Agent (GPA) Prescription**

The results of study analysis, predictor of gastroprotective agent (GPA) use in OA and RA patients using NSAIDs in 2010 is presented in Table II. Totally, 791 prescriptions consisted of same NSAID with GPA concomitantly. Predictor factors of GPA use are female patients; age  $\geq$  65 years; patients who were prescribed oxicam, antiplatelet; patients with a history of gastrointestinal disorders; and prescribing NSAIDs with duration of  $\geq$  3 months.

### **Gender (Female)**

In Table II, 544 (44.3%) prescriptions were females using concomitant use between NSAID and GPA. P-value of 0.014 means that there is a relationship between the prescription of GPA and gender. The value of OR = 1.28 (95% CI 1.05 to 1.55), means that when females were prescribed NSAIDs had risk to get GPA prescription 1.28 times greater than men.

### **The Range of Age**

One of main predictor factor in concomitant use of NSAIDs with GPA was patient age  $\geq$  65 years. They had risk to get GPA prescription 1.27 times greater than in the age group  $<$  65 years.

### **The Type of NSAIDs**

The table II describes that 764 (42.3%) prescriptions consist of NSAIDs that was concomitant with GPA. Only the use of NSAID oxicam and diclofenac natrium types that have relationship with GPA prescription. The amount of prescription consisting oxicam group concomitant with GPA were 406 (35.8%) prescriptions, and 385 (52.3%) prescriptions did not use oxicam with p value = 0.000. It means that there was relationship between prescribing GPA with the prescribing oxicam. OR value of 0.51 (95% CI: 0.42-0.61) means that if the patients were prescribed oxicam they had risk to get GPA prescription 0.51 times. Another class of NSAIDs was diclofenac sodium, 308 (59.1%) prescriptions have used diclofenac sodium concomitant with GPA. The p value of 0.000 means that there was relationship between GPA prescription with diclofenac sodium. OR value of 2.6 (CI 95%: 2.11 – 3.19) means that if the patients were prescribed diclofenac sodium they had risk to get GPA prescription 2.6 times.

### **The Dose of NSAIDs**

NSAID prescribing in high doses ( $>$  1 DDD) was a moderate risk factor in the increasing occurrence of side effects of NSAIDs on the gastrointestinal tract. It means that a concomitant use of NSAIDs  $>$  1 DDD with GPA is needed (Lanza *et al.*, 2009). In this research, NSAIDs  $>$  1 DDD concomitant with GPA were 38 (40.9%) prescriptions with p value of 0.777. This p value indicates that there was no relationship between GPA prescription with NSAID prescription with doses  $>$  1DDD.

Tabel I. Characteristics of gastroprotective agent uses of OA and RA patients who receive NSAIDs in 2010

Characteristics of drugs prescribing	Jumlah	(%)
Total Prescribes (N total) (%)	1871	(100)
Total Prescribes GPA	828	(44.3)
- Ranitidine	650	(34.7)
- Lanzoprazole	143	(7.6)
- Lain-lain *	35	(1.9)
The Use of GPA > 1	37	(2.0)
GPA Doses ≤1 DDD	803	(42.9)
- Ranitidine	648	(34.6)
- Lanzoprazole	127	(6.8)
- The Others *	28	(1.5)
GPA Doses >1DDD	25	(1.3)
- Lanzoprazole	16	(0.9)
- The Others **	9	(0.5)

GPA (Gastroprotective Agent)

\*{ Sucralfate, Antacid, Rebammipid, Omeprazole}; \*\*{Sucralfate, Antacid, Ranitidin}

Van der Linden *et al.* (2009) explained that the NSAIDs > 1.25 DDD concomitant with GPA (PPI) was 60.2% cases. RR = 1.28 (CI 95%: 1.13 – 1.45), it means that patients who were prescribed with NSAIDs > 1.25 DDD had risk 1.28 times getting PPI than prescribed with NSAID ≤ 1.25 DDD. It means that the use of NSAIDs > 1 DDD should need simultaneous use of GPA that can transform and reduce side effects of NSAIDs.

#### The Use of NSAIDs More Than 1 types

In the study, the use of NSAIDs more than 1 types (combination) were 129 prescriptions concomitant with GPA, where 662 prescriptions used 1 type of NSAIDs prescription. The p value of 0.003 means that there was a relationship between GPA prescription with the NSAIDs combination prescription. The OR value of 1.49 (95% CI: 1.14 - 1.94) means if patients prescribed with NSAIDs combination so that they had risk 1.49 times to get GPA prescription than patients who get one type NSAIDs prescription.

