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CHARACTERISTICS OF ADVERSE DRUG REACTION DUE TO NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN THAILAND, 2015–2019

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CHARACTERISTICS OF ADVERSE DRUG REACTION DUE TO NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN THAILAND, 2015–2019

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【要旨 ABSTRACT】

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for treating pain and inflammation. Spontaneous adverse drug reaction (ADR) reports represent a rich data source for the detection of unknown and rare ADRs. This study aimed to analyze the characteristics of ADRs due to NSAIDs reported from 2015 to 2019 in Thailand.

Material and Methods: This was a cross-sectional study that was conducted using the National ADR database (Thai Vigibase). All ADR reports of NSAIDs for systemic use from 2015 to 2019 were included in the study. The reports in which the causality assessment was unlikely or those with missing information on senders of the reports, unidentified patients, suspected drugs, or reactions were also excluded. Patient characteristics, drug use information, adverse reaction information, and source of senders were collected from the database.

Results: Between 2015 and 2019, the total number of reports on ADRs and ADRs due to NSAIDs was 214,189 and 32,857, respectively. The annual number of ADR reports due to NSAIDs from 2015 to 2019 decreased from 7,008 to 5,922. Ibuprofen was the most frequently reported drug (n=12,645). The majority of patients were in the age group of 40–59 years (30.6%). Almost half of all patients had no history of drug allergies or underlying diseases. Serious DRs were recorded in 20.7% of the total ADRs due to NSAIDs. Angioedema was the most frequently reported adverse reaction (22.9%). Most patients recovered without sequalae (62.7%), but 16.5% did not recover. Of the 20 fatal cases, four cases had a history of drug allergy, and seven experienced severe drug-induced skin reactions. The time for the onset of the adverse reaction ranged from less than 24 hours to 36 days.

Conclusions: The number of ADR reports due to NSAIDs decreased; however, 16.5% of the cases did not exhibit recovery, and 20 patients died. A system to minimize the risk of ADRs should be established in Thailand.

Keywords: Adverse drug reaction, NSAIDs, spontaneous ADR reports, Thailand, Thai Vigibase.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications for treating pain and inflammation.[1-5] NSAIDs reduce the production of biochemicals involved in inflammation, pain, and fever through inhibiting cyclooxygenases (COXs). The two COX isoforms (COX-1 and COX-2) are the main targets of NSAIDs.[6,7] COX-1 is expressed in most tissues, including the gastrointestinal (GI) mucosa, platelets, endothelium, kidneys, and uterus, and functions as a housekeeping enzyme that maintains homeostasis.[8,9] However, COX-2 is induced during inflammation.[10] The gastrointestinal side effects of inhibiting COX-1 are the well-known adverse drug reactions (ADRs) associated with the use of NSAIDs.[1,11] A previous study has shown that the most frequently reported serious ADRs due to NSAIDs are cutaneous diseases followed by gastrointestinal, hepatic, renal, and cardiovascular events.[12] Several studies also demonstrated the risks of ADRs accompanied with some NSAIDs; valdecoxib increased the risk of thrombotic adverse events[13], and rofecoxib exerted a risk of a heart attack.[14] As a result, these drugs were ceased from the global market.

Reporting the ADRs of post-marketing products is an important surveillance system for drug safety. The Spontaneous Reporting System (SRS) is widely used worldwide,[15,16] although it may exhibit some limitations, such as incomplete information and under-reporting.[15,17] Using cumulative and large number of reports from multiple sources, unknown ADRs may be identified. An in-depth analysis of such big data may be helpful to ensure the safety of drug use by the public, to determine which drug needs regulation and management, and to set individual drug priorities in drug safety surveillance.[18,19]

In Thailand, Thai Vigibase was initiated in 1984, which is the national spontaneous reporting database regulated by the Health Product Vigilance Center. The health professionals and marketing authorization holders in the public and private

sectors submit the reports of ADRs that are identified throughout the country.[16] Thai Vigibase accepts only a valid report according to the documentation grading criteria outlined by the Thai Food and Drug Administration. The minimum data needed for a valid report include an identifiable patient, an identifiable sender, at least one suspect drug, and at least one adverse event.[20]

Thai Vigibase revealed that the second highest ADR was caused by ibuprofen in 2019.[10] However, very little is known about the characteristics of ADRs among NSAID users in Thailand. This is the first study on ADRs due to NSAIDs for systemic use in Thailand. This study aimed to analyze the characteristics of ADRs due to NSAIDs using the reports submitted to Thai Vigibase from 2015 to 2019.

