Original Article

Factor-Associated in Pattern of Non-Steroidal Anti-Inflammatory Drug-Induced Cutaneous Adverse Drug Reactions in the Elderly

Papapit Tuchinda MD[1], Leena Chularojanamontri MD[1], Pattriya Chanyachailert MD[1], Kanokvalai Kulthanan MD[1], Kowit Jongjarearnprasert MS[2], Panadda Uthaitas B.Pharm[2]

[1]Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[2]Department of Pharmacy, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly prescribed medications in elderly, which can frequently cause cutaneous adverse drug reactions (ADRs).

Objective: The present study aimed to investigate demographic data of elderly patients who had cutaneous reactions from NSAIDs and determine the risk factors that induce serious reactions.

Materials and Methods: A retrospective analysis involving elderly patients aged 60 years or over with cutaneous ADRs suspected from NSAIDs attending the ADR Center, Siriraj Hospital, Mahidol University, Thailand, over a 4-year period. Demographic data, concurrent medications, clinical course of cutaneous ADRs and causative NSAIDs were analyzed.

Results: A total of 101 patients were included. Cutaneous ADRs from NSAIDs occurred more commonly in females (65.3%). Angioedema alone was the most common cutaneous ADRs (29.7%) followed by urticaria with and without angioedema (26.7%). Forty-one patients (40.6%) were categorized as serious ADRs. Systemic reactions were significantly associated with non-selective COX inhibitors as compared to preferential and selective COX-2 inhibitors (p = 0.046). A history of severe cutaneous ADRs is significantly associated with severity of cutaneous ADRs to NSAIDs in elderly (p<0.001).

Conclusion: Preferential and selective COX-2 inhibitors may be a good option for elderly due to lower risk of cutaneous ADRs. Early signs and symptoms of severe reactions should be addressed in this group of patients.

Keywords: cutaneous, adverse reaction, NSAID, elderly, geriatric

J Med Assoc Thai 2018; 101 (6): 713-9
Website: http://www.jmatonline.com

The proportion of the population aged 60 and over is increasing substantially. This group of people tends to have more medical comorbid conditions and concurrent use of over five medications in consequence of the complex therapeutic regimens[1]. The multivariable analysis study showed that polypharmacy was the significant predictor of adverse drug reactions (ADRs). In addition, pharmacodynamic and pharmacokinetic alterations in elderly patients, from decreasing hepatic drug clearance and the decline of renal function, can increase risks and mortality rates of ADRs in elderly[2-4].

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently prescribed medications worldwide[5]. About half of NSAIDs were prescribed for elderly patients[6]. Most previous reports about NSAID-induced ADRs were non-dermatologic conditions involving gastrointestinal system such as abdominal pain, dyspepsia, nausea and vomiting[7]. For cutaneous reaction, the rate of NSAID-induced cutaneous ADRs in general population varied from 0.3% - 0.7%[8,9]. In Thai patients, 19% of culprit drugs inducing urticaria were NSAIDs[10]. However, clinical knowledge of NSAID-induced cutaneous ADRs in elderly is limited. Accordingly, the present study aimed to investigate demographic data of elderly patients who had cutaneous reactions from NSAIDs and determine the risk factors that induce serious and non-serious reactions in elderly patients.

Correspondence to:

Tuchinda, P. Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University
2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-2-4194333, **Fax:** +66-2-4115031
Email: papapitt@gmail.com

Materials and Methods

The present cross-sectional retrospective study was approved by the Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Bangkok,

How to cite this article: Tuchinda P, Chularojanamontri L, Chanyachailert P, Kulthanan K, Jongjarearnprasert K, Uthaitas P. Factor-associated in pattern of non-steroidal anti-inflammatory drug-induced cutaneous adverse drug reactions in the elderly. J Med Assoc Thai 2018;101:713-9.

