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Risk Factors for the Incidence of Overdose of Etoricoxib Drug in Outpatient at Hospital in Indonesia

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ABSTRACT: Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID) commonly prescribed for the treatment of various inflammatory conditions. However, the risk of overdose associated with the use of etoricoxib in outpatient polyclinic settings remains a significant concern. This study aimed to investigate the potential risk factors contributing to the incidence of etoricoxib overdose in outpatient polyclinic patients. A retrospective observational study was conducted, analyzing data from medical records of patients who had experienced etoricoxib overdose in outpatient polyclinics. The study population included patients who had been prescribed etoricoxib and presented with signs of overdose. The analysis revealed several potential risk factors contributing to the incidence of etoricoxib overdose in outpatient polyclinic patients. Factors such as age, multiphatology and polypharmacy were found to be associated with an increased risk of overdose (P value = 0,001). Additionally, the study highlighted the importance of pharmacist intervention to reducing the risk of etoricoxib overdose in this clinical setting.

KEYWORDS: *DRP; etoricoxib; overdoses; pain; pharmacist intervention.*

1. INTRODUCTION

Etoricoxib is a class of selective non-steroidal anti-inflammatory drugs (NSAIDs) approved by the Medicines Agency (EMEA) for the acute and chronic treatment of signs and symptoms of OA and RA, treatment of ankylosing spondy-litis (AS), treatment of acute gouty arthritis, relief of acute and chronic pain, and treatment of primary dysmenorrhea (Ducan et al, 2003). Etoricoxib is a novel bipyridine COX-2 selective inhibitor Unlike celecoxib, valdecoxib and parecoxib, etoricoxib is a methyl sulfone and does not contain a sulfonamide group which is associated with an increased risk of hypersensitivity reactions[1]. The maximum dose of etoricoxib for Osteoarthritis disease is 60 mg - 90 mg per day, in rheumatoid arthritis disorders the recommended dose is 90 mg per day and and in acute gouty arthritis disorders the recommended dose is 120 mg per day [2]. The basis for the use of etoricoxib doses is to start with a low dose of etoricoxib (60 mg once a day) where the dose shows similar efficacy to diclofenac sodium 150 daily, etoricoxib and diclofenac in general have a good safety profile and can be tolerated well for a 6-week treatment period. In general, etoricoxib and diclofenac sodium increase the risk of side effects if used at doses exceeding the therapeutic dose, these side effects can be GI disorders with a prevalence of 12.9%, peripheral edema, hypertension, angina pectoris and congestive heart failure (CHF) with a prevalence of 3.5% [3]. This problem of over-dosing and adverse events is one form of Drug Related Problems (DRPs).

NSAIDs are commonly ingested in overdose in many areas of the world. The 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS) showed that analgesics were the most common category of drug in acute overdose in adult patients (10%) and the second most

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common in pediatric patients (9%). Acetaminophen alone or in combination products was the most common analgesic in acute overdose (42%), with NSAIDs contributing to 33% of reported analgesic acute ingestions. Ibuprofen is the most common NSAID taken in overdose (81%), followed by naproxen (11%). This data has not changed significantly in the last decade [4].

The situation is similar in the United Kingdom acetaminophen is the most common agent involved in poisoning enquiries to both the National Poisons Information Service telephone service (10.2% telephone calls) and accesses to the online TOXBASE database (6.3% accesses). The second most common agent is the NSAID ibuprofen (4.7% telephone enquiries and 3.7% TOXBASE accesses) [5]. Meanwhile, in Indonesia, there is no data related to the overdose of NSAID drugs, especially selective NSAIDs in the form of etoricoxib in hospital settings. One of the hospitals in Banyuasin Regency is one of the main referrals for diseases such as gout, osteoarthritis, rheumatoid arthritis, low back pain that are not treated in primary health facilities where the disease uses therapeutic management in the form of selective NSAIDs such as etoricoxib, and based on the study of drug use in the hospital, etoricoxib is the most widely used NSAIDs compared to other NSAIDs, which is 48.5%.