#### The Use of NSAIDs Concomitant with Corticosteroid

The amount of the use of NSAIDs concomitant with corticosteroids were 164

(50.6%) prescriptions with GPA. The p value of 0.001 means there was relationship between GPA prescription by prescribing of NSAIDs concomitant with corticosteroid. The prescription of NSAIDs concomitant with corticosteroid on the patients had risk 1.5 times prescribed with GPA. The value of OR was 1.5 (95% CI: 1.18 - 1.91). In this study, only the use of corticosteroid methylprednisolone type has a relationship with GPA prescription.

The amount of the use of NSAIDs concomitant with methylprednisolone were 160 prescriptions with GPA, and 631 prescriptions without methylprednisolone. The p value of 0.001 means there was a relationship between GPA prescription with NSAIDs prescription concomitant with methylprednisolone. The value of OR 1.49 (95% CI: 1.17 - 1.9) means that if patients get NSAIDs prescription concomitant with methylprednisolone had risk 1.49 times prescribed with GPA. The p value of concomitant use between NSAIDs and dexamethasone were 0.425. This fact means that there was no relationship between GPA prescription and NSAID concomitant with dexamethasone.

Tabel II. Analysis of the result GPA predictor factors in OA and RA patients who received NSAIDs in 2010

<b>Concomitant Use of NSAIDs with GPA (N total)</b>	<b>791</b>		<b>p</b>	<b>OR</b>	<b>CI</b>
Predictor Factors	Yes (%)	No (%)			
-Females	544 (44.3)	247 (38.4)	0.014	1.28	1.05 – 1.55
-Age ≥ 65 tahun	267 (46.3)	524 (40.5)	0.019	1.27	1.04 – 1.54
-NSAIDs and analgesic	764 (42.3)	27 (39.1)	0.590	1.15	0.7– 1.87
- <i>Oxicam</i>	406 (35.8)	385 (52.3)	0.000	0.51	0.42 – 0.61
- Sodium Diclofenac	308 (59.1)	483 (35.8)	0.000	2.6	2.11 – 3.19
- The Others *	8 (25.8)	783 (42.6)	0.061	0.47	0.21 – 1.06
-The Other Analgesic (Paracetamol)	167 (46,4)	624 (41,3)	0,079	1,23	0,98 – 1,55
-NSAIDs Doses >1DDD	38 (40.9)	730 (42.4)	0.777	0.94	0.62 – 1.44
- <i>Oxicam</i>	33 (42.9)	758 (42.3)	0.916	1.03	0.65 – 1.63
- The Others **	6 (33.3)	785 (42.4)	0.440	0.68	0.25 – 1.82
-The Use of NSAIDs > 1	129 (50.8)	662 (40.9)	0.003	1.49	1.14 – 1.94
-Concomitant Use of NSAIDs with Corticosteroid	164 (50.6)	627 (40.5)	0.001	1.5	1.18 – 1.91
- Methylprednisolone	160 (50.5)	631 (40.6)	0.001	1.49	1.17 – 1.9
- Dexamethason	4 (57.1)	787 (42.2)	0.425	1.82	0.41 – 8.18
-Concomitant Use of NSAIDs with Antiplatelet	54 (54)	737 (41.6)	0.015	1.65	1.1 – 2.47
- Aspirin	47 (51.6)	744 (41.8)	0.064	1.49	0.98 – 2.27
- Clopidogrel	7 (53.8)	784 (42.2)	0.397	1.6	0.54 – 4.77
-GI Disorders (%)	216 (67.9)	575 (37)	0.000	3.6	2.79 – 4.66
- Dyspepsia	194 (71.9)	597 (37.7)	0.000	4.29	3.23 – 5.7
- Gastritis	22 (45.8)	769 (42.2)	0.613	1.16	0.65 – 2.06

p (p value); OR (Odds Ratio); CI (Confidence Interval 95%)

\*{Mefenamic Acid, Aspirin, Propionate (ibuprofen, ketoprofen), Methampiron}

\*\*{ Mefenamic Acid, Sodium Diclofenac, Ketoprofen }

**The Use of NSAIDs Concomitant with Antiplatelet**

The amount of the use of NSAIDs concomitant with antiplatelet were 54 prescriptions with GPA. The p value was 0.015 which means that there was a relationship between GPA prescription with the use of NSAIDs concomitant with antiplatelet. The prescription of NSAIDs concomitant with antiplatelet to the patients had risk 1.65 times prescribed with GPA. The value of OR was 1.65 (95% CI: 1.1 – 2.47).

**History of Gastrointestinal Disorders**

The use of NSAIDs in patients with history of gastrointestinal disorders were 216 prescriptions concomitant with GPA, whereas

575 prescriptions without gastrointestinal history. The p value of 0.000 means there was a relationship between GPA prescription with NSAID prescription in patients with a history of gastrointestinal. The OR value was 3.6 (95% CI: 2.79 - 4.66) meaning that if patients with a history of gastrointestinal got NSAIDs prescription, they had risk 3.6 times prescribed with GPA. The risk would increase 4.29 times with a history of gastrointestinal disorder (dyspepsia) which the OR value of 4.29 (CI95%: 3.23-5.7).

**Duration of NSAIDs Use**

Duration of the use of NSAIDs was shown in table III. The use of NSAIDs with

Tabel III. The duration result analysis of the use of NSAIDs as a factor GPA usage in patients with OA and RA in 2010

Predictor Factor	The patient use NSAIDs concomitant with GPA (N total) 318		p	OR	CI
	Yes (%)	No (%)			
- Duration of NSAIDs $\geq$ 3 months	19 (45.2)	299 (61.9)	0.034	0.51	0.27-0.96
- Meloxicam	69 (82.1)	249 (56.5)	0.000	3.55	1.97-6.39
- The Others *	48 (88.9)	270 (57.3)	0.000	5.96	2.5-14.19

p (p value); OR (Odds Ratio); CI (Confidence Interval 95%); \* (Paracetamol Diclofenac Sodium, Ibuprofen)

duration  $\geq$  3 months was 19 prescriptions concomitant with GPA. In 299 prescriptions, NSAIDs was used with duration  $<$  3 months. The p value of 0.034 means there was a relationship between GPA prescription with NSAID prescription with a duration  $\geq$  3 months. The OR value of 0.51 (CI 95%: 0.27 - 0.96) means NSAIDs prescription with duration  $\geq$  3 months had risk 0.51 times greater to get GPA prescription than patients who got NSAIDs with duration  $<$  3 months. The use of NSAIDs  $>$  3 months in meloxicam type is the most influence on GPA prescription. Duration of prescription of meloxicam  $\geq$  3 months had risk 3.55 times of GPA prescription in which the value of OR was 3.55 (95% CI: 1.97-6.39).

Lanza *et al.* (2009), in the Guidelines for Prevention of NSAID-related Ulcer Complications mentioned that patients who have risk of gastrointestinal disorders using NSAIDs classified into 3 groups. The first group was low risk, i.e. patients without risk factors. The second group was moderate risk, i.e. patients over the age of 65 years, the use of high doses of NSAIDs, a history of ulcers, concomitant use of other NSAIDs drugs { aspirin (low dose), corticosteroids, anticoagulants}. Third group was high risk groups to which patients who had the history of ulcers or patients who had 2 risk of moderate risk group.

Davies and Saleh (2000) mentioned that long-term NSAID users (OA and RA patients) had risk 2-4% of developing symptomatic ulcers, gastrointestinal bleeding or perforation, and 40-70% long-term impact on the use of

intestinal bleeding. These facts mean that the use of NSAIDs in patients who have risk factors need to be prescribed with GPA concomitantly. Prescribing GPA aims to reduce gastrointestinal side effects in patients

Altman (2000) mentioned that prevention of NSAID complications were done with the use of type COX-2 inhibitors NSAID or NSAIDs in combination with the GPA. In this study, every patient who had risk factors of gastrointestinal disorders, when prescribed with NSAIDs would have risk to be prescribed with GPA. However, prescription of NSAIDs  $>$  1 DDD was no relationship with GPA prescription. Previous studies reported that all risk factors of GPA prescription when patients who receive NSAID would have risk to get GPA. Van der Linden *et al.* (2009), the use of NSAIDs  $>$  1.25 DDD had risk to get GPA (PPI) 1.28 times greater than prescription of NSAID  $\leq$  1.25 DDD.

## CONCLUSION

There were several predictor factors of GPA prescription in patient using NSAIDs, except the prescription of NSAIDs  $>$  1 DDD that was no relationship with GPA prescription. These factors are female patients; age  $\geq$  65 years; patients who were prescribed oxcam, antiplatelet; patients with a history of gastrointestinal disorders; and prescribing NSAIDs with duration of  $\geq$  3 months. History of gastrointestinal (dyspepsia) in patients was the most influential factor in the consideration of a doctor to prescribe GPA.

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