MATERIALS AND METHODS

Study design

This cross-sectional study was conducted using the data of Thai Vigibase from January 2015 to December 2019. All reports of ADRs suspected to be caused by NSAIDs use itself or due to drug interactions between NSAIDs and other drugs were included in this study. The reports in which the causality assessment was unlikely or those with missing information on the senders of reports, identification of patient, suspected drugs, or reactions were excluded from the analysis. There were 214,189 reports of all ADRs that occurred from 2015 to 2019, of which 32,974 were ADRs caused due to NSAIDs. A total of 32,857 ADRs caused due to NSAIDs were included in the study after excluding 117 ADRs due to the above reasons.

Data of ADR reports

The following information was extracted from the Thai Vigibase database: (1) patient characteristics (sex, age, history of drug allergy, and underlying disease), (2) drug use information (names of drugs, reasons for usage, role of drugs, and date of starting

and discontinuing drugs), (3) adverse event information (adverse reaction, affected organ system, seriousness, date of onset and offset, causality assessment of ADRs, and outcome), and (4) source of senders.

Roles of drugs were categorized into suspect, concomitant, and interacting.[21] All ADRs and organ system affected by ADRs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology.[22] Seriousness was categorized into serious or non-serious. Serious ADRs included one of the followings: life-threatening, requiring hospitalization or extension of hospital stay, resulting in death, persistent or significant disability.[23] Outcomes of ADRs were categorized into six groups: recovered without sequelae, recovered with sequelae, recovering, not recovered, fatal, and unknown.[21] Causality assessment of ADR was used to estimate the strength of relationship between drug exposure and occurrence of ADR, and it was categorized into four groups: certain, probable, possible, and unlikely.[24] In this study, only ADRs for which the causality was certain, probable, or possible were included. Senders were organizations that sent the reports, and they could be the primary source or different from the primary source. Sources of senders were categorized into the following categories: hospitals and clinics in the public and private sectors, pharmaceutical companies, pharmacies, and others, including governmental public health offices.

Statistical analysis

Descriptive statistics were used to describe the characteristics of ADRs and to determine the frequencies and percentages for categorical data. Microsoft Excel version 2019 and IBM SPSS version 27 (IBM SPPS Inc., New York, USA) were used for the statistical analyses.

Ethical issue

The study protocol was approved by the Ethical Review Committee for Research

in Human Subjects of the Ministry of Public Health (approval number: 18/2563).

RESULTS

Between 2015 and 2019, the annual number of ADR reports decreased from 44,952 to 37,886 (Fig. 1). The annual number of ADR reports due to NSAIDs with causality assessment as certain, probable, or possible also decreased from 7,008 in 2015 to 5,922 in 2019. The proportion of ADRs caused due to NSAIDs in all ADR reports was stable (15.0–15.6%) during these five years. The total number of reports on ADRs and ADRs caused due to NSAIDs was 214,189 and 32,857 (15.3%) from 2015 to 2019.

Fig. 2 shows the number and seriousness of ADRs based on types of NSAIDs. The most frequently drug reported was ibuprofen (n=12,645), followed by diclofenac (n=7,795), and naproxen (n=2,741). Some patients were administered two or more NSAIDs. The least reported drug was etodolac (n=3). Less than half of ADRs caused by each NSAID were classified as serious ADRs (8.1–46.2%).

Table 1 shows the characteristics of patients and ADRs in 32,857 ADR reports associated with NSAIDs from 2015 to 2019. More ADRs were reported in female patients (64.3%) than in male patients, and the majority of patients were in the age group of 40–59 years (30.6%). Almost half of all patients had no history of drug allergy (49.8%) or underlying disease (46.3%). Most ADRs were non-serious (72.5%), and 20.7% of all ADRs were serious. Regarding the causality assessment, 66.4% were probable, followed by possible (29.2%), and certain (4.4%). Almost all reports were submitted by either the hospitals or clinics (99.8%). The others (less than 1%) were submitted by the pharmacies, pharmaceutical companies, Thai Food and Drug Administration, and provincial public health offices. Most reports were from the provinces (83.2%). The median time period of the occurrence of ADRs was 3.5 (interquartile range, 13.8) days. Regarding the outcomes of ADRs, recovery without sequelae was the most common (62.7%) followed by not recovered (16.5%) and recovering (9.5%). Eight patients died

after the occurrence of ADRs caused by NSAIDs, but 12 patients were reported to have died due to other causes. The outcomes of 1,828 ADRs (5.6%) were unknown.

The top 10 reported reasons for administering NSAIDs are listed in Table 2. The major reason was pain management, such as unspecified pain (9.3%), muscle strain (5.5%), and myalgia (5.3%). NSAIDs were also used to treat unspecified fever (3.5%) and common cold (1.5%).

