Original article

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SAFETY OF TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) USING THE THAI HEALTH PRODUCT VIGILANCE CENTER DATABASE

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ABSTRACT

This study sought to determine the characteristics of adverse events (AEs) reported in patients using topical non-steroidal anti-inflammatory drugs (NSAIDs) in Thailand as per the Thai Health Product Vigilance Center Database (Thai Vigibase). All AE reports from 1984 to 2016, involving topical NSAIDs and registered in Thailand, were retrieved from the Thai Vigibase. The following information on patient demographics was extracted from each report: age, gender, history of drug allergy, concomitant diseases, suspected drugs, timing of drug exposure, concomitant drugs, suspected reactions, time to onset of AEs, seriousness, and causality assessment. Descriptive statistics were used for data analyses. Results identified 179 AEs as reported by hospitals. The mean age was 47.2±17.2 years and 56.4% were female. Diclofenac (49.2%), ketoprofen (25.4%), and piroxicam (21.5%) were the three most commonly suspected drugs. Eighteen AE reports (10.1%) were classified as serious with 14 cases (7.8%) requiring hospitalization or prolonged hospitalization, and 2 cases (1.1%) resulted in death related to toxic epidermal necrolysis (TEN) and eczema. Of the 179 total reports, 249 AEs were found. Overall, skin and appendage disorders were the most common AEs reported (77.1%), followed by the body as whole - general disorders (8.8%), application site disorders (6.8%), gastrointestinal system disorders (2.4%), and disorders of the central and peripheral nervous system (1.6%). Most AEs (88.9%) occurred during the first week of treatment, of which 39.2% manifested within 24 hours after application. The causality of most reported events was classified as probable (57.5%). The most frequent skin AEs were pruritus and rash. In conclusion, topical NSAIDs were potentially associated with a risk of skin AEs. However, systemic AEs were uncommon. Further studies are needed to investigate the safety of topical NSAIDs for long-time use and in patients with severe or unstable comorbidities.

Keywords: topical non-steroidal anti-inflammatory drugs (NSAIDs), adverse events, Thai Vigibase

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Introduction

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been developed as an alternative to oral NSAIDs that are formulated for direct application to the painful area. They are widely available, advertised, and used extensively for pain relief for many years in some parts of the world, including Europe and Asia.[1] Topical NSAIDs are widely recommended in international guidelines as a first option for the symptomatic management of musculoskeletal pain, such as knee osteoarthritis (OA)[2-4], and OA in patients aged 75 years or older.[4,5] Recent systematic reviews (SR) and meta-analyses (MA) indicated that topical NSAIDs were superior to placebo for relieving pain due to musculoskeletal conditions.[6,7] There was an increase in local AEs with topical diclofenac compared with placebo or oral NSAIDs, but no increase with topical ketoprofen.[6] Up to 39% of patients using a topical NSAID reported a local AE, including dry skin, erythema, irritation, paresthesia, and pruritus, compared with 25% of patients receiving a placebo, whereas systemic AEs were up to 17.5%.[8] Systemic AEs did not differ from placebo[7,9] and were less frequent than with oral NSAIDs.[6] These results showed differences in the incidence of some AEs between oral and topical NSAID uses. However, some SR and MA focused on randomized controlled trials[6-9] which provided the most reliable estimates of treatment effects, the interpretation of safety data should be cautious from efficacy trials due to the absence of rigorous data collection on AEs, and the scanty incidence of rare AEs or events with significant latency.[10]

