International Medical Case Reports Journal

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CASE SERIES

Clinical Presentations and Characteristics of NSAIDs Hypersensitivity in a Tertiary Care Hospital in Indonesia: A Case Series

Adi Nurmesa[1,2], Neily Zakiyah[1,3], Widya Norma Insani[1,3]

[1]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, 40132, Indonesia; [2]Department of Pharmacy, Dr Rivai Abdullah Regional General Hospital, Banyuasin, 30961, Indonesia; [3]Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, 40132, Indonesia

Correspondence: Neily Zakiyah, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, 40132, Indonesia, Email neily.zakiyah@unpad.ac.id

Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely administered in all age groups due to their effectiveness in reducing fever, relieving pain, and reducing inflammation. However, they have also been identified as the second most common cause of drug-induced hypersensitivity reactions, after beta-lactam antibiotics. Adverse reactions to NSAIDs can range from expected pharmacological side effects such as gastritis to severe allergies, including anaphylaxis. It is important to distinguish true hypersensitivity reactions from other side effects to ensure proper management and patient safety. Four patients aged 35–60 years were treated with NSAIDs for pain management and subsequently developed hypersensitivity reactions to NSAIDs such as ketorolac, ketoprofen, and diclofenac sodium in the type of allergic reactions such as NSAIDs-induced urticaria/angioedema (NIUA). This case series provides valuable insights into the clinical presentations and potential mechanisms of NSAID hypersensitivity in the documented cases in one of the hospitals in Indonesia. It highlights important areas for future investigation, including the need for larger, controlled studies to better understand incidence, risk factors, and generalizability to broader populations.

Keywords: hypersensitivity, NSAID, pain, analgesic, allergic reaction

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used in a variety of therapeutic settings. These drugs serve a variety of purposes, including pain relief, fever reduction, and treatment of inflammatory conditions (eg arthritis). However, recent studies have highlighted NSAIDs as a major cause of hypersensitivity reactions.[1] The occurrence of these reactions in the general population ranges between 0.6% and 2.5%, with higher rates among women, individuals with chronic urticaria, and those with asthma. The prevalence of acetylsalicylic acid (ASA) hypersensitivity is reported to range from 0.5% to 1.9% of the general population and comprises 25% among patients with asthma and nasal polyposis, and 27%-35% among patients with chronic urticaria.[2] In the United States, NSAIDs hypersensitivity accounts for 18.3% of all adverse drug reactions (ADRs).[2] Similarly, a study from Portugal found that 8% of adults and 6% of children were allergic to at least one drug, with NSAIDs as the second most common trigger of hypersensitivity. Further supporting these findings, research from North India identified NSAIDs as a leading cause of skin-related hypersensitivity reactions, along with quinolone antibiotics, amoxicillin, and corticosteroids.[3,4] Studies conducted in hospitals in East Java also reported that NSAID hypersensitivity constituted 14.3% of drug hypersensitivity cases.[5] In Indonesia, a retrospective observational study conducted in Karawang Regency found that the prevalence of potentially inappropriate drug use, including NSAIDs hypersensitivity, was high among elderly patients. Similarly, a study conducted in a regional hospital in West Nusa Tenggara province examining drug-related problems among patients with gastric disorders indicated the occurrence of ADRs, with some cases associated with NSAIDs hypersensitivity.[6] Unwanted drug reactions from NSAIDs are called NSAID ADRs which can include gastrointestinal disorders, bleeding, nephrotoxic and hypersensitivity

Received: 2 September 2024
Accepted: 15 January 2025
Published: 25 January 2025

reactions. Type A adverse drug reactions are dose-dependent, predictable, and pharmacologically mediated (>80%) ranging from mild to severe, and type B drug hypersensitivity reactions (DHR), which are not dose-dependent, unpredictable, and often occur in predisposed patients.[7] Hypersensitivity reactions can differ based on symptoms, time of onset, existing chronic conditions, and pathophysiologic mechanisms or biochemical pathways.[8] Common classification systems for NSAIDs intolerance include NSAIDs-exacerbated respiratory disease (NERD), two allergic types (single NSAID-induced delayed reaction [SNIDR] and single NSAID-induced urticaria/angioedema or anaphylaxis [SNIUAA],[9,10] and two skin types (NSAIDs-induced urticaria/angioedema [NIUA/NECD]).[9,10] The authors reported four cases of NSAIDs hypersensitivity in a hospital inpatient setting and conducted a brief review of the literature on this topic. This study aims to describe the clinical presentations and characteristics of NSAIDs hypersensitivity among patients treated in tertiary healthcare facilities in Indonesia who experienced hypersensitivity reactions to NSAIDs.