Table 3 shows the top 20 reactions based on the preferred terms of the MedDRA coding system. The most frequently reported reaction was angioedema (22.9%), followed by urticaria (14.9%), and maculopapular rash (10.8%). Additionally, anaphylactic reactions were observed in 2.4% of all reactions. Adverse events classified based on organ systems are listed in Table 4. Skin and subcutaneous tissue were the most frequently reported organ system disorders (65.1%), followed by eye disorders (9.2%), immune system disorders (7.5%), general disorders and administration site conditions (6.6%), and gastrointestinal (5.3%) disorders.

The characteristics of patients whose adverse reactions did not recover are listed in Table 5. Most patients were female (65.4%) and in the age group of 40-59 years (29.3%). A total of 259 patients (4.8%) were 0-9 years old. Almost half of the patients had no history of drug allergy (49.7%) or underlying disease (47.2%). The causality of ADRs was assessed as probable for 66.6%, possible for 28.9%, and certain for 4.5%. The median time period for the onset of the adverse reaction was less than 24 hours (interquartile range, 1). The median time period for drug exposure was less than one day (interquartile range, 1). Most patients (86.3%) had one suspected drug per report.

The details of the 20 fatal cases are summarized in Table 6. Patients were divided into two groups based on the last observation: death was possibly related (n=8) and unrelated (n=12) to the event. Four out of the 20 patients had a history of drug allergy, especially two cases (cases 6 and 19) had a history of allergy to NSAIDs. The causality assessment of ADRs was probable in 12 cases, possible in seven cases, and certain in

one case. The time for the onset of the reaction ranged from less than 24 hours to 36 days. Seven of the eight patients who died possibly related to the event exhibited severe drug-induced skin reactions, such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Ibuprofen was the most commonly reported drug (n=6), followed by piroxicam (n=5), and diclofenac (n=4). One patient (case 17) was administered two suspected NSAIDs (diclofenac and ketorolac).

DISCUSSION

To the best of my knowledge, this is the first study to analyze ADRs caused by all types of NSAIDs reported in Thai Vigibase. In this study, four important results were obtained. First, the number of ADR reports decreased continuously from 2015 to 2019. Second, ibuprofen was the most commonly administered drug causing ADRs, followed by diclofenac. Third, angioedema was the most commonly reported drug, followed by urticaria. Fourth, the majority of fatal cases exhibited severe drug-induced skin reactions, such as SJS and TEN.

There was a decreasing trend in the number of reports of all ADRs and ADRs caused due to the use of NSAIDs from 2015 to 2019. The plausible reasons may include first, the incidence of ADRs might have actually decreased, since the Ministry of Public Health requested the hospitals to follow the "National Patient and Personnel Safety Goals" policy, which included an activity for patient safety to prevent ADRs and medication errors;[25] and second, the senders might be short of time to report ADRs. A previous study on healthcare workers attitude towards reporting ADRs revealed that the hospital staff paid less attention to the ADR reporting system than general practices.[26] Third, there might be other problems or lack of understanding regarding the ADR reporting system in the hospitals. Vallano and colleagues demonstrated that the limitations behind proper functioning of the hospitals Pharmacovigilance (PV) system were the lack of information of the system, low accessibility of the system to the staff, less utility of the

reporting system, and lack of tools, such as reporting forms.[27] However, Thai Vigibase is a widely used and effective method for collecting information regarding the suspected ADRs. Under-reporting is still an important issue associated with this system that persists and needs to be resolved.[27,28]

Ibuprofen is the most commonly administered drug reported in Thailand. According to the National Guideline for Essential Medicines, ibuprofen is recommended as the first-line treatment for several indications in Thailand.[29] In one study that included 149 patients with a history of NSAID hypersensitivity conducted at the University hospital in Denmark between 2002 and 2011, aspirin, ibuprofen, and diclofenac were reported as the top three drugs causing hypersensitive reactions.[30] It was also found that the frequent use of NSAIDs was associated with the occurrence of hypersensitive reactions.[30]

Angioedema was the most commonly reported ADR, followed by urticaria. These two are the most commonly recognized cutaneous reactions caused due to NSAIDs and clinical manifestations, such as hypersensitivity, that are unpredictable and occur mostly in susceptible individuals.[31,32]

Most fatal cases exhibited severe drug-induced skin reactions. The mortality rate was high among patients with severe drug-induced skin reactions due to the complications that occurred during the acute phase, including septicemia,[33] with mortality rates of 5% and 40% for SJS and TEN, respectively.[34]

Although some ADRs caused due to NSAIDs are idiosyncratic and cannot be predicted through pharmacology, it is important to establish a system to prevent the development of serious illnesses following any ADR. Early detection of prodromal signs and discontinuation of drugs may help decrease the mortality rate.[35] In Thailand, patients can procure some of NSAIDs at pharmacies without presenting a prescription but on the pharmacist's advice. Healthcare professionals should be aware of the potential risks of ADRs caused by NSAIDs and educate the patients about ADRs.