Research on the problem of DRPs related to the overdose of etoricoxib is still not widely done, especially for outpatients. This study identifies the types of DRPs in the form of excessive doses in the prescription of etoricoxib, on an outpatient basis in all polyclinics in one of the hospitals in Banyuasin Regency in the January 2022 Period. The development of this study is expected to provide information on the description of the incidence of DRPs in the form of over-dosage in drug prescribing on an outpatient basis in all polyclinics in one of the hospitals in Banyuasin Regency and can be used as reference data for the development of clinical information systems. In addition, it is hoped that this research can be a reference for pharmacists to identify, prevent and limit DRPs in patients.

2. METHODS

This study was an analytic study using a cross-sectional research design to determine the influence of risk factors on the incidence of overdoses etoricoxib therapy in polyclinic outpatients at one of the hospitals in Banyuasin Regency in January 2022 This study was carried out because there are still cases of Drug Related Problems related to overdoses of etoricoxib at outpatient pharmacy satellite in the January 2022 period, so studies related to the incidence factors of etoricoxib overdose are needed. The study subjects were all outpatients who met the inclusion and exclusion criteria. The data used were sourced from electronic medical records and electronic prescriptions of patients, data collection was carried out in the pharmacy hospital department.

The total population of patients with etoricoxib prescriptions in the period January 2022 was 180 patients. The sampling method used is simple random sampling Sample calculation using the slovin formula :

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

$$n = \frac{180}{1 + (180.\,0{,}05^2)}$$

$$n = \frac{180}{1 + 0{,}45}$$

$$n = 124{,}1 \sim 124$$

Description:
n = Number of population
N = Z score at 95% confidence = 1.96

E = margin of error

So that the minimum sample size in this study was 180 prescription with dual therapy NSAID sheets.
The inclusion inclusion criteria are :

1. Patients with age ≥ 18 years
2. Outpatient polyclinic with prescriptions overdoses etoricoxib therapy
3. Doses etoricoxib therapy > 120 mg/day

The exclusion criteria are incomplete electronic medical record data.
The variables in the study are independent variables consisting of risk factors for age, gender, type of drug, comorbidities. The dependent variable, which consists of the incidence of overdoses etoricoxib therapy.

3. RESULTS AND DISCUSSION

The first characteristic of the test subjects was age, the minimum and maximum ages of the patients were 20 and 74 years old. The etoricoxib overdoses and etoricoxib non-overdoses groups had similar characteristics, with most patients falling into the elderly category. Patients with age > 60 years in the etoricoxib overdose group were 86 patients, and the group that did not overdose etoricoxib were 2 patients, with the total number of patients in the elderly group being 88 patients, while at the age of ≤ 60 years in the etoricoxib overdose group were 6 patients, and the group that did not overdose etoricoxib were 30 patients, with the total number of patients in the non-elderly group being 36 patients.

Gender was the second patient characteristic in this study. Patients with etoricoxib overdoses in this study were mostly female with a total of 52 patients, while male patients were 40 patients, while patients who did not overdose on etoricoxib in this study were mostly female with 19 patients, while male patients were 13 patients (table I). This study also analyzed the number of types of diagnoses written in each patient (table I). A total of 4 patients had a single diagnosis without comorbidities while 120 patients had more than 1 type of diagnosis. The diagnosis received by the patient was the diagnosis written 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 due to chronic diseases suffered by patients. The data related to polypharmacy of patients with overdoses were 90 patients and non-polypharmacy etoricoxib overdose patients were 2 patients, while data related to polypharmacy in patients not overdosed etoricoxib were 32 patients, and in cases of non-polypharmacy etoricoxib overdose were 0 patient.

Tabel 1. Characteristics of the Incidence of Overdose of Etoricoxib Drugs in Polyclinic Outpatients at One of the Hospitals in Indonesia.

Characteristics	Etoricoxib Overdose	Etoricoxib Not Overdosed
Age		
Erderly	86 (69, 4%)	2 (1,6 %)
Non Elderly	6 (4,8%)	30 (24,2%)
Female		
Gender		
Male	40 (32,3%)	13 (10,5%)
Female	52 (41,9%)	19 (15,3%)
Pathological Conditions		
Multipathology	89 (71,8%)	31 (25%)
Monopathology	3 (2,4%)	1 (0,8%)
Number of medicine types		
Polypharmacy	90 (72,6%)	0 (0%)
Non Polypharmacy	2 (1,6%)	32 (25,8%)

Table 2. Risk Factors for the Incidence of an Overdose of Etoricoxib Drugs in Polyclinic Outpatients at One of the Hospitals in Indonesia.