Case Presentation

Data collection on the clinical presentations of NSAIDs hypersensitivity cases was carried out retrospectively on medical record data of inpatients at Dr. Rivai Abdullah Regional General Hospital, Banyuasin, Indonesia, with a period of two years from January 2022 - January 2024. There were four cases of NSAIDs hypersensitivity described in this case presentation. The sociodemographic characteristics of hospitalized patients who experienced NSAIDs hypersensitivity events are described in Table 1.

Table 1 Sociodemographic Characteristics of Patients With NSAIDs Hypersensitivity

Characteristics	Number (%)
Age	
18–35	0 (0%)
35–60	4 (100%)
>60	0 (0%)
BMI (kg/m2)	
< 25	0 (0%)
> 25	4 (100%)
Gender	
Male	2 (50%)
Female	2 (50%)
Comorbidities	
With comorbidities	1 (25%)
No Comorbidities	3 (75%)
NSAIDs Causing Allergies	
Diclofenac Potassium	1 (25%)
Ketorolac	2 (75%)
Ketoprofen	1 (25%)

Case 1

A 44-year-old male patient, with a body mass index (BMI) of 30.08 kg/m^2 came to the Emergency Department with complaints of low back pain after falling from a ladder while installing ceiling cables in his house. The male patient had vital signs: blood pressure 131/84 mmHg, pulse frequency 87 beats/minute, respiratory frequency 20 beats/minute, and body temperature 36 C. The patient was brought to the hospital inpatient room starting on January 24, 2022, with a history of laboratory examination results as follows: Hb 13.2 gr/dl, hematocrit 37 vol%, leukocytes 9300 mm, platelets 291,000 mm, erythrocytes 4.5 million/mm, basophils 1%, eosinophils 2%, neutrophils 55%, lymphocytes 33%, monocytes 9%, blood sugar 91 mg/dl, creatinine 0.4 mg/dl, ureum 30 mg/dl, sodium 140 mmol/l, and potassium 4.4 mmol/l. When the male patient was hospitalized, he was treated with ketorolac 30 mg twice daily injection, diclofenac potassium 50 mg twice daily, omeprazole 40 mg/mL once daily injection, calcitriol 0.5 mg once daily, pregabalin 75 mg twice daily, and mecobalamin three times daily. On January 24, 2022, when the patient was admitted to the hospital, the male patient had complaints of angioedema under the right and left eyes after 30 minutes of using potassium diclofenac 50 mg. After allergic symptoms, the drug potassium diclofenac 50 mg was stopped. The male patient then received antiallergic therapy in the form of diphenhydramine injection and dexamethasone 5 mg/mL twice a day. To reduce pain symptoms in male patients, diclofenac potassium therapy was replaced with another drug, etoricoxib 90 mg. The male patient was then monitored for signs and symptoms of allergy after discontinuation of diclofenac potassium, administration of antiallergic therapy, and replacement of analgesic therapy. The monitoring results showed improvement in the symptoms of diclofenac potassium hypersensitivity. To assess the causality of this case, the Naranjo algorithm was used, resulting in a score of 7 (probable).

Case 2

A pregnant female patient with a BMI of 27.39 kg/m^2 presented seeking maternal care for her first child. The female patient presented with vital signs, including body temperature of 36° C, blood pressure of 128/83 mmHg, pulse frequency of 93 beats/min, respiratory frequency of 20 beats/min, and oxygen saturation of 100%. The female patient then underwent relevant laboratory tests; the results were as follows: hemoglobin 11.4 g/L, hematocrit 34 vol%, leukocytes 8100 mm, platelets 339. 000 mm, erythrocytes 4.1 million/mm, basophils 0%, eosinophils 2%, neutrophils 68%, lymphocytes 20%, monocytes 10%, total blood sugar 76 mg/dl, creatinine 04 mg/dl, ureum 11 mg/dl, bleeding time 2 min, and clotting time 8 minutes, Alanine Aminotransferase (ALT) 16 U/L, Aspartate Aminotransferase (AST) 10 U/L, sodium 144 mmol/l, potassium 4.3 mmol/l, chloride 109 mmol/l.