Thailand. Patients aged 60 years and over were defined as elderly patients according to the definition of the United Nations[11]. Elderly patients who were suspected to have cutaneous ADRs from NSAIDs and evaluated by the ADR center of Siriraj Hospital were included from January 2011 to December 2014. The NSAID reactions were diagnosed by well-trained dermatologists and pharmacologists. The standardized causality assessment was categorized using the World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) system as follows [12]:

1. *Certain* means that the ADR has occurred corresponding with the time period of drug intake, and the reaction could not be explained by a pre-existing disease, other concomitantly used drugs or other chemical substances. In addition, after the patients discontinued the medication, the reaction improved or disappeared. On the contrary, if the medication was rechallenged, the reaction recurred. Furthermore, the adverse reaction could be explained pharmacologically or phenomenologically by an objective evidence.
2. *Probable or Likely* means that the ADR has occurred reasonably with the time period of drug intake, and the reaction could probably not be explained by a pre-existing disease, other concomitantly used drugs or other chemical substances. When the patients discontinued the medication, the reaction improved or disappeared. However, the information about medication re-administration may be unavailable.
3. *Possible* means that the ADR has occurred reasonably with the time period of drug intake and could also be explained by a pre-existing disease, other concomitantly used drugs or other chemical substances. The information about medication re-administration may be unavailable or unclear.
4. *Unlikely* means that the ADR could not be occurred with the time period of drug intake and probably be explained by a pre-existing disease, other concomitantly used drugs or other chemical substances.
5. *Conditional or Unclassified* means that the ADR was occurred, however, additional proper assessment data are required.
6. *Unassessable or Unclassifiable* means that the ADR was suggested despite insufficient or contradictory information for a judgment. Data cannot be supplemented or verified.

Demographic data including history of atopy, urticaria, previous drug reactions, pre-existing diseases, concurrent medications, clinical course of cutaneous ADRs and possible causative NSAIDs were recorded. Patients having a history of previous other NSAID reactions were classified as multiple NSAID reactions. For the patients who were prescribed five or more medications were defined as receiving multidrug therapy or polypharmacy[13]. The cutaneous manifestations were categorized into serious cutaneous reactions and non-serious cutaneous reactions. Angioedema with or without urticaria, drug hypersensitivity syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, drug-induced vasculitis and anaphylaxis were considered to be serious drug reactions[14].

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation (SD) and median (minimum, maximum) for quantitative data, and presented as number (percentages) for categorical data. The chi-square test or Fisher's exact test were used to evaluate the correlations between categorical variables. Logistic regression was used for multivariate analysis. An independent sample t-test and Mann-Whitney U-test were used for comparing mean age and median duration between two categorical variables respectively. The results were considered statistically significant at $p \leq 0.05$. Statistical analysis was performed using the SPSS software version 22.0 (SPSS Inc, Chicago, IL).

Ethics consideration

The present study was approved by the Siriraj Institutional Review Board, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Results

Over the four-year period, 101 of 1,799 NSAID-induced ADRs patients reported to have cutaneous reactions. All of these reactions were new events and detected by physicians reported to ADRs center. Therefore, the incidence of cutaneous ADRs from NSAIDs over four years was 5.6%. Table 1 showed

Table 1. Demographic and clinical data of patients classified by suspected NSAID groups (n =101)