Risk Factors	Etoricoxib Overdose	Etoricoxib No Overdose	P- Value
Age			
Erderly	86 (69, 4%)	2 (1,6 %)	0,001
Non Elderly	6 (4,8%)	30 (24,2%)	
Gender			
Male	40 (32,3%)	13 (10,5%)	0,779
Female	52 (41,9%)	19 (15,3%)	
Pathological Conditions			
Multipathology	89 (71,8%)	31 (25%)	0,001
Monopathology	3 (2,4%)	1 (0,8%)	
Number of medicine types			
Polypharmacy	90 (72,6%)	0 (0%)	0,001
Non Polypharmacy	2 (1,6%)	32 (25,8%)	

P< 0,05, Using Pearson Chi-Square Tests

The results of the bivariate analysis showed a relationship between age, pathological conditions and polypharmacy on the incidence of excessive doses of etoricoxib with the same p value of 0.001, while gender had no relationship with the incidence of excessive doses of etoricoxib with a p value of 0.779 (Table 2). These results are in line with research conducted by Al Musawe et al 2020 which states 72.09% of the study group used polypharmacy with a poor socio-demographic profile where Polypharmacy has negative consequences if it is related to the quality of life of elderly patients [6], overdoses of etoricoxib can increase the risk of etoricoxib side effects including side effects in the form of myocardial infarction events, gastrointestinal disorders and renal disorders [7]. This overdose can also be caused by the high scale of pain felt by the patient so that it requires a maximum dose in the management of its therapy.

The therapeutic, and many of the toxic, effects of the NSAIDs result from reversible inhibition of the enzymes in the cyclooxygenase (COX) group. This results in a decrease in the synthesis of prostaglandins and thromboxane A2, from the precursor arachidonic acid, Prostaglandins have a wide variety of effects within the body. They act on the thermoregulatory center within the hypothalamus to produce fever and are involved in the regulation of inflammatory mediators and the sensitization of pain fibers [8]. Therefore, NSAID inhibition of these effects is responsible for the therapeutic effects of NSAIDs as antipyretic, anti-inflammatory and analgesic agents. However, prostaglandins also play an integral role in maintaining gastrointestinal mucosal integrity and renal blood flow and are also important in mediating platelet aggregation.4 These effects are responsible for many of the adverse effects seen with the therapeutic use of NSAIDs – in particular dyspepsia, gastric/duodenal ulceration and renal impairment. The gastrointestinal adverse effects of NSAIDs arise because they inhibit formation of prostaglandins that are cytoprotective within the stomach [9].

The majority of the NSAIDs act nonspecifically on cyclooxygenase, in the early 1990s, two isoenzymes of cyclooxygenase (COX-1 and COX-2) were identified 5 COX-1 is present in most tissues throughout the body, whilst COX-2 is induced by inflammatory mediators and is therefore predominantly present at sites of inflammation. In light of this, more recently developed NSAIDs have been produced to act more specifically on the COX-2 isoenzyme with the intention of maintaining the beneficial clinical effects, whilst reducing associated gastrointestinal and renal side-effects relating to COX-1 inhibition. However, recently a number of studies have shown that therapeutic use of the COX-2 selective NSAIDs like etoricoxib is associated with an increased risk of cardiovascular disease and a number of these agents have been withdrawn [10] (Hillis, 2002), [11]. However, the pattern of toxicity associated with COX-2 specific overdose appears to be similar to that

seen with the standard non-COX specific NSAIDs [12]. The potential mechanisms by which etoricoxib may increase the risk of cardiovascular events are multifaceted. Selective inhibition of COX-2 leads to an imbalance between the production of thromboxane A2 (a potent vasoconstrictor and platelet aggregation inducer) and prostacyclin (PGI2), which play critical roles in maintaining vascular homeostasis. Thromboxane A2 is a potent vasoconstrictor and platelet aggregator, while prostacyclin is a vasodilator and inhibitor of platelet aggregation. This imbalance can promote a prothrombotic state, increasing the risk of myocardial infarction and stroke [12].

