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Characteristics of adverse drug reactions due to nonsteroidal anti-inflammatory drugs: a cross-sectional study

Cholticha Sonsupap[1,2], Pattreya Pokhakul[2], Tetsuyoshi Kariya[1], Yunosuke Suzuki[1], Nobuyuki Hamajima[1] and Eiko Yamamoto[1]

[1]*Department of Healthcare Administration, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[2]*Health Product Vigilance Center, Food and Drug Administration, Ministry of Public Health, Nonthaburi, Thailand*

ABSTRACT

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 cross-sectional study aimed to analyze the characteristics of ADRs due to NSAIDs in Thailand. All ADR reports of NSAIDs for systemic use from 2015 to 2019 were extracted from the national database in Thailand. Patient characteristics, drug use information, adverse event information, and source of senders in 32,857 reports were analyzed. The annual number of ADR reports due to NSAIDs decreased from 7,008 in 2015 to 5,922 in 2019. The most frequently reported drug was ibuprofen (n=12,645, 38.5%) followed by diclofenac (n=7,795, 23.7%), most patients were 40–59 years old, and the major adverse reaction was angioedema (n=7,513, 22.9%). Serious reactions were recorded in 20.7% (n=6,801) of the total ADRs. Most patients (n=20,593, 62.7%) recovered without sequelae, but there were 5,420 patients (16.5%) who could not recover and 3,109 patients (9.5%) who were recovering. Eight patients (0.02%) died of Stevens-Johnson syndrome (n=3), toxic epidermal necrolysis (n=4), and anaphylactic shock (n=1), which were possibly related to ADRs. The number of ADR reports due to NSAIDs decreased from 2015 to 2019 in Thailand. Serious ADRs and death cases accounted for 20.7% and 0.02%, respectively. Most fatal cases exhibited severe drug-induced skin reactions.

Keywords: nonsteroidal anti-inflammatory drug, adverse drug reaction, Thailand

Abbreviations:
NSAID: nonsteroidal anti-inflammatory drug
ADR: adverse drug reaction
COX: cyclooxygenases
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

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Corresponding Author: Eiko Yamamoto, MD, PhD
Department of Healthcare Administration, Nagoya University Graduate School of Medicine,
65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
Tel: +81-52-744-1985, Fax: +81-52-744-2302, E-mail: yamaeiko@med.nagoya-u.ac.jp

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 mucosa, platelets, endothelium, kidneys, and uterus, and functions as a housekeeping enzyme that maintains homeostasis.[8,9] On the other hand, COX-2 is induced during inflammation.[10] The gastrointestinal side effects of inhibiting COX-1 are 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 removed from the global market.

Reporting the ADRs of post-marketing products is an important surveillance system for drug safety. The spontaneous reporting system is widely used worldwide,[15,16] although it may exhibit some limitations, such as incomplete information and under-reporting.[15,17] By using cumulative and a 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. 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 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 alone 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 due to NSAIDs. A total of 32,857 ADRs due to NSAIDs were included in the study after excluding 117 ADRs due to the above reasons. The study protocol was approved by the Ethical Review Committee for Research in Human Subjects of the Ministry of Public Health on October 28, 2020 (approval number: 18/2563).

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 systems affected by ADRs were coded according to the Medical Dictionary for Regulatory Activities terminology.[22] Seriousness was categorized into serious or non-serious. Serious ADRs included one of the following: 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: hospitals and clinics in the public and private sectors, pharmaceutical companies, pharmacies, and others, including governmental public health offices.

Statistical analyses

Descriptive statistics were used to describe the characteristics of ADRs and to determine the frequencies and percentages for categorical data. Reporting odds ratio (ROR) was calculated by disproportionality analysis. Disproportionality signals were defined as having an ROR value of more than 1 with lower limit of 95% confidence interval of more than 1 and the number of reports for interested adverse event-drugs being more than or equal to 3.[25] Microsoft Excel version 2019 and IBM SPSS version 27 (IBM SPPS Inc, New York, USA) were used for the statistical analyses.

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 due to NSAIDs in all ADR reports was stable (15.0–15.6%) from 2015 to 2019. The total number of reports on ADRs and ADRs due to NSAIDs from 2015 to 2019 was 214,189 and 32,857.