Even though topical NSAIDs are recommended as an initial treatment option for pain relief due to their safety profile[5,11], serious AEs associated with topical NSAIDs have gradually been reported during the last two decades. AEs such as photosensitivity reactions with topical ketoprofen gel in several countries[12-14], and hepatotoxicity associated with topical diclofenac uses[15-17] have been reported. Therefore, a postmarketing surveillance system is an essential mechanism in identifying AEs and their characteristics in the large number of patients being exposed to these medications, which may lead to regulatory actions to improve patient safety. In Thailand, the drug surveillance system was established in 1983 under the Health Product Vigilance Center (HPVC), Thai Food and Drug Administration (Thai FDA), Ministry of Public Health. In 1984, the HPVC developed Thai Vigibase as a national pharmacovigilance database collecting all case reports submitted from a spontaneous reporting system, intensive monitoring programs, and clinical trials nationwide via an AE reporting form or online reporting system. A total of more than 50,000 reports are presently received and evaluated annually[18], and the Thai Vigibase now contains over 800,000 reports.[19] Although a spontaneous reporting system has some limitations such as underreporting and limited quality of reports, Thai Vigibase is still a powerful data source to identify and describe the characteristics of patients and AEs associated with health products in Thailand in several surveillance studies.[20-22]

In Thailand, topical NSAIDs have been allowed to become easily accessible and widely available to patients at drug stores as over-the-counter (OTC) drugs. Although OTC drugs are believed to be relatively safe, their inappropriate use may lead to patient harm. Consequently, as a regulatory tool for the FDA, safety-related sections including contraindications, warnings, and precautions in the patient package insert (PPI) are essential information for patients or users to aware of the safety profile and enable them to decide whether to use or stop using such medication.[23] This information should be clear, accurate, complete, and updated continuously for the safe use of medications.[24] Therefore, previously approved safety-related content in PPIs could be occasionally revised, resulting from safety updates on new AEs.[25]

In Thailand, a legal warning, which is mandatory written warning about the predictable or

unpredictable adverse drug reactions in the PPI or box at approval, may be applied. Besides, the Drug Safety Advisory Subcommittee, under the Drug Committee of the Thai FDA, is assigned to decide the significance of various safety signals and give recommendations to add or revise the legal warnings after a drug's authorization.[26] The regulatory requirements of written legal warning in the PPI or box of topical NSAIDs, announced in the Notification of the Ministry of Public Health (volume 42, 2010), were the same as those for orally administered conventional NSAIDs.[27] Hence, based on topical NSAIDs' safety updates, the written legal warning of topical NSAIDs may differ from that of oral NSAID preparations and should be considered to revise its content. Nevertheless, the safety information regarding the frequency of AE results from topical NSAIDs and the types of AEs occurring among large populations are still limited.

This study aimed to determine the characteristics of AEs reported in patients using topical NSAID products in Thailand using the Thai Health Product Vigilance Center database. The findings may be useful for considering the revision of written legal warnings in the PPI of topical NSAIDs in Thailand.

Materials and methods

Data source

This retrospective study used the Thai Vigibase, which included all case reports of suspected AEs submitted by healthcare professionals throughout the country to the HPVC since the launch of the database in 1984 through December 2016. The Thai FDA permitted database access with patient anonymity, and we presented specific cases with only general demographic characteristics to ensure patient identity anonymously.

Criteria for the selection of case reports

All case reports of patients using any topical NSAID products in a single or combined formulation in Thailand were retrieved. Of those reports, patients had to use topical NSAIDs registered in Thailand and not as liquid ophthalmic, nasal, or otic preparations. During the study period, there were 166 topical NSAID products in six active ingredients or generic names with eight formulations, including diclofenac gel, ibuprofen cream and gel, indomethacin spray and gel, ketoprofen gel, piroxicam gel, and nimesulide gel registered in Thailand.[28] Report quality was assessed using WHO-Uppsala Monitoring Centre (WHO-UMC) documentation grading, which classified quality into four grades (0, 1, 2, and 3) depending on data completeness.[29,30] To be classified as grade 1, reports must include data on patient identification, at least one suspected drug, and at least one adverse event term with additional information on onset and treatment dates. For grade 2, treatment indication must be additionally provided, and for grade 3, detail on confirming positive rechallenge has to be given. All reports that provide information less than grade 1 level are classified as grade 0. Our study included only report quality grades 1-3 for the completeness of data analysis. Finally, reports with topical NSAIDs being suspected drugs were selected in the analysis. Figure 1 shows the study flow diagram for case selection.

