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RISK FACTORS FOR DUPLICATION OF NSAIDs WITHOUT GASTROPROTECTIVE IN ONE OF THE HOSPITALS IN INDONESIA

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ABSTRACT

The use of dual NSAIDs without gastroprotective is one of the drug related problems that often occurs in hospitals, the purpose of giving dual NSAIDs is to increase the effectiveness of pain relief in reducing pain in patients. However, the use of dual NSAIDs without gastroprotective increases the risk of side effects on the gastrointestinal tract, kidneys, and cardiovascular system. This study aimed to examine the risk factors for duplication of NSAID therapy without gastroprotective in the outpatient pharmacy unit at a type C hospital in Banyuasin district. This analytical study used a cross-sectional research design to determine the influence of risk factors on the incidence of duplication of NSAIDs therapy without gastroprotective in the outpatient polyclinic. Data were analyzed using Pearson Chi Square analysis. The results of the bivariate analysis showed that older age, polypharmacy, and multipathology were factors associated with the incidence of NSAID duplication in outpatients with p values (OR) of 0.047 (1.101), 0.025 (2.63), 0.025 (2.63), and 0.025 (2.63), respectively.

Keywords: Therapeutic duplications, Ibuprofen, Diclofenac, Gastroprotective agent

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory, antipyretic, and analgesic properties (Ghlichloo and Gerriets 2021). The large number of NSAIDs used has also been reported to result in duplication of treatment. In South Korea over 59 million ambulatory care visits have NSAID/analgesic prescription and 13,3% of them have therapeutic duplications (TDs), with the most frequently found duplication were diclofenac/aceclofenac sodium (12,4% of TDs), diclofenac/talniflumate (11.2 %), and diclofenac/loxoprofen sodium (10.7 %) (Kang et al., 2016). The use of two NSAIDs is directly aimed at increasing the analgesic effect that resulted, previous studies show that efforts to be able to increase the analgesic effect is to use two NSAIDs or increase the dose to the maximum dose but this is at risk of increasing the incidence of drug related problems of NSAID drugs such as the use of NSAIDs without gastroprotective and over-dose use of NSAIDs (Nurmesa A, 2024). According to research, the long-term use of NSAIDs can also increase mortality risk factors (Campbell et al., 2022). However, NSAIDs are known to adversely affect the gastric mucosa and renal, cardiovascular, hepatic, and hematologic systems (Ghlichloo & Gerriets, 2021; Wongrakpanich et al., 2018).

Gastrointestinal complications that occur due to the long-term use of NSAIDs include GI bleeding, peptic ulcer disease, and small bowel mucosal disease injuries (Tai &

McAlindon, 2021). GI bleeding can be fatal and can even cause mortality (Straube et al., 2009). Therefore, gastroprotective use has been recommended in patients taking NSAIDs for those at risk of gastrointestinal side effects and with a longer duration of NSAIDs use (Lee et al., 2016; Shabani et al., 2020).

Health professionals, such as pharmacists, play an important role in increasing drug use safety (Azwar & Pelajar, 2016). The pharmacist's role in safe medication use is to prevent medication errors by making dose adjustments, therapeutic duplication reviews, and medication reconciliation (Alzahrani et al., 2021; Zhang et al., 2023). Several studies have been published on duplicate NSAIDs (Kang et al., 2013; Syarifah, 2015; Trenaman et al., 2021). However, the study only presented data on the duplication of NSAIDs and did not provide information on gastroprotective use in patients receiving duplication of NSAID treatment. Therefore, this study aimed to examine the risk factors for duplication of NSAID therapy without gastroprotective in the outpatient pharmacy unit at a type C hospital in Banyuasin district.

RESEARCH METHODS

Research Procedure

This study was an analytic study using a cross-sectional research design to determine the influence of risk factors on the incidence of duplication of NSAIDs therapy without gastroprotective in polyclinic outpatients at one of the hospitals in Banyuasin Regency in March-June 2022. The study participants were outpatients who met the inclusion and exclusion criteria. The data used were sourced from electronic medical records and electronic prescriptions of patients, and data collection was carried out at the pharmaceutical installation.

The total population of patients with dual therapy NSAID prescriptions in the period March-June 2023 was 138. The sampling method used was a simple random sampling sample calculation using the Slovin formula:

$$\text{n} = \frac{N}{1 + Ne^2}$$

$$\text{n} = \frac{138}{1 + (138.\,0{,}05^2)}$$

$$\text{n} = \frac{138}{1 + 0{,}345}$$

$$n = 102{,}6 \sim 103$$

Description:

n = Number of population

N = Z score at 95% confidence = 1.96

E = margin of error

Thus, the minimum sample size in this study was 103 patients who received dual therapy NSAID sheets.