Additionally, COX-2 inhibition may also impair endothelial function, leading to increased vascular resistance and blood pressure. This is particularly problematic in patients with pre-existing cardiovascular disease, where endothelial dysfunction is already a key pathogenic factor [12]. Furthermore, etoricoxib has been associated with fluid retention and edema, which can lead to increased blood pressure and exacerbate pre-existing cardiovascular conditions. The combination of these factors contributes to the overall increased risk of cardiovascular events associated with etoricoxib use [13]. While the precise mechanisms are not fully elucidated, the available evidence suggests that the cardiovascular risks associated with etoricoxib may be dose-dependent, with higher doses conferring greater risk [14]. Careful patient selection, close monitoring, and consideration of cardiovascular risk factors are essential when prescribing etoricoxib. Attributed to its effects on the balance of vasoactive substances, impaired endothelial function, and potential for fluid retention and edema[15]. It is important for healthcare providers to carefully consider the potential cardiovascular risks of etoricoxib when prescribing this medication, especially for patients with underlying cardiovascular disease or risk factors. Close monitoring for signs of cardiovascular events, such as chest pain, shortness of breath, or sudden changes in blood pressure, is crucial for patients taking etoricoxib [16]. In addition to considering the cardiovascular risks, healthcare providers should also assess the overall benefits and risks of etoricoxib for each individual patient, taking into account their specific medical history, concomitant medications, and treatment goals. This personalized approach can help optimize the use of etoricoxib while minimizing the potential for cardiovascular complications [13]. It is important for healthcare providers to carefully consider the potential cardiovascular risks when prescribing etoricoxib, especially in patients with known cardiovascular disease or risk factors. Close monitoring of blood pressure and signs of fluid retention is essential in patients taking etoricoxib. Additionally discussing alternative treatment options with lower cardiovascular risk may be warranted in certain patient populations [16].

Seeing the results of this study, pharmacist intervention is needed in reducing drug related problems in the form of pharmacist led intervention either in the form of a team or independently, several studies show the relationship and impact of pharmacist intervention on reducing drug related problems in several populations and research settings. The geriatric patients are at high risk of Drug Related Problems (DRPs) due to multi-morbidity associated polypharmacy, age related physiologic changes, pharmacokinetic and pharmacodynamics alterations. These patients often excluded from premarketing trials that can further increase the occurrence of DRPs. Drug related problems were substantially high among geriatric inpatients. Patients with polypharmacy and co-morbidities had a much higher chance of developing DRPs. Hence, special attention is needed to prevent the occurrence of DRPs in these patients. Moreover, clinical pharmacists' intervention was found to reduce DRPs in geriatric inpatients. The prescriber acceptance rate of clinical pharmacists' intervention was also substantially high [17]. Base research by Albayrak et al, 2022 the importance of the clinical pharmacist in the determination and analysis of DRPs was emphasized. Clinical pharmacy services should be implemented widely to increase patient safety [18]. Clinical pharmacists have a crucial role in minimizing drug related problems. Particularly, there should be a greater emphasis on patient counseling and patient follow-up [19], and the from study, shows that especially designed services such as pharmacotherapy clinics run by clinical pharmacists are necessary to detect and resolve DRPs in an effective

way. The high compliance rate of the patients indicates patients' confidence in the clinical pharmacist services provided in the pharmacotherapy clinic. The low acceptance rate of the physicians highlights the need to improve interprofessional collaboration between clinical pharmacists and physicians in an outpatient setting [20]. Pharmacists had a valuable role to perform MTM services for ambulatory elderly patients, not only in identifying and solving the DRPs, but also in improving clinical outcomes and cost-saving effect [21].

The advantage of this study is that it can see the relationship between polypharmacy, multipathology and age which has a significance to the incidence of etoricoxib overdose, this study also describes the number of incidents of etoricoxib overdose in one of the hospitals in Indonesia and describes the toxicological risk of etoricoxib overdose. The limitation of this study is a short period of retrospective data collection, the number of research samples is still small, and there is still a need for multivariate analysis of the most significant factors for the incidence of etoricoxib overdose.

4. CONCLUSION

Age, multipathology and polypharmacy have a significant relationship with the incidence of etoricoxib overdose (p value = 0.001), the incidence of etoricoxib overdose can increase side effects in the form of gastrointestinal disorders, renal failure and cardiovascular risk, pharmacist intervention is needed to be able to reduce the incidence of drug-related problems related to etoricoxib overdose in hospital settings.