Data extraction

All reports that indicated topical NSAID products as a suspected drug were identified. For each report, the following information was extracted: patient demographics (age, gender, history of drug allergy, concomitant diseases), suspected drugs, the timing of drug exposure, concomitant drugs, suspected reactions, time to onset of AEs, seriousness, causality assessment and quality of reports.

The number of reports and AEs classified by topical NSAIDs will be counted. AEs from each product were classified by the organ system affected. According to the WHO Adverse Reaction Terminology (WHO-ART) classification, each preferred term is categorized into a primary system organ class and up to two subsidiary system organ

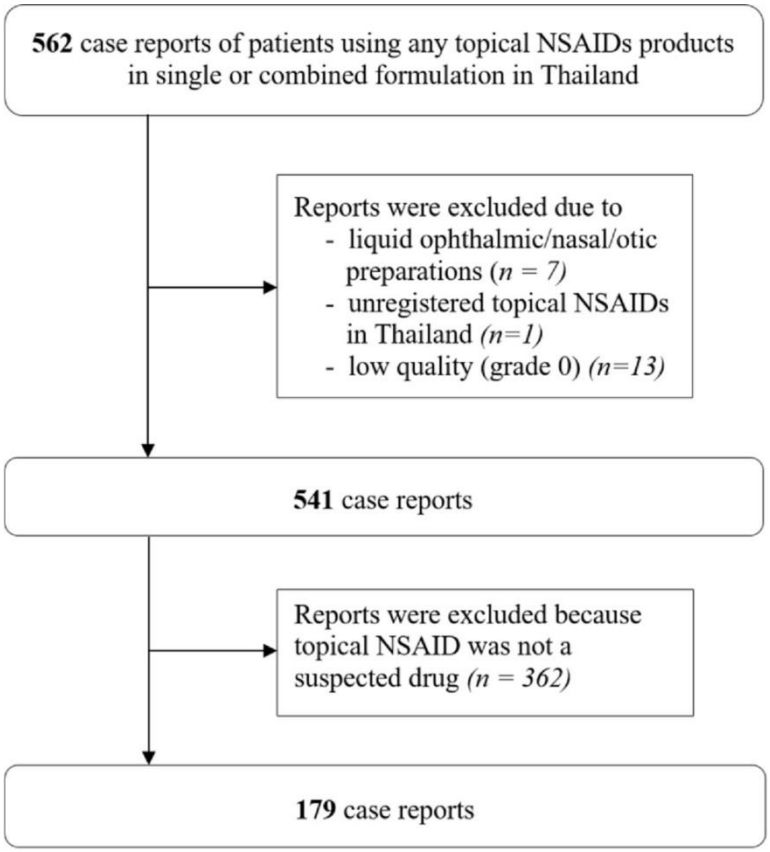

Figure 1 Study flow diagram

classes.[30] We used the matched pair of the primary system organ class and preferred term in our analysis. AEs were classified as serious or non-serious. Serious AEs were subclassified into hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, life-threatening, and death. Causality assessment was carried out using Naranjo's algorithm by health professionals at the time of report submission.[31] The algorithm consists of 10 questions answered as either Yes, No, or Do not know. Different point values (-1, 0, +1, or +2) are assigned to each answer. Total scores range from -4 to +13; the reaction is considered certain or definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and unlikely or doubtful if 0 or less.[31]

Data analyses

All variables were analyzed using descriptive statistics to determine the total number of reports. These reports included the mean age and number in each age group, gender, history of drug allergy, concomitant diseases, type and formulation of topical NSAIDs. The number of concomitant drugs, the distribution of AEs associated with each type of topical NSAIDs used, causality assessment, time of drug exposure, time to onset of reaction, seriousness and quality of reports are also considered. The data were managed using Microsoft Excel® and subsequently imported into IBM SPSS Statistics for Windows, version 17 for analysis.

Results

A total of 179 case reports of AEs associated with topical NSAID products in single formulation registered in Thailand were included in data analysis.

