



อุบัติการณ์และลักษณะทางคลินิกของปฏิกิริยาภูมิไวเกิน ที่เกิดจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์: การศึกษาแบบภาคตัดขวางย้อนหลัง

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Incidence and Clinical Characteristics of Nonsteroidal Anti-inflammatory Drugs (NSAIDs)-Induced Hypersensitivity Reactions: A Retrospective Cross-sectional Study

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บทคัดย่อ

ภูมิหลังและวัตถุประสงค์: การใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์เพื่อบรรเทาอาการปวดเล็กน้อยโดยที่ไม่ได้รับคำแนะนำจากบุคลากรทางการแพทย์ อาจมีการใช้ในข้อบ่งใช้ที่ไม่เหมาะสม ซึ่งเพิ่มความเสี่ยงต่อการเกิดภาวะปฏิกิริยาภูมิไวเกิน อย่างไรก็ตาม ยังมีข้อมูลจำกัดเกี่ยวกับอุบัติการณ์และลักษณะทางคลินิกของการเกิดภาวะปฏิกิริยาภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ ในการปฏิบัติทางคลินิกจริง ดังนั้นการศึกษานี้มีวัตถุประสงค์ เพื่อประเมินอุบัติการณ์และลักษณะทางคลินิกของภาวะปฏิกิริยาภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ในผู้ป่วยที่เข้ารับการรักษาที่โรงพยาบาลศรีนครินทร์

วิธีการศึกษา: เป็นการศึกษาแบบภาคตัดขวางย้อนหลัง โดยใช้ข้อมูลจากเวชระเบียนอิเล็กทรอนิกส์ในช่วงระหว่างวันที่ 1 มกราคม พ.ศ. 2564 ถึงวันที่ 31 ธันวาคม พ.ศ. 2566 ผู้ป่วยที่มีการบันทึกการเกิดปฏิกิริยาภูมิไวเกินแบบเฉียบพลันภายหลังได้รับยาในกลุ่มยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ถูกคัดเลือกเข้าศึกษา การประเมินความสัมพันธ์เชิงสาเหตุของยา ไข้ นานโซ อลกอริทึม และทำการวิเคราะห์ข้อมูลทั้งเชิงพรรณนาและเชิงอนุมาน เพื่อประมาณอุบัติการณ์ของการเกิดปฏิกิริยาภูมิไวเกิน และประเมินความสัมพันธ์ระหว่างชนิดของยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์กับความรุนแรงของปฏิกิริยา

ผลการศึกษา: ในผู้ป่วยจำนวนทั้งหมด 1,349 ราย ที่พบว่ามีการแพ้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ เป็นผู้หญิง ร้อยละ 70.50 อายุเฉลี่ย 51.96 ± 16.32 ปี ยาไอบูโพรเฟน เป็นสาเหตุของการเกิดปฏิกิริยามากที่สุด 491 ราย ร้อยละ 36.40 รองลงมา ไดโคลฟีแนค 254 ราย ร้อยละ 18.83 นาพรอกเซน 119 ราย ร้อยละ 8.82 แอสไพริน 97 ราย ร้อยละ 7.19 และ ซิลิโคกซิบ

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90 ราย ร้อยละ 6.67 ปฏิกริยาส่วนใหญ่มีความรุนแรงระดับปานกลาง 1,213 ราย ร้อยละ 89.90 ขณะที่เหตุการณ์รุนแรงพบ 82 ราย ร้อยละ 6.07 เหตุการณ์ส่วนใหญ่จัดเป็นไม่รุนแรง 1,232 ราย ร้อยละ 91.33 โดยต้องเข้ารับการรักษาในโรงพยาบาล 70 ราย ร้อยละ 5.19 และพบภาวะคุกคามต่อชีวิต 2 ราย ร้อยละ 0.14 การประเมินความสัมพันธ์เชิงสาเหตุ พบว่าส่วนใหญ่จัดอยู่ในระดับน่าจะใช่ 685 ราย ร้อยละ 50.78 อาจจะใช่ 649 ราย ร้อยละ 48.11 ในขณะที่ระดับแน่นอน พบได้น้อย 14 ราย ร้อยละ 1.03 และมีเพียง 1 ราย ร้อยละ 0.07 อยู่ในระดับน่าจะสงสัย ลักษณะอาการที่พบมากที่สุดเป็นอาการทางผิวหนัง โดยเฉพาะผื่นและอาการคัน ร้อยละ 24.54 การบวมได้ขึ้นผิวหนัง ร้อยละ 24.46 ส่วนแอนาฟิแล็กซิส พบ 82 ราย ร้อยละ 6.07 ภาวะปฏิกิริยาทางผิวหนังที่รุนแรงพบได้น้อย ได้แก่ SJS ร้อยละ 0.44 DRESS ร้อยละ 0.29 และ AGEP ร้อยละ 0.29 นอกจากนี้ไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างชนิดยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์กับความรุนแรงของปฏิกิริยา ($p > 0.05$)

สรุป: ปฏิกริยาภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์ ส่วนใหญ่มีความรุนแรงระดับปานกลางและไม่จัดเป็นเหตุการณ์ร้ายแรง โดย ไบพูโพรเฟนเป็นยาที่พบเกี่ยวข้องกับการเกิดปฏิกิริยามากที่สุด รองลงมาคือ ไดโคลฟีแนค และ นาพรอกเซน ผลการศึกษานี้สะท้อนถึงความสำคัญของการเฝ้าระวังและการดำเนินการป้องกันอย่างเหมาะสม เพื่อลดความเสี่ยงของการเกิดภาวะภูมิไวเกินจากการใช้ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์

คำสำคัญ: ยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์, ปฏิกริยาภูมิไวเกิน, การเกิดภูมิไวเกินจากยาต้านการอักเสบที่ไม่ใช่สเตียรอยด์

Abstract

Background and objective: Widespread self-medication for minor pain has led to extensive use of nonsteroidal anti-inflammatory drugs (NSAIDs), sometimes for inappropriate indications, potentially increasing the risk of hypersensitivity reactions (HSRs). Real-world data on the incidence and clinical characteristics of NSAID-induced HSRs remain limited. This study aimed to estimate the incidence and characterize the clinical patterns of NSAID-induced HSRs at Srinagarind Hospital.

Methods: A retrospective cross-sectional study was conducted using electronic medical records from January 1, 2021, to December 31, 2023. Patients with documented immediate HSRs following NSAID exposure were identified. Causality was assessed using the Naranjo algorithm. Descriptive and inferential analyses were performed to estimate incidence and evaluate associations between NSAID type and reaction severity.

Results: Total of 1,349 patients with NSAID-associated HSRs were included; 70.5% were female, with a mean age of 51.96 ± 16.32 years. Ibuprofen accounted for the largest proportion of reactions (491, 36.40%), followed by diclofenac (254, 18.83%), naproxen (119, 8.82%), aspirin (97, 7.19%), and celecoxib (90, 6.67%). Most reactions were moderate (1,213, 89.90%), with severe events in 82 cases (6.07%). The majority were non-serious (1,232, 91.33%), with hospitalization in 70 cases (5.19%) and life-threatening reactions in 2 (0.14%). Causality was mainly classified as probable (685, 50.78%) or possible (649, 48.11%), while definite reactions were rare (14, 1.04%) and only one case (0.07%) was classified as doubtful. Cutaneous manifestations predominated, particularly rash and itching (24.54%) and angioedema (24.46%); anaphylaxis occurred in 82 cases (6.07%). Severe cutaneous adverse reactions were uncommon (SJS 0.44%, DRESS 0.29%, AGEP 0.29%). No significant associations were observed between NSAID type and reaction severity ($p > 0.05$).

Conclusion: NSAID-induced HSRs were predominantly moderate and non-serious. Ibuprofen was the most frequently implicated drug, followed by diclofenac and naproxen, underscoring the importance of vigilant monitoring and preventive strategies to reduce NSAID-related hypersensitivity.

Keywords: nonsteroidal anti-inflammatory drugs, hypersensitivity reactions, NSAID-induced HSRs

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed and self-administered medications worldwide because of their well-established analgesic, anti-inflammatory, and antipyretic properties. They are commonly used for both acute and chronic conditions, particularly in musculoskeletal disorders, postoperative pain, and chronic inflammatory diseases. However, patterns of NSAID utilization are influenced by cultural factors, healthcare accessibility, and regulatory policies. In Thailand, NSAIDs are not classified as over-the-counter (OTC) medications and must be dispensed under pharmacy supervision. Nevertheless, unauthorized sales in non-pharmacy retail outlets have been reported and are considered illegal.

Inappropriate NSAID use includes prescribing without clear indications, excessive dosing, prolonged use beyond guideline recommendations, concomitant use of multiple NSAIDs, and prescribing in high-risk populations without adequate monitoring or gastroprotective strategies. The magnitude of this issue is substantial. Previous studies have shown that a significant proportion of adult outpatients receive NSAIDs despite having established risk factors such as advanced age, chronic kidney disease (CKD), cardiovascular disease, hypertension, diabetes mellitus, or concomitant use of nephrotoxic or anticoagulant medications. These prescribing patterns may expose patients to preventable adverse clinical outcomes. Importantly, the consequences of inappropriate NSAID use extend far beyond hypersensitivity reactions (HSRs). Although drug HSRs remain clinically relevant, more common and clinically significant complications include acute kidney injury, progression of CKD, gastrointestinal bleeding, peptic ulcer disease, heart failure exacerbation, destabilized hypertension, and increased cardiovascular events. NSAIDs are broadly classified according to their mechanism of action into cyclooxygenase-1 (COX-1) inhibitors (e.g., diclofenac, indomethacin, piroxicam, ibuprofen, naproxen, and

mefenamic acid) and cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib and etoricoxib). Differences in COX selectivity may influence both therapeutic efficacy and adverse event profiles, including HSRs.

The prevalence of hypersensitivity to NSAIDs has been estimated to range from 1.5% to 3% in the general population, and NSAIDs account for up to 20% of all adverse drug reactions [1]. In adult patients with asthma, aspirin intolerance occurs in approximately 4.3% to 11% of cases, and in those with both asthma and nasal polyposis, the prevalence increases to 25.6–40% [1,2]. Aspirin intolerance is also more frequently observed in patients with chronic idiopathic urticaria (CIU), and NSAIDs are among the leading causes of drug-induced anaphylaxis [3]. Additional risk factors for NSAID hypersensitivity include female gender, young adulthood, atopy [4], and intermittent NSAIDs use for acute pain relief [5]. Clinical studies conducted at tertiary allergy centers in Thailand have described the clinical characteristics of patients with suspected NSAID hypersensitivity and identified common manifestations such as angioedema and cross-reactivity to multiple NSAIDs [6,7]. In addition, recent advances in pharmacogenetics have improved the understanding of drug HSRs, indicating that genetic variations influencing drug metabolism and immune pathways may contribute to interindividual differences in susceptibility to NSAID-induced HSRs. These insights may facilitate improved risk prediction and personalized therapeutic strategies [1].

Despite increasing awareness of the risks associated with NSAID use, real-world data quantifying the incidence and clinical spectrum of NSAID-induced HSRs in adult outpatient populations remain limited, particularly in tertiary care settings in Southeast Asia. Moreover, comparative data evaluating hypersensitivity patterns in relation to NSAID exposure in routine clinical practice are scarce. Therefore, this study was undertaken to address these knowledge gaps. The primary objective was to estimate the incidence rate of NSAID-induced HSRs among patients receiving NSAID therapy. The secondary objectives were to

characterize the clinical phenotypes and patterns of NSAID-induced HSRs, evaluate their severity spectrum, and delineate the extent of organ-system involvement associated with these reactions.

Methods

Study design and setting: This retrospective cross-sectional study was conducted at the Department of Pharmacy, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. Data were obtained from the hospital's electronic medical record system for the period between 1 January 2021 and 31 December 2023.

Study population: Adult patients (≥ 18 years) who received at least one NSAID during the study period at Srinagarind Hospital were screened according to predefined eligibility criteria. Patients who subsequently developed suspected HSRs were included in the analysis. HSRs were identified using diagnostic codes (ICD-10) from electronic medical records and confirmed through clinical documentation and causality assessment using the Naranjo algorithm. Patients were categorized according to NSAIDs type into COX-1 inhibitor and COX-2 inhibitor groups. Eligible patients were required to have no evidence of baseline acute kidney injury and no significant laboratory abnormalities, including creatinine clearance, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and estimated glomerular filtration rate (eGFR). Patients were excluded if key clinical data were incomplete or if the temporal relationship between NSAIDs exposure and reaction onset was unclear. Individuals with terminal illness, an expected survival of less than three months, or other conditions deemed inappropriate for inclusion by the investigators were also excluded.

Assessment of NSAID hypersensitivity: NSAID-induced HSRs were evaluated based on clinical symptoms, and causality was assessed using the Naranjo algorithm. To determine the likelihood that the suspected NSAID caused the reaction. This algorithm consists of a structured 10-item questionnaire assessing factors such as the temporal relationship between drug exposure and symptom onset,

improvement after drug withdrawal (dechallenge), recurrence after re-exposure (rechallenge), alternative causes, previous history of similar reactions, and objective clinical evidence. Each response was assigned a weighted score, and the total scores are classified the likelihood of an adverse drug reaction as definite (≥ 9), probable (5–8), possible (1–4), or doubtful (≤ 0). This standardized approach was used to identify the suspected culprit NSAID and ensure consistent documentation of HSRs.

Statistical analysis: Descriptive statistics summarized patient demographics. Categorical variables were expressed as frequencies and percentages, while continuous variables were reported as means $\pm$ standard deviations (SD). Causality between NSAIDs exposure and HSR was assessed using the Naranjo algorithm, as described in the methods section. Statistical significance was defined as a two-sided p-value < 0.05 . All analyses were performed using Stata version 18.0 (StataCorp, College Station, TX, USA). Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Medicine, Khon Kaen University (Approval No. HE681190).

Results

Baseline characteristics

A total of 1,349 participants were included in the analysis as presented in Table 1. The majority of participants were female ($n = 951$, 70.50%), while male participants comprised 29.50% ($n = 398$). The mean age was 51.96 ± 16.32 years. The mean body weight and height were 62.31 ± 13.91 kg and 159.61 ± 11.62 cm, respectively. According to the eGFR staging, nearly half of the patients were classified in stage 1 ($n = 184$, 49.33%), followed by stage 2 ($n = 141$, 37.80%). The remaining patients were divided among stage 3a ($n = 25$, 6.70%), stage 3b ($n = 10$, 2.68%), stage 4 ($n = 6$, 1.61%), and stage 5 ($n = 7$, 1.88%). The mean serum creatinine level was recorded at 1.01 ± 1.25 mg/dL. The most common primary diagnosis was musculoskeletal system and connective tissue disorders ($n = 255$, 19.03%), followed by cancer ($n = 111$, 8.28%) and skin and subcutaneous tissue disorders ($n = 109$, 8.13%).

Other notable categories included respiratory system diseases (n = 105, 7.84%), genitourinary system diseases (n = 105, 7.84%), digestive system diseases (n = 75, 5.60%), metabolic diseases (n = 55, 4.10%), nervous system disorders (n = 55, 4.10%), and

cardiovascular diseases (n = 53, 3.96%). Less frequent conditions included infectious and parasitic diseases (n = 34, 2.54%), mental and behavioral disorders (n = 24, 1.79%), essential hypertension (n = 17, 1.27%) and other diagnosis accounted for 25.52% (n = 342).

Table 1 Demographic data (n = 1,349)

Demographic data	n (%)
Gender	
Female	951 (70.50)
Male	398 (29.50)
Age (years)	51.96±16.32
Weight (kg)	62.31±13.91
Height (cm)	159.61±11.62
eGFR stage (1.73 mL/min/m²)	
Stage 1	184 (49.33)
Stage 2	141 (37.80)
Stage 3a	25 (6.70)
Stage 3b	10 (2.68)
Stage 4	6 (1.61)
Stage 5	7 (1.88)
Creatinine (mg/dl)	1.01±1.25
Diagnosis	
Cancer	111 (8.28)
Cardiovascular disease	53 (3.96)
Essential (primary) hypertension	17 (1.27)
Metabolic disease	55 (4.10)
Musculoskeletal system and connective tissue	255 (19.03)
Respiratory system	105 (7.84)
Digestive system	75 (5.60)
Genitourinary system	105 (7.84)
Skin and subcutaneous tissue	109 (8.13)
Nervous system	55 (4.10)
Mental and behavioral disorders	24 (1.79)
Infectious and parasitic disease	34 (2.54)
Other diagnosis	342 (25.52)

Note: Data are presented as n (%) for categorical variables and mean ± standard deviation (SD) for continuous variables. eGFR = estimated glomerular filtration rate (mL/min/1.73 m²). eGFR stages were classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines which eGFR classification was based on patients with available laboratory data. Diagnoses were categorized according to the International Classification of Diseases, 10th Revision (ICD-10).

In terms of severity, most adverse drug reactions (ADRs) were moderate, with significant variation observed across different agents. Ibuprofen accounted for the largest proportion of moderate reactions (446 cases, 37.14%), followed by diclofenac (220 cases, 18.32%) and naproxen (109 cases, 9.07%). Severe reactions were most frequently associated with ibuprofen (31 cases, 37.80%) and diclofenac (25 cases, 30.49%), while naproxen (7 cases, 8.54%), etoricoxib (8 cases, 9.76%), and mefenamic acid (4 cases, 4.88%) contributed to smaller numbers.

Regarding seriousness, the majority of ADRs were classified as non-serious (ranging from 17.96% to 37.09% across different agents). However, hospitalization due to ADRs was most common with diclofenac (24 cases, 34.29%) and ibuprofen (25 cases, 35.71%). Life-threatening events were rare, occurring only in cases involving diclofenac (1 case, 50.00%) and naproxen (1 case, 50.00%). Serious events classified as “other” were most frequently associated with ibuprofen (14 cases, 40.00%) and diclofenac (8 cases, 22.86%). Based on causality classification assessed using the Naranjo algorithm, the majority of reactions were categorized as probable (ranging from 18.71% for diclofenac to 35.67% for ibuprofen) or possible (with ibuprofen showing the highest number of cases at 244, or 46.39%). Definite ADRs were uncommon, with the highest occurrences in diclofenac (4 cases, 28.57%) and ibuprofen (3 cases, 21.43%). Doubtful ADRs were rare, recorded only in conjunction with diclofenac (1 case, 100%). Most reactions were mild to moderate and non-serious across all NSAIDs. Ibuprofen accounted for the highest proportion of reported reactions, followed by diclofenac. Diclofenac and ibuprofen showed relatively higher proportions of severe and serious HSRs; however, the associations between NSAID type and reaction severity ($p = 0.081$), seriousness ($p = 0.435$), or causality classification ($p = 0.787$) was not statistically significant as presented in Table 2.

The distribution of HSRs associated with individual NSAIDs as presented in Table 3. Overall, cutaneous manifestations were the most frequently reported reactions, with rash and itching, angioedema, generalized skin eruption, and allergic urticaria

accounting for the majority of cases across most NSAIDs.

Rash and itching represented the most common presentation overall, accounting for 32.98% of aspirin-related reactions, 28.09% of celecoxib, 22.80% of diclofenac, 19.05% of etoricoxib, and 25.73% of ibuprofen-associated reactions. Similarly, angioedema was frequently observed, particularly with ibuprofen (30.29%), etoricoxib (25.00%), naproxen (25.42%), and diclofenac (23.20%). Allergic urticaria was also commonly reported across multiple NSAIDs, including diclofenac (13.20%), mefenamic acid (12.22%), and celecoxib (10.11%).

Systemic reactions were less frequent but clinically significant. Anaphylaxis occurred most commonly with diclofenac (12.80%), followed by naproxen (8.47%) and ibuprofen (4.98%), whereas only sporadic cases were observed with other NSAIDs. Respiratory manifestations such as bronchospasm and wheezing were uncommon, with bronchospasm occurring primarily in association with ibuprofen (1.66%) and diclofenac (2.00%).

Severe cutaneous adverse reactions were rare. Stevens–Johnson syndrome (SJS) was reported in a small number of cases associated with etoricoxib (3.57%), mefenamic acid (1.11%), naproxen (0.85%), and parecoxib (1.32%). Drug reaction with eosinophilia and systemic symptoms (DRESS) occurred only in a few cases related to ibuprofen (0.62%) and parecoxib (1.32%), while acute generalized exanthematous pustulosis (AGEP) was observed only with diclofenac, ibuprofen, and naproxen.

Other reactions, including palpitations, edema/eczema, mucositis, dizziness, and gastrointestinal symptoms, were reported with varying frequencies but generally represented a smaller proportion of events. Certain rare manifestations, such as drug-induced hepatitis, hypotension, petechiae, and localized drug eruptions, were reported only sporadically. Overall, the data demonstrate that cutaneous HSRs predominated across all NSAIDs classes, whereas severe systemic and life-threatening reactions were relatively uncommon but occurred with several commonly prescribed agents, particularly diclofenac and ibuprofen.

Table 2 Incidence and characteristics of HSRs associated with NSAID use

NSAIDs	Severity			Seriousness					Causality classification					
	Total usage	Mild	Moderate	Severe	Non-serious	Hospitalization-		Life-threatening	Serious-		Definite	Probable	Possible	Doubtful
						initial	prolonged		Other					
Aspirin	97(7.19)	4(7.41)	92(7.66)	1(1.22)	93(7.70)	0(0.00)	0(0.00)	0(0.00)	4(11.43)	0(0.00)	0(0.00)	43(6.29)	54(10.27)	0(0.00)
Celecoxib	90(6.67)	6(11.11)	82(6.83)	2(2.44)	86(7.12)	2(2.86)	0(0.00)	0(0.00)	2(5.71)	2(14.29)	2(14.29)	45(6.58)	43(8.17)	0(0.00)
Diclofenac	254(18.83)	9(16.67)	220(18.32)	25(30.49)	217(17.96)	24(34.29)	4(33.33)	1(50.00)	8(22.86)	4(28.57)	4(28.57)	128(18.71)	121(23.00)	1(100.00)
Etoricoxib	86(6.38)	3(5.56)	75(6.24)	8(9.76)	77(6.37)	4(5.71)	2(16.67)	0(0.00)	3(8.57)	2(14.29)	2(14.29)	48(7.02)	36(6.84)	0(0.00)
Ibuprofen	491(36.40)	14(25.93)	446(37.14)	31(37.80)	448(37.09)	25(35.71)	4(33.33)	0(0.00)	14(40.00)	3(21.43)	3(21.43)	244(35.67)	244(46.39)	0(0.00)
Indomethacin	2(0.15)	0(0.00)	2(0.17)	0(0.00)	2(0.17)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.15)	1(0.19)	0(0.00)
Ketorolac	8(0.59)	0(0.00)	8(0.67)	0(0.00)	8(0.66)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	7(1.02)	1(0.19)	0(0.00)
Mefenamic acid	90(6.67)	5(9.26)	81(6.74)	4(4.88)	86(7.12)	4(5.71)	0(0.00)	0(0.00)	2(5.71)	1(7.14)	1(7.14)	49(7.16)	40(7.60)	0(0.00)
Meloxicam	35(2.59)	3(5.56)	32(2.66)	0(0.00)	35(2.90)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	12(1.75)	23(4.37)	0(0.00)
Naproxen	119(8.82)	3(5.56)	109(9.07)	7(8.54)	109(9.02)	7(10.00)	0(0.00)	1(50.00)	2(5.71)	1(7.14)	1(7.14)	69(10.09)	49(9.32)	0(0.00)
Parecoxib	77(5.71)	7(12.96)	66(5.50)	4(4.88)	71(5.88)	4(5.71)	2(16.67)	0(0.00)	0(0.00)	1(7.14)	1(7.14)	39(5.70)	37(7.03)	0(0.00)
Total	1349(100.00)	54(4.00)	1213(89.92)	82(6.08)	1232(91.33)	70(5.19)	120(8.9)	2(0.15)	35(2.59)	14(1.04)	14(1.04)	685(50.78)	649(48.11)	1(0.07)

Note: Data are presented as number (%). Percentages in the total row were calculated based on the overall number of NSAID-induced HSRs (N = 1,349). Statistical comparison between NSAID type and each reaction category was performed using the chi-square test. p-values represent the association between NSAID type and: severity of HSRs (p = 0.081), seriousness of reactions (p = 0.435), causality assessment (p = 0.787). No statistically significant differences were observed (all p > 0.05).

Tablet 3 Clinical manifestations of HSRs associated with NSAID use

HSRs, n (%)	Aspirin	Celecoxib	Diclofenac	Etoricoxib	Ibuprofen	Indomethacin	Ketololac	Mefenamic acid	Meloxicam	Naproxen	Parecoxib
AGEP	0(0.00)	0(0.00)	2(0.80)	0(0.00)	1(0.21)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.85)	0(0.00)
Allergic urticaria	8(8.51)	9(10.11)	33(13.20)	3(3.57)	47(9.75)	1(50.00)	2(25.00)	11(12.22)	3(9.38)	11(9.32)	7(9.21)
Anaphylaxis	3(3.19)	3(3.37)	32(12.80)	3(3.57)	24(4.98)	0(0.00)	0(0.00)	5(5.56)	0(0.00)	10(8.47)	2(2.63)
Angioedema	17(18.09)	17(19.10)	58(23.20)	21(25.00)	146(30.29)	0(0.00)	1(12.50)	20(22.22)	6(18.75)	30(25.42)	14(18.42)
Blister	1(1.06)	0(0.00)	0(0.00)	0(0.00)	1(0.21)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.85)	1(1.32)
Bronchospasm	3(3.19)	1(1.12)	5(2.00)	0(0.00)	8(1.66)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	2(1.69)	1(1.32)
Burn	2(2.13)	0(0.00)	1(0.40)	1(1.19)	1(0.21)	0(0.00)	0(0.00)	1(1.11)	0(0.00)	0(0.00)	3 (3.95)
Chest pain, Dyspnea	1(1.06)	0(0.00)	1(0.40)	0(0.00)	3(0.62)	0(0.00)	0(0.00)	1(1.11)	1(3.12)	0(0.00)	0(0.00)
Dizziness / Vertigo, Nausea / Vomiting	0(0.00)	1(1.12)	1(0.40)	1(1.19)	3(0.62)	0(0.00)	0(0.00)	1(1.11)	1(3.12)	1(0.85)	1(1.32)
DRESS	0(0.00)	0(0.00)	0(0.00)	0(0.00)	3(0.62)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(1.32)
Drug induced pharmacology effects	1(1.06)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Palpitation	6(6.38)	2(2.25)	19(7.60)	4(4.76)	31(6.43)	0(0.00)	1(12.50)	7(7.78)	0(0.00)	7(5.93)	3(3.95)
Edema/Eczema	8(8.51)	11(12.36)	13(5.20)	8(9.52)	34(7.05)	0(0.00)	0(0.00)	6(6.67)	3(9.38)	9(7.63)	2(2.63)
Erythema multiforme, unspecified	1(1.06)	2(2.25)	1(0.40)	0(0.00)	1(0.21)	0(0.00)	0(0.00)	0(0.00)	1(3.12)	0(0.00)	2(2.63)
Fixed drugs eruption	1(1.06)	2(2.25)	2(0.80)	6(7.14)	1(0.21)	0(0.00)	0(0.00)	1(1.11)	1(3.12)	0(0.00)	9(11.84)
Generalized skin eruption due to drugs and medicaments	10(10.64)	14(15.73)	22(8.80)	15(17.86)	39(8.09)	0(0.00)	1(12.50)	11(12.22)	9(28.12)	17(14.41)	5(6.58)
Hepatitis	0(0.00)	0(0.00)	1(0.40)	0(0.00)	1(0.21)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Hypotension	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.85)	0(0.00)
Localized skin eruption due to drugs and medicaments, unspecified	0(0.00)	0(0.00)	0(0.00)	0(0.00)	6(1.24)	1(50.00)	0(0.00)	1(1.11)	0(0.00)	1(0.85)	0(0.00)

Tablet 3 Clinical manifestations of HSRs associated with NSAID use (Cont.)

HSRs, n (%)	Aspirin	Celecoxib	Diclofenac	Etoricoxib	Ibuprofen	Indomethacin	Ketololac	Mefenamic acid	Meloxicam	Naproxen	Parecoxib
Mouth irritation	0(0.00)	1(1.12)	0(0.00)	0(0.00)	1(0.21)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.85)	0(0.00)
Mucositis	0(0.00)	1(1.12)	2(0.80)	3(3.57)	4(0.83)	0(0.00)	0(0.00)	0(0.00)	1(3.12)	0(0.00)	2(2.63)
Petechiae	1(1.06)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	2(2.63)
Rash and Itching	31(32.98)	25(28.09)	57(22.80)	16(19.05)	124(25.73)	0(0.00)	3(37.50)	24(26.67)	6(18.75)	25(21.19)	20(26.32)
Severe Headaches, Hypertension	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.21)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
SJS	0(0.00)	0(0.00)	0(0.00)	3(3.57)	0(0.00)	0(0.00)	0(0.00)	1(1.11)	0(0.00)	1(0.85)	1(1.32)
Wheezing	0(0.00)	0(0.00)	0(0.00)	0(0.00)	2(0.41)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Note: Data are presented as n (%). Percentages were calculated using the total number of hypersensitivity reactions associated with each individual NSAID as the denominator. A single patient may have experienced more than one HSRs. Abbreviations: AGEP (acute generalized exanthematous pustulosis); DRESS (drug reaction with eosinophilia and systemic symptoms); SJS (Stevens–Johnson syndrome); NSAIDs (nonsteroidal anti-inflammatory drugs), HSRs (hypersensitivity reactions).

Discussion

From a policy perspective, promoting rational drug use (RDU) for NSAIDs is essential to reduce the risk of drug-related adverse reactions, including HSRs. Healthcare providers should carefully evaluate the indications for NSAIDs therapy, use the lowest effective dose for the shortest duration, and assess patients' history of drug allergy before prescribing. In addition, strengthening pharmacovigilance systems and educating patients about the appropriate use of NSAIDs may help prevent inappropriate use and improve medication safety. However, this study comprehensively evaluated the spectrum of HSRs associated with various NSAIDs, revealing considerable variability in clinical manifestations across different agents. The incidence observed in this study is comparable to findings reported in previous studies from other populations. Several studies conducted in different countries have reported varying incidences of NSAID-induced HSRs, which may be influenced by genetic background, prescribing patterns, and differences in healthcare systems. In Thailand, previous pharmacovigilance studies have also reported similar patterns of HSRs associated with commonly used NSAIDs. These variations highlight the potential influence of ethnic and regional differences in drug utilization and susceptibility to ADRs.

Rash and itching were the most prevalent symptoms, which is consistent with previous studies indicating that cutaneous manifestations are the dominant clinical phenotypes of NSAID hypersensitivity, particularly NSAID-induced urticaria/angioedema (NIUA) [8,9]. The relatively high incidence of angioedema, particularly with ibuprofen (30.29%), diclofenac (23.20%), and naproxen (25.42%), underscores the importance of monitoring for potentially severe swelling that may compromise airway patency [10]. The higher number of HSRs associated with ibuprofen observed in this study may be related to its widespread use in clinical practice rather than indicating that it carries the highest risk among NSAIDs. Ibuprofen is commonly prescribed due to its

availability and perceived safety profile, which may increase the likelihood of reported reactions. Anaphylaxis, a life-threatening systemic reaction, was most frequently reported with diclofenac (12.80%), followed by ibuprofen and naproxen. This aligns with previous evidence indicating diclofenac as a common culprit for severe NSAID hypersensitivity [11]. The occurrence of rare but serious cutaneous adverse reactions such as SJS and AGEP emphasizes the critical need for early recognition and prompt discontinuation of the offending agent [12]. Etoricoxib association with SJS (3.57%) in our cohort is noteworthy and warrants cautious use in susceptible populations. Other symptoms, including bronchospasm, palpitations, and edema/eczema, although less frequent, contribute to the heterogeneity of NSAID hypersensitivity and highlight the multifaceted nature of these reactions. The presence of mucositis and fixed drug eruptions further reflects the complex immunopathology underlying NSAID-induced adverse events. These manifestations are generally classified as delayed-type HSRs mediated by drug-specific T lymphocytes. Previous case series have documented NSAIDs as potential causative agents of fixed drug eruptions, underscoring the diverse spectrum of cutaneous phenotypes associated with NSAID hypersensitivity [13]. The findings also underscore the challenges in clinical management due to the overlap of symptoms among different NSAIDs and the variability in individual patient responses. These findings highlight the importance of individualized patient assessment, including a detailed medical history and physical examination, as key components of the diagnostic management of drug hypersensitivity. When available, diagnostic testing such as drug provocation tests, skin tests, and in vitro assays may further support the identification of culprit drugs and guide safer NSAID use [14]. Moreover, variation in the incidence of HSRs among different NSAIDs may be explained by differences in their pharmacological properties and pathogenic mechanisms. Many NSAID-induced HSRs are thought to be related to

COX-1 inhibition, which can shift arachidonic acid metabolism toward increased leukotriene production, leading to inflammatory and allergic manifestations. In addition, some reactions may involve immunological mechanisms that are specific to certain drugs. These differences may contribute to the variability in HSRs rates observed among different NSAIDs. However, no statistically significant association was observed in this study. Thus, this finding should be interpreted with caution because the imbalance in sample size among the groups may have limited the statistical power to detect a true association.

This study has several limitations that should be considered when interpreting the findings. First, due to the retrospective design, the study relied on information recorded in medical records, which may have resulted in incomplete clinical data. Second, there may be reporting bias, as not all ADRs are consistently documented or reported. In addition, the imbalance in sample size among some groups may have limited the statistical power of the analysis. Therefore, the findings should be interpreted with caution. A system perspective, strategies to improve medication safety should include strengthening pharmacovigilance systems and encouraging more consistent reporting of adverse drug reactions. In addition, promoting RDU policies for NSAIDs, increasing awareness among healthcare professionals regarding drug hypersensitivity, and implementing routine screening of patients' history of drug allergies before prescribing NSAIDs may help reduce inappropriate use and prevent HSRs. In conclusion, NSAID-induced HSRs presents with a wide range of clinical manifestations, varying by specific agent. Awareness of these patterns is crucial for clinicians to enhance diagnosis, patient counseling, and therapeutic decision-making, thereby minimizing adverse outcomes.

Conclusion

NSAID-induced HSRs encompass a broad clinical spectrum, ranging from mild cutaneous symptoms such as rash and itching to severe manifestations including anaphylaxis and SJS. The incidence and type of reactions vary significantly among different NSAIDs, with agents like diclofenac and ibuprofen showing higher frequencies of serious events. Clinicians should maintain high vigilance when prescribing NSAIDs, particularly in patients with prior hypersensitivity. Early recognition and prompt management of adverse reactions are crucial to improving patient safety. Further prospective research is warranted to elucidate underlying mechanisms and optimize diagnostic and therapeutic strategies.

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Conflict of Interest

Author(s) declared none.

References

1. Minaldi E, Cahill K. Recent updates in understanding NSAID hypersensitivity. *Curr Allergy Asthma Rep* 2023;23(3):181-8. doi:10.1007/s11882-023-01064-3.
2. Blanca-Lopez N, Soriano V, Garcia-Martin E, Canto G, Blanca M. NSAID-induced reactions: classification, prevalence, impact, and management strategies. *J Asthma Allergy* 2019;12:217-33. doi:10.2147/JAA.S164806.
3. Jalali J, Wild L, Oberhelman K, Yusin J. A rare case of anaphylaxis to ibuprofen: NSAID allergy in a stroke patient. *Ann Allergy Asthma Immunol* 2024;133(6 Suppl):S117-8. doi:10.1016/j.anai.2024.08.502.

4. Sánchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000;84(1):101-6. doi:10.1016/S1081-1206(10)62748-2.
5. Strom BL, Carson JL, Morse ML, West SL, Soper KA. The effect of indication on hypersensitivity reactions associated with zomepirac sodium and other nonsteroidal anti-inflammatory drugs. *Arthritis Rheum* 1987;30(10):1142-8. doi:10.1002/art.1780301009.
6. Wongsu C, Sompornrattanaphan M, Tantilipikorn P, Thongngarm T. Clinical characteristics and aspirin desensitization in Thai patients with a suggestive history of NSAID-exacerbated respiratory disease. *Asian Pac J Allergy Immunol* 2022;40(3): 247-53. doi:10.12932/AP-150619-0583.
7. Yuenyongviwat A, Chantaravisarut N, Phattara-pongdilok W, Koosakulchai V, Jessadapakorn W, Sangsupawanich P. Characteristics and contributing factors related to nonsteroidal anti-inflammatory drugs hypersensitivity. *Int Arch Allergy Immunol* 2021;182(2):139-45. doi:10.1159/000510364.
8. Blanca-Lopez N, Soriano V, Garcia-Martin E, Canto G, Blanca M. NSAID-induced reactions: classification, prevalence, impact, and management strategies. *J Asthma Allergy*. 2019 Aug 8;12:217-233. doi:10.2147/JAA.S164806.
9. Quiralte J, del Robledo Ávila M, Cimbollek S, Quiralte-Castillo J. Clinical Phenotypes in NSAID-Induced Urticaria/Angioedema [Internet]. *Urticaria - Diagnosis and Management*. IntechOpen; 2021. doi:10.5772/intechopen.96718
10. Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol* 2017;140(2):321-33. doi:10.1016/j.jaci.2017.06.012.
11. Kowalski ML, Makowska JS, Blanca M, Bavbek S, Bochenek G, Bousquet J, et al. Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs): classification, diagnosis and management. *Allergy* 2011;66(7):818-29. doi:10.1111/j.1398-9995.2011.02557.
12. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol* 2011;7(6): 803-15. doi:10.1586/eci.11.66.
13. Aouam K, Fadhel NB, Fredj NB, Chaabane A, Belhadjali H, Boughattas NA, et al. Nonsteroidal anti-inflammatory drugs-induced fixed drug eruptions: a case series. *Clin Transl Allergy* 2014;4(Suppl 3):P82. doi:10.1186/2045-7022-4-S3-P82.
14. Popiołek I, Blasiak M, Kozak A, Pietak E, Bulanda M, Porebski G. Diagnostic value of oral provocation tests in drug hypersensitivity reactions induced by nonsteroidal anti-inflammatory drugs and paracetamol. *Diagnostics (Basel)* 2022;12:3074. doi:10.3390/diagnostics12123074.

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