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Universitas Islam Indonesia

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# QUALITY OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS PRESCRIBING FOR OUTPATIENT AT A PRIVATE HOSPITAL IN CENTRAL OF JAVA

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## ABSTRAK

Obat antiinflamasi non-steroid (AINS) banyak digunakan dalam pengobatan berbagai penyakit yang melibatkan proses inflamasi dan merupakan grup terbesar dari agen farmasetik yang digunakan secara luas di seluruh dunia. Beberapa studi telah melaporkan bahwa komplikasi pada saluran pencernaan merupakan reaksi obat yang tidak dikehendaki (ROTD) yang paling sering terjadi terkait penggunaan AINS. Penelitian ini dilakukan dengan tujuan untuk mengetahui kuantitas dan kualitas persepsian obat golongan AINS untuk pasien rawat jalan di salah satu rumah sakit. Penelitian dilakukan dengan menggunakan sampel data persepsian obat selama satu tahun, yaitu selama periode 1 Juli 2006 sampai 30 Juni 2007. Data penggunaan obat golongan AINS dikumpulkan dari catatan penggunaan obat di instalasi farmasi rumah sakit meliputi jenis obat, bentuk sediaan, kekuatan, serta jumlah penggunaan. Pengukuran kuantitas penggunaan obat AINS dilakukan dengan menggunakan satuan unit DDD (*Defined Daily Dose*) yang dinyatakan dalam DDD/1000 kunjungan pasien rawat jalan (KPRJ). Kualitas persepsian obat AINS diukur berdasarkan kriteria keamanan relatif obat AINS terhadap saluran pencernaan yang dianalisis berdasarkan data kuantitas penggunaan obat AINS menggunakan metode *Drug Utilization 90%* (DU90%). Hasil penelitian menunjukkan bahwa keseluruhan AINS yang digunakan meliputi 7 jenis dengan 22 nama dagang. Kuantitas AINS yang digunakan adalah sebesar 182,5 DDD/1000 kunjungan pasien, yang artinya adalah setiap pasien mendapatkan AINS sebesar 1,8 DDD. Jenis AINS yang termasuk dalam segmen DU90% adalah asam mefenamat (62,8%), ketorolak (15,4%), ketoprofen (8,6%), dan diklofenak (8,5%). Berdasarkan tingkat keamanan obat golongan AINS terhadap saluran pencernaan, kualitas persepsian obat golongan AINS untuk pasien rawat jalan di rumah sakit ini sudah cukup baik, karena AINSs yang digunakan sebagian besar merupakan AINS dengan risiko moderat dan rendah terhadap gangguan saluran pencernaan, yakni asam mefenamat dan diklofenak dengan persentase penggunaannya sebesar 71,3%.

Kata kunci: AINS, ATC/DDD, DU90%

## ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are used widely for a variety of diseases, primarily for musculo-skeletal diseases. NSAIDs are also one of the most common causes of adverse drug reactions (ADRs) reported in many clinical and epidemiological studies, notably dyspepsia and gastrointestinal bleeding. There are no important differences among NSAIDs with regard to efficacy, and the choice of first line treatment should be based on their relative toxicity, primarily on gastrointestinal system. This study aims to know quality of NSAIDs prescribing for outpatient at a private hospital in Central of Java based on relative toxicity on GI tract by determine the number of drugs that account for 90% of the use. Utilization of NSAIDs during one year (1 July 2006 – 30 June 2007) was measured as number of DDD (defined daily dose). The drugs that accounted for 90% of the use (drug utilization 90%; DU90%) and proportion of NSAIDs with high risk (ketoprofen, piroxicam) and low risk (ibuprofen, diclofenac) with respect to GI toxicity was determined in order to assess the quality of prescribing. There were 8 agents of NSAIDs by substance was used during the study period with total quantity was 22938.09 DDDs. Four of

NSAIDs were found in the DU90% segment and mefenamic acid was the most prescribed drug. The high risks drugs (piroxicam and ketoprofen) made up 19.76% of NSAIDs within DU90% segment, compared with 18.51% for low risk drug (diclofenac). Result of this study indicates that in respect to gastrointestinal toxicity, the quality of NSAIDs prescribing for outpatients in the hospital was quite good, because the most prescribed NSAIDs were mefenamic acid and diclofenac with moderate and low risk, respectively, to gastrointestinal system.