Figure 2 shows the number and seriousness of ADRs based on types of NSAIDs. The most frequently reported drug was ibuprofen (n=12,645, 38.5%), followed by diclofenac (n=7,795, 23.7%), and naproxen (n=2,741, 8.3%). 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 (n=21,126, 64.3%) than in male patients, and the majority of patients were in the age group of 40–59 years (n=10,056, 30.6%). Almost half of all patients had no history of drug allergy (n=16,365, 49.8%) or underlying disease (n=15,196, 46.3%). Most ADRs were non-serious (n=23,827,

72.5%), and 20.7% (n=6,801) of all ADRs were serious. Regarding the causality assessment, 66.4% (n=21,807) were probable, followed by possible (n=9,597, 29.2%), and certain (n=1,453, 4.4%). Almost all reports were submitted by either the hospitals or clinics (n=32,776, 99.8%). The others (n=81, 0.2%) were submitted by the pharmacies, pharmaceutical companies, Thai Food and Drug Administration, and provincial public health offices. Most reports were from the provinces (n=27,351, 83.2%). The median time period of the occurrence of ADRs was 3.5

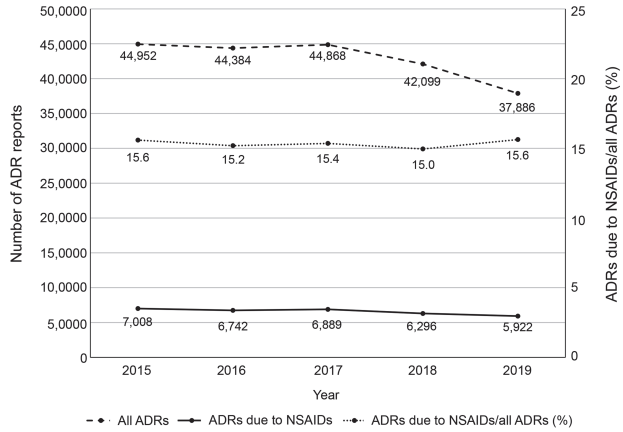

Fig. 1 The trend of reporting all adverse drug reactions and adverse drug reactions due to non-steroidal anti-inflammatory drugs from 2015 to 2019

NSAID: non-steroidal anti-inflammatory drug
ADR: adverse drug reaction

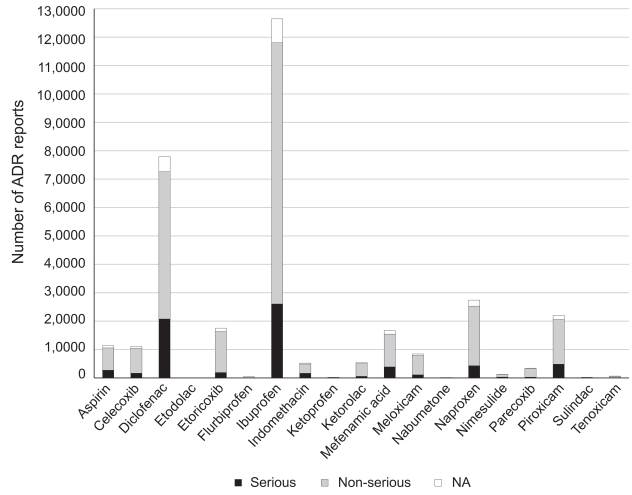

Fig. 2 The number of adverse drug reactions according to types of non-steroidal anti-inflammatory drugs and seriousness from 2015 to 2019

ADR: adverse drug reaction
NA: not available

(interquartile range, 13.8) days. Regarding the outcomes of ADRs, recovery without sequelae was the most common (n=20,593, 62.7%) followed by not recovered (n=5,420, 16.5%) and recovering (n=3,109, 9.5%). Eight patients (0.02%) 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.

Table 1 Characteristics of patients and ADRs due to NSAIDs 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)

Outcome[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)
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 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 shows the top 20 reactions based on the preferred terms of the Medical Dictionary for Regulatory Activities coding system. The most frequently reported reaction was angioedema (n=7,513, 22.9%), followed by urticaria (n=4,902, 14.9%) and maculopapular rash (n=3,556, 10.8%). Additionally, anaphylactic shocks were observed in 798 (2.4%) of all reactions. Adverse events classified based on organ systems are listed in Table 3. Skin and subcutaneous tissue were the most frequently reported organ system disorders (n=26,725, 65.1%), followed by eye disorders (n=3,790, 9.2%), immune system disorders (n=3,064, 7.5%), general disorders and administration site conditions (n=2,725, 6.6%), and gastrointestinal disorders (n=2,164, 5.3%).