The characteristics of these 179 case reports are shown in Table 1. The ages ranged from 5 to 90 years, with a mean age of 47.2±17.2 years old, and more than half of the cases occurred in patients older than 45. Most reported cases involved female

(56.4%), and 34 cases (19.0%) had a history of drug allergies. Of which, 16 cases had the previous history of NSAID allergy. Four cases occurred a similar reaction to prior NSAID allergy, whereas 12 cases did not report a detailed history of allergic reactions. Approximately 83% of all cases had no concomitant diseases, and the three most common were myalgia/ muscle strain/ myositis (4/ 179, 2. 2%), hypertension (3/179, 1.7%), and diabetes (3/179, 1.7%).

Diclofenac (49.2%), ketoprofen (25.4%), and piroxicam (21.5%) were the three most commonly suspected drugs. All topical products containing NSAID as a single active agent, and most dosage forms (72.4%) were cream/gel/ointment/paste, and 5.5% were spray. Most patients (113/179, 63.1%) had no concomitant drugs. Of 145 total items of concomitant drugs in all cases, most of them were anti- inflammatory and antirheumatic products (59/ 145, 40. 7%), followed by muscle relaxants (22/ 145, 15. 2%), analgesic (16/ 145, 11. 0%), and antacids/ antiflatulents and anti- peptic ulcerants (10/145, 6.9%). They were administered orally (79.2%), injectable (1.4%), and topical (1.4%).

All cases were reported from the hospitals. For the causal relationship of AEs and the suspected topical NSAID drugs according to the Naranjo Algorithm, 57. 5% were assessed as probable, followed by possible (36. 9%) and certain (5. 6%). Regarding report quality, most case reports were graded at quality level 2 (47.5%) and 1 (46.4%).

The patterns of AEs are shown in Table 2. Most AEs (29.3%) had a drug exposure time of less than or equal to one day, with a mean exposure of 4.3 days. The majority of AEs (88.9%) were observed within one week of starting treatment. Of these, 39.2% developed within 24 hours. The most prolonged onset timing of AEs was five months after the first use of treatment. Most AE reports (88.3%) were classified as non-serious, whereas eighteen AE reports (10.1%) were classified as serious with 14 cases (7.8%) requiring hospitalization or prolongation of hospitalization, and two deaths (1.1%) were reported. It was found that 66.7% (12/18) and 33.3% (6/18) of serious case reports had causality assessment at the 'probable' and 'possible' level, respectively, and no certain serious case.

The first fatal case of a 90-year-old female developed symptoms of toxic epidermal necrolysis (TEN) on the same day of starting diclofenac spray used for muscle strain, and she stopped such medication the next day. She had none of the previous histories of drug allergy, comorbidities, and current concomitant drugs. She died after stopping diclofenac spray for six days. The causality assessment revealed the ADR to be 'probable' level. In the other case, a 39-year-old male with no comorbidities presented with eczema after one-day topical diclofenac exposure, and then he stopped such medication. He also took oral nimesulide and oral tolperisone, but they were not reported as suspected drugs. There was no detail on a history of drug allergy, the severity of eczema, and the alternative causes of death in such a case. Such a report was graded at quality level 1 with a 'possible' level.

Table 3 shows the number of AEs and reports for individual topical NSAID products. Of the 179 total reports in this study, we found 249 total AEs related to 181 topical NSAID products. The most frequently reported topical NSAID products relating to such AEs were diclofenac 49.2%, followed by ketoprofen 25.4%, piroxicam 21.5%, nimesulide 2.8%, and indomethacin 1.1%. Overall, skin and appendage disorders were the most common AEs reported (192/249, 77.1%), followed by the body as a whole – general disorders 8.8%, application site disorders 6.8%, gastrointestinal system disorders 2.4%, and central and peripheral nervous system 1.6%, as shown in table 4.

The most frequently reported skin AEs were rash and pruritus. Most skin AEs (172/192, 89.6%) were classified as non-serious. Serious skin AEs (18/192, 9.4%) were maculopapular rash/macular rash/rash, angioedema, urticaria, TEN, eczema, pruritus, bullous eruption, and drug eruption. The causality of most skin AEs were classified as probable (61.5%), followed by possible (32.8%), and certain (5.7%). All certain skin AEs were non-serious.