Characteristics	Number of patients (n = 101 (%)	Non-selective COX inhibitors; (n = 57) Number of patients (%)	Preferential and selective COX-2 inhibitors; (n = 44) Number of patients (%)	*p*-value Univariate analysis	*p*-value, Multivariate analysis
Sex					
Female	66 (65.3)	36 (63.2)	30 (68.8)	0.599	
Male	35 (34.7)	21 (36.8)	14 (31.1)		
Age					
Mean age±SD (years)	67.5±7.2	66.9±6.5	68.3±8.0	0.339	
History of atopy (n = 46)*	28/46 (60.9)	13/19 (68.4)	15/27 (55.6)	0.379	
Allergic rhinitis	25/46 (54.3)	10/17 (58.8)	15/29 (51.7)	0.641	
Asthma	13/46 (28.3)	7/17 (41.2)	6/29 (20.7)	0.181	
Atopic conjunctivitis	7/46 (15.2)	4/18 (22.2)	3/28 (10.7)	0.407	
History of chronic urticaria	2 (2.0)	0	2 (3.5)	0.503	
Previous drug allergy	34 (33.7)	21 (36.8)	13 (29.5)	0.442	
Previous drug allergy with cutaneous reaction	31 (30.7)	20 (35.1)	11 (25.0)	0.276	
Previous drug allergy with systemic reaction	9 (8.9)	5 (8.8)	4 (9.1)	1.000	
Single NSAID reactions	92 (91.1)	50 (87.7)	42 (95.5)	0.292	
Multiple NSAID reactions	9 (8.9)	7 (12.3)	2 (4.5)		
Underlying diseases					
Hypertension	57 (56.4)	32 (56.1)	25 (56.8)	0.946	
Orthopedic diseases	48 (47.5)	24 (42.1)	24 (54.5)	0.214	
Dyslipidemia	42 (41.6)	18 (31.6)	24 (54.5)	0.020	0.003
Diabetes	21 (20.8)	16 (28.1)	5 (11.4)	0.040	0.011
Malignancy	16 (15.8)	7 (12.3)	9 (20.5)	0.265	
Rheumatologic diseases	11 (10.9)	6 (10.5)	5 (11.4)	1.000	
Cerebrovascular diseases	7 (6.9)	4 (7.0)	3 (6.8)	1.000	
Liver diseases	7 (6.9)	3 (5.3)	4 (9.1)	0.696	
Coronary heart diseases	6 (5.9)	4 (7.0)	2 (4.5)	0.694	
Gastrointestinal diseases	6 (5.9)	3 (5.3)	3 (6.8)	1.000	
Renal diseases	5 (5.0)	3 (5.3)	2 (4.5)	1.000	
Multidrug therapy	46 (45.5)	24 (42.1)	22 (50.0)	0.430	
Cutaneous reaction					
Non-serious cutaneous reaction	60 (59.4)	30 (52.6)	30 (68.2)	0.115	
Serious cutaneous reaction	41 (40.6)	27 (47.4)	14 (31.8)	0.115	
Systemic reaction	25 (24.8)	18 (31.6)	7 (15.9)	0.070	0.046
Respiratory	17 (16.8)	12 (21.1)	5 (11.4)	0.197	
Anaphylaxis	5 (5.0)	3 (5.3)	2 (4.5)	1.000	
Gastrointestinal	3 (3.0)	3 (5.3)	0	0.255	

COX, cyclo-oxygenase enzymes; NSAID, non-steroidal anti-inflammatory drug

*A history of atopic diseases was recorded in only 46 patients in the study

demographic data of 101 elderly patients with cutaneous ADRs suspected from NSAIDs. Females were more common than males (65.3% and 34.7%, respectively). The mean age was 67.5±7.2 years, ranged from 60 to 90 years. Of 46 elderly patients, whose histories of atopy were recorded, allergic rhinitis was the most common atopic disease, followed by asthma and atopic conjunctivitis, (54.3%, 28.3%, and

15.2%, respectively). A history of previous drug allergy with systemic reactions was reported in 9 patients. The culprit drugs were sulfonamide, allopurinol, NSAIDs, gemfibrozil, gabapentin, and tolperisone.

Thirty-four patients (33.7%) and 9 patients (8.9%) reported a history of previous drug reactions from other drugs apart from NSAIDs and a history of multiple NSAID reaction, respectively. Almost 60% of the patients had non-serious cutaneous reactions. Respiratory tract was the most common organ involvement in patients who developed systemic reactions. Systemic reactions occurred significantly higher in patients received non-selective COX inhibitors as compared to preferential and selective COX-2 inhibitors, ($p = 0.046$).

In aspect of NSAID classification, as shown in Table 2, the most frequent NSAID used which probably induced cutaneous ADRs was etoricoxib (22.8%). Majority of these elderly patients were categorized by WHO-UMC assessment as "probable" (73.3%), however, no ADR was considered to be certain because of concerning about performing a re-challenge especially in elderly. Angioedema alone was the most common cutaneous reactions from NSAIDs in elderly (29.7%), (Table 3). There was no statistical significant difference between type of cutaneous reactions and groups of NSAIDs.

Among elderly patients with serious cutaneous reactions, female predominated than male ($p = 0.027$). There were no significant associations between serious cutaneous ADRs and age, history of atopy, urticaria, number of underlying diseases and multidrug therapy in the elderly patients. The culprit drugs caused serious cutaneous reactions in the present study were in order of frequency as follows; angioedema (caused by ibuprofen, naproxen, diclofenac, etoricoxib, aspirin, meloxicam, indomethacin, piroxicam, cerecoxib and parecoxib, respectively), anaphylaxis (caused by etoricoxib, ibuprofen and aspirin, respectively), and acute generalized exanthematous pustulosis (caused by ibuprofen). However, among multiple NSAID reactors, prevalence of serious cutaneous ADRs was shown to be significantly higher than prevalence of non-serious cutaneous ADRs ($p = 0.028$). Furthermore, patients with history of serious cutaneous drug reactions had a significant increased risk to develop serious cutaneous ADRs from NSAIDs ($p < 0.001$).