This study had some limitations. First, ADR data might be under-reported, which is often found in the case of SRS.[15,27] Conversely, the number of reports be high when there were recent warnings about a drug or soon after marketing authorization. Second, the senders might not provide the information on all concomitant drugs administered to the patients. According to the criteria for a valid case report submitted to Thai Vigibase, at least one suspected drug is required in each report. Therefore, all concomitant drugs may not be reported, although they might have caused ADRs due to the drug-drug interactions.

Conclusively, the number of ADRs and ADRs caused due to NSAIDs decreased annually in Thailand from 2015 to 2019. Ibuprofen was the most frequently reported drug in the ADR reports. The most common ADR caused due to NSAIDs was angioedema, followed by urticaria. Of the 20 fatal cases, most cases exhibited severe skin reactions, such as SJS and TEN. The Thai Vigibase system was useful to better understand ADRs in Thailand. However, to prevent severe illness and deaths caused due to NSAIDs, a system for early detection of ADRs must be established in the near future.

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CONFLICT OF INTEREST

There was no conflict of interest.

FIGURE LEGENDS

Fig. 1. The trend of reporting all ADRs and ADRs due to NSAIDs from 2015 to 2019.

The number of reports and ADRs caused due to the use of NSAIDs in Thai Vigibase decreased annually from 2015 to 2019. The proportion of annual reports of ADRs caused due to the use of NSAIDs accounted for 15.0–15.6% of all reports recovered for those five years. These reports included ADRs for which the causality was certain, probable, and possible, but not unlikely.

Fig. 2. The number and seriousness of ADRs based on the type of NSAIDs.

The most frequently administered drug was ibuprofen (n=12,645), and 2,606 ADRs (20.6%) were reported to be serious. Most ADRs were non-serious and less than half of ADRs caused by each NSAID were reported as serious (8.1–46.2%).

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Table 1 Characteristics of patients and ADRs due to NSAIDs in Thai Vigibase from 2015 to 2019 (N=32,857)

Characteristics	N	(%)
Sex		
Male	11,679	(35.5)
Female	21,126	(64.3)
NA	52	(0.2)
Age (years)		
0-9	1,719	(5.2)
10-19	2,397	(7.3)
20-39	9,113	(27.7)
40-59	10,056	(30.6)
≥ 60	4,418	(13.5)
NA	5,154	(15.7)
History of drug allergy		
No	16,365	(49.8)
Yes	6,740	(20.5)
NA	9,752	(29.7)
Underlying disease		
No	15,196	(46.3)
Yes	3,751	(11.4)
NA	13,910	(42.3)
Seriousness of ADR		
Serious[a]	6,801	(20.7)
Non-serious	23,827	(72.5)
NA	2,229	(6.8)
Causality assessment		
Certain	1,453	(4.4)
Probable	21,807	(66.4)
Possible	9,597	(29.2)
Sender source		
Hospital/clinic	32,776	(99.8)
Pharmacy	51	(0.2)
Pharmaceutical company	27	(0.0)
Other[b]	3	(0.0)
Sender region		
Bangkok	5,495	(16.8)
Province	27,351	(83.2)
NA	11	(0.0)
Period of having ADR (days)[c]		
Median (IQR)	3.5 (13.8)	
Outcomes[d]		
Recovered without sequelae	20,593	(62.7)
Recovered with sequelae	1,887	(5.7)
Recovering	3,109	(9.5)
Not recovered	5,420	(16.5)
Died	20	(0.1)

Characteristics	N	(%)
Possibly related to the event	8	
Unrelated to the event	12	
Unknown	1,828	(5.6)

ADR, adverse drug reaction; NA, not available; IQR, interquartile range.

[a]Serious means that life-threatening, requiring hospitalization or extension of hospital stay, resulting in death or persistent or significant disability.

[b]Other includes Thai Food and Drug administration and governmental public health offices.

[c]7,962 reports were included.

[d]Outcome of the event at the last observation.

Table 2 Top 10 reported reasons for administering NSAIDs (N=32,857)

Reason	N	(%)
Pain, unspecified	3,064	(9.3)
Muscle strain	1,811	(5.5)
Myalgia	1,742	(5.3)
Acute pain	2,388	(7.3)
Low back pain	1,231	(3.7)
Fever, unspecified	1,149	(3.5)
Headache	914	(2.8)
Common cold	509	(1.5)
Pain in the joint	500	(1.5)
Pain in the limb	245	(0.7)

NSAIDs, nonsteroidal anti-inflammatory drugs.
Some patients had two or more kinds of NSAIDs.