Table 1 Characteristics of patients and adverse event reports among topical NSAID product users

Characteristics	Number of patients/reports (%)
Patient demographics (n=179)	
Age (year), mean ± SD	47.2 ± 17.2
<15	8 (4.5)
15-30	21 (11.7)
31-45	41 (22.9)
46-60	54 (30.2)
61-75	32 (17.9)
>75	6 (3.4)
Not reported	17 (9.5)
Gender	
Female	101 (56.4)
Male	76 (42.5)
Not reported	2 (1.1)
History of drug allergy[a]	
No	115 (64.2)
Yes	34 (19.0)
NSAIDs[b]	16
Antibiotics	13
Analgesics	4
Topical analgesics	2
Elastic bandage	1
Others	6
Not reported	30 (16.8)
Concomitant diseases[c]	
No	149 (83.2)
Yes	27 (15.1)
Myalgia/muscle strain/myositis	4
Hypertension	3
Diabetes mellitus	3
HIV	1
Gout	1
Rectal cancer	1
Allergic rhinitis	1
Chronic urticaria	1
Rheumatoid arthritis	1
Not specified	12
Not reported	3 (1.7)

Table 1 Characteristics of patients and adverse event reports among topical NSAID product users (continued)

Characteristics	Number of patients/reports (%)
Topical NSAIDs and concomitant drugs	
Type of topical NSAIDs (n=181)[d]	
Diclofenac	89 (49.2)
Ketoprofen	46 (25.4)
Piroxicam	39 (21.5)
Nimesulide	5 (2.8)
Indomethacin	2 (1.1)
Type of topical NSAID dosage forms (n=181)[d]	
Cream/gel/ointment/paste	131 (72.4)
Spray	10 (5.5)
Emulsion/suspension	2 (1.1)
Not reported	38 (21.0)
Number of concomitant drugs (items), (n=179)	
mean ± SD, median	0.8 ± 1.2, 0
None	113 (63.1)
1 item	19 (10.6)
2 items	25 (14.0)
3 items	14 (7.8)
4 items	6 (3.4)
5 items	2 (1.1)
Adverse event reports	
Source of reports (n=179)	
Hospitals Under Ministry of Public Health	
Community hospitals	55 (30.7)
General hospitals	49 (27.4)
Regional hospitals	29 (16.2)
Private hospitals	20 (11.2)
Other hospitals	24 (13.4)
Not reported	2 (1.1)
Causality assessment (n=179)	
Certain	10 (5.6)
Probable	103 (57.5)
Possible	66 (36.9)
Quality of reports (n=179)	
Grade 3	11 (6.1)
Grade 2	85 (47.5)
Grade 1	83 (46.4)

[a] Each case may have > 1 medication causing drug allergy, [b] unknown type of dosage form,

[c] Each case may have > 1 concomitant disease, [d] Each case may have > 1 suspected topical NSAID

Table 2 Patterns of adverse events among topical NSAID product users

Characteristics	Number of reports (%)
Adverse event reports	
Time of exposure (days), mean ± SD (n=181)	4.3 ± 9.5
≤ 1 day[a]	53 (29.3)
2 – 4 days	77 (42.5)
5 – 7 days	23 (12.7)
8 days – 1 month	11 (6.1)
> 1 – 6 months	8 (4.4)
Not reported	9 (5.0)
Time to onset (days), mean ± SD (n=181)	4.2 ± 13.6
Within 1 week of use	
First day of use	71 (39.2)
2 – 4 days of use	76 (42.0)
5 – 7 days of use	14 (7.7)
8 days – 1 month of use	12 (6.6)
> 1 – 6 months of use	7 (3.9)
Not reported	1 (0.6)
Seriousness (n=179)	
Serious	18 (10.1)
Hospitalization or Prolongation of hospitalization	14 (7.8)
Life threatening	0
Death	2 (1.1)
Not specified	2 (1.1)
Non-serious	158 (88.3)
Not reported	3 (1.7)