Table 2. Non-steroidal anti-inflammatory drugs causing cutaneous reactions (n = 101)

Drug groups	Suspected drugs	No. of drugs (%)
COX-1/ COX-2 inhibitors (n=57)	Naproxen	19 (18.8)
	Ibuprofen	13 (12.9)
	Diclofenac	12 (11.9)
	Aspirin	6 (5.9)
	Piroxicam	5 (5.0)
	Indomethacin	1 (1.0)
	Tenoxicam	1 (1.0)
Preferential COX-2 inhibitors (n=6)	Meloxicam	6 (5.9)
Selective COX-2 inhibitors (n=38)	Etoricoxib	23 (22.8)
	Celecoxib	13 (12.9)
	Parecoxib	2 (2.0)

COX, cyclo-oxygenase enzymes

Discussion

Because of polypharmacy and pharmacodynamics and pharmacokinetics alterations, an advance age was a significant risk factor for ADRs[15]. Prevalence of NSAID-induced cutaneous ADRs was 9.5% in Thai elderly patients[16]. Moreover, 16.5% of the Australian patients aged 60 years or older were admitted to the hospital due to ADRs from analgesic drugs including NSAIDs[17]. In previous ADRs studies either in elderly or in NSAIDs hypersensitivity, females had a higher incidence of ADRs from NSAIDs than males which were similar to our study[16,18,19]. It has been suggested that pharmacokinetic, immunological and hormonal differences and multiple drug use by female may explain the higher incidence[1,20]. Another risk factor for NSAIDs-induced cutaneous ADRs was atopic condition[21]. We found that patients with cutaneous ADRs to NSAIDs tended to have concomitant atopic diseases (60.9%) which is higher than the prevalence of atopy in Thai elderly (4.8%)[22]. However, it should be noted that the history of atopic diseases was recorded in only 46 patients in our study.

Previous study in Thai patients reported that ibuprofen was the most frequent suspected causative NSAID inducing cutaneous ADRs (25.7%) and etoricoxib was less frequently reported (7.3%)[18]. In contrast, our findings showed that etoricoxib was the most common culprit drug of cutaneous ADRs in elderly (22.8%). Ibuprofen was found to be the suspected drug in 12.9% of the patients. However, it should be noted that amount of etoricoxib prescriptions in elderly from our institute were approximately three times higher than ibuprofen prescriptions (28,984 and 8,949, respectively). Cutaneous ADRs proportion

Table 3. Cutaneous reactions caused by suspected non-steroidal anti-inflammatory drugs (n = 101).

Type of cutaneous reactions	Total; (n =101) No. of patients (%)	Non-selective COX inhibitors; (n = 57) No. of patients (%)	Preferential and selective COX-2 inhibitors; (n = 44) No. of patients (%)	*p*-value
Angioedema alone	30 (29.7)	21 (36.8)	9 (20.5)	0.074
Maculopapular rash	19 (18.8)	9 (15.8)	10 (22.7)	0.376
Urticaria	17 (16.8)	7 (12.3)	10 (22.7)	0.164
Angioedema and urticaria	10 (9.9)	5 (8.8)	5 (11.4)	0.774
Pedal edema	8 (7.9)	2 (3.5)	6 (13.6)	0.076
Fixed drug eruption	6 (5.9)	5 (8.8)	1 (2.3)	0.228
Erythematous reaction	5 (5.0)	2 (3.5)	3 (6.8)	0.315
Eczematous drug eruption	4 (4.0)	2 (3.5)	2 (4.5)	1.000
Photosensitivity dermatitis	3 (3.0)	3 (5.3)	0	0.225
AGEP	1 (1.0)	1 (1.8)	0	1.000
Mucositis	1 (1.0)	0	1 (2.3)	0.436

AGEP, acute generalized exanthematous pustulosis; COX, cyclo-oxygenase enzymes

among elderly from etoricoxib was lower than from ibuprofen (0.00079 and 0.0015, respectively). Accordingly, physicians may prefer to prescribe selective COX-2 inhibitors in order to avoid common side effects of non-selective COX-2 inhibitors, such as abdominal pain, dyspepsia, nausea and headache, in elderly patients[7]. Our study demonstrated that Asian patients had some similar findings of cutaneous NSAID reactions as Caucasian patients[23-26]. Firstly, both of them tended to have cutaneous ADRs to non-selective COX inhibitors rather than preferential and selective COX-2 inhibitors. Secondly, patients who took non-selective COX inhibitors had a higher proportion of angioedema (with and without urticaria) than those who took COX-2 selective inhibitors (45.6% and 31.9%, respectively)[27]. Lastly, systemic reaction was significantly higher in patients using non-selective COX inhibitors. It may be explained that COX-1 enzyme which is associated with the mechanism of angioedema and urticaria is not inhibited by selective COX-2 inhibitors[28].