On April 25, 2022, the female patient underwent cesarean section after receiving oxytocin injection therapy. The day after, on April 26, 2022, the patient was given prophylactic antibiotics, cefazolin therapy, at a single dose of 1 gram, along with dexamethasone twice daily. After the cesarean section, the patient received postoperative therapy that included ceftriaxone (1 gram) twice daily, ketorolac injection (30 mg) three times daily, and tranexamic acid injection (500 mg) twice daily. About 30 minutes after receiving ketorolac, the patient reported experiencing allergic symptoms, including a reddish rash and bumps on the neck, arms and legs. In addition, the patient complained of angioedema in both eyes and swelling of the forehead. After experiencing allergic symptoms, ketorolac was discontinued. The patient was then given antiallergic therapy, including injections of diphenhydramine and dexamethasone 5 mg/mL twice a day. To manage pain symptoms, ketorolac therapy was replaced with etoricoxib 90 mg tablet. The female patient was closely monitored for signs and symptoms of allergy after discontinuation of ketorolac, administration of antiallergic therapy, and transition to the new analgesic therapy. Monitoring results showed improvement in hypersensitivity symptoms previously caused by 30 mg ketorolac injection. In addition, the monitoring results showed an improvement in the symptoms of hypersensitivity to ketorolac injection. To assess the causal relationship of this case, Naranjo's algorithm was used and resulted in a score of 7 (probable).

Case 3

A 45-year-old man with a BMI of 32.32 kg/m² was brought to the hospital after experiencing chest pain in the morning. The pain was localized, and the patient did not report any additional symptoms such as cough, runny nose, nausea, or vomiting. She had a history of hypertension and was prescribed captopril 12.5 mg twice daily and spironolactone

12.5 mg once daily. Her vital signs were blood pressure 125/79 mmHg, body temperature 36°C, heart rate 86 beats/min, respiratory rate 20 beats/min, and oxygen saturation 96%.

During hospitalization, the patient received the following medications: ketoprofen 100 mg twice daily, clopidogrel 75 mg once daily, diazepam 2 mg once daily, captopril 12.5 mg three times daily, ranitidine injections twice daily, and spironolactone 25 mg once daily. However, less than 30 minutes after receiving ketoprofen 100 mg on February 7, 2022, the patient developed angioedema under both eyes. After the allergic symptoms, ketoprofen was immediately stopped, and the patient was given anti-allergic therapy in the form of diphenhydramine injection and dexamethasone 5 mg/mL twice a day. To manage pain symptoms, ketoprofen 100 mg was replaced with methylprednisolone 4 mg. The patient was carefully monitored for signs of allergic reaction after discontinuation of ketoprofen 100 mg tablets and initiation of antiallergic therapy. The monitoring results showed improved symptoms of hypersensitivity to ketoprofen 100 mg tablets. The probable cause in this case was assessed using the Naranjo algorithm, which resulted in a score of 7 (probable).

Case 4

A 45-year-old woman with a BMI of 22.89 kg/m2 came to the hospital with a complaint of a lump in her right breast. Her vital signs were recorded as follows: blood pressure 94/54 mmHg, body temperature 36.9°C, heart rate 60 BPM, and respiratory rate 20 beats/min. The patient underwent laboratory examination consisting of large tissue anatomical pathology and then underwent surgical removal of the lump in her right breast. The patient was prescribed ceftriaxone 1 gram twice daily and ketorolac injection 30 mg once daily for therapy. On August 1, 2023, the patient experienced swelling of her fingers and hands after receiving therapy. The next day, on August 2, 2023, the swelling increased and affected her lips and nose due to hypersensitivity to ketorolac 30 mg. The patient was then given antiallergic therapy in the form of diphenhydramine injection and dexamethasone 5 mg/mL twice a day. To relieve pain symptoms, the 30 mg ketorolac injection was replaced with 1000 mg paracetamol infusion. The patient's allergic signs and symptoms were monitored after discontinuation of ketorolac injection, administration of antiallergic therapy, and switching to a different analgesic therapy. Monitoring results showed improvement in hypersensitivity symptoms to ketorolac injection 30 mg. In addition, monitoring showed improvement in symptoms related to potassium diclofenac hypersensitivity. The Naranjo algorithm was used to assess the causality of this case, which resulted in a score of 7 (probable). The results of the four cases in this case series are presented below and summarized in Table 2.