[a] patient started and stopped the medication on the same day

Table 3 The number of reports and adverse events associated with individual topical NSAID products submitted to the Health Product Vigilance Center

Topical NSAIDs	Number of reports (%)[a]	Number of adverse events (%)[b]
Diclofenac	89 (49.2)	118 (47.4)
Ketoprofen	46 (25.4)	71 (28.5)
Piroxicam	39 (21.5)	53 (21.3)
Nimesulide	5 (2.8)	5 (2.0)
Indomethacin	2 (1.1)	2 (0.8)
Total	181 (100)	249 (100)

[a] Some reports have > one topical NSAID, [b] Some reports have > one adverse event.

Table 4 Adverse events of reported topical NSAID products classified by organ system according to WHO Adverse Reaction Terminology

System organ class	n (%) [n=249][a]	Detail of adverse events (n)[a]
Skin and appendages disorders	192 (77.1)	Pruritus (33), rash maculopapular (29), rash (29), urticaria (18), rash erythematous (23), angioedema (11), eczema (7), fixed eruption (6), itching (4), papular rash (3), bullous eruption (3), dermatitis (3), burn (2), eczema allergic (2), macular rash (2), papulovesicular rash (2), dermatitis allergic (1), dermatitis exfoliative (1), drug eruption (1), photosensitivity allergic reaction (1), rash follicular (1), rash impetiginous (1), rash psoriaform (1), rash purpuric (1), rash pustular (1), skin dry (1), skin erythema desquamative (1), skin ulceration (1), toxic epidermal necrolysis (1), urticaria aggravated (1), vesicular rash (1)
Body as a whole – general disorders	22 (8.8)	Face oedema (6), oedema (5), oedema eyelid (5), anaphylaxis (2), oedema periorbital (2), oedema legs (1), oedema of extremities (1)
Application site disorders	17 (6.8)	Dermatitis contact (11), application site reactions (6)
Gastrointestinal system disorders	6 (2.4)	Nausea (3), vomiting (3)
Central and peripheral nervous system disorders	4 (1.6)	Dizziness (2), burning sensation (1), paraesthesia (1)
Platelet, bleeding and clotting disorders	2 (0.8)	Thrombocytopenia (1), purpura (1)
Cardiovascular disorders, general	1 (0.4)	Shock (1)
Heart rate and rhythm disorders	1 (0.4)	Palpitation (1)
Musculo-skeletal system disorders	1 (0.4)	Arthritis (1)
Respiratory system disorders	1 (0.4)	Dyspnoea (1)
Special senses other, disorders	1 (0.4)	Taste loss (1)
Vision disorders	1 (0.4)	Conjunctivitis (1)
Total	249 (100)	

[a] Number of events from 179 total reports (some reports have more than one suspected topical NSAIDs and/or one adverse event)

Approximately 90% (172/192) of skin AEs were observed within one week after topical NSAID uses, including rashes, pruritus/itching, eczema, urticaria, fixed eruption, dermatitis, angioedema, and allergic photosensitivity. Of these, 41.7% (80/192) of skin AEs developed within 24 hours of treatment, including most serious skin AEs (13/18) such as TEN, angioedema, urticaria, and eczema. The majority of

concomitant drugs in patients with skin AEs were also anti-inflammatory and antirheumatic products (32.0%), followed by muscle relaxants (15.6%), analgesic (14.8%).