The study by Kasemsarn, et al., the rate of severe cutaneous ADRs from NSAIDs in general population was not different from in elderly patients in our study (47.2% and 40.6%, respectively)[18]. However, the rate of NSAID-induced severe cutaneous ADRs (40.6%) in the elderly in our study was higher than the rate of overall drug-induced severe cutaneous ADRs in elderly according to Kasemsan et al. study (16.5%)[16]. It may be explained that angioedema, which was categorized as a severe reaction, was the most common cutaneous manifestations of ADRs from NSAIDs. We also found that multiple NSAIDs reactors and history of severe cutaneous ADRs may be the risk factors of the serious cutaneous ADRs.

It was suggested that elderly patients were possible at risk for serious ADRs due to alterations in pharmacokinetics, pharmacodynamics, and drug interactions in their bodies[5,15]. The NSAIDs are relatively lipid soluble and predominantly cleared by hepatic metabolism resulting in inactive metabolites being excreted in urine[29]. According to an increase in adipose tissue storages and pharmacokinetic alteration in the geriatric patients, hepatic blood flow is likely to be reduced by 40% to 45% resulting in increasing dose of unbound plasma concentration. In accordance with the age-related renal deterioration, higher drug levels of NSAIDs in elderly may lead to severe ADRs[5]. Previous study from India found that advance age (>80 years) was a significant risk factor for ADRs[15]. However, we could not find the relationships between hepatic and renal diseases and cutaneous ADRs from NSAIDs. In the present study, age older than 75 years (17 patients) was not at significant risk factor to develop serious cutaneous ADRs. There is a limitation of our study which has to be pointed out. Some patients who were prescribed NSAIDs from our hospital and developed cutaneous ADRs might seek treatment from other hospitals. Thus, the incidence of cutaneous ADRs from NSAIDs in the elderly from our study may be lower than the real situation.

Conclusion

Due to the lower rate of cutaneous ADRs, preferential and selective COX-2 inhibitors may be the preferred option for elderly patients. Physician should be aware that multiple NSAID reactors and patients who have had previous severe cutaneous reactions from other drugs may be susceptible to develop severe reactions to NSAIDs.

What is already known on this topic?

Alterations in pharmacokinetics and pharmacodynamics in elderly patients were a possible risk for serious ADRs from NSAIDs.

What is this study add?

Elderly patients who were prescribed with non-selective COX inhibitors were significantly at increased risk of systemic reaction.

Acknowledgment

We would like to acknowledge Ms. Suthipol Udomphunthurak for statistical advice and analysis. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Funding