Keywords: DDD, DU90%, Nonsteroidal anti-inflammatory drugs, NSAIDs, prescribing



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## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in the world because of their efficacy in reducing pain and inflammation. Their efficacy has been documented in a number of clinical disorders, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, dysmenorrhea, dental pain and headache. As a group, NSAIDs are excellent analgesics and are even more efficacious than intramuscular morphine for acute pain (Ong *et al.*, 2007). A major factor limiting the use of NSAIDs is gastrointestinal toxicity. It has been estimated conservatively that the number of NSAIDs-related death among patients with rheumatoid arthritis or osteoarthritis is similar to the number of deaths from acquired immunodeficiency syndrome and considerably greater than number of deaths from multiple myeloma, asthma, cervical cancer, or Hodgkin's disease. Therefore, to identify the factors that increase risk of NSAIDs-related gastrointestinal complications and to determine methods for reducing this risk are very important (Wolfe *et al.*, 1999). Since there are no important differences among these drugs with regard to efficacy, the choice of first-line treatment should be based on their relative toxicity. In general, ibuprofen has the lowest risk for gastrointestinal toxicity among NSAIDs, while diclofenac and naproxen have intermediate risks, and piroxicam and ketorolac carry the greatest risk (Ong *et al.*, 2007).

To measure the quality of NSAIDs prescription with regarding to their gastrointestinal risks is very important in order to reduce NSAIDs-related morbidity and mortality. It was well accepted that the quality of drug prescribing is related to the number of drugs that account for 90% of drug use (Drug Utilization 90% or DU90%) and that the number as well as the drugs in this segment may serve as simple indicators of the quality of drug prescribing (Wettermark *et al.*, 2003). The DU90% is a simple method to assess the quality of drug prescribing, which may be can be adapted to provide comparative data between healthcare facilities. When properly used, DU90% method has shown to be a valuable tool in general practice for assessing the overall quality in prescribing and to form the basis for more specific analysis using disease, or patient, specific quality indicators. High quality of NSAIDs prescribing is associated with the use of relatively low risk for gastrointestinal toxicity (Bergman *et al.*, 1998).

This research was aimed at knowing the quality of NSAIDs prescription for outpatients at a private hospital in Central of Java based on NSAIDs gastrointestinal relative toxicity, by determining the number of drugs that account for 90% of the use (DU90%).

## METHODS

Utilization of NSAIDs for outpatients during one year (1 July 2006 – 30 June 2007) was measured as number of DDD (defined daily dose). Data on NSAIDs use were collected from pharmacy department of the hospital. In this research, DDDs for NSAIDs listed in the ATC index with DDDs 2006 was used. The drugs were recorded by trade names, and the information obtained included generic names, strength and quantity (e.g. number of tablets) prescribed. Each drug was then given its chemical name and a code according to the ATC classification. This classification comprises 5 levels. The first level is the anatomical group, the second is the therapeutic group, the third is a therapeutic subgroup, the fourth the chemical form, and the fifth is a chemical subgroup. Raw data were entered into Microsoft Excel and converted into DDD. The drugs that accounted for 90% of the use (drug utilization 90%; DU90%) and proportion of NSAIDs with high risk (ketoprofen, piroxicam, ketorolac), moderate risk (mefenamic acid, meloxicam, phenylbutazone), and low risk (ibuprofen, diclofenac) with respect to GI toxicity was determined in order to assess the quality of prescribing. High quality was assumed to be associated with a limited number of drugs and a

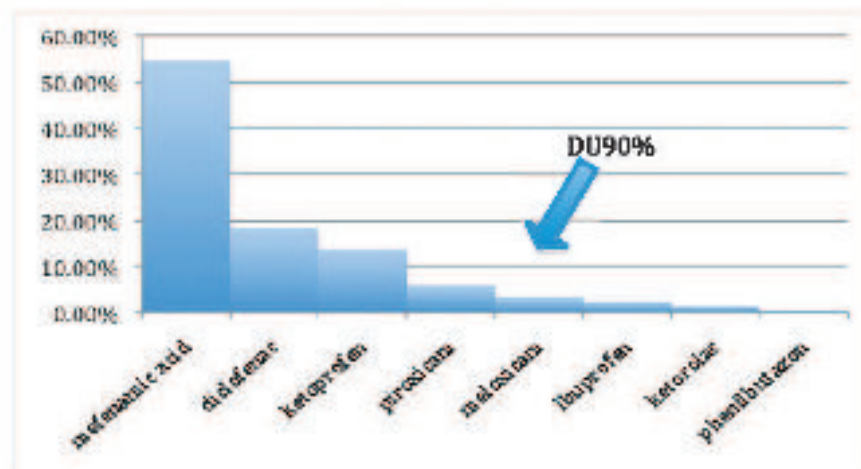
higher number of drugs with low risk for gastrointestinal toxicity within DU90% segment (Palcevski, *et al.*, 2002)

## RESULTS AND DISCUSSION

There were 8 agents of NSAIDs by substance was used during the study period with total quantity was 22938.09 DDDs. Mefenamic acid was the most used agent during the study period. The overall NSAIDs used during the study period are listed in Table 1.