Discussion

This is the first study to accumulate and determine the characteristics of AEs reported in patients using topical NSAID products in Thailand. Our findings revealed a total of 179 reports involving 181 topical NSAID products with 249 AEs. Diclofenac, ketoprofen, and piroxicam were the most frequently reported, but there was no ibuprofen report. Besides the number of reports depending on the drug effects themselves, it may also result from the number of products under the same generic name available in the market. All diclofenac, ketoprofen, and piroxicam products became approximately 90%, especially diclofenac products were around 50%, whereas ibuprofen products were only 1.2% of all available topical NSAID products.[28]

Based on our findings, skin and appendage disorders were the most commonly reported AEs of topical NSAIDs. The most frequent skin AEs were pruritus and rash and were classified as non-serious. This is consistent with previous studies, indicating that local skin AEs were reported commonly in topical NSAID uses[6,8], and were mostly mild and transient.[6,7] Although AEs could be related to other contributing factors, we found almost all patients experiencing skin AEs without concomitant skin diseases, except one with underlying chronic urticaria. Approximately 90% of skin AEs in this study were observed within one week of topical NSAID uses, including rashes, pruritus/itching, and dermatitis. This was because the most common skin drug reactions are caused by immunologic mechanisms in nature which usually take 7-10 days to become allergic to a drug.[32] Additionally, around 40% of skin AEs developed within 24 hours of treatment, including angioedema, urticaria, and eczema. Such AEs could occur through type I hypersensitivity reaction which usually begin within minutes to hours after drug exposure.[32] It is important to note that most serious skin AEs in this study were observed within 24 hours of application. Although the majority of skin AEs were non-serious and could be managed without hospitalization, the patients should be informed to alert for the signs and symptoms of serious skin manifestations to early detect serious skin AEs and discontinued such topical NSAIDs at the first appearance of skin rash or any other signs of hypersensitivity.

There were formerly concerns about gastrointestinal (GI) complications with topical NSAID use due to the high risk of such events in patients taking oral NSAIDs. Previous studies suggested that GI-related AEs with topical NSAIDs did not differ from placebo[6,9], but were less frequent than with oral NSAIDs.[6,8] One case-control study indicated no significant independent associations between topical NSAID use and upper GI bleeding and perforation.[33] Our findings lend support to previous studies. There were few GI-related AEs reported, and all were nausea or vomiting with non-serious conditions. There were no reports of GI bleeding, ulceration, or perforation in the database. However, such a case-control study had some limitations as they did not control the previous medical history of GI events. Although the existing data on topical NSAID use in patients with a history of GI complications are still limited, they are more likely to be used than oral NSAIDs in patients with GI comorbidities, particularly treatments for knee OA.[3] Nevertheless, patients need to be provided the warning information related to GI complications to avoid using if they have a history of GI bleeding, ulceration, or perforation.

For the safety of topical NSAIDs in patients with an elevated risk of NSAID-related AEs, such as the elderly and those with comorbidities, a previous study suggested that the rate of cardiovascular and renal AEs in topical diclofenac-treated patients did not differ according to age, and comorbid hypertension, type 2 diabetes, or cerebrovascular or cardiovascular disease.[34] However, only diclofenac

gel may not represent all topical NSAIDs well, and the protocol of this study excluded patients with severe or unstable illness, such as severe cardiovascular disease. Our study found edema approximately 8% (20/249) of all AEs, and all cases had no concomitant cardiovascular or renal disease. Nevertheless, it could not conclude that topical NSAIDs were the real cause of edema in these cases since almost half of the case reports had some concomitant drugs, particularly oral NSAIDs, that can cause fluid retention or edema. Although there is evidence supporting topical NSAIDs' safety in patients with comorbidities, there is no adequate evidence for long term use and in patients with severe or unstable comorbidities. Also, patients need to be provided with warning information to be aware of the prolonged use of topical NSAIDs to avoid cardiovascular and renal AEs.

The particular attention in patients with a history of NSAID allergy should be discussed. We found four topical ketoprofen case reports occurring similar reactions to the previous history of NSAID allergy, including eyelid edema, angioedema, and urticaria. Regarding histories of allergies, the first and second cases had a reaction related to a single NSAID, including ibuprofen and naproxen. The third case had a reaction induced by diclofenac, ibuprofen, and aspirin. Lastly, a reaction was induced by ibuprofen and mefenamic acid. According to available recorded data, the first and second cases should have avoided NSAIDs belonging to propionic acid derivatives, since the reactions occurred due to a single NSAID and manifested with urticaria or angioedema in patients without a history of chronic urticaria or asthma. Their reactions could be single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA).[35,36] For other cases, the patients should not have used culprit NSAIDs as well as other NSAIDs with strong COX-1 inhibitory activity since their reactions occurred due to at least two NSAIDs with different chemical structure and manifested with angioedema in patients without history of chronic spontaneous urticaria. Their reactions could be NSAIDs-induced urticaria/angioedema (NIUA).[35,36] However, we found the same reactions recurred due to topical ketoprofen, belonging to the same propionic acid derivatives, in those cases. Our findings strongly support topical NSAID's current legal warning that a patient should not use that topical NSAID product if he/she has known an allergic reaction to aspirin, the same or other NSAIDs.