This study was not supported by any grants.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivela SL, Isoaho R. Use of medications and polypharmacy are increasing among the elderly. J Clin Epidemiol 2002; 55: 809-17.
2. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem 2010; 17: 571-84.
3. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev 2004; 56: 163-84.
4. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009; 4: e4439.
5. Johnson AG, Day RO. The problems and pitfalls of NSAID therapy in the elderly (Part I). Drugs Aging 1991; 1: 130-43.
6. Lee SH, Han CD, Yang IH, Ha CW. Prescription pattern of NSAIDs and the prevalence of NSAID-induced gastrointestinal risk factors of orthopaedic patients in clinical practice in Korea. J Korean Med Sci 2011; 26: 561-7.
7. Moore N, Ganse EV, Le Parc JM, Wall R, Schneid H, Farhan M, et al. The PAIN Study: paracetamol, aspirin and ibuprofen new tolerability study: a large-scale, randomised clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. Clin Drug Investig 1999; 18: 89-98.
8. Oberholzer B, Hoigne R, Hartmann K, Capaul R, Egli A, Wymann R, et al. Incidence of drug side effects by symptoms and syndromes. From the experiences of the Comprehensive Hospital Drug Monitoring and the Swiss Drug Side Effect Center. As an example: allergic and pseudo-allergic reactions with mild analgesics and NSAID. Ther Umsch 1993; 50: 13-9.
9. Hunziker T, Kunzi UP, Braunschweig S, Zehnder D, Hoigne R. Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. Allergy 1997; 52: 388-93.
10. Rutnin NO, Kulthanan K, Tuchinda P, Jongjarearnprasert K. Drug-induced urticaria: causes and clinical courses. J Drugs Dermatol 2011; 10: 1019-24.
11. United Nations, Department of Economic and Social Affairs, Population Division. World population ageing (ST/ESA/SER.A/390) [Internet]. New York: United Nations; 2015 [cited 2016 Sep 26]. Available from: http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf.
12. World Health Organization. Causality assessment of suspected adverse reactions [Internet]. Geneva: WHO; 2012 [cited 2016 Sep 26]. Available from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf.
13. Kennerfalk A, Ruigomez A, Wallander MA, Wilhelmsen L, Johansson S. Geriatric drug therapy and healthcare utilization in the United kingdom. Ann Pharmacother 2002; 36: 797-803.
14. Mockenhaupt M. Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. J Dtsch Dermatol Ges 2009; 7: 142-60.
15. Mandavi, D'Cruz S, Sachdev A, Tiwari P. Adverse drug reactions & their risk factors among Indian

ambulatory elderly patients. Indian J Med Res 2012; 136: 404-10.
16. Tuchinda P, Chularojanamontri L, Sukakul T, Thanomkitti K, Nitayavardhana S, Jongjarearnprasert K, et al. Cutaneous adverse drug reactions in the elderly: a retrospective analysis in Thailand. Drugs Aging 2014; 31: 815-24.
17. Burgess CL, Holman CD, Satti AG. Adverse drug reactions in older Australians, 1981-2002. Med J Aust 2005; 182: 267-70.
18. Kasemsarn P, Kulthanan K, Tuchinda P, Dhana N, Jongjarearnprasert K. Cutaneous reactions to non-steroidal anti-inflammatory drugs. J Drugs Dermatol 2011; 10: 1160-7.
19. Schubert B, Grosse Perdekamp MT, Pfeuffer P, Raith P, Brocker EB, Trautmann A. Nonsteroidal anti-inflammatory drug hypersensitivity: fable or reality? Eur J Dermatol 2005; 15: 164-7.
20. Rademaker M. Do women have more adverse drug reactions? Am J Clin Dermatol 2001; 2: 349-51.
21. Sanchez-Borges M, Capriles-Hulett A. Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. Ann Allergy Asthma Immunol 2000; 84: 101-6.
22. Jiamton S, Leeyaphan Ch, Prasertworonun N, Omcharoen V. Skin diseases among elderly attending out-patient dermatologic clinic, Siriraj Hospital. Siriraj Med J 2014; 66: 219-24.
23. Celik G, Pasaoglu G, Bavbek S, Abadoglu O, Dursun B, Mungan D, et al. Tolerability of selective cyclooxygenase inhibitor, celecoxib, in patients with analgesic intolerance. J Asthma 2005; 42: 127-31.
24. García-Rodríguez RM, Hinojosa M, Camacho-Garrido E, Berges Gimeno P, Martín García C. Celecoxib, safe in NSAID intolerance. Allergy 2002; 57: 1085-6.
25. Pacor ML, Di Lorenzo G, Biasi D, Barbagallo M, Corrocher R. Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal anti-inflammatory drugs. Clin Exp Allergy 2002; 32: 397-400.
26. Quiralte J, Sáenz de San Pedro B, Florido JJ. Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. Ann Allergy Asthma Immunol 2002; 89: 63-6.
27. Downing A, Jacobsen J, Sorensen HT, McLaughlin JK, Johnsen SP. Risk of hospitalization for angio-oedema among users of newer COX-2 selective inhibitors and other nonsteroidal anti-inflammatory drugs. Br J Clin Pharmacol 2006; 62: 496-501.
28. Sanchez-Borges M, Capriles-Hulett A, Caballero-Fonseca F. NSAID-induced urticaria and angioedema: a reappraisal of its clinical management. Am J Clin Dermatol 2002; 3: 599-607.
29. Day RO, McLachlan AJ, Graham GG, Williams KM. Pharmacokinetics of nonsteroidal anti-inflammatory drugs in synovial fluid. Clin Pharmacokinet 1999; 36: 191-210.