Table 2 Summary of NSAID Hypersensitivity Case Series

	Case 1	Case 2	Case 3	Case 4
Assessment during Registration	Lower back pain	Maternity care until cesarean section	Angina pectoris with essential (primary) hypertension, and Obesity	Benign tumors of the breast
Hypersensitivity Reaction	Angioedema under the right and left eyes	A reddish rash with papules on the neck, arms and legs and angioedema affecting both eyes and forehead.	Angioedema under the right and left eyes.	The patient showed symptoms of edema of the fingers and hands, as well as swelling of the lips and nose.
NSAIDs	Diclofenac potassium	Ketorolac injection	Ketoprofen injection	Ketorolac injection
Hypersensitivity Therapy	Dexamethasone and Diphenhydramine.	Dexamethasone	Dexamethasone and Diphenhydramine.	Dexamethasone and Diphenhydramine.
Therapeutic Replacement Analgesics	Etoricoxib 90 mg tablet	Etoricoxib 90 mg tablet	Paracetamol infusion	Paracetamol Infusion

(*Continued*)

Table 2 (Continued).

	Case 1	Case 2	Case 3	Case 4
History of Urticaria or Angioedema	No history	No history	No history	No history
Onset of Hypersensitivity	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes	Less than 30 minutes
DPT (Drug Provocation Test)	No	No	No	No
Types of Hypersensitivity	Non-steroidal inflammatory drug-induced urticaria/ angioedema (NIUA)	Non-steroidal inflammatory drug-induced urticaria/angioedema (NIUA)	Non-steroidal inflammatory drug-induced urticaria/ angioedema (NIUA)	Non-steroidal inflammatory drug-induced urticaria/angioedema (NIUA)
Naranjo Score	7 (probable)	7 (probable)	7 (probable)	7 (probable)

Discussion

From the four cases in this study, we found that patients experiencing NSAIDs hypersensitivity ranged in age from 35 to 60 years, with an equal gender distribution (two male and two female patients). While our small sample size limits broader conclusions, other studies have reported a higher prevalence of NSAIDs hypersensitivity in women compared to men.[11] This difference may be attributed to women's higher likelihood of using medications, including NSAIDs, which increases the potential for hypersensitivity reactions.[12] Additionally, immune-mediated drug hypersensitivity reactions (DHRs) in women are influenced by hormonal and genetic sex differences, which are known to enhance immune responses. Factors such as pregnancy, autoimmune conditions (more prevalent in women), and multiple drug intolerance syndromes further amplify the risk of drug hypersensitivity.[13] This study also observed that all four patients had a BMI > 25 kg/m², categorizing them as overweight or obese. Obesity has been associated with an increased risk of drug hypersensitivity due to its role in systemic inflammation, altered immune responses, and predictors such as body fat percentage (BFP). Previous research has demonstrated that BFP is a significant predictor of drug hypersensitivity (OR, 1.12; 95% CI, 1.02–1.24; p=0.02).[14] These findings suggest that obesity may play a role in NSAID hypersensitivity, potentially through inflammatory mediators and cytokine pathways. Although our study did not specifically assess genetic predispositions, pharmacogenetic factors likely contribute to the observed hypersensitivity. Variations in genes encoding enzymes like CYP450 and UDP-glucuronosyltransferase (UGT) may affect the metabolism of NSAIDs and alter cyclooxygenase (COX) pathway function. Mutations in cytokine signaling pathways, histamine metabolism, IgE activation, and HLA (human leukocyte antigen) or MHC class II receptors may also increase susceptibility. Epigenetic changes further modulate these processes, highlighting the complex interplay of genetic predisposition and environmental factors.[15]

The type of NSAIDs hypersensitivity reaction in the four patients was NSAIDs-induced urticaria/angioedema (NIUA), with the main reactions felt by the patients being angioedema in the eyes, reddish rash with papules on the neck, arms, and legs, oedema of the fingers and hands, and swelling of the lips and nose. The diverse clinical manifestations of NSAIDs hypersensitivity can be attributed to various underlying mechanisms. One mechanism is COX-1 inhibition, which leads to activation of mast cells and eosinophils, along with the release of inflammatory mediators. This is further compounded by increased production of leukotrienes due to increased levels of 5-lipoxygenase (5-LO) and related enzymes.[16] In addition, there appears to be decreased production of PGE2, which normally helps regulate mast cell activation that can result in NSAIDs hypersensitivity reactions.[17] NIUA presents with hives and swelling caused by a cross-over non-reactive immune response (triggered by IgE or T cell pathways).[18]

Facial swelling, known as facial angioedema, is the most commonly seen symptom associated with the A444-C variant of LTC4 synthase, a protein important in leukotriene production.[19] Basically, the mechanism of NSAIDs is by blocking the production of prostaglandin E2 and shifting metabolism to the lipoxygenase pathway through cyclooxygenase (COX) inhibition. There are two forms of COX: COX-1, which is consistently present and involved in maintaining a stable internal environment, and COX-2, which is only produced when needed and is responsible for mediating inflammation. The therapeutic benefits of NSAIDs are largely derived from their ability to block COX-2, and the most common side effects are the result of COX-1 inhibition.[16]

In this study, NSAIDs drugs that can cause hypersensitivity events include diclofenac sodium, ketoprofen and ketorolac. In previous studies reported the incidence of hypersensitivity to diclofenac sodium was 19.4%.[11] Previous case studies showed that the incidence of diclofenac sodium hypersensitivity in India was NIUA.[12] While in previous case studies the clinical presentations of hypersensitivity to ketoprofen was SNIDHR (single non-steroidal anti-inflammatory drug hypersensitivity reaction) with the main reaction being photoallergic.[20] In this case series, it was found that ketorolac is the NSAIDs that causes the most NSAIDs hypersensitivity, this occurs because of the use of ketorolac analgesics which are widely used in hospitals in patients with moderate pain levels, such as postoperative pain. Ketorolac injection has a pharmacokinetic profile in the form of peak serum levels within 1 to 3 minutes, causing a rapid analgesic effect. Ketorolac is metabolized in the liver and excreted through the kidneys.[21] Previous case report studies in Iran showed that ketorolac allergic reactions were in the form of anaphylactic reactions.[22] A similar case report study in Korea also showed a similar allergic reaction to ketorolac, namely anaphylactic reaction,[23] and a case study in a pediatric case also showed an allergic reaction in the form of anaphylaxis to the use of ketorolac.[24]

In this study, the causality test used the Naranjo algorithm with the results in the four case studies being "probable". The Naranjo algorithm has advantages in assessing the causality of side effects of NSAIDs including being easy to use, being able to assess the relationship between dose and drug side effects, providing quantifiable score results that represent the probability of drug-related side effects and considering the historical context of previous drug side effects. The drawbacks of the Naranjo algorithm include the limited scope of the Naranjo algorithm, as it does not consider the temporal properties of the drug and the pharmacological properties of the drug, and the lack of standardization as each person's assessment will result in a different assessment, as it depends on expertise and experience.[25]

Therefore, other more comprehensive tests are needed that can assess hypersensitivity reactions to NSAIDs, such as the DPT (Drug Provocation Test) test. The DPT test is a test that can be used to accurately identify in patients the presence of allergies to drugs. This test has advantages because the DPT test not only produces allergic symptoms but other adverse clinical manifestations, reduces repeated empirical desensitization and can prove the presence of cross-reactivation of drugs that cause hypersensitivity such as NSAIDs. DPT testing is important in the diagnosis and management of drug allergy patients.[26] As for NSAIDs hypersensitivity testing with the skin testing method, it is still not universally accepted due to variations in the results of each test, and the lack of specificity and sensitivity in skin test results in patients who are hypersensitive to NSAIDs.[27] While in vitro tests in the form of leukotriene measurements and basophil activity tests are other options for assessing NSAIDs hypersensitivity, these in vitro methods are still not reliable and recommended due to the unavailability of specific and sensitive in vitro data for NSAIDs, even in vitro tests are not better when compared to skin tests.[28]

In all four-case series, the management of NSAIDs hypersensitivity was to use corticosteroid therapy in the form of dexamethasone and antihistamine, in the form of diphenhydramine. These two drugs can effectively reduce the symptoms of hypersensitivity, leading to patient improvement. Systemic corticosteroids and systemic antihistamines can relieve symptoms, especially for itching. In severe cases, short-term systemic corticosteroid treatment may be required. In 47.1% of cases, corticosteroids and antihistamines were the most commonly administered drugs.[29] Management of hypersensitive NSAIDs discontinuation and replacement with another NSAIDs is key in the management of NSAID hypersensitivity to improve patient safety. In this case series, discontinuing NSAIDs and switching to other NSAIDs can reduce allergic reactions and improve patient safety. In this case series, the problematic NSAIDs was replaced with etoricoxib and paracetamol.

Etoricoxib, a potent and specific COX-2 inhibitor, is considered a safe option as long as the NIUA reaction is affected by COX-1 inhibition and the imbalance between leukotrienes and prostaglandins. However, it is important to exercise

caution when prescribing etoricoxib, especially for patients with a history of heart disease, due to the potential risk of cardiovascular problems.[30] The patient group experienced very little reaction from acetaminophen (paracetamol), probably because this drug minimally inhibits COX-1. Studies, such as the study by Kowalski et al suggest the use of acetaminophen for patients sensitive to NSAIDs.[31] A previous retrospective study with a sample size of 104 people with a history of NSAIDs hypersensitivity who were given OPT (*Oral Provocation* Testing) intervention showed the results that etoricoxib and paracetamol were safe treatments in cases of NSAIDs hypersensitivity with the risk of cross-hypersensitivity reactions.[32] Another study involving 74 people with a history of NSAIDs allergy showed that etoricoxib is a safe alternative to NSAIDs in patients who have a history of NSAIDs allergy with comorbidities such as atopic and chronic urticaria.[33]

Long-term management to prevent NSAIDs hypersensitivity events is to recognize the risk of NSAIDs hypersensitivity with a history of asthma, chronic rhinosinusitis, nasal polyposis, chronic urticaria, and angio-oedema.[34] The need for patient education to recognize early signs of NSAIDs hypersensitivity such as rash, hives, rash, wheezing and swelling,[35] avoid self-medication with NSAIDs without consulting a pharmacist or doctor and the need for hypersensitivity testing before prescribing NSAIDs[36] and consider recommending paracetamol as the primary therapeutic option in patients with a history of NSAIDs hypersensitivity.[31] This case series emphasizes the importance of being more attentive and aware of potential NSAIDs hypersensitivity, especially in resource-limited settings where these drugs are frequently used. Further studies such as cohort trials are needed to elucidate the mechanisms and risk factors underlying these potentially life-threatening reactions. Rapid identification and discontinuation of the offending drug is the most important therapeutic measure to manage NSAIDs hypersensitivity.

We acknowledge several limitations in this study. First, the use of a case series design inherently limits the ability to draw definitive conclusions about the incidence and risk factors for NSAIDs hypersensitivity. Case series are descriptive and exploratory in nature, aiming to identify patterns and generate hypotheses rather than establish causality or generalizable findings. Additionally, the small sample size (four cases) further restricts the assessment of incidence and limits the generalizability of the findings. This is a common challenge in studying rare conditions like NSAIDs hypersensitivity, where larger cohorts are often difficult to obtain.

Another limitation is the exclusive use of the Naranjo algorithm to analyze the causality of NSAIDs hypersensitivity. The study did not incorporate additional diagnostic testing methods, such as in vitro tests, skin tests, or DPT, which could provide a more comprehensive assessment. The DPT, for instance, is a valuable tool for evaluating causal relationships and assessing the risk of cross-reactions in NSAIDs hypersensitivity.[26] This test involves administering the suspected drug in incremental doses until an allergic reaction occurs, providing critical insights into hypersensitivity mechanisms. In this study, DPT was not conducted because it was not included in the hospital's clinical pathway protocol. Furthermore, the feasibility of performing DPT is limited due to several factors. These include the possibility of false positive and false negative results, the potential risk of resensitization, challenges in interpreting subjective symptoms, and the absence of objective and reliable biomarkers (eg, serum tryptase). Additionally, DPT requires experienced personnel and a well-equipped clinical setting, which may not always be available. Despite being the gold standard, DPT also has numerous contraindications that further limit its practical application.[26]

The reliance on the Naranjo algorithm alone also presents challenges. While useful, this tool has several limitations. It heavily depends on the temporal relationship between drug use and the onset of adverse reactions, does not account for the specific mechanisms of allergic reactions, and is less effective in assessing rare or complex adverse reactions.[25] Moreover, it does not consider potential contributing factors such as cross-reactions, genetic polymorphisms, or environmental influences, which are essential in understanding NSAIDs hypersensitivity.[37]

Future studies should address these limitations by employing larger, more diverse cohorts and incorporating additional diagnostic tools to enhance the reliability and generalizability of the findings.

Another limitation is the lack of assessment of long-term patient outcomes and recurrence risks to better understand the efficacy of management strategies for NSAIDs hypersensitivity. In this particular hospital setting, follow-up care after discharge is sometimes unavailable due to logistical constraints and the structure of the healthcare system. Resource limitations, time constraints, and the absence of a dedicated follow-up program for discharged patients often hinder long-term monitoring. In many cases, follow-up care is delegated to general practitioners or outpatient clinics, and there is

limited coordination between inpatient care providers and outpatient teams, making it challenging to systematically track long-term outcomes. Additionally, some patients may not have agreed to or been able to attend follow-up appointments after discharge, further limiting the ability to assess recurrence risks or the effectiveness of the chosen management strategies over time. These challenges highlight the practical barriers faced in implementing structured follow-up protocols in certain healthcare settings.

Conclusion

There were four cases of NSAIDs allergy in an Indonesian hospital, all classified as NSAIDs-induced urticaria/angioedema (NIUA). The main symptoms were angioedema and urticaria, with hypersensitivity reactions occurring within 30 minutes of NSAIDs administration. Therefore, caution is needed in prescribing NSAIDs, especially in high-risk populations such as patients with a history of hypersensitivity and comorbidities. The implementation of a pharmacovigilance program to monitor NSAID-related adverse reactions in Indonesian hospitals may help collect more robust data and improve patient safety.

Ethics Approval and Informed Consent

This study was approved by the research ethics committee of Padjadjaran University, with registration number 481/UN6. KEP/EC/2024. A written consent form for publication of this data has been provided by the patient.

Consent for Publication

All patients provided written informed consent for their case details to be published.

Funding

This study is supported by a grant from Universitas Padjadjaran, Indonesia.

Disclosure

The authors declare no conflicts of interest related to this research.

References

1. Demir S, Olgac M, Unal D, et al. Evaluation of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs according to the latest classification. *Allergy*. 2015;70(11):1461–1467. doi:10.1111/all.12689
2. Thong BY-H. Nonsteroidal anti-inflammatory drug hypersensitivity in the Asia-Pacific. *Asia Pacific Allerg*. 2018;8(4):e38. doi:10.5415/apallergy.2018.8.e38
3. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol*. 2005;5(4):309–316. doi:10.1097/01.all.0000173785.81024.33
4. Inbaraj S, M M, n S M, et al. Pharmacovigilance of the cutaneous drug reactions in outpatients of dermatology department at a tertiary care hospital. *J Clin Diagn Res*. 2012;6(10):1688. doi:10.7860/JCDR/2012/4809.2645
5. Hidajat D, Lindriati NLPN, Purwaningsih NWD. Reaksi Hipersensitivitas pada kulit akibat obat anti inflamasi non steroid. *Jurnal Kedokteran*. Indonesian. 2019;8(3):6.
6. Al-Worafi YM. Drug safety in Indonesia. *Elsevier BV, 279-285 Elsevier BV*. 2020;2.
7. Kathuria P, Rai M. Management of drug allergy-clinical update. *Ind J Allerg, Asthma Immunol*. 2022;36(1):4–17. doi:10.4103/ijaai.ijaai_34_22
8. Canto MG, Andreu I, Fernandez J, et al. Selective immediate hypersensitivity reactions to NSAIDs. *Curr Opin Allergy Clin Immunol*. 2009;9(4):293–297. doi:10.1097/ACI.0b013e32832db943
9. Tosepu R, Effendy DS. Description of gastritis characteristics at the batalaiworu health center, Muna Regency, Southeast Sulawesi Province, Indonesia in 2021. *KnE Life Sciences*. 2022;214–222.
10. Pérez-Alzate D, Cornejo-García JA, Pérez-Sánchez N, et al. Immediate Reactions to More Than 1 NSAID must not be considered cross-hypersensitivity unless tolerance to ASA Is Verified. *J Invest Allergol Clin Immunol*. 2017;27(1):32–39. doi:10.18176/jiaci.0080
11. Knopf H, Grams D. Medication use of adults in Germany: results of the German health interview and examination survey for adults (DEGS1). *Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz*. 2013;56(5–6):868–877. doi:10.1007/s00103-013-1667-8
12. Jeyamani VPS, Gowri R, Bhuvaneshwari G et al. Diclofenac Induced Hypersensitivity: a Case Study. *Res J Pharm Biol Chem Sci*. 2018;9(2):247–249.
13. Lee EY, et al. Drug allergy in women. *J Allerg Clin Immunol in Pract*. 2023.
14. de Castro ED, Pinhão S, Paredes S, et al. Obesity markers in patients with drug allergy and body fat as a predictor. *Ann Allergy Asthma Immunol*. 2021;127(1):100–108. doi:10.1016/j.anai.2021.03.014
15. Trinh HKT, Pham LD, Le KM, et al. Pharmacogenomics of hypersensitivity to non-steroidal anti-inflammatory drugs. *Front Genetics*. 2021;12:647257. doi:10.3389/fgene.2021.647257

16. Kaur G, Singh KP, Saji AM, Sethi A, Sharma A. Diclofenac-induced hypersensitivity reaction in a patient suffering from rheumatoid arthritis: a case report. *Pharmaspire*. 2018;10:164–166.
17. Picado C. The role of cyclooxygenase in acetylsalicylic acid sensitivity. *ALLERG CLIN IMMUNOL INTERNATIONAL*. 2006;18(4):154. doi:10.1027/0838-1925.18.4.154
18. Rebelo Gomes E, Geraldes L, Gaspar Â, et al. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs among adults: clinical features and risk factors for diagnosis confirmation. *Int Arch Allergy Immunol*. 2017;171(3–4):269–275. doi:10.1159/000452627
19. Sánchez-Borges M, Park H-S. NSAID hypersensitivity. *J Allerg Clin Immunol in Pract*. 2019;7(2):746–747. doi:10.1016/j.jaip.2018.10.037
20. Rosan T, Ljubojević Hadžavdić S. Ketoprofen-induced photoallergic reaction. *Acta Dermatovenerologica Croatica*. 2022;30(3):197–198.
21. Mallinson TE. A review of ketorolac as a prehospital analgesic. *J Paramed Pract*. 2017;9(12):522–526. doi:10.12968/jpar.2017.9.12.522
22. Yousefi H, Sahebi A, Farahani M, et al. Anaphylaxis as a rare side effect of ketorolac; a case report. *Archiv Acad Emerg Med*. 2020;8(1).
23. Chung HS, Kim ES, You YJ, et al. Anaphylactoid reaction after injection of ketorolac in a loading dose for patient-controlled analgesia-A case report. *Korean J Anesthesiol*. 2010;58(6):565–568. doi:10.4097/kjae.2010.58.6.565
24. Ratchataswan T, Mbuthia J. A CASE OF ANAPHYLAXIS TO KETOROLAC IN A PEDIATRIC PATIENT. *Ann Allergy Asthma Immunol*. 2023;131(5):S105–S106. doi:10.1016/j.anai.2023.08.312
25. Murayama H, Sakuma M, Takahashi Y, et al. Improving the assessment of adverse drug reactions using the Naranjo Algorithm in daily practice: the Japan Adverse Drug Events Study. *Pharmacol Res Perspect*. 2018;6(1):e00373. doi:10.1002/prp2.373
26. Soyer O, Sahiner UM, Sekerel BE. Pro and contra: provocation tests in drug hypersensitivity. *Int J mol Sci*. 2017;18(7):1437. doi:10.3390/ijms18071437
27. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of rheumatology/arthritis foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220–233. doi:10.1002/art.41142
28. Mayorga C, Celik G, Rouzaire P, et al. In vitro tests for drug hypersensitivity reactions: an ENDA / EAACI drug allergy interest group position paper. *Allergy*. 2016;71(8):1103–1134. doi:10.1111/all.12886
29. Jares EJ, Sánchez-Borges M, Cardona-Villa R, et al. Multinational experience with hypersensitivity drug reactions in Latin America. *Ann Allergy Asthma Immunol*. 2014;113(3):282–289. doi:10.1016/j.anai.2014.06.019
30. Martín Arias LH, Martín González A, Sanz Fadrique R, et al. Cardiovascular risk of nonsteroidal anti-inflammatory drugs and classical and selective cyclooxygenase-2 inhibitors: a meta-analysis of observational studies. *J Clin Pharmacol*. 2019;59(1):55–73. doi:10.1002/jcph.1302
31. Kowalski ML, Asero R, Bavbek S, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy*. 2013;68(10):1219–1232. doi:10.1111/all.12260
32. Angeletti F, Meier F, Zöller N, Meissner M, Kaufmann R, Valesky EM. Hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs)–a retrospective study. *J Dtsch Dermatol Ges*. 2020;18(12):1405–1414.
33. Llanora GV, Loo EX, Gerez IF, Cheng YK, Shek LP.Etoricoxib: a safe alternative for NSAID intolerance in Asian patients. *Asian Pac J Allergy Immunol*. 2013;31(4):330. doi:10.12932/AP0290.31.4.2013
34. Wöhrl S. NSAID hypersensitivity–recommendations for diagnostic work up and patient management. *Allergo J Int*. 2018;27(4):114–121. doi:10.1007/s40629-018-0064-0
35. Mirakian R, Ewan PW, Durham SR, et al. BSACI guidelines for the management of drug allergy. *Clin Exp Immunol*. 2009;39(1):43–61. doi:10.1111/j.1365-2222.2008.03155.x
36. Matte G, Shuster J, Guevremont C, et al. Standardization and updating of a drug allergy testing program: the McGill experience and impact on pharmacy activities. *Canadian J Hospital Pharm*. 2020;73(1):45. doi:10.4212/cjhp.v73i1.2957
37. Blumenthal KG, Lai KH, Huang M, et al. Adverse and hypersensitivity reactions to prescription nonsteroidal anti-inflammatory agents in a large health care system. *J Allerg Clin Immunol in Pract*. 2017;5(3):737–743.e3. doi:10.1016/j.jaip.2016.12.006