The strength of our study is the experience of using the Thai Health Product Vigilance Center database with a large number of case reports submitted from various settings throughout the country. Nevertheless, several limitations exist in our study and should be discussed. Firstly, underreporting may affect our analysis for several reasons. First, we included case reports with topical NSAIDs being a suspected drug, not a concomitant drug, to avoid unconfirmed AEs. However, outcome reporting bias could occur because healthcare providers sometimes overlooked topical NSAIDs as a cause of AEs due to a better safety profile than systemic preparations. Second, topical NSAIDs are often patient self-medicated drugs because they are not included in the Thai National List of Essential Medicines and have also been widely available at drug stores as OTC drugs. Consequently, these products may not be recorded in the current patient medication profile of the hospital database, leading to missing medication history to identify and report AEs. Finally, as patient self-medicated drugs, if a non-serious AE occurs, the patient may decide to go to a community pharmacy instead of a hospital and are likely to seek advice from a community pharmacist. However, our findings showed no report from community pharmacies. Further efforts may be needed to promote adverse drug reaction reporting among community pharmacists who contribute to enhancing AE reports related to self-medicated or OTC drugs.

Secondly, similar to other pharmacovigilance studies[20-22], the limited quality of reports, especially incomplete data, is one major issue of the

pharmacovigilance database. We were unable to obtain precise data of some of the variables, such as historical details of allergy symptoms, a specific type of drug formulation, dosage regimen, and concomitant disease states, leading to being unable to identify relationships between AEs and particular risk factors entirely. Most case reports in our study were graded at quality level 2 (47.5%) and 1 (46.4%), but only 6.1% at level 3. Based on this finding, further attempts are continually needed to improve the completeness of reporting.

Recently, the Thai FDA has been interested in current evidence on topical NSAIDs-related AEs in order to consider revising written legal warnings in the PPI of those products. Our findings provided additional evidence for considering such revision to the Drug Safety Advisory Subcommittee of the Thai FDA. The new legal warning related to skin disorders should be added in the PPI of topical NSAIDs due to the potential risk of skin AEs in the Thai population. The legal warning concerning the history of NSAID allergy should remain unchanged. Due to a few reported AEs of GI system, renal system, liver diseases, and platelet and clotting system, alternative pieces of evidence should be provided together to consider the revision of those written legal warnings.

Current regulatory requirements of written legal warnings in the PPI of topical NSAIDs has announced in the Notification of the Ministry of Public Health (volume 55, 2015).[37] The legal warning related to skin disorders has been added as it is the likely cause for most cases, whereas former information related to GI system, renal system, liver diseases, and platelet and clotting system (including dengue), have been changed contents from contraindication to warning from a decision of the subcommittee due to their predictable adverse drug reaction.

Although there is evidence supporting topical NSAIDs' safety in patients with comorbidities, more studies are needed with long-term follow-up, and with severe or unstable comorbidities. Further efforts may also be needed to encourage community pharmacists to report AEs related to self-medicated or OTC drugs.

Conclusion

Our findings demonstrated that topical NSAIDs were potentially associated with a risk of skin AEs in the Thai population. The most frequent skin AEs were pruritus and rash, while systemic AEs were uncommon. Most AEs were classified as non-serious and developed within one week of topical NSAID therapy. There remain further studies to investigate topical NSAIDs' safety for long-term use and in patients with severe or unstable comorbidities.

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