The inclusion criteria were as follows.

1. Patients with age ≥ 18 years
2. Outpatient polyclinic with prescriptions dual NSAID therapy as analgetic therapy

The exclusion criterion was incomplete electronic medical record data.

The study variables were independent variables consisting of risk factors for age, gender, type of drug, and comorbidities. The dependent variable consisted of the incidence of duplication of NSAIDs therapy without gastroprotective. Data collection was performed using secondary data in the form of patient medical records and prescriptions for hospitalized patients.

Data Analysis

This study used statistical analysis of *Chi-square* (bivariate) with a confidence level of 95% to compare whether the risk factors of age, gender, drug type, comorbidities, and polypharmacy affect the incidence of duplication of NSAIDs therapy without gastroprotective. The relationship was considered meaningful if the significance level was less than 0.05.

RESULTS AND DISCUSSION

Based on the studies conducted, the samples included in this study were patients aged 20–80 years. In this study, it was also found that patients who received duplication of NSAIDs therapy without gastroprotective and duplication of NSAIDs therapy with gastroprotective had similar characteristics, namely, the majority of patients aged > 60 years (elderly), as many as 42 patients in the group of duplication of NSAIDs therapy without gastroprotective, and the group of duplication of NSAIDs therapy with gastroprotective, as many as 31 patients, with a total of 73 patients in the elderly group. At the age of ≤ 60 years (non elderly), as many as 16 patients in the group with duplication of NSAIDs therapy without gastroprotective. At the age of ≤ 60 years (non-elderly), there were 16 patients in the group with duplication of NSAIDs therapy without gastroprotective and 14 patients in the group with duplication of gastroprotective therapy, with a total of 30 patients in the non-elderly group.

In this study, female patients received duplicate NSAID therapy without gastroprotective more often than male patients, with a total of 34 patients (58.6%), while male patients received 24 patients (41.4%). Patients with duplication of NSAIDs therapy with gastroprotective in this study were mostly female (23 patients, 51.1%), while 22 patients (48.9 %) were male (Table I). This study also analyzed the number of diagnoses suffered by patients consisting of monopathological, namely patients with one type of diagnosis and multipathological, namely patients with 2 or more diagnoses in this study Patients with monopathological conditions were 31 patients (30.1%) and multipathological were 72 patients (69.9%). The diagnosis received by the patient was made by the doctor during the patient's treatment during the study period. The number of patients with more than one diagnosis is related to complications experienced by patients with chronic diseases.

Table I. Patient Characteristics of Duplicate NSAID Therapy Without Gastroprotective

Characteristics	Case Group (n=58)	Control Group (n=45)
Age (Years)		
20-30	2 (3,45)	3(6,67)
31-50	4 (6,90)	3 (6,67)
51-59	10 (17,24)	8 (17,78)
60-80	42 (72,41)	31 (68,89)
Gender		
Male	24 (44,45)	22 (48,89)
Female	34 (58,62)	23 (51,11)
Pathologic conditions		
Multi-phatology	45 (77,59)	27 (60)
Mono-phatology	13 (22,41)	19 (40)
Number of drugs		
≥5	45 (77,59)	27 (60)
<5	13 (22,41)	19 (40)

This study also found polypharmacy in patients who took ≥4 drugs (Bradley et al., 2014). There were 45 patients in the group of patients with duplication of NSAIDs therapy without gastroprotective and 13 patients with duplication of NSAIDs therapy without

gastroprotective non-polypharmacy, while data related to polypharmacy in patients with duplication of NSAIDs with gastroprotective were 27 patients with duplication of NSAIDs with non-polypharmacy gastroprotective were 19 patients. Research conducted by Breadley et al, 2014 showed that the incidence of potential irrational prescriptions in the elderly age group was related to polypharmacy and excessive use of NSAIDs (Abdu et al., 2020; Bradley et al., 2014).

The most common duplication of NSAIDs without gastroprotective therapy was diclofenac sodium with ibuprofen (n=29 cases), and the least common was mefenamic acid with diclofenac potassium and ibuprofen and ketoprofen (n=1 case) (Table II).