Table 3 Top 20 reactions based on the preferred terms of the MedDRA coding system (N=32,857)

Adverse drug reaction	N	(%)
Angioedema	7,513	(22.9)
Urticaria	4,902	(14.9)
Maculo-papular rash	3,556	(10.8)
Periorbital edema	3,433	(10.4)
Rash	3,249	(9.9)
Pruritus	1,903	(5.8)
Anaphylactic reaction	1,873	(5.7)
Rash erythematous	1,133	(3.4)
Face oedema	1,121	(3.4)
Edema mouth	1,079	(3.3)
Dyspnea	853	(2.6)
Fixed eruption	840	(2.6)
Anaphylactic shock	798	(2.4)
Chest pain	690	(2.1)
Edema	296	(0.9)
Stevens-Johnson syndrome	223	(0.7)
Mouth ulceration	208	(0.6)
Palpitations	198	(0.6)
Conjunctivitis	191	(0.6)
Edema peripheral	173	(0.5)

MedDRA; Medical Dictionary for Regulatory Activities.
One or more adverse drug reactions could be selected.

Table 4 Classification of adverse events by the MedDRA coding system (N = 41,038)[a]

System organ class	Number (%)	Preferred term (number)
Skin and subcutaneous tissue disorders	26,725 (65.1)	angioedema (8,067), urticaria (5,426), rash maculo-papular (4,157), rash (3,674), pruritus (2,230), rash erythematous (1,333), fixed eruption (931), Stevens-Johnson syndrome (302), dermatitis bullous (105), erythema multiforme (89), eczema (47), purpura (41), dermatitis exfoliative (36), drug reaction with eosinophilia and systemic symptoms (35), skin exfoliation (28), acute generalized exanthematous pustulosis (26), toxic epidermal necrolysis (26), rash vesicular (23), skin disorder (22), miliaria (21), dermatitis (20), photosensitivity reaction (18), acne (13), hyperhidrosis (11), dermatitis contact (10), henoch-schonlein purpura (4), erythema (3), rash follicular (3), skin necrosis (3), systemic lupus erythematosus rash (3), alopecia (2), cold urticaria (2), erythema nodosum (2), skin discoloration (2), skin reaction (2), skin ulcer (2), butterfly rash (1), chloasma (1), drug eruption (1), dry skin (1), pseudoporphyria (1), psoriasis (1)
Eye disorders	3,790 (9.2)	periorbital edema (3,709), eye pain (21), lacrimation increased (15), eyelid edema (14), visual impairment (11), corneal edema (7), blepharitis (4), eye disorder (1), eye edema (1), eyelid disorder (1), eyelid retraction (1), macular edema (1), papilledema (1), retinal edema (1), ulcerative keratitis (1), xerophthalmia (1)
Immune system disorders	3,064 (7.5)	anaphylactic reaction (2,102), anaphylactic shock (898), anaphylactoid reaction (47), eosinophilic, hypersensitivity (16), granulomatosis with polyangiitis (1)
General disorders and administration site conditions	2,725 (6.6)	face edema (1,237), chest pain (771), edema (338), edema peripheral (197), pyrexia (37), fatigue (33), generalized edema (18), gravitational edema (15), mucosal inflammation (13), pain (11), chills (8), enanthema (8), mucosal ulceration (6), condition aggravated (3), drug ineffective (3), feeling of body temperature change (3), injection site inflammation (3), injection site pain (3), application site reaction (2), asthenia (2), drug tolerance decreased (2), injection site reaction (2), malaise (2), chest discomfort (1), crying (1), drug interaction (1), influenza like illness (1), injection site bruising (1), injection site dermatitis (1), injection site necrosis (1), edema mucosal (1)

Table 4 Classification of adverse events by the MedDRA coding system (N = 41,038)[a] (continued)