Table 2 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 edema	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 3 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)
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 edema (4), respiratory disorder (4), respiratory failure (4), stridor (4), epistaxis (3), pulmonary edema (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), 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)
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)
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 (including 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.

The characteristics of patients who possibly died from the event are summarized in Table 4. Two out of the eight patients had a history of drug allergy, especially one case (case No. 6) had a history of allergy to NSAIDs. Seven patients exhibited severe drug-induced skin reactions, such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Piroxicam was the most commonly reported drug (n=4), followed by ibuprofen (n=3). Twenty-four pairs of each NSAIDs-adverse event were detected as new signals. The top three highest ROR values were etoricoxib–oliguria (ROR, 22.97; 95% CI, 8.16–64.65), parecoxib-cardiac arrest (ROR, 15.53; 95% CI, 5.77–41.79) and etoricoxib-pharyngeal edema (ROR, 12.83; 95% CI, 3.99–41.23) (Table 5). New signals were defined when those adverse events due to NSAIDs met the criteria for the disproportionality signals (ROR value > 1 with lower limit of 95% CI > 1 and the number of reports for interested adverse event-drugs ≥ 3), and the events were not listed on the drug labels.

Table 4 Characteristics of patients who possibly died from the event

No.	Sex	Age (years)	History of drug allergy	Under-lying disease	Drug	Role	Event	Time to onset (days)	Causality
1	M	66	Allopurinol, orphenadrine	NA	Piroxicam, cimetidine	S S	SJS	36 36	Possible
2	M	11	No	Epilepsy	Phenobarbital, ibuprofen, amoxicillin, traditional medicine	S S S S	TEN	23 1 2 19	Possible
3	M	74	NA	NA	Piroxicam, gabapentin	S S	SJS	16 16	Possible

4	F	56	No	NA	Carbamazepine, clindamycin, ibuprofen	S S S	TEN	7 7 7	Possible
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, paracetamol	S C	Anaphy- lactic shock	<1 <1	Probable

M: male
F: female
NA: not available
S: suspected
C: concomitant
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

Table 5 Reporting odd ratio of new signals of NSAIDs

Drug	Preferred term[a]	Number of reports[b]	ROR	95% CI
Etoricoxib	oliguria	4	22.97	8.16–64.65
Parecoxib	cardiac arrest	4	15.53	5.77–41.79
Etoricoxib	pharyngeal edema	3	12.83	3.99–41.23
Sulindac	cheilitis	5	12.48	5.14–30.27
Etoricoxib	genital ulceration	10	8.94	4.74–16.85
Parecoxib	lacrimation increased	3	8.94	2.86–27.91
Celecoxib	hiccups	4	7.63	2.81–20.70
Parecoxib	choking	6	6.29	2.81–14.06
Ibuprofen	lacrimation increase	62	5.01	3.79–6.63
Diclofenac	laryngeal edema	5	4.41	1.73–11.26
Parecoxib	flushing	16	3.97	2.42–6.50
Etoricoxib	thermal burn	15	3.85	2.31–6.42
Celecoxib	choking	13	3.21	1.86–5.55
Diclofenac	lacrimation increase	24	2.68	1.77–4.07
Aspirin	choking	11	2.50	1.38–4.53
Ibuprofen	choking	83	2.08	1.66–2.61
Meloxicam	fixed eruption	96	2.05	1.67–2.51
Meloxicam	eczema	13	1.89	1.09–3.26
Mefenamic acid	fixed eruption	205	1.78	1.55–2.05
Etoricoxib	cheilitis	17	1.71	1.06–2.76
Mefenamic acid	anaesthesia oral	29	1.68	1.16–2.42
Etoricoxib	anaesthesia oral	20	1.67	1.07–2.60
Celecoxib	anaesthesia oral	19	1.64	1.04–2.58
Aspirin	fatigue	37	1.41	1.02–1.95

[a]Preferred term of adverse events by the MedDRA coding system.
[b]All the reports containing NSAIDs that were identified as suspected or drug interaction were extracted from the Thai VigiBase, and each report may contain more than one event or drug.