Table II. Characteristics of Duplication of NSAID Therapy Without Gastroprotective Agents

NSAID Duplication Without Gastroprotective	Total (%)
Ketoprofen and Mefenamic Acid	14 (23,7)
Diclofenac Sodium and Mefenamic Acid	10 (17)
Diclofenac Sodium and Ibuprofen	29 (49,2)
Diclofenac Potasium and Mefenamic Acid	1 (1,7)
Ketoprofen and Ibuprofen	1 (1,7)
Ketoprofen and Mefenamic Acid	3 (5)

Table III. Risk Factors for The Incidence of Duplication of NSAID Therapy Without Gastroprotective in Polyclinic Outpatients at One of The Hospitals in Indonesia

Risk Factors	Case Group	Control Group	P Value	OR : Odds Ratio
Ages				
Erderly	42	31	0,047	1,101
Non Elderly	16	14		
Gender				
Male	24	22	0,751	0,706
Female	34	23		
Pathologic conditions				
Multi-phatology	45	25	0,025	2,63
Mono-phatology	13	19		
Number of drugs				
Polypharamacy	45	25	0,025	2,63
Non Polypharmacy	13	19		

P< 0,05, Using Perason *Chi-Square* Tests

Based on the bivariate test, the relationship between duplication of NSAID therapy without gastroprotective and age has a p value of 0.047, which means there is an association between the incidence of duplication of NSAID therapy without gastroprotective and the age of the elderly (Elderly), which is in line with the relationship between multipathology and duplication of NSAID therapy (p value = 0.025) and polypharmacy (p value = 0.05) (Table III), indicating that there is an association between multipathological conditions and polypharmacy in patients with duplication of NSAID therapy without gastroprotective. This is in line with the research conducted by Abdu et al 2020 which states that there is a relationship between multipathological events such as diabetes or hypertension with polypharmacy and the use of NSAID in the elderly age group (Abdu et al., 2020). In this study, it was influenced by the large number of drugs received by outpatients with more than one diagnosis condition and varying severity of pain, which could increase the use of duplicate NSAID drug therapy without gastroprotective. The factor that had no relationship

between the gender factor with incidence of duplication of NSAID therapy without gastroprotective was p = 0.751 (Table III).

NSAIDs are anti-inflammatory drugs that can be used for pain therapy; however, they are associated with peptic ulcer disorders, bleeding risk, and increased blood pressure. NSAID groups with a relatively low risk of peptic ulcer disorders included celecoxib and ibuprofen, while those with a moderate risk for peptic ulcer disorders included meloxicam, diclofenac, and ketoprofen. NSAIDs with a high risk of peptic ulcer disorders are naproxen, indomethacin, and diflunisal, and those with the highest risk of peptic ulcer side effects are piroxicam and ketorolac (Drini, 2017). Based on these data, a strategy is needed to reduce the incidence of drug side effects and the risk of gastrointestinal disorders such as dyspepsia, bleeding, and ulcers, namely, by using NSAIDs with other drugs such as misoprostol, H2-Blockers or PPIs, or by using selective NSAIDs, namely the COX-2 selective inhibitor group (Wongrakpanich et al., 2018). This is in line with a study conducted by Tai et al 2021 which shows that the strategy of adding gastroprotective agents in the form of Proton Pump Inhibitors (PPI) can reduce the risk of peptic ulcer, GI tract, and gastric bleeding in risk groups including age over 65 years, use of non-selective NSAIDs, use of high doses of NSAIDs, long-term use of NSAIDs, and use of NSAIDs along with other drugs such as anticoagulants, corticoteroids, antiplatelets, and SSRIs (Tai & McAlindon, 2021).

These strategies are very useful for preventing the risk of side effects of NSAID on the digestive tract, especially in geriatric patients (elderly). The risk factors that can exacerbate the side effects of NSAIDs are age > 65 years, history of peptic ulcer disease, heart disease, and concurrent use of other drugs such as antiplatelet agents, anticoagulants, and corticosteroids (De Groot et al., 2013). This is because the non-selective NSAID class works by inhibiting COX1, which is an enzyme that plays a role in producing pain mediators in the form of prostaglandins, which also act as natural protective agents in the stomach. Long-term inhibition of gastric acid secretion is necessary to prevent drug side effects in the form of gastroduodenal ulcers during the use of NSAID class drugs (Wehling, 2014). In the event of patients with a high risk of adverse drug effects on the gastrointestinal tract, it is recommended to combine it with other drugs such as misoprostol or high doses of PPIs, or use selective NSAIDs. The concurrent use of NSAIDs with gastoprotective drugs has been shown to be pharmacometrically more cost-effective than NSAID monotherapy. The most recommended combination is NSAIDs with PPIs, which has been shown to be the most cost-effective compared to other gastroprotective drugs (De Groot et al., 2013).

CONCLUSION

Most cases of NSAID duplication without gastroprotective are between diclofenac and ibuprofen, which is 29 cases; based on bivariate tests, factors such as pathology and polypharmacy are factors that have an association with the incidence of NSAID duplication in outpatients.

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