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REFERENCES

[1]. Takemoto, J.K., et al., *Clinical pharmacokinetic and pharmacodynamic profile of etoricoxib.* Clinical pharmacokinetics, 2008. **47**: p. 703-720.
[2] Balazcs, E., et al., *A randomized, clinical trial to assess the relative efficacy and tolerability of two doses of etoricoxib versus naproxen in patients with ankylosing spondylitis.* BMC Musculoskeletal Disorders, 2016. **17**: p. 1-12.
[3] Tang, H.-y., et al., *Efficacy of etoricoxib for ankylosing spondylitis: A protocol for systematic review of randomized controlled trial.* Medicine, 2019. **98**(15): p. e15155.
[4] Service, N.P.I.S.a.F.Y.R.N.P.I., *National Poisons Information Service and Five Year Review National Poisons Information Service*. 2009.
[5] Bronstein, A.C., et al., *2009 annual report of the American Association of Poison Control Centers' national poison data system (NPDS): 27th annual report.* Clinical Toxicology, 2010. **48**(10): p. 979-1178.
[6] AL-Musawe, L., et al., *Polypharmacy, potentially serious clinically relevant drug-drug interactions, and inappropriate medicines in elderly people with type 2 diabetes and their impact on quality of life.* Pharmacology research & perspectives, 2020. **8**(4): p. e00621.
[7] Franco-de la Torre, L., et al., *Analgesic efficacy of etoricoxib following third molar surgery: A meta-analysis.* Behavioural Neurology, 2021. **2021**(1): p. 9536054.
[8] Rosano, T.G., *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning, Matthew J. Ellenhorn, Seth Schonwald, Gary Ordog, and Jonathan Wasserberger. Baltimore, MD: Williams and Wilkins, 1997, 2047 pp., $199, ISBN 0–683-30031–8*. 1998, Oxford University Press.
[9] Heim, H.-K. and K. Broich, *Selective COX-2 inhibitors and risk of thromboembolic events–regulatory aspects.* Thrombosis and haemostasis, 2006. **96**(10): p. 423-432.
[10] Hillis, W.S., *Areas of emerging interest in analgesia: cardiovascular complications.* American journal of therapeutics, 2002. **9**(3): p. 259-269.
[11] Baron, J.A., et al., *Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial.* The Lancet, 2008. **372**(9651): p. 1756-1764.

[12] Kirkby, N.S., et al., *Cyclooxygenase-2 selectively controls renal blood flow through a novel PPARβ/δ-dependent vasodilator pathway.* Hypertension, 2018. **71**(2): p. 297-305.
[13] Recinella, G., et al., *Probable Etoricoxib-Induced severe thrombocytopenia: a case report.* Medical Principles and Practice, 2019. **28**(4): p. 387-389.
[14] Rabie, A.S.I., et al. *Clinical consequences for individuals treated with tocilizumab for serious COVID-19 Infection*. in *Healthcare*. 2023. MDPI.
[15] Walker, C., *Are all oral COX-2 selective inhibitors the same? A consideration of celecoxib, etoricoxib, and diclofenac.* International journal of rheumatology, 2018. **2018**(1): p. 1302835.
[16] Kwiatkowska, B., et al., *Status of etoricoxib in the treatment of rheumatic diseases. Expert panel opinion.* Reumatologia/Rheumatology, 2017. **55**(6): p. 290-297.
[17] Hailu, B.Y., et al., *Drug related problems in admitted geriatric patients: the impact of clinical pharmacist interventions.* BMC geriatrics, 2020. **20**: p. 1-8.
[18] Albayrak, A., et al., *Clinical pharmacist assessment of drug-related problems among intensive care unit patients in a Turkish university hospital.* BMC Health Services Research, 2022. **22**(1): p. 79.
[19] Osoro, I., et al., *Pharmacist interventions in minimizing drug related problems in diabetes with co-existing hypertension: a five-year overview and ground report from India.* International Journal of Public Health, 2023. **68**: p. 1605808.
[20] Shahrami, B., et al., *Identification of drug-related problems followed by clinical pharmacist interventions in an outpatient pharmacotherapy clinic.* Journal of Clinical Pharmacy and Therapeutics, 2022. **47**(7): p. 964-972.
[21] Wang, X., et al., *Impact of pharmacist-led medication therapy management in ambulatory elderly patients with chronic diseases.* British journal of clinical pharmacology, 2021. **87**(7): p. 2937-2944.