DISCUSSION

To the best of our knowledge, this is the first study to analyze ADRs caused by all types of NSAIDs reported in Thai VigiBase. In this study, four important findings 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 due to NSAIDs from 2015 to 2019. There are some possible reasons for the decrease in ADRs as well as ADRs due to NSAIDs. First, the Ministry of Public Health requested all hospitals to follow the "National Patient and Personnel Safety Goals" policy, which included an activity for patient safety to prevent ADRs and medication errors.[26] Government regulations and policies might be effective in reducing ADRs.[27] Second, healthcare workers might not report all ADRs, because a previous study on healthcare workers attitude towards reporting ADRs revealed that hospital staff paid less attention to the ADR reporting system than general practices.[28] Third, there might be lack of understanding regarding the ADR reporting system among healthcare workers or other problems in the hospitals. Vallano and colleagues demonstrated that the pharmacovigilance system in the hospitals did not work properly due to a lack of information of the system, low accessibility to the system by the staff, less utility of the reporting system, and a lack of tools, such as reporting forms.[29] In any reporting system, under-reporting is an important issue that needs to be resolved.[29,30]

Ibuprofen was the most commonly administered drug reported in Thailand. According to the National Guidelines for Essential Medicines, ibuprofen is recommended as the first-line treatment for several indications in Thailand.[31] In a study that included 149 patients with a history of NSAID hypersensitivity at the university hospital in Denmark between 2002 and 2011, aspirin, ibuprofen, and diclofenac were reported as the top three drugs that caused hypersensitive reactions. Not only ibuprofen but also all NSAIDs should be prescribed carefully, because frequent use of NSAIDs is associated with the occurrence of hypersensitive reactions.[32]

In this study, angioedema was the most commonly reported ADR, followed by urticaria and these two reactions are the most commonly recognized cutaneous reactions due to NSAIDs.[33] Clinical manifestations, such as hypersensitivity, are unpredictable and occur mostly in susceptible people. In this study, most fatal cases exhibited severe drug-induced skin reactions. The mortality rate was high among patients with severe drug-induced skin reactions due to complications that occurred during the acute phase, including septicemia.[34] The mortality rates of patients who had SJS and TEN was reported to be 5% and 40%, respectively.[35] In this study, 299 cases had SJS or TEN and seven cases (2.3%) of them died of the events. There are some risk factors for developing SJS and TEN including a genetic factor which is related to specific human leukocyte antigens and some medications including NSAIDs.[36-38] The prodromal symptoms are fever, chills, fatigue, headache, cough, and sore throat and the symptoms can appear within 1–12 weeks after taking responsible drugs.[39] Early detection of prodromal signs and discontinuation of drugs may help decrease the mortality rate from severe drug-induced skin reactions.[40]

Some ADRs due to NSAIDs are idiosyncratic and cannot be predicted through pharmacology. However, it is important to establish a system to prevent the development of serious illnesses following any ADRs. Medication error should be prevented by checking a patient's allergy history before prescribing or dispensing medication. In Thailand, patients can buy some types of NSAIDs at pharmacies without a prescription but with advice by pharmacists. A central database system which allows all hospitals and pharmacies in Thailand to access the data of each patient's allergy

history needs to be developed. Furthermore, healthcare professionals should be aware of the potential risks of ADRs caused by NSAIDs and they also should provide appropriate instructions and education about ADRs to patients.

This study had some limitations. First, ADR data might be under-reported, but under-reporting is often found in spontaneous reporting systems.[26,29] Conversely, the number of reports may increase after issuing a warning on a drug or soon after marketing authorization. Second, the senders might not report the information on all concomitant drugs that were 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.

The annual number of ADRs and ADRs due to NSAIDs in Thailand decreased from 2015 to 2019. Ibuprofen was the most frequently reported drug in the ADR reports. The most common ADR due to NSAIDs was angioedema, followed by urticaria. Most fatal cases exhibited severe skin reactions, such as SJS and TEN. The Thai VigiBase system was useful in understanding ADRs due to NSAIDs in Thailand. To prevent serious ADRs and deaths caused by NSAIDs, a system for the early detection of ADRs and stopping preventable ADRs should be established.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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