**Table 1.** The overall NSAIDs prescribed during the study period expressed as number of DDDs and percentage

ATC code	Drug	Consumption in number of DDDs	Consumption in percentage
M01AA01	Phenilbutazon	89	0.43
M01AB05	Diclofenac	4244	18.52
M01AB15	Ketorolac	291	1.27
M01AC01	Piroxicam	1370	5.98
M01AC06	Meloxicam	743	3.24
M01AE01	Ibuprofen	517	2.26
M01AE03	Ketoprofen	3183	13.81
M01AG01	Mefenamic acid	12488	54.49



**Figure 1.** The percentage of NSAIDs use and agent of NSAIDs included within DU90% segment

As shown in Figure 1, there were four of NSAIDs were found in the DU90% segment and mefenamic acid was the most prescribed drug. According to relative risk for gastrointestinal toxicity, mefenamic acid has a moderate risk. Piroxicam and ketoprofen (the high risks) made up 19.78% of NSAIDs within DU90% segment, compared with 18.51% for low risk drug (diclofenac) and 54.49% for moderate risk (mefenamic acid). The use of meloxicam, ibuprofen, ketorolac, and phenilbutazon were not included within DU90% segment, and the meaning is that their use in this hospital is low. Surprisingly, the use of ibuprofen as a safest agent of NSAIDs was not included within DU90% segment and its use was very low (2.26%). In respect to gastrointestinal toxicity, the quality of outpatient NSAIDs prescribing in the hospital was low, based on the total consumption for the high risk NSAIDs was more than the low risk NSAIDs, and there were two agents with high risks within DU90% segment.

Many of clinical trials show that NSAIDs have an excellent analgesic effect, but their efficacy was limited by their toxicity, especially on gastrointestinal tract. Therefore, many of recent

guidelines for the management of osteoarthritis (OA) and rheumatoid arthritis (RA) recommend using acetaminophen as first line oral pharmacotherapy. The recommendation is based on studies showing comparable efficacy of acetaminophen to NSAIDs in short-term, symptomatic treatment of mild to moderate joint pain due to OA and RA, in addition to its more favorable safety profile (Lee *et al.*, 2004). However, recent clinical trials have found NSAIDs to be more efficacious than acetaminophen in some group of patients with OA and RA. In overall NSAIDs, ibuprofen was associated with the lowest relative risk for gastrointestinal toxicity, followed by diclofenac, although the use of ibuprofen in a higher doses were associated with relative risks similar to those with naproxen and indomethacin (Henry *et al.*, 1996). In this study, the use of ketorolac was also very low (1.27%). The risk with ketorolac was distinctly higher than with the remaining NSAIDs and this suggest an unfavorable risk-benefit assessment for outpatient use of ketorolac compared with other NSAIDs (Rodriguez *et al.*, 1998).

According to data from medical record division, the most diagnosed medical problems for outpatient during study period was obstetric-gynecology problem, which may be mostly is related to childbirth. NSAIDs are commonly needed for pain relieving in perinatal care, both for vaginal or sectio cesarian delivery. The overall of ten most diagnosed medical problems during study period are listed in Table 2.

**Table 2.** The ten most medical problems for outpatient during study period

No.	Medical diagnosis	No. of cases (%)
1	Obsgyn	4688 (29.5)
2	Thypoid fever	3221 (20.3)
3	Hypertension	1410 (8.9)
4	Acute respiratory infections	1278 (8.1)
5	Acute bronchitis	1265 (7.9)
6	Unspecific diarrhea	1123 (7.1)
7	Post-stroke	1054 (6.6)
8	Heart failure	528 (3.3)
9	Bronchopneumonia	681 (4.3)
10	Head trauma	643 (4.1)

NSAIDs commonly are prescribed during perinatal care, especially for pain relieving resulted from delivery process. Mefenamic acid, for example, is commonly used for pain relieving in women with vaginal delivery, as there is a high risk for trauma during delivery process. On the other hand, in women with sectio cesarian delivery ketorolac is preferred as it has a higher analgesic effect.

As for the therapeutic approach to reduce gastrointestinal toxicity, any medications such as proton pump inhibitors (PPIs), misoprostol, and cyclooxygenase 2 selective (COX-2) inhibitors are all effective. However, PPIs and COX-2 selective inhibitors may be preferable to misoprostol due to their once daily dosing, and their lower rate of treatment-related adverse events.

This study assesses the quality of NSAIDs prescribing by using an aggregate data on NSAIDs utilization from hospital pharmacy department. It should be noted that the increasing risk for serious gastrointestinal complications will be more probable in patient with several risk factors including: the age over 65, history of previous peptic ulcer disease, taking corticosteroids, taking anticoagulants, and also taking aspirin (Ong *et al.*, 2007). One limitation of this study is that complete patient information was not known and also the average prescribed daily dose. The prescribed daily dose may be higher or lower than the DDDs, therefore the results of this study are important to be followed up to get accurate information about the quality of NSAIDs prescription. Several reasons which will influence the NSAIDs prescribing such as cultural traditions, differences in market, education, marketing and pricing were important to be studied.

## CONCLUSIONS

In respect to gastrointestinal toxicity, the quality of NSAIDs prescribing for outpatients in the hospital was quite good, because the most prescribed NSAIDs were mefenamic acid and diclofenac with moderate and low risk, respectively, to gastrointestinal system.



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