System organ class	Number (%)	Preferred term (number)
Gastrointestinal disorders	2,164 (5.3)	edema mouth (1,216), mouth ulceration (246), nausea (167), vomiting (142), anesthesia oral (74), gastrointestinal hemorrhage (44), abdominal pain (39), dry mouth (35), dyspepsia (31), stomatitis (31), cheilitis (23), diarrhea (22), tongue edema (18), glossitis (11), flatulence (7), gastritis (7), gingival bleeding (6), melaena (6), gingival hypertrophy (4), mouth cyst (4), tongue ulceration (4), gastric ulcer (3), gastroesophageal reflux disease (3), hematemesis (3), dysphagia (2), tongue disorder (2), abdominal distension (1), anal ulcer (1), aphthous ulcer (1), breath odor (1), duodenal ulcer hemorrhage (1), faces discolored (1), gastrointestinal disorder (1), hypoesthesia oral (1), mouth hemorrhage (1), esophagitis (1), saliva altered (1), salivary hypersecretion (1), tongue discoloration (1), toothache (1)
Respiratory, thoracic and mediastinal disorders	1,243 (3.0)	dyspnea (973), bronchospasm (91), choking (69), asthma (33), throat tightness (11), cough (9), asphyxia (6), dysphonia (5), obstructive airways disorder (5), bradypnea (4), pharyngeal oedema (4), respiratory disorder (4), respiratory failure (4), stridor (4), epistaxis (3), pulmonary oedema (3), respiratory depression (3), hypoventilation (2), apnea (1), bronchospasm paradoxical (1), hemoptysis (1), hiccups (1), hyperventilation (1), hypoxia (1), laryngeal edema (1), pulmonary congestion (1), respiratory acidosis (1), sputum increased (1)
Infections and infestations	316 (0.8)	conjunctivitis (206), rhinitis (43), rash pustular (27), pharyngitis (18), cellulitis (5), meningitis (4), eye infection (2), genital infection (2), laryngitis (2), pneumonia (2)ll abscess (1), gastroenteritis (1), gingivitis (1), infection (1), orchitis (1)
Nervous system disorders	314 (0.8)	dizziness (147), hypoesthesia (67), dysesthesia (21), headache (20), syncope (16), paranesthesia (10), dystonia (7), tremor (6), tongue paralysis (4), neuropathy peripheral (3), muscle contractions involuntary (2), paralysis (2), apraxia (1), asterixis (1), cerebrovascular disorder (1), coma (1). hyperkinesia (1), migraine (1), parosmia (1), seizure (1), taste disorder (1)

Table 4 Classification of adverse events by the MedDRA coding system (N = 41,038)[a] (continued)

System organ class	Number (%)	Preferred term (number)
Cardiac disorders	270 (0.7)	palpitations (222), tachycardia (26), angina pectoris (7), bradycardia (4), cardiac arrest (3), cardiac failure (3), arrhythmia (2), myocardial infarction (2), atrioventricular block (1)
Vascular disorders	138 (0.3)	flushing (58), hypotension (46), hypertension (18), vasculitis (9), hot flush (3), circulatory collapse (1), hematoma (1), hemorrhage (1), peripheral ischemia (1)
Renal and urinary disorders	62 (0.2)	acute kidney injury (19), renal impairment (16), hematuria (6), azotemia (5), urinary retention (4), dysuria (3), oliguria (2), tubulointerstitial nephritis (2), chronic kidney disease (1), cystitis hemorrhagic (1), nephritis (1), urethral syndrome (1), urinary incontinence (1)
Injury, poisoning and procedural complications	40 (0.1)	thermal burn (39), fracture (1)
Musculoskeletal and connective tissue disorders	40 (0.1)	muscular weakness (11), myalgia (9), back pain (6), arthralgia (5), arthropathy (2), pain in extremity (2), arthritis (1), muscle atrophy (1), muscle spasms (1), systemic lupus erythematosus (1), tendonitis (1)
Reproductive system and breast disorders	34 (0.1)	genital ulceration (13), edema genital (11), pruritus genital (3), balanoposthitis (2), genital pain (2), genital rash (1), penis disorder (1), perineal pain (1)
Psychiatric disorders	22 (0.1)	insomnia (7), confusional state (5), agitation (4), anxiety (2), completed suicide (1), eating disorder (1), intentional self-injury (1), nervousness (1)
Investigations	21 (0.1)	weight increased (14), urine analysis abnormal (3), blood creatine phosphokinase increased (2), international normalized ratio increased (2)

Table 4 Classification of adverse events by the MedDRA coding system (N = 41,038)[a] (continued)

System organ class	Number (%)	Preferred term (number)
Hepatobiliary disorders	20 (0.0)	hepatitis (15), hepatocellular injury (3), hepatitis cholestatic (2)
Ear and labyrinth disorders	13 (0.0)	tinnitus (4), ear pain (3), vertigo (3), hypoacusis (2), ototoxicity (1)
Surgical and medical procedures	12 (0.0)	local anesthesia (12)
Blood and lymphatic system disorders	11 (0.0)	agranulocytosis (2), methemoglobinemia (2), thrombocytopenia (2), eosinophilia (1), hemolytic anemia (1), lymphadenopathy (1), thrombocytopenic purpura (1), thrombocytosis (1)
Congenital, familial and genetic disorders	8 (0.0)	vascular malformation (7), lipidosis (1)
Metabolism and nutrition disorders	4 (0.0)	hyperkaliemia (2), lactic acidosis (1), lipedema (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.0)	angiofibroma (1), angiosarcoma (1)

MedDRA; Medical Dictionary for Regulatory Activities.

[a]41,038 events from 32,857 cases were included because 15,364 reports had more than one event or drug.

Table 5 Characteristics of patients whose adverse reactions did not recover (N = 5,420)

Characteristic		N	(%)
Sex of patients			
Male		1,869	(34.5)
Female		3,545	(65.4)
NA		6	(0.1)
Age of patient (years old)			
0–9		259	(4.8)
11-19		377	(7.0)
20-39		1,335	(24.6)
40–59		1,589	(29.3)
≥ 60		743	(13.7)
NA		1,117	(20.6)
History of drug allergy			
No		2,692	(49.6)
Yes		1,006	(18.6)
NA		1,722	(31.8)
Underlying disease			
No		2,561	(47.2)
Yes		531	(9.8)
NA		2,328	(43.0)
Causality of ADR			
Certain		242	(4.5)
Probable		3,612	(66.6)
Possible		1,566	(28.9)
Time to onset (days) [a]			
Median (IQR)	0.0 (1)		
Time of exposure (days) [b]			
Median (IQR)	0.0 (1)		
Number of suspected drugs per report			
1		4,676	(86.3)
2		631	(11.6)
3		92	(1.7)
≥4		21	(0.4)

ADR, adverse drug reaction; NA, not available; IQR, interquartile range.

[a]5,330 reports were included.

[b]5,286 reports were included.

Table 6 Characteristics of 20 fatal cases

Case no.	Sex	Age (years)	History of drug allergy	Under-lying disease	Drug	Role	Event	Time to onset (days)	Causality
Death possibly related to the event									
1	M	66	allopurinol and orphe-nadrine	NA	piroxicam	S	SJS	36	possible
					cimetidine	S		36	
2	M	11	No	epilepsy	phenobarbital	S	TEN	23	possible
						S		1	
					ibuprofen	S		2	
					amoxycillin	S		19	
					traditional medicine				
3	M	74	NA	NA	piroxicam	S	SJS	16	possible
					gabapentin	S		16	
4	F	56	No	NA	carbamazepine	S	TEN	7	possible
						S		7	
					clindamycin	S		7	
					ibuprofen				
5	M	40	NA	NA	piroxicam	S	TEN	2	probable
6	M	69	piroxicam	NA	ibuprofen	S	TEN	<1	probable
7	F	79	NA	NA	piroxicam	S	SJS	<1	certain
8	F	36	No	NA	diclofenac	S	anaphy- lactic shock	<1	probable
					paracetamol	C		<1	
Death unrelated to the event									
9	F	73	No	NA	piroxicam	S	rash erythe-matous	7	possible
10	M	61	No	CKD and kidney stone	diclofenac	S	SJS	7	probable
					ofloxacin	C		7	
					hyoscine-n-butylbromide	C		7	
						C		7	

Case no.	Sex	Age (years)	History of drug allergy	Under-lying disease	Drug	Role	Event	Time to onset (days)	Causality
11	M	77	No	gout	doxazosin mesylate nimesulide	S	acute kidney injury	5	possible
12	F	66	NA	NA	indomethacin	S	anaphy-lactic reaction	2	possible
13	M	75	NA	NA	diclofenac	S	rash erythe-matous angioe-dema	11	probable
14	M	NA	tolperisone	NA	ibuprofen	S	anaphy-lactic reaction	<1	probable
15	M	4	No	No	ibuprofen	S	rash maculo-papular	<1	probable

Table 6 Characteristics of 20 fatal cases (continued)

Case no.	Sex	Age (years)	History of drug allergy	Under-lying disease	Drug	Role	Event	Time to onset (days)	Causality
16	F	29	NA	NA	ibuprofen	S	angioedema	<1	probable
17	M	33	NA	NA	diclofenac ketorolac	S S	rash	<1 <1	probable
18	F	57	No	No	naproxen	S	urticaria	<1	probable
19	F	52	diclofenac and mefenamic acid	Hyperli-pidemia	naproxen	S	rash erythe-matous	<1	probable
20	M	41	No	No	mefenamic acid	S	urticaria	<1	probable

NA, not available; S, suspected; C, concomitant; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; CKD, chronic kidney disease

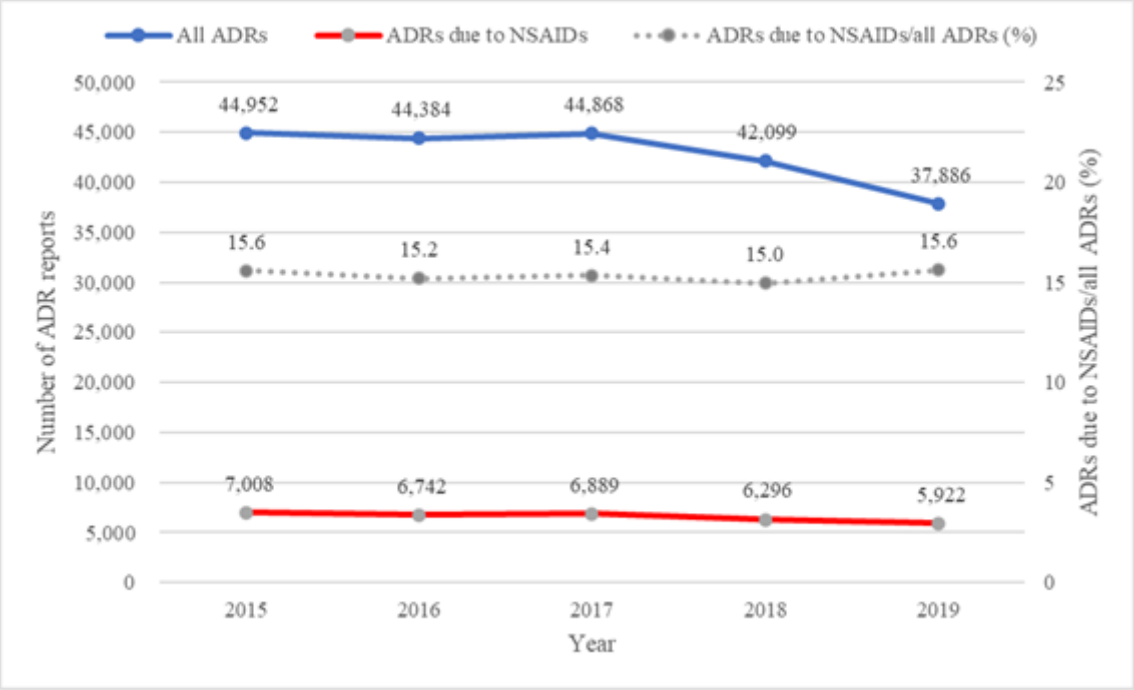

Fig. 1 The trend of reporting all ADRs and ADRs due to NSAIDs from 2015 to 2019.

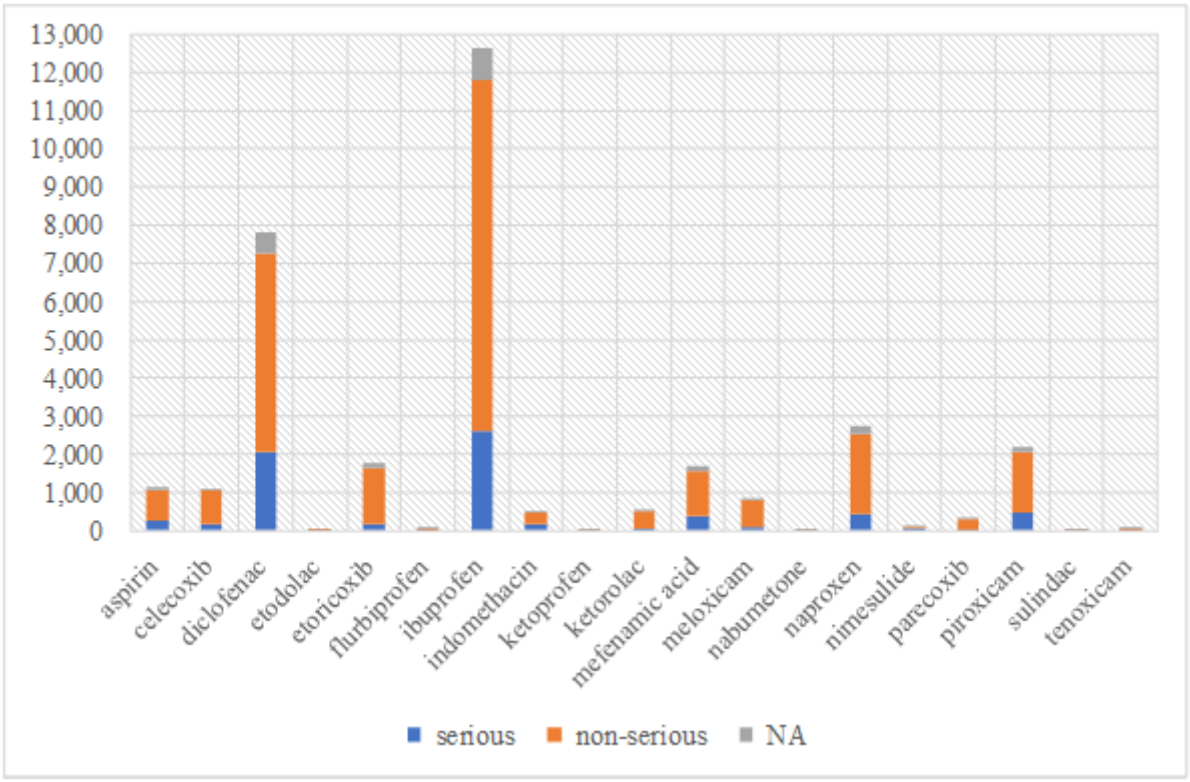

Fig. 2 The number and seriousness of ADRs based on the type